THE SYNTHESIS AND REACTIONS

OF

STEROID EPOXIDES

by

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T O M Y P A R E N T S

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NOTE

The configuration of the hydrogen atoms at the ring junctions will be 5α,8β,9α and 14α, unless otherwise specified.

In the diagrams the configurations are shown as follows:

A solid line indicates a β-configuration

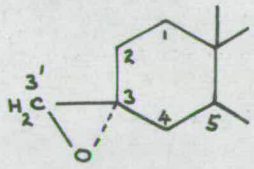
A broken line indicates a α-configuration

A wavy line indicates an unknown configuration or a mixture of isomers.

A dotted line indicates a partially formed bond.

The nomenclature, adopted by Bladon and McMeeken,[86] for exocyclic steroid epoxides has been followed.

The exocyclic carbon at C-3 will be named the 3' position,

e.g. 

is 3β-methyl-3α,3'-epoxy-5α-cholestane.

Summary

The stereochemical results of the epoxidation with dimethyloxosulphonium methylide and dimethylsulphonium methylide of 5α-cholestan-3-one, 2α-methyl-5α-cholestan-3-one, 2,2-dimethyl-5α-cholestan-3-one, 5α-cholestan-2-one and 5α-androstan-17-one and the epoxidation with peracids and the alkaline hydrogen peroxide-benzonitrile system of the methylene-derivatives of these five ketones have been studied. Dimethyloxosulphonium methylide with the A-ring-ketones gave mainly epoxides resulting from equatorial attack, while its reaction with the 17-ketone involved attack from the α-side. Attack of 5α-cholestan-3-one and 2,2-dimethyl-5α-cholestan-3-one with dimethylsulphonium methylide was mainly axial, whilst the epoxidation of 2α-methyl-5α-cholestan-3-one and 5α-cholestan-2-one with the same reagent involved principally equatorial attack. The reaction of 5α-androstan-17-one with dimethylsulphonium methylide gave the 17β,20-epoxide. Peracid attack of the 3-methylene-steroids was mainly axial, while that of 2-methylene-5α-cholestan and 17-methylene-5α-androstane was predominantly from the α-side. Epoxidation of the A-ring-methylene-steroids with the alkaline hydrogen peroxide-benzonitrile system involved predominantly equatorial attack, whilst 17-methylene-5α-androstane with this reagent gave the 17α,20-epoxide. The addition of hypohalous acids to 3-methylene-5α-cholestane has been studied. The epoxidation of A-nor-5α-cholestan-2-one with dimethyloxosulphonium methylide and the peracid epoxidation of 2-methylene-A-nor-5α-cholestane and 3-methylene-4,4-dimethyl-cholest-5-ene have been carried out.

The reactions of methylene-epoxides under basic conditions

involved attack at the exocyclic carbon atom, while with acids or reagents involving coordination to the epoxide oxygen as the first stage attack took place at the more heavily substituted steroid-ring carbon atom.

The stereochemistry of the intermediate amino-alcohols produced in the Tiffeneau reactions of 5α-cholestan-3-one, 2α-methyl-5α-cholestan-3-one and 2,2-dimethyl-5α-cholestan-3-one has been deduced from the corresponding 3-methylene-epoxides by cleavage with N_3^-, followed by reduction of the 3-azidomethyl-3-alcohols.

The epoxidation of cholest-4-en-3-one with dimethylsulphonium methylide was unsuccessful, alumina chromatography of the crude product allowing for the isolation of an α,β-unsaturated-5α-cholestan-3-aldehyde. The synthesis of 3β-methyl-3α,3'-epoxy-5α-cholestan-2-one from 2,2-ethylenedioxy-5α-cholestan-3-one has been carried out. 2-Methylene-5α-cholestan-3β-ol was prepared from 2-N-piperidino-methylene-5α-cholestan-3-one and the peracid epoxidation of the 2-methylene-3β-ol and its 3β-acetate was carried out, followed by modifications of the C-3 functional groups of the epoxides. The reactions of these 3-oxygenated-2-methylene-epoxides with acidic reagents involved cleavage of the bond between the epoxide oxygen atom and the exocyclic carbon atom.

The epoxidation of the 3-ethylidene-5α-cholestanes and 3-isopropylidene-5α-cholestane with peracid involved predominantly axial attack, whilst epoxidation of these compounds with the alkaline hydrogen peroxide-benzonitrile system showed a preference for equatorial attack to take place. The epoxide derivatives of the 3-ethylidene-5α-cholestanes all gave 3β-acetyl-5α-cholestane on

rearrangement with BF_3, the β-epoxides also giving some 3α-methyl-5α-cholestan-3β-aldehyde. The BF_3 catalysed rearrangements of the two 3-isopropylidene-epoxides have been carried out. The α-epoxide gave 4,4-dimethyl-A-homo-5α-cholestan-3-one and 3β-methyl-3α-acetyl-5α-cholestane, while the β-epoxide gave 3α-methyl-3β-acetyl-5α-cholestane. As part of the proof of the structure of the ring enlargement product from the α-epoxide, the methylation of A-homo-5α-cholestan-4-one was carried out.

The synthesis and the BF_3-catalysed rearrangements of the epoxides of 2-isopropylidene-A-nor-5α-cholestane have been carried out.

The α- and β-epoxides of 2,3-dimethyl-5α-cholestane have been prepared and treated with BF_3, the α-epoxide giving 2β-methyl-2α-acetyl-A-nor-5α-cholestane and the β-epoxide the corresponding 2α-methyl-2β-acetyl-compound.

Finally the reaction of 2α,3α-epoxy-5α-cholestane with methyl magnesium iodide was found to involve rearrangement to 5α-cholestan-3-one.

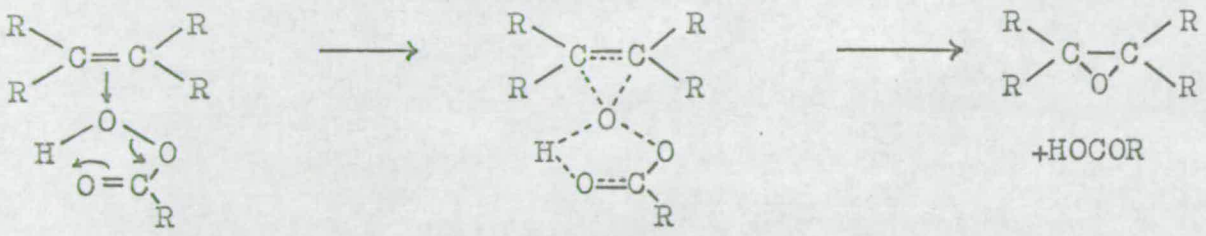
INTRODUCTION

The chemistry of the epoxide group in steroid systems has been extensively investigated. The methods of synthesis and ring-opening reactions of particular steroid epoxides illustrate the influence that steric, electronic, and conformational factors can have upon the chemical reactions of the epoxide system. In the work presented in this thesis the synthesis and reactions of some exocyclic and tetrasubstituted steroid epoxides are reported. Examples were chosen in order to illustrate three aspects of epoxide chemistry; stereochemistry of epoxidation, nucleophilic substitution reactions of epoxides, and Lewis acid catalysed rearrangement reactions of epoxides.

A literature review of the available information relevant to these three aspects of epoxide chemistry has been made.

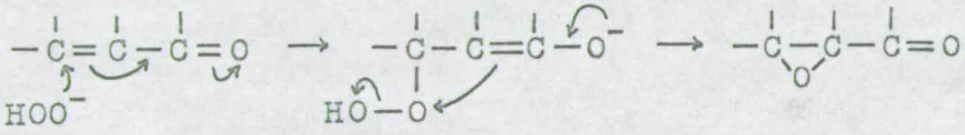
Stereochemistry of Epoxidation

Of the many methods available for epoxide synthesis the most frequently used are peracid (1)[1] and alkaline hydrogen peroxide (2)[1] oxidation of olefins, cyclodehydrohalogenation of halohydrins with alkali (3, X = halogen),[1] and cyclisations which involve other leaving groups than halogen such as the base treatment of monoalkyl- or monoarylsulphonate esters of 1,2-diols (3, X = $-OSO_2R$). To these methods can be added two recently reported procedures which offer interesting and useful routes to epoxides. The first method consists of the treatment of olefins with benzonitrile and hydrogen peroxide in methanol at a pH ca.8.[2,3] Here the peroxide and benzonitrile co-react to give the reactive peroxybenzimidic acid (4) which in the absence of an olefin will oxidise the hydrogen peroxide itself to oxygen (4).[2] The mechanism for epoxidation by this reagent has not yet been rigorously established but has been assumed to be similar to the Bartlett[1] mechanism for peracid epoxidations (1).[3] The second of the newer methods involves the reaction of aldehydes and ketones with certain sulphur ylides.[3,4,5,6] Of the ylides that have been used for epoxide synthesis, dimethyloxosulphonium methylide (5a) and dimethylsulphonium methylide (5b) have so far been the most prominent.[3,4,5] It has been found that these two ylides differ both in their reactivity and in their reactions.[4] For while the less reactive oxosulphonium ylide interacts with the carbonyl group of aromatic and nonconjugated aldehydes and ketones to form epoxides and with α,β-unsaturated ketones to form cyclopropyl



(1)

$$H_2O_2 + OH^- \rightleftharpoons HO_2^- + H_2O$$



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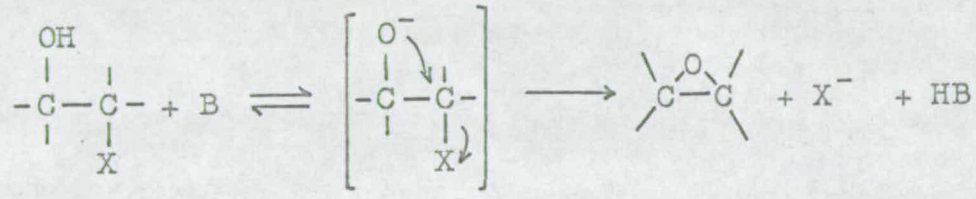
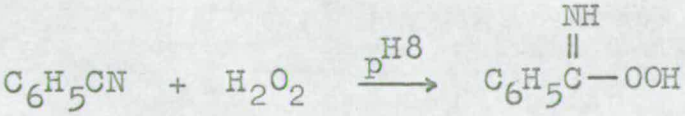
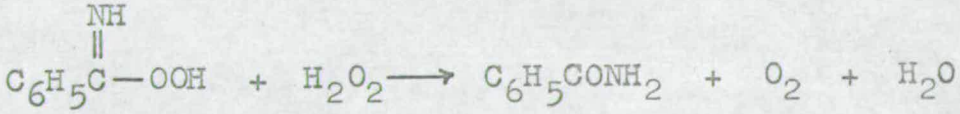


B = a base.

(3)

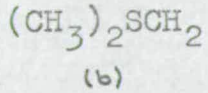




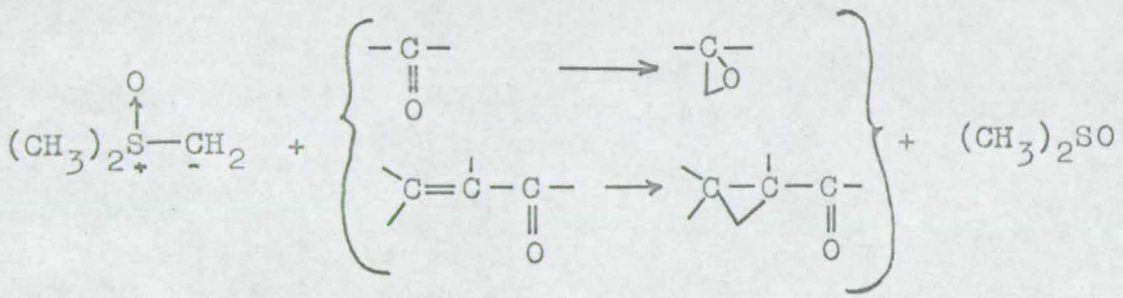
(4)

(a)

(5)



(b)



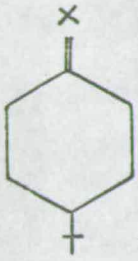
(6)

ketones (6), the sulphonium ylide is extremely labile with a half-life of a few minutes at room temperature and gives only epoxides even from α,β-unsaturated ketones.

(a) Epoxides from olefins

Turning now to the stereochemical aspects of epoxidation, it is a general rule that the attacking species, be it peracid or halonium ion, will tend to approach the site of the reaction from the less hindered side of the molecule. This directive influence is clearly seen in the peracid epoxidation of steroid olefins. In A/B-trans steroids, for example, the screening of the β-face of the molecule by the angular C-19 and C-18 methyl groups causes attack by peracid predominantly from the less hindered α-face resulting in the formation of α-epoxides. Thus 5α-cholest-1-ene,[7] 5α-cholest-2-ene,[8] and 5α-cholest-3-ene[9] all give exclusively α-epoxides on treatment with peracids. With cholest-5-ene, however, some ca.27% of the β-epoxide is formed on peracid epoxidation.[10] The formation of the β-epoxide is attributed to the effect which the 5,6-double bond has upon the conformation of rings A and B. The trigonal carbon atoms at C-5 and C-6 cause the 19-methyl group to become pseudoaxial thereby reducing the screening effect on the incoming reagent. However it must be noted that cholest-4-ene in which the methyl group at C-10 is also pseudoaxial gives only the α-epoxide.[11]

The results from the peracid epoxidation of several rigid methylenecyclohexane systems have recently been published.[3,12,13] With relatively unhindered compounds such as 4-t-butyl-methylenecyclo-



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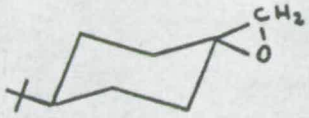

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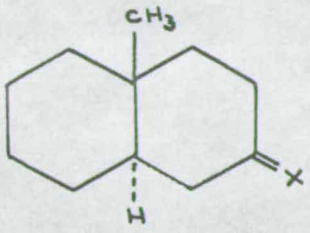
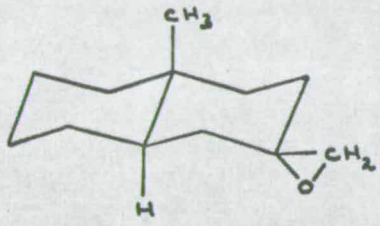
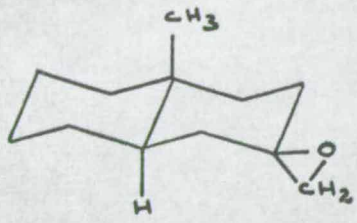


(10)



(11)



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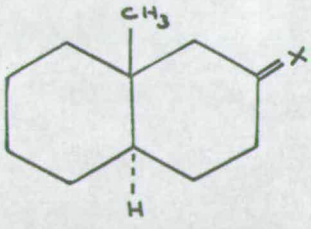

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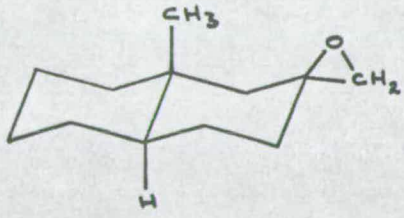

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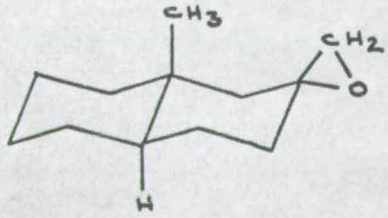


(15)

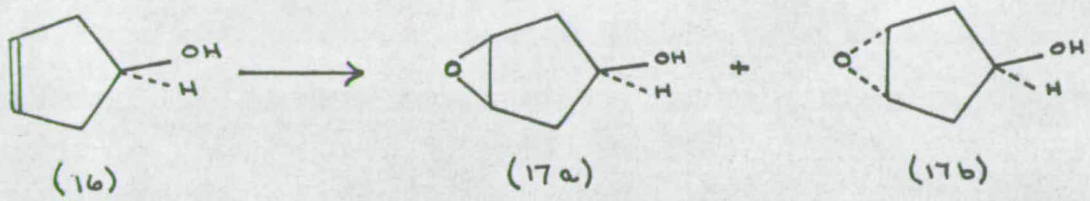
hexane (7, X = CH_2) and trans-10-methyl-2-methylene-decahydronaphthalene (10, X = CH_2) peracid attack is predominantly axial to give the two epoxides (8) and (11), while equatorial attack is observed with the more hindered trans-9-methyl-2-methylene-decahydronaphthalene (13, X = CH_2) giving the epoxide (15).[3] Explanations similar to those used to elucidate the stereochemistry of the metal hydride reduction of cyclohexanones have been put forward to explain these epoxide formations since the results obtained from the epoxidations of the methylene-compounds when compared with the reduction products of the corresponding ketones (7, 10, 13, X = O) are found to be stereochemically very similar.[3] There have been two explanations put forward in order to account for the stereochemistry of metal hydride reduction of cyclohexanones.[14,15,16] The first[14] involves two factors, "steric approach control" and "product development control." Here equatorial approach is assumed to involve approach from the less hindered side, and is found in relatively hindered cyclohexanones where there is substantial steric interference between a β-axial substituent and the attacking species in the transition state, with the less stable axial alcohol resulting. With unhindered cyclohexanones, on the other hand, the stable equatorial alcohols are predominantly formed, and it is assumed that the relative stability of the product is reflected in the transition state with formation of the more stable product. Thus while the result of the epoxidation of the more hindered olefin (13, X = CH_2) in which there is one 1,3-interaction with hydrogen and one 1,3-interaction with the angular methyl group is presumably due to

"steric approach control" the other methylene-cyclohexanes would appear to give products resulting from "product development control" indicating that the epoxides are more stable with their methylene groups "equitorial."

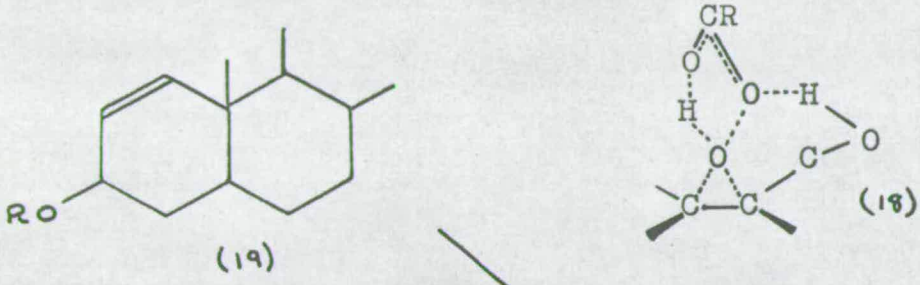
In the second explanation[15,16] it is suggested that unhindered cyclohexanones are not symmetrical above and below the plane of the carbonyl group and that while equitorial substituents on the carbons α to the carbonyl group are more or less in the plane of the carbonyl group thereby giving little steric interference to attacking reagents the axial substituents on the same α-carbon atoms are perpendicular to the plane of the carbonyl group and will tend to interfere with the close approach of a reagent from the equitorial side. If the transition state for the reaction is reached at some distance from the carbonyl group, however, the axial hydrogens on the β-carbons will become sterically more important resulting in a decrease in axial attack. Applying this hypothesis to the peracid epoxidation results would therefore indicate that the peracid must closely approach the double bond in the transition state.

From the epoxidation reactions with the unhindered methylene-cyclohexanes[3] it was found that the amount of axial attack is somewhat solvent dependent, the use of methylene chloride and chloroform giving the least amount of axial attack. This is ascribed to a tighter solvation of the transition state which will consequently increase the bulk of the reagent making a sterically controlled process more important.

Steric factors are not, however, the only influences on the



(16) (17a) (17b)



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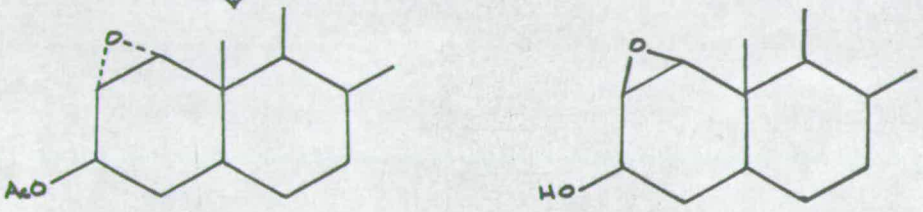
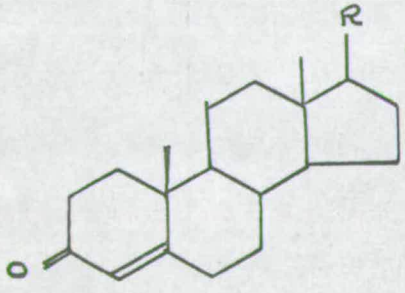
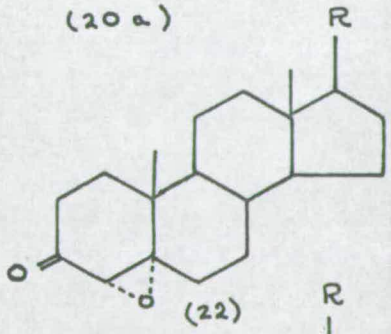


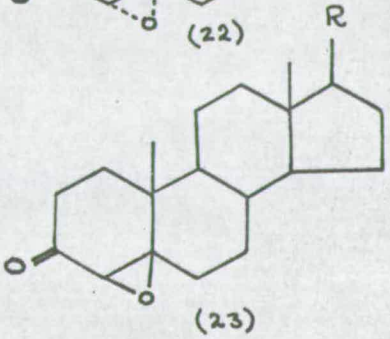
(20b) (20a)



(21)



(22)

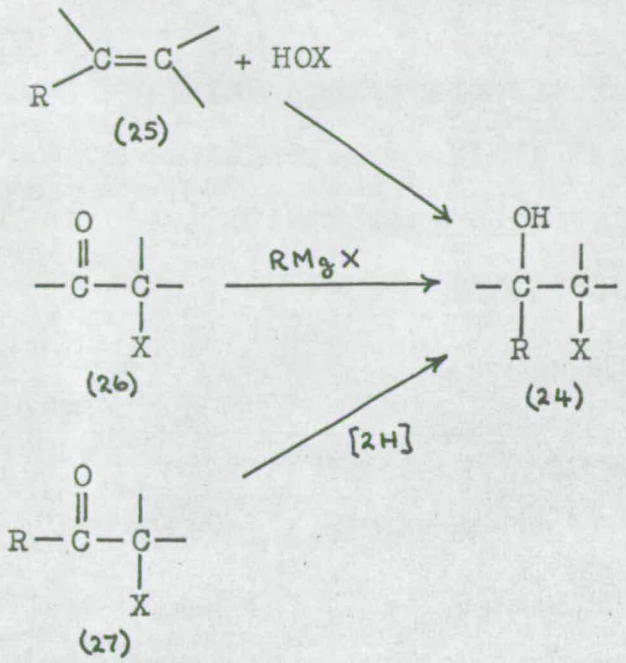


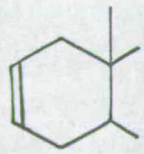
(23)

stereochemistry of peracid epoxidation. With α,β- or β,γ-unsaturated alcohols peracid attack produces an epoxide in which the epoxide oxygen usually assumes a position on the same side of the molecule as the hydroxyl group (eg. (17a)).[12,17,18] This can naturally give an epoxide oxygen on either the more or less hindered side of the molecule, depending on the position of the hydroxyl group. This has been explained in terms of hydrogen bonding between the peracid and the hydroxyl group (18), which holds the reagent on the same side as the hydroxyl group with the result that finally a cis-epoxy-alcohol is produced. One of the best steroid examples of this is the epoxidation with perbenzoic acid of 5α-cholest-1-en-3β-ol (19, R = H) in which the 1β,2β-epoxide (20a) is formed, whereas 3β-acetoxy-5α-cholest-1-ene (19, R = Ac) yields the corresponding 1α,2α-epoxide (20b).[18d] This type of reaction has been found in some cases to be solvent controlled,[17] for while epoxidation of cyclo-pentenol (16) gives high yields of cis-epoxide (17a) in cyclopentane or acetonitrile as solvent, more trans-compound (17b) is produced in ether or methanol. This is probably due to the hydroxyl group hydrogen bonding with the oxygenated solvents rather than the peracid

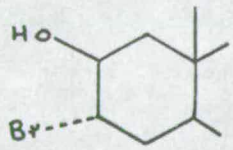
Long range directive effects have also been observed in olefin epoxidation.[17] Thus the alkaline hydrogen peroxide of 17-substituted Δ^4-3-keto-steroids (21) gives 100% β-epoxide (23) as the normal product except where the 17-substituent is a hydroxy- or acetoxy-group when, because of polar effects, up to 30% of the product is the α-epoxide (22).

So far only one stereochemically significant epoxidation with

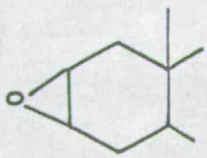




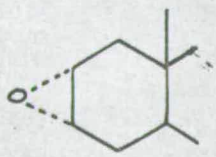
(28)



(29)



(30)

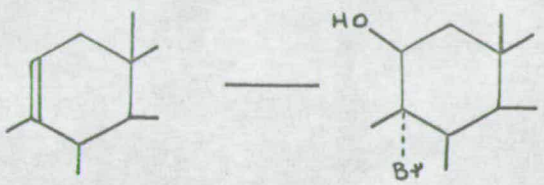


(31)

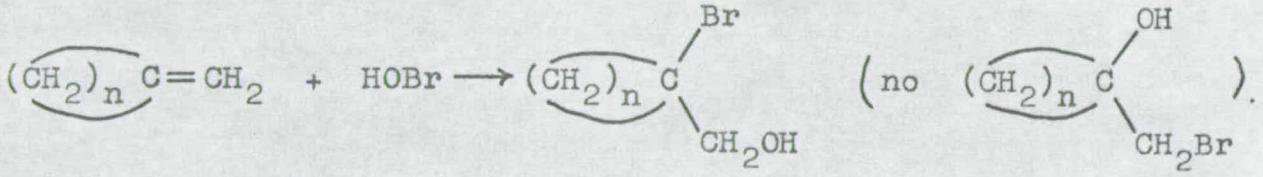
the alkaline hydrogen peroxide-benzonitrile system has been carried out.[3] Epoxidation with this reagent of the same rigid methylene-cyclohexanes used in the study of peracid epoxidation (p.3) in all cases gives predominantly equatorial oxygen transfer. These results can be explained by assuming that the reagent has considerable steric bulk thus attacking the double bonds by a sterically controlled process and/or that the transition state for the addition is formed at a distance from the double bond such that the β-axial hydrogens become sterically important.

There are three well established methods for the synthesis of the intermediate halohydrins (24) necessary in the cyclodehydrohalogenation technique; the addition of a hypohalous acid to an olefin (25), reduction of α-halo-carbonyl compounds (26) and addition of organo-metallic reagents to α-halo-carbonyl compounds (27).[1] In all cases the hydrogen atom and hydroxyl-group must be trans to one another for cyclisation to an epoxide to take place, the reaction being particularly favoured when the groups are trans diaxial to one another.[1] This necessity for trans arrangement of groups also applies for those cyclisations involving leaving groups other than halogen.[1]

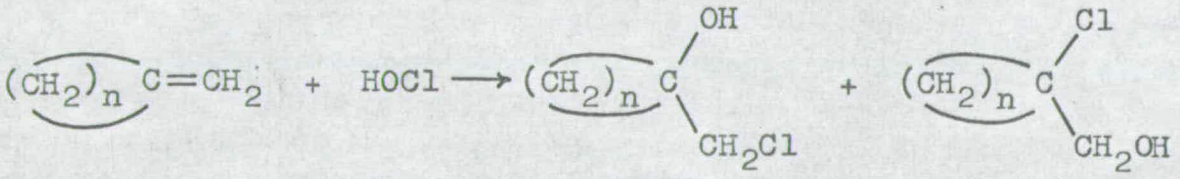
The stereochemistry of epoxidation starting from α-halo-carbonyl compounds depends on the configuration of the halogen atom in the starting material (and need not be considered further). With the addition of a hypohalous acid to an olefin the principle of attack from the less hindered side again predominates,[1] attack of the halonium ion producing a halohydrin with the oxygen atom on the more


HO
Br

(32) (33)

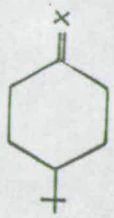

(CH2)n C=CH2 + HOBr
Br
CH2OH
(no
OH
CH2Br
).

(34)

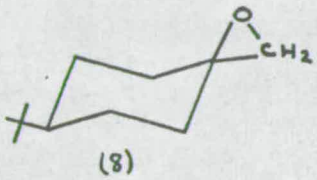

(CH2)n C=CH2 + HOCl
OH
CH2Cl
+
Cl
CH2OH

(35)

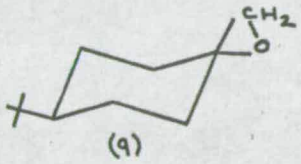
hindered side of the molecule. This therefore results in the formation of epoxides isomeric in configuration to those obtained by peracid epoxidation of the same olefin. For example hypobromous acid generated from N-bromosuccinimide and perchloric acid with 5α-cholest-2-ene (28) gives 3α-bromo-5α-cholestan-2β-ol (29),[19] which on treatment with alkali produces 2β,3β-epoxy-5α-cholestane (30)[20] while as has already been mentioned peracid attack of this olefin gives the α-epoxide (31).[8] Also well illustrated in this example is the stereochemistry of the addition to the 2,3-double bond, the trans diaxial bromohydrin and not the diequatorial compound being produced. Endocyclic olefins in general give trans diaxial addition compounds, the unsymmetrically substituted ^{9,11}-steroids (32) give, for example, the 9α-bromo, 11β-alcohols (33).[21] This is in marked contrast to addition of hypohalous acids to unsymmetrically substituted acyclic olefins where Markovnikov's rule is usually obeyed to give a compound with the halogen atom on the less substituted carbon atom.[22] Again of particular relevence to this work is the addition of hypohalous acids to methylenecycloalkanes.[23] Here ring size has an influence for while hypobromous acid gives only 1-bromo-cycloalkylmethanols (34), hypochlorous acid gives mixtures of chlorohydrins. The 1-chloro-compounds predominate for four- and six-membered rings and the chloromethylcycloalkanols predominating with the five- and seven-membered rings (35).



(7)



(8)



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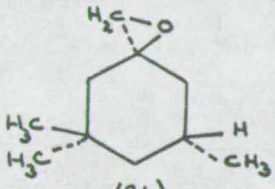

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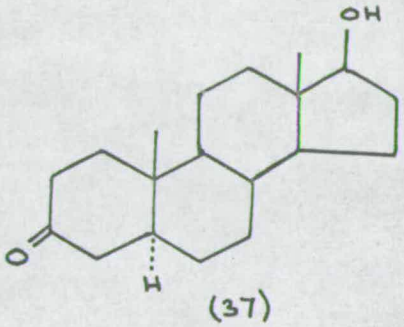

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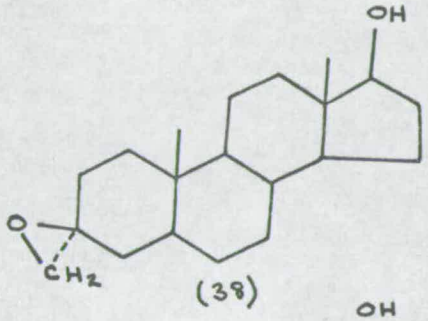

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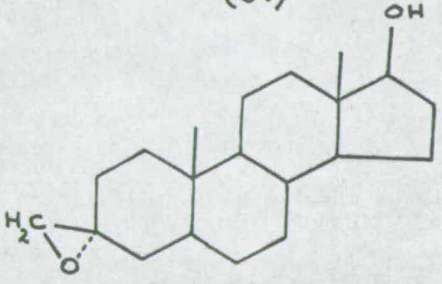

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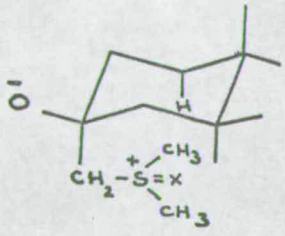
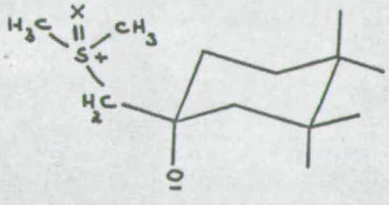


(40)

a. without X

b. X = O



(41)

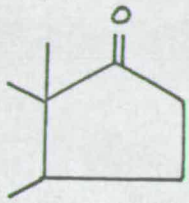
a. without X

b. X = O

(b) Epoxides from ketones

The stereochemical results for the epoxidation of the carbonyl groups of aldehydes and ketones with dimethyloxosulphonium methylide and dimethylsulphonium methylide are interesting. It has been shown that in this respect a real difference exists between these two ylides. For while the oxosulphonium ylide on addition to cyclohexanones reacts by equatorial attack the sulphonium ylide shows a preference for axial attack.[4] Examples include the reaction with 4-t-butylcyclohexanone which with the oxosulphonium ylide gives a 90% yield of the epoxide (9), while with the sulphonium ylide a mixture of the two epoxides (8) and (9) is produced in which the epoxide with cis t-butyl and epoxide oxygen atom (8) predominates (ratio of cis:trans 87:13). Transfer of methylene to 3,3,5-trimethylcyclohexanone with the oxosulphonium ylide is also stereospecific with only epoxide (36) being formed. The same starting material on reaction with the sulphonium ylide gives a mixture of epoxides with the axial methylene epoxide comprising 55% of the mixture.

Several non-conjugated steroid ketones have been treated with these reagents as a means of producing exocyclic steroid epoxides.[5] With 5β-steroid-3-ketones single epoxides seem to be produced on treatment with dimethyloxosulphonium methylide. Unfortunately, however, the configuration of these epoxides has not been established.[5b] Dihydrotestosterone (37) on the other hand with the oxosulphonium ylide gives a 79% yield of the α-epoxide (39) while the sulphonium ylide reacts with the ketone to give a 90% yield of the β-epoxide (38).[5f] The explanation for these results is based upon the assumption that initial attack on the carbonyl group by the ylides will take



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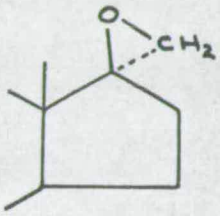
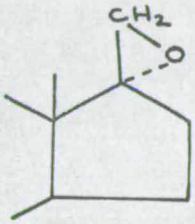


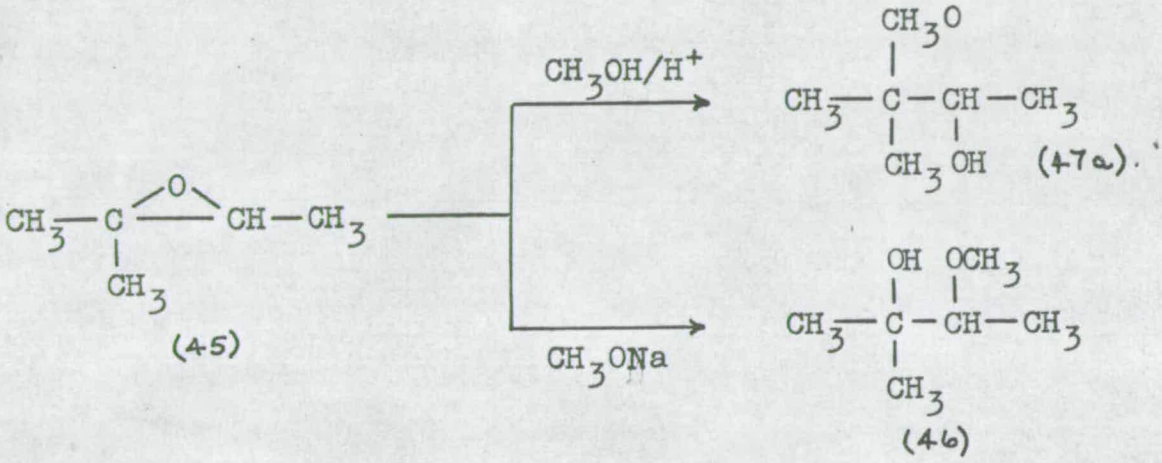
(43)

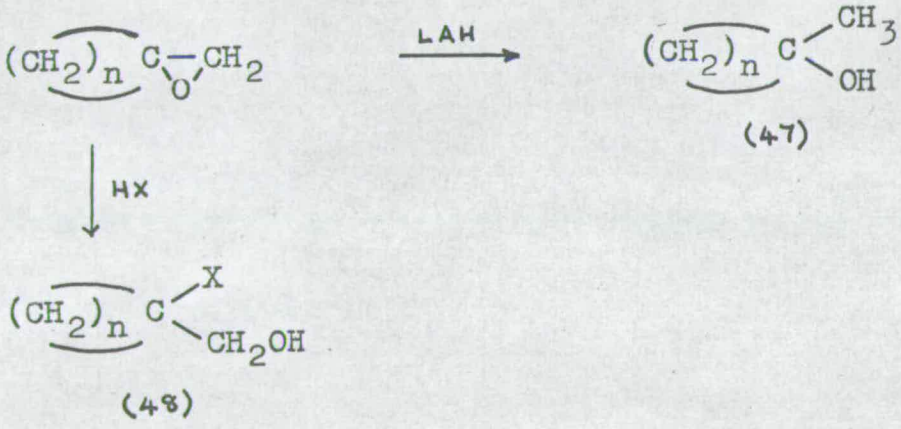


(44)

place from the α-side to give intermediates (40a) and (40b) with the intermediate formed from the more reactive sulphonium ylide less likely to revert to starting materials than (40b) which is formed from the relatively stable oxosulphonium ylide. Then since epoxide generation from (40a) or (40b) involves S_N2 backside displacement of sulphonium group by oxyanion a trans coplanar arrangement of oxygen and sulphur is required. With intermediates (40a) and (40b) severe non-bonded interactions between the groups attached to sulphur and the 1α- and 5α-hydrogens will occur and will be more severe with (40b). However, an intermediate of the form (41) will be relatively free of non-bonded interactions and thus while the same intermediates (40a) and (40b) are initially formed from either ylide only (40a) goes to a product. The other intermediate (40b) participates in an equilibrium among starting materials, (40b), and (41b), only the later going to products.

With 17-keto-steroids (42) ylide attack takes place to give 17β,20β-epoxides (43)[5a,b,c,d,e] but even here there is a difference between the ylides, the sulphonium methylide is almost 100% stereospecific whilst the oxosulphonium methylide always gives a little of the α-epoxide (44).[5a,b,c,e]


CH3OH/H+
CH3ONa
(45)
(47a)
(46)

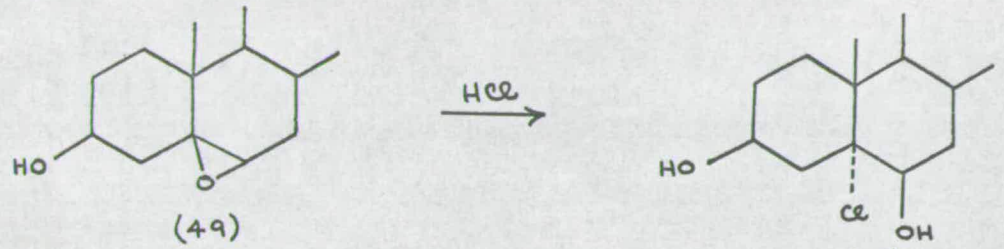

LAH
HX
(47)
(48)

Epoxide Nucleophilic Substitution Reactions

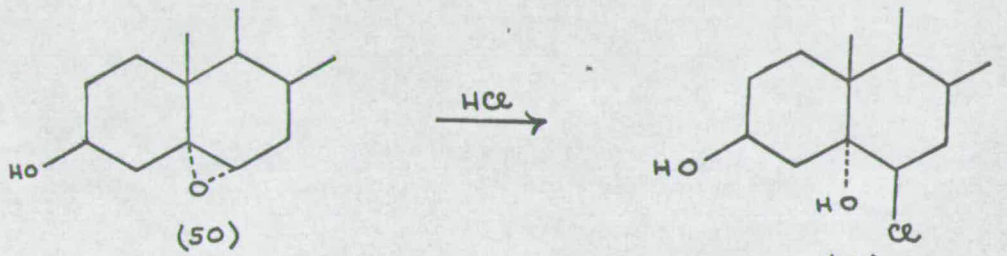
Ring opening reactions of epoxides involve nucleophilic attack on one of the epoxide carbons with displacement of the epoxide oxygen and are therefore nucleophilic substitution reactions. Most of these reactions take place with inversion of configuration at the site under attack although some examples with retention of configuration are known.[1,24]

It is most convenient to consider separately ring opening reactions which take place under basic or neutral conditions from those carried out under acidic conditions. In the former case simple nucleophilic attack at one of the epoxide carbons with subsequent ring opening is the most likely procedure whilst under acidic conditions epoxide oxygen protonation will first take place with a resultant weakening of both carbon-oxygen bonds. Thus bond breaking is relatively easy under acidic conditions and with backside push by the attacking nucleophile ring opening is a fairly rapid process.

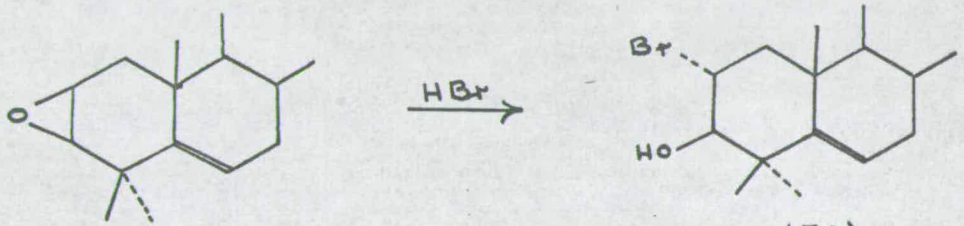
Orientation studies of nucleophilic substitution reactions of unsymmetrically substituted acyclic epoxides show in fact that there is a difference in the mechanisms of substitution under basic or neutral conditions and under acidic conditions.[24] For example treatment of 2,3-epoxy-2-methylbutane (45) with sodium methoxide gives 3-methoxy-2-methyl-2-butanol (46) whilst the addition of methanol, catalysed by sulphuric acid or boron trifluoride, to the same epoxide gives chiefly 3-methoxy-3-methyl-2-butanol (47a).[25] With the basic reagent steric hindrance will inhibit attack at the more highly substituted carbon whilst the different product resulting from reaction under acidic conditions indicates that the transition



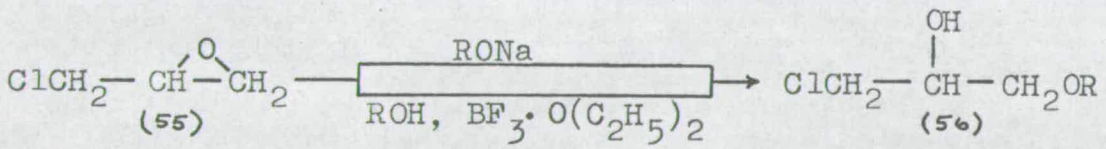
(49) (51)



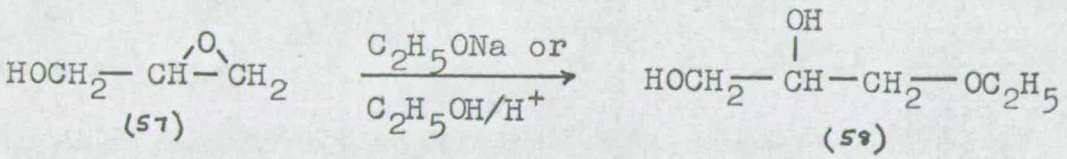
(50) (52)



(53) (54)



R=CH_3, C_2H_5, n-C_3H_7, iso-C_3H_7, n-C_4H_9, iso-C_4H_9, n-C_5H_{11}.

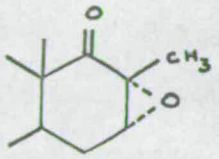


state here must involve some degree of positive charge on the more highly alkylated carbon which can be stabilised by the electron releasing effects of the two methyl groups. Since inversion takes place, a fully developed carbonium ion is unlikely, and thus both reactions can be regarded as involving S_N2 type mechanisms.

With exocyclic epoxides a similar orientation distinction can be made between neutral or basic and acidic reaction conditions. With lithium aluminium hydride reduction of methylenecycloalkane epoxides gives tertiary alcohols (47)[26] whilst cleavage of the same type of epoxides with hydrogen halides produces mainly 1-halocycloalkanemethanols (48).[23]

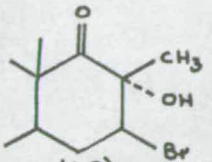
In nucleophilic substitution reactions of steroid epoxides conformational effects are usually more important than primary steric, or electronic effects. This is also true for other endocyclic epoxides. Of the very many examples of this effect in steroid epoxides one which best illustrates the difference between substitution reactions with acyclic and alicyclic epoxides is the cleavage of 5β,6β-epoxy- and 5α,6α-epoxy-steroids (49) and (50) with hydrogen chloride to the trans diaxial chlorohydrins (51) and (52) respectively.[27] Indeed, there are very few examples where diaxial cleavage is not observed for steroid epoxides in which there are no strong polar group influences. One exception, however, to the diaxial opening rule exists in the case of acid cleavage of 4,4-dimethyl-2β,3β-epoxy-steroids (53) where the trans diequitorial derivatives (54) are formed, this being due to the original epoxides existing in preferred half-boat conformations.[28]

The orientation during the ring-opening of unsymmetrically



(59)

HBr →



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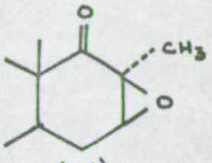
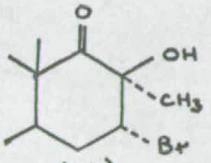


(61)

HBr →



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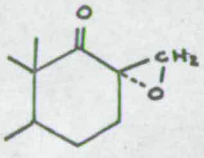
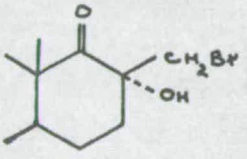


(63)

HBr →



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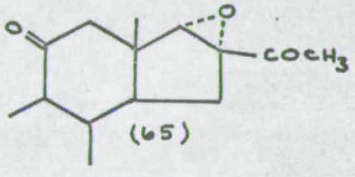
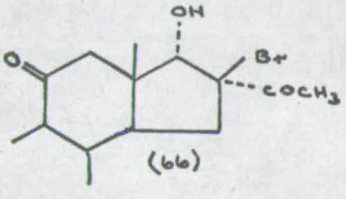


(65)

HBr →



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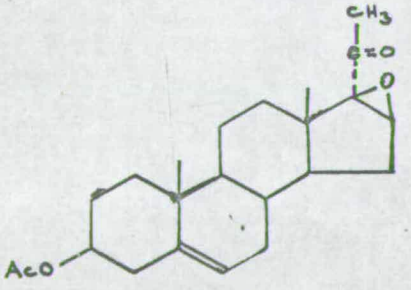
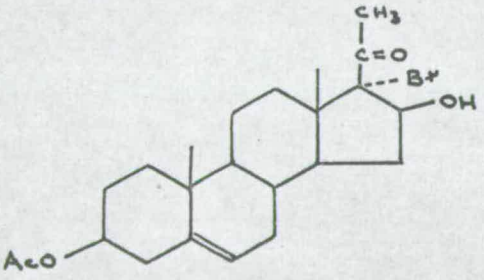


(67)

HBr →



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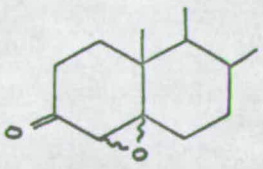

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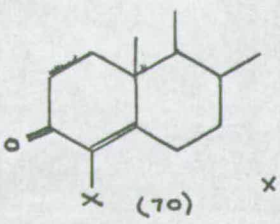


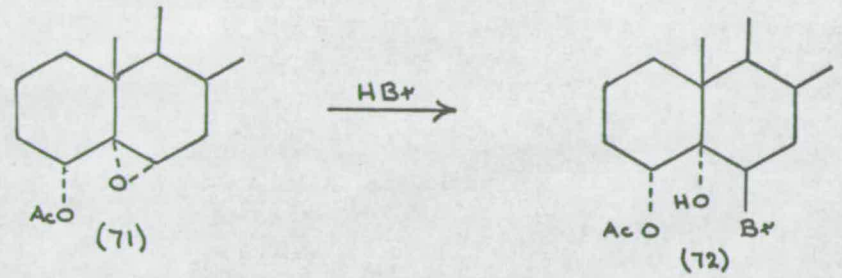
(70)

X = halogen.

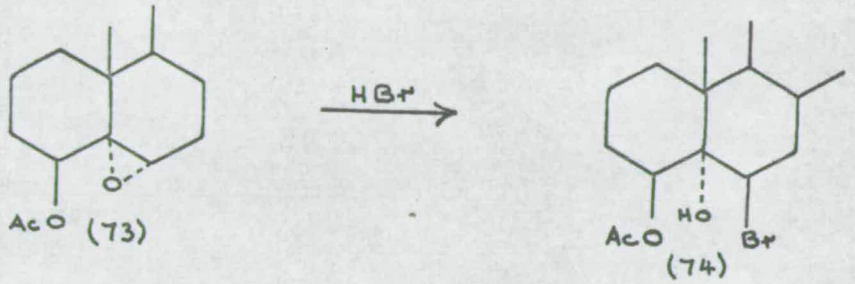
substituted epoxides is greatly influenced by adjacent polar groups. An electron withdrawing group tends to inhibit attack at the epoxide carbon next to it. For example with epichlorohydrin (55) the electronegativity of the chlorine atom overcomes the normal tendency for attack to take place at the more highly alkylated carbon atom under acidic conditions and with various alcohols gives the same products (56) as with the corresponding sodium alkoxides.[29] Similarly glycidol (57) has been converted into 1-ethoxy-2,3-propandiol (58) on treatment with either sodium ethoxide or ethanol in the presence of an acid.[30]

Such a general rule cannot however be applied to steroid epoxides with an adjacent electron withdrawing group. Here factors other than electronic can influence the course of the reaction. A survey of some examples can illustrate this point taking acid-catalysed ring-opening reactions of α,β-epoxy-ketones as the first examples.

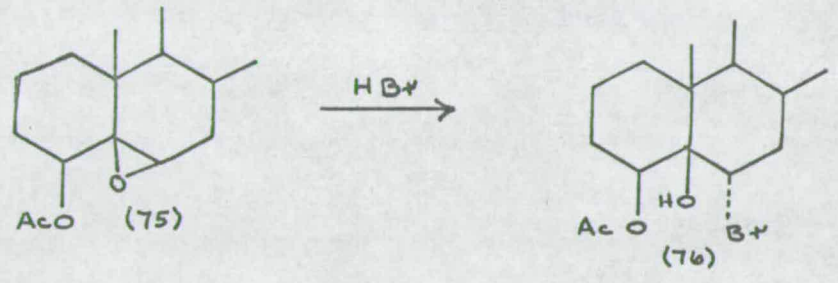
The 16α,17α-epoxy-17β-methyl-17α-ketone (59) gives a bromohydrin (60) on treatment with hydrogen bromide in which there is a diequatorial orientation of bromine and hydroxyl group and the corresponding β-epoxide (61) cleaves to give a product (62), with the same reagent, in which the hydroxyl group is also α to the ketone.[31] The exocyclic epoxide (63) similarly gives the bromohydrin in which the bromine is on the exocyclic carbon atom (64).[32] However, 3α-acetoxy-16α,17α-epoxy-16β-acetyl-5β-androstan-11-one (65) with hydrogen bromide in acetic acid gives a bromohydrin (66) with the hydroxyl group β to the carbonyl group.[33] Again, epoxide (67) cleaves with hydrogen bromide to give the 17α-bromo-16β-alcohol (68) in which the substituents are quasi-axial.[34] Obviously for these



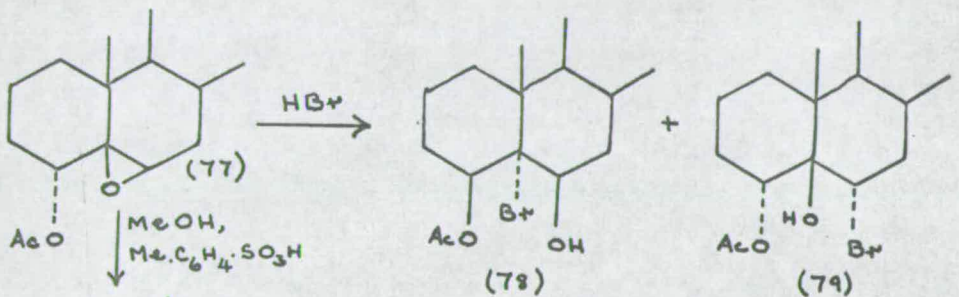
(71) (72)



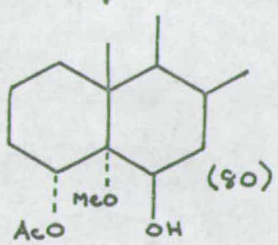
(73) (74)



(75) (76)

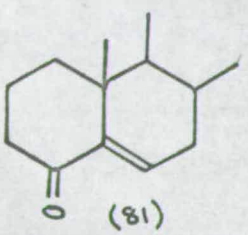


(78) (79)



(80)

(75) $\xrightarrow[Me.C_6H_4.SO_3H]{MeOH}$



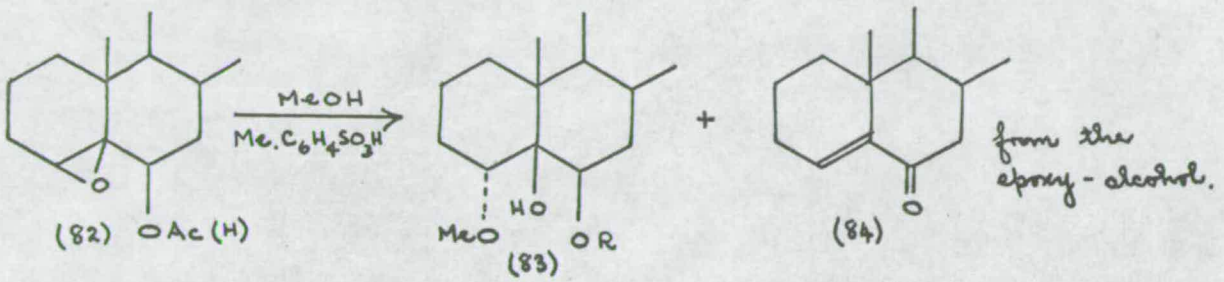
(81)

last two examples steric and conformational factors are of importance. This type of behaviour is not confined to cyclopentane epoxides, however, for the α- and β-epoxy-derivatives of testosterone (69) both give on treatment with hydrogen halides, the 4-halo-compounds (70).[35]

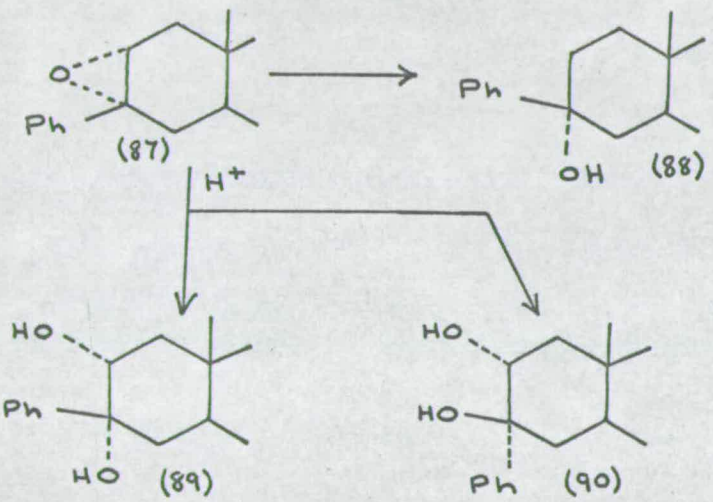
Several α-hydroxy- (and α-acetoxy-) steroid epoxides have also been subjected to acid catalysed nucleophilic substitution reactions.[36,37] Again results cannot solely be explained in terms of the inductive (-I) effect of the hydroxyl-(acetoxyl-) group.

Hydrobromic acid cleavage of 4α- and 4β-acetoxy-5α,6α-epoxides (71) and (73) gives the expected 5α-hydroxy-6β-bromo-compounds (72) and (74), and the 4β-acetoxy-5β,6β-epoxide (75) similarly gives the expected trans-diequatorial bromohydrin (76). However, 4α-acetoxy-5β,6β-epoxy-cholestane (77) gives with hydrobromic acid a mixture of the trans-diaxial 5α-bromo-6β-alcohol (78) and the trans-diequatorial 6β-bromo-6β-hydroxy-derivative (79). The same epoxide (77) on treatment with methanol and toluene-p-sulphonic acid gives only the 5α-methoxy-6β-ol (80). The reagent used for epoxide cleavage seems to be of considerable importance since the acid catalysed addition of methanol to the 4β-acetoxy-5β,6β-epoxide gives cholest-5-en-4-one (81).

At the same time the reactions of the four isomeric 4,5-epoxy-6-hydroxy-cholestanes under acidic conditions were investigated.[37] With the exception of the 4β,5β-epoxy-6β-ol (82) the epoxides with methanol and toluene-p-sulphonic acid yield products resulting from C-4-O bond cleavage. The cis-β-epoxy-alcohol (82) does show

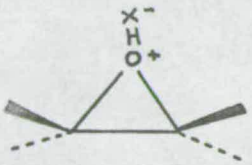

MeOH
Me.C6H4SO3H
(82) OAc(H)
MeO
HO
OR
(83)
(84)
from the epoxy-alcohol.


H
H+
(85)
(86)

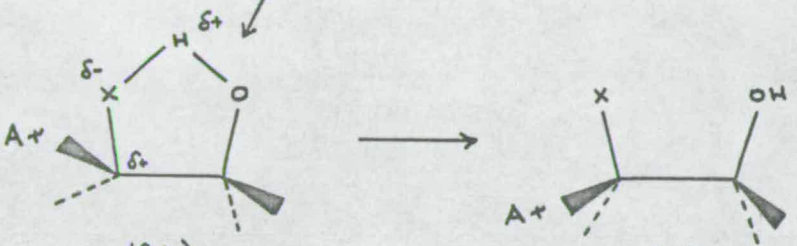

Ph
(87)
(88)
OH
H+
HO
(89)
(90)

some C-4-oxygen cleavage (83) but this product is accompanied by some cholest-4-en-6-one (84). This can only be explained by C-5-oxygen bond cleavage concerted with hydride migration from C-4. A similar mechanism to this is also proposed for formation of cholest-5-en-4-one from 5β,6β-epoxy-4β-hydroxy-cholestane. In both cases a boat conformation is required [ring A for the 5,6-epoxide, ring B for the 4,5-epoxide] for a trans antiparallel arrangement of the 4α- or 6α-hydrogen and the C-5-oxygen bond.

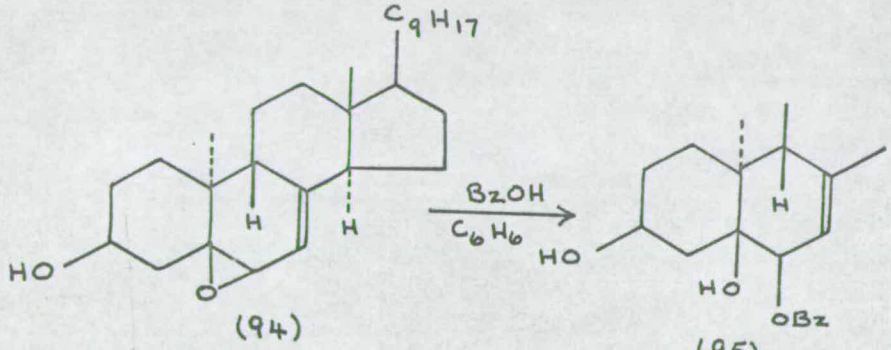
The presence of conjugated groups favours attack at the adjacent carbon both under acidic and basic or neutral conditions.[24] Under acidic conditions the positive charge (or partial positive charge) is stabilised by conjugative electron release from a π-orbital or atomic p-orbital. In some cases there is good evidence for a high degree of carbonium ion development and a two step reaction, backside attack by the nucleophile not being part of the driving force for the reaction. 3-Phenyl-2α,3α-epoxy-5α-cholestane (87) which reacts with lithium aluminium hydride in the normal fashion to give 3β-phenyl-5α-cholestan-3α-ol (88) undergoes an abnormal reaction with dilute perchloric acid in aqueous acetone, the main product being 3β-phenyl-5α-cholestan-2α,3β-diol (90).[38] The proposed mechanism requires cleavage to the C-3 carbonium ion followed by the nucleophile then attacking in the main from the less hindered side of the molecule. This is one of the few steroid epoxides giving retention of configuration on nucleophilic substitution. In fact cis ring opening is frequently observed with aryl substituted epoxides when the reaction is carried out under



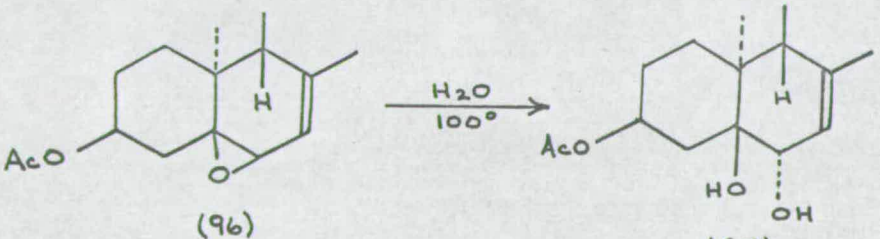
(91)



(92) (93)



(94) (95)

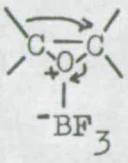


(96) (97)

acidic conditions.[24,39] This has been interpreted as being due to the formation of an ion pair by the protonated epoxide and acid anion (91) which is enclosed in a "cage" of solvent with consequent nucleophilic attack by the anion taking place from the only available direction, i.e. from the same side as the epoxide oxygen.[24,39] However, this clearly should be possible with any acid catalysed epoxide nucleophilic substitution reaction. Since, cis opening has so far only been observed for epoxides carrying unsaturated substituents such as aryl groups or double bonds this would tend to indicate that the transition state must have considerable carbonium ion character and could thus be represented as (92)[39] which would account very well for cis opening to a product with overall retention (93). A good example is the opening of trans-stilbene epoxide with hydrogen chloride in chloroform to give only threo chlorohydrin[40] (complete retention). It is interesting, however, that cis-stilbene epoxide gives up to 80% inversion under the same conditions. Here, if a transition state of type (92) were involved, there would be a fair degree of eclipsing between the two aryl groups and rotation around the carbon-carbon bond to the more stable trans form might take place prior to chlorohydrin formation.[39]

Another steroid epoxide giving retention of ring opening is the ring B epoxide (94).[41] Acid catalysed reaction with benzoic acid in benzene gives mainly the 6β-ester (95) and it is supposed that the presence of the 7,8-double bond leads to considerable carbonium ion development at C-6 with the direction of attack of the nucleophile due either to attack preferentially occurring from

the less hindered side or to a partial bond intermediate. It is interesting to note that cleavage of the corresponding 3β-acetoxy-epoxide (96) with boiling water yields mainly the diol (97) accompanied by a little 6β-alcohol (95 with C-3 acetate, C-6-OH). Compound (97) is the result of a S_N2 type reaction with inversion at C-6.



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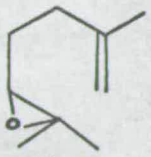

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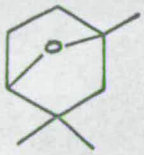

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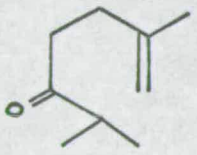

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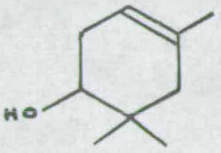

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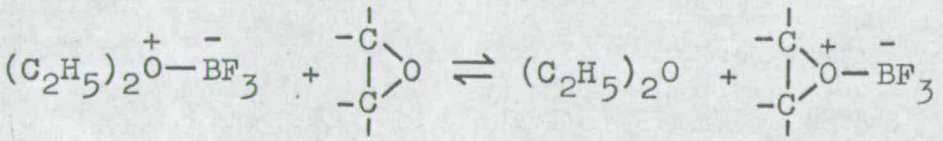

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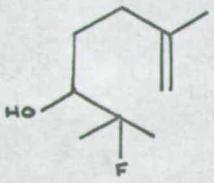


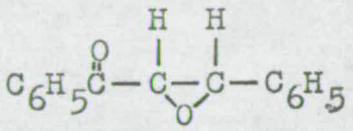
(104)

EPOXIDE REARRANGEMENT REACTIONS

A convenient method for the rearrangement of an epoxide to its isomeric ketonic products is to treat the epoxide in a suitable solvent with a Lewis acid such as boron trifluoride (98). The first step in this type of reaction involves co-ordination of the Lewis acid with the epoxide oxygen bringing about polarisation of the carbon-oxygen bonds with consequent migration of one of the substituents to an electron difficient centre. Which bond breaks and which group migrates depends on steric, electronic, and conformational factors. Clearly these rearrangements can also involve either a transition state with bond polarisation and concerted group migration or a two step reaction in which full carbonium ion development first takes place. The nature of the substituents on the epoxide have a bearing on the degree to which a carbonium ion is involved, it being most favoured in epoxides with adjacent conjugative substituents and least favoured where a positive charge at a secondary centre would be involved.

Products from epoxide rearrangement reactions can often only be explained in a satisfactory manner by attributing their formation to a two-step carbonium ion mechanism. Goldsmith,[42] for example, found that reaction of Geraniolene monoepoxide (99) with boron trifluoride in benzene as solvent gives the three products, (100), (101), and (102). Compound (101) results from a transition state with full development of a positive charge.

This example[42] also illustrates well two other points which can often be observed in boron trifluoride catalysed epoxide



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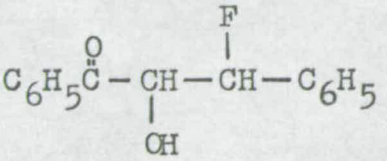

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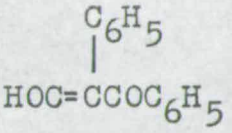

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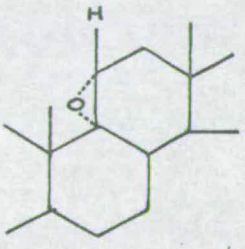

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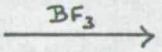

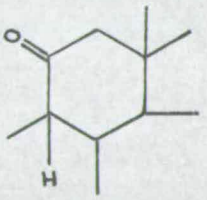

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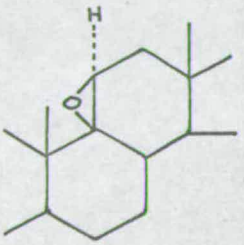

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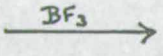
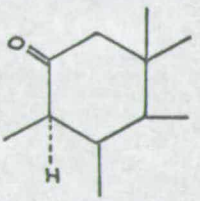
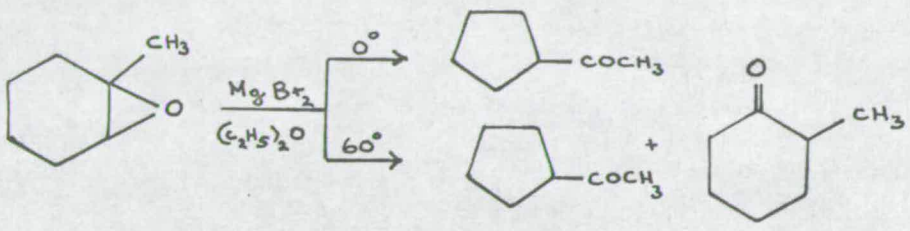




(111)

rearrangement reactions. When ether is substituted for benzene as the reaction solvent the overall reaction is much slower than that for benzene. After fifteen minutes some 17% of the starting material remains unchanged with ether whilst in benzene total conversion to products occurs in this time. Other workers[43] have explained this solvent dependence of reaction rate in terms of the equilibrium shown in (103) making it obvious that the concentration of boron trifluoride-epoxide complex will be increased by the use of an inert solvent. Again using ether as solvent the reaction products are different,[42] for as well as some starting material and compounds (101) and (102) the fluorohydrin (104) is also produced. The rate of fluorohydrin formation is much faster than that of ketone formation when roughly equivalent amounts of epoxide and catalyst are used. Preferential fluorohydrin formation on treating epoxides with boron trifluoride has been found in many instances[10,44,45,59,68,71] and is usually solvent-dependent.[10,44,45] For example the epoxy-ketone (105)[45] with a limited amount of boron trifluoride-etherate in ether leads to fluorohydrin formation (106) whilst in benzene the dicarbonyl compound (107) is formed.

In many cases treatment of these fluorohydrins with a further quantity of boron trifluoride leads to the same ketonic products that are formed during boron trifluoride treatment of the original epoxide in benzene. With fluorohydrin (104) for example treatment with boron trifluoride-etherate in ether gives (101).[42] With benzene, the fluorohydrin on treatment with more boron trifluoride undergoes fragmentation to volatile products. Usually, however,



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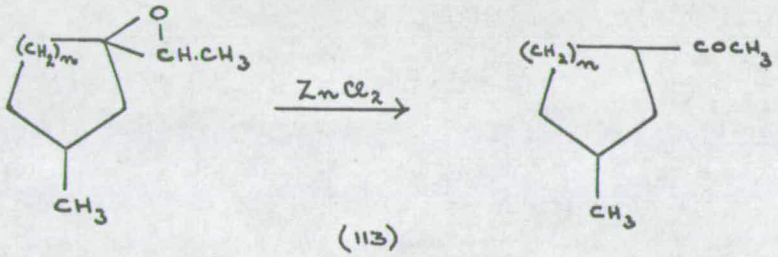

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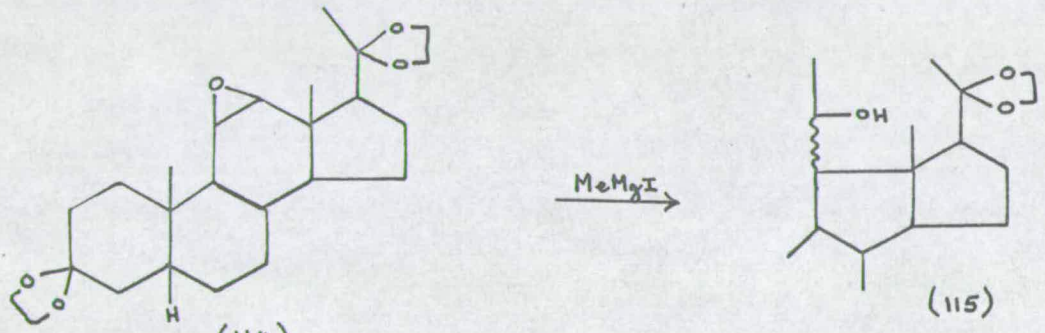
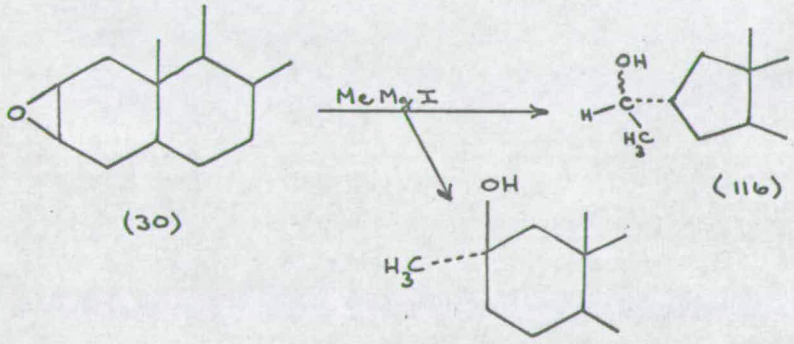


(114) (115)



(30) (116) (117)

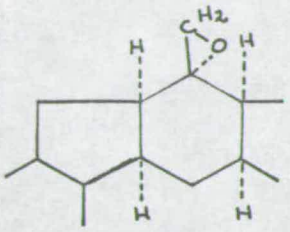
either solvent gives the same results for this type of secondary transformation. Further details of preferential fluorohydrin formation and mechanisms for their subsequent conversion to ketonic products will be given when the effect of polar groups on epoxide rearrangement is discussed.

In trisubstituted steroid epoxides, without a polar substituent in the vicinity of the epoxide group, ketone formation results from a hydride shift. Moreover migration of hydrogen is stereospecific, with the 9,11-epoxides for example, the ketone with a β-hydrogen at C-9 (110) is formed from the α-epoxide (108) while the β-epoxide (109) gives the corresponding 9α-compound (111).[10,46] It is interesting that whereas the reaction with the β-epoxide is complete in five minutes the α-epoxide requires seventy five hours for complete isomerisation. This long reaction time for the α-epoxide is probably due to the 9β-configuration of the product requiring that either ring B or ring C is in a boat conformation.

Competition between alkyl migration and hydrogen shift is only observable outside the steroid field. Thus 1-methyl-1,2-epoxycyclohexane with magnesium bromide gives either acetylcyclopentane or a mixture of acetylcyclopentane and 2-methylcyclohexanone depending on the reaction conditions (112).[47]

On treatment with zinc chloride epoxide derivatives of ethylidenecycloalkanes rearrange to acetyl compounds (113) with no evidence of competing methyl migration or ring enlargement.[48]

With disubstituted epoxides there is a chance of two competing hydride migrations. Excluding exocyclic methylene epoxides there



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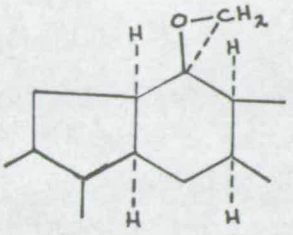

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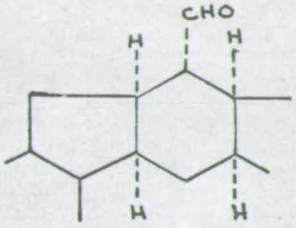

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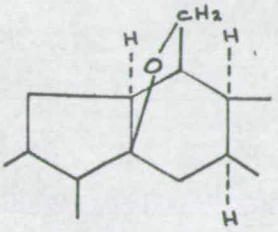

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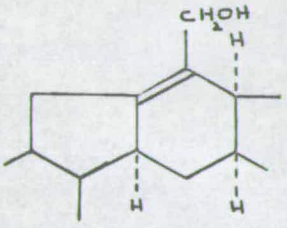

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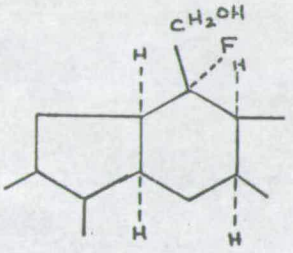

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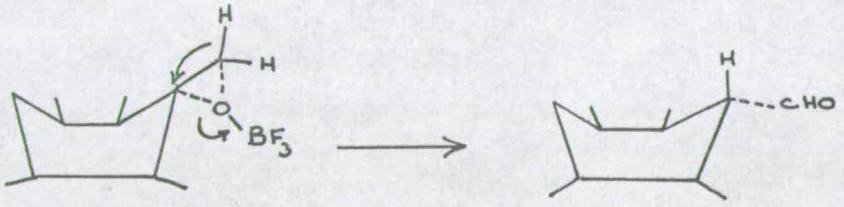

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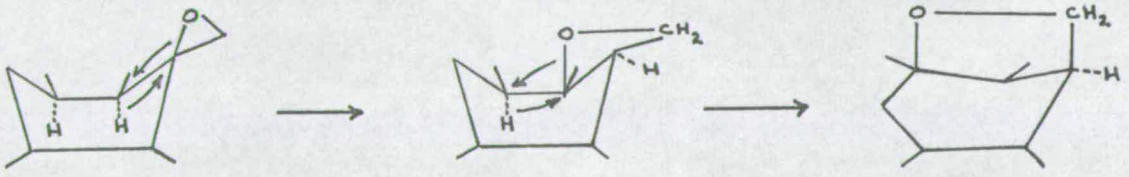
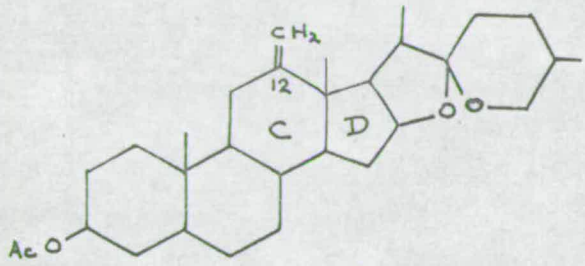


(125)

are two examples of rearrangement of steroid epoxides of this type.[49,50] Addition of methyl magnesium iodide to the 11β,12β-epoxide (114) results principally in rearrangement to a C-nor-11-hydroxyethyl-compound (115), in which C-11-oxygen bond cleavage and 12,13-bond migration are both involved.[49] 2β,3β-Epoxy-5α-cholestane (30) with methyl magnesium iodide[50] gives ring contraction products (116) and the Grignard derivative of 5α-cholestan-2-one (117) which can only come from C-3-oxygen bond cleavage.

Rearrangement with Lewis acids of simple exo-methylene epoxides such as methylenecyclohexane epoxide,[51] β-pinene epoxide,[53] and camphene epoxide[53] results in formation of aldehydes as the only products.

The rearrangement of similar epoxides in the steroid system has been the subject of two recent reports.[54,55] 17aα,18-Epoxy-C-nor-D-homo-spirostan (118)[54] on treatment with either boron trifluoride or perchloric acid gives mainly an 18α-aldehyde (120), since it does not epimarise with base. In both cases minor products are isolated, two of unknown structure with boron trifluoride and the 18-hydroxy-$\Delta^{13(17a)}$-olefin (122) with perchloric acid. The 17aβ,18-epoxide (119)[54] with boron trifluoride in benzene gives three products identified as a cyclic ether (121), a fluoro-alcohol whose probable structure is given as the 17aα-fluoro-compound (123), and the 18-hydroxy-$\Delta^{13(17a)}$-olefin (122). The same reaction carried out in ether gives a mixture of cyclic ether (121) and the 18-hydroxy-olefin (122), while perchloric acid converts the epoxide into the 18-hydroxy-olefin (122).



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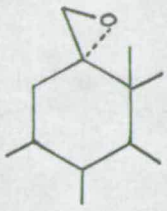

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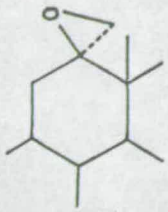

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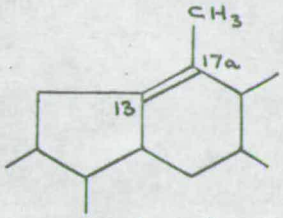
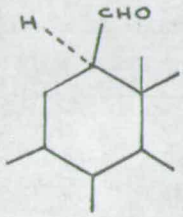


(122a)



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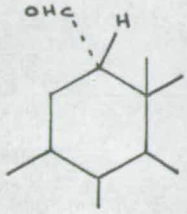

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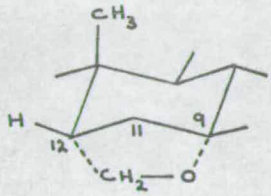

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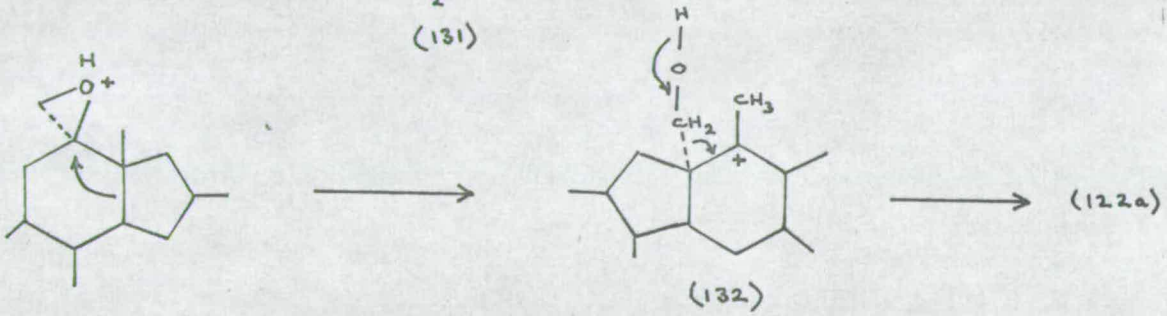

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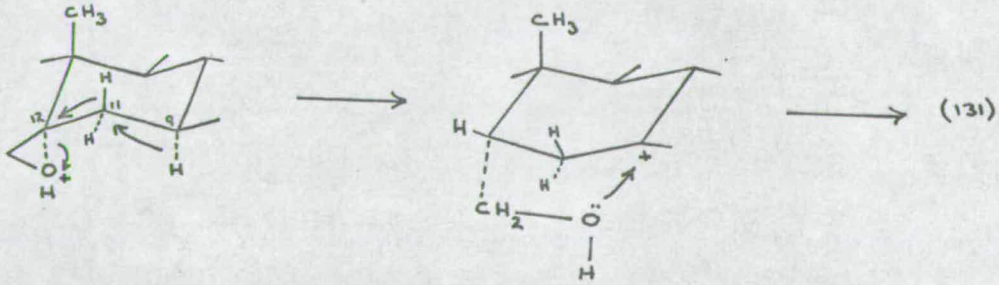
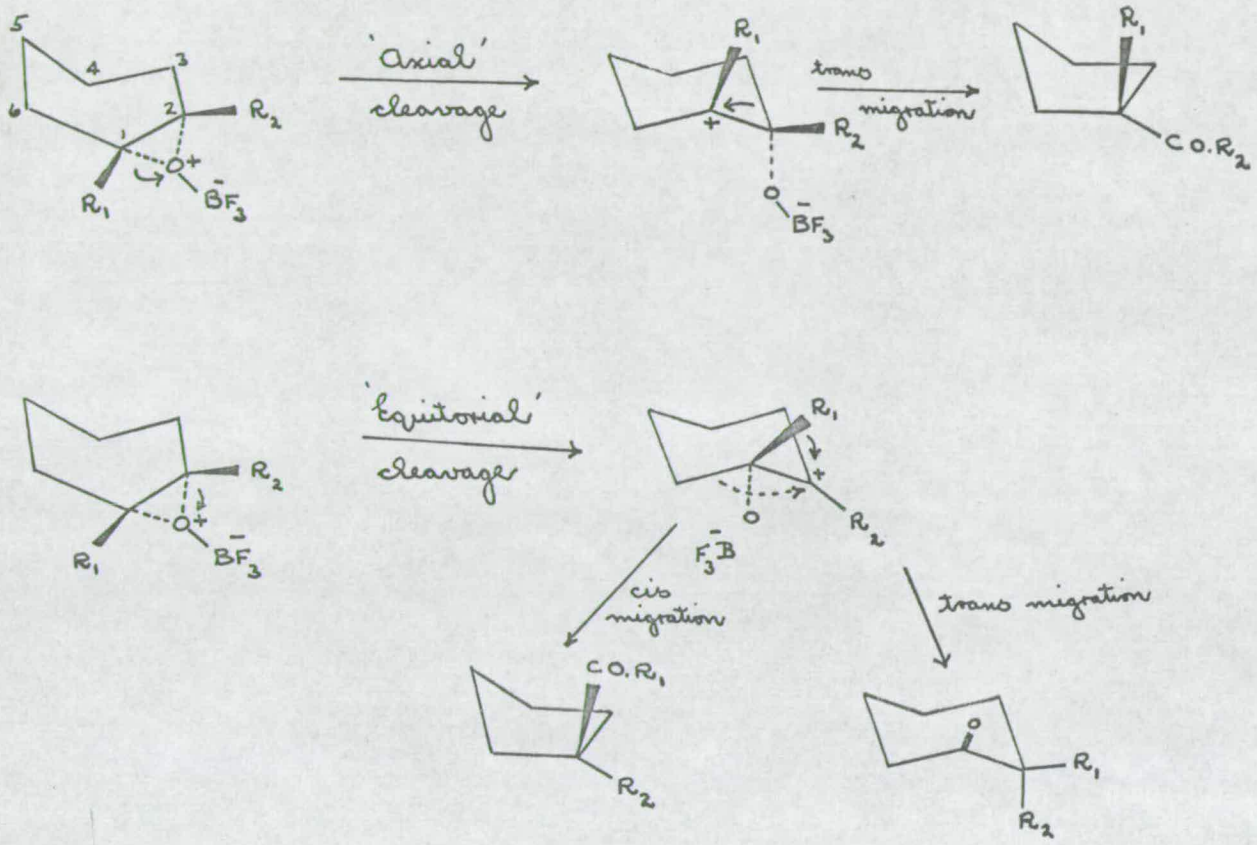


(133)

Formation of the 18-aldehyde from the 17aα,18-epoxide is a concerted process as shown in (124). The simultaneous formation of the 18-hydroxy-olefin requires a cis-elimination and is presumed to involve full carbonium development at C-17a. The cyclic ether is thought to involve a two step process involving a four-membered ring as an unstable intermediate (125), this intermediate can also give the 18-hydroxy-olefin by 13α-proton loss.

The same workers[55] have investigated the boron trifluoride and perchloric acid reactions of the 12,12'-epoxy-derivatives ((127) and (128)) of 12-methylene-tigogenin (126). The 12β,12'-epoxide (128) with BF_3 in benzene gives after chromatography the C-nor-D-homo-$\Delta^{13(17a)}$-olefin (122), followed by the 12β-aldehyde (129) and an unknown unsaturated alcohol. Replacing the solvent by ether gives the same major products along with an unknown diol. Treatment of the epoxide (128) with aqueous perchloric acid gives the olefin (122) plus a minor product tentatively assigned as the cyclic ether (133). The α-epoxide (127) with boron trifluoride in benzene also produces a mixture of products from which the 12α-aldehyde (130) is obtained directly by crystallisation. Chromatography of the residue which from n.m.r. contains both aldehydes gives the $\Delta^{13(17a)}$-olefin (122) and the 12β-aldehyde (129). The same products, but in different yields, are obtained using ether as the solvent. Reaction of the compound (127) with perchloric acid gives 65% of the cyclic ether (131), 10% aldehyde (129), and a new unknown unsaturated compound.

The formation of the C-nor-D-homo-$\Delta^{13(17a)}$-olefin from both



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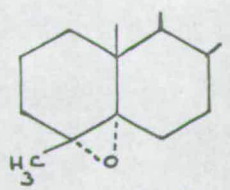

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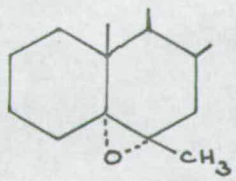
(a)



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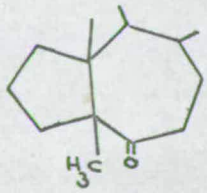

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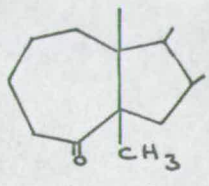
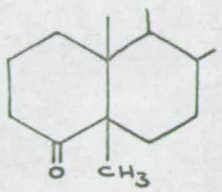


(138)

epoxides is envisaged[55] as involving C_{12}-O bond cleavage and migration of the electron pair of the C_{13}-C_{14} bond to give the intermediate (132), fragmentation with loss of formaldehyde then produces the olefin. Both in this instance and for the formation of the 12β-aldehyde the electron shifts involved can be concerted with C_{12}-O bond cleavage only for the 12β,12'-epoxide. Formation of the 12β-aldehyde and the $^{13(17a)}$-olefin from the 12α,12'-epoxide requires a C-12 carbonium ion intermediate since the stereochemical requirements for a concerted rearrangement are not possible in this case. Only the less stable 12α-aldehyde results from a concerted mechanism with the 12α,12'-epoxide. Thus it appears that a two step carbonium ion reaction pathway can compete effectively with the concerted rearrangement when the latter leads to the less stable isomer. The possible mode of formation of the cyclic ether from the perchloric acid reactions is given in fig. (133) for the α-epoxide. Formation of the ether (131) from the β-epoxide is thought to involve a C-12-carbonium ion intermediate.

With tetrasubstituted epoxides rearrangement in theory could involve migration by any one of the four substituent groups, and in fact complex product mixtures have been obtained from reactions of this type.[54,57,58,59] Kirk and Hartshorn[56] have put forward a scheme to help rationalise such results. In it transition states involving some degree of positive charge are proposed arising from either "axial" or "equatorial" cleavage (134) (this need not involve full development of a positive charge and can be concerted with substituent migration). The ring assumes the "chair" conformation



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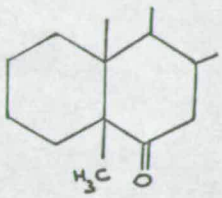

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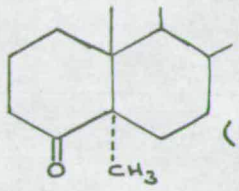

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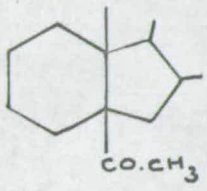

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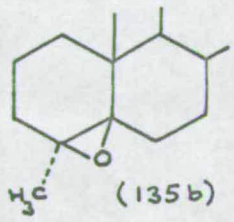

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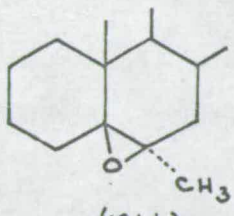

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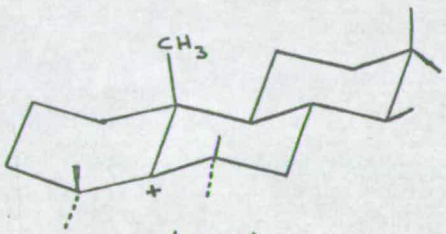

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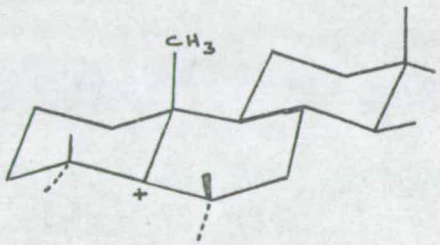
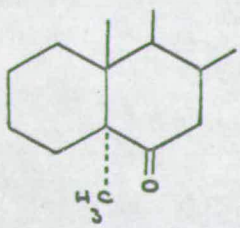
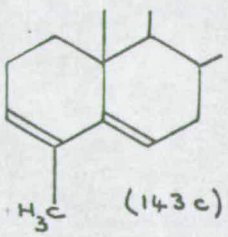


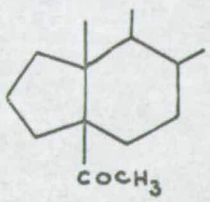
(135d)



(143a)



(143c)



(143b)

closest to the conformation of the epoxy-compound, so that non-bonded interactions are minimised, rotation of groups about the 1,2-bond during this initial step determining which groups will migrate. Axial cleavage permits trans-attack by C-3, while equatorial cleavage favours trans-migration of group R_1, although cis-attack is possible if migration of R_1 is unfavourable (134).

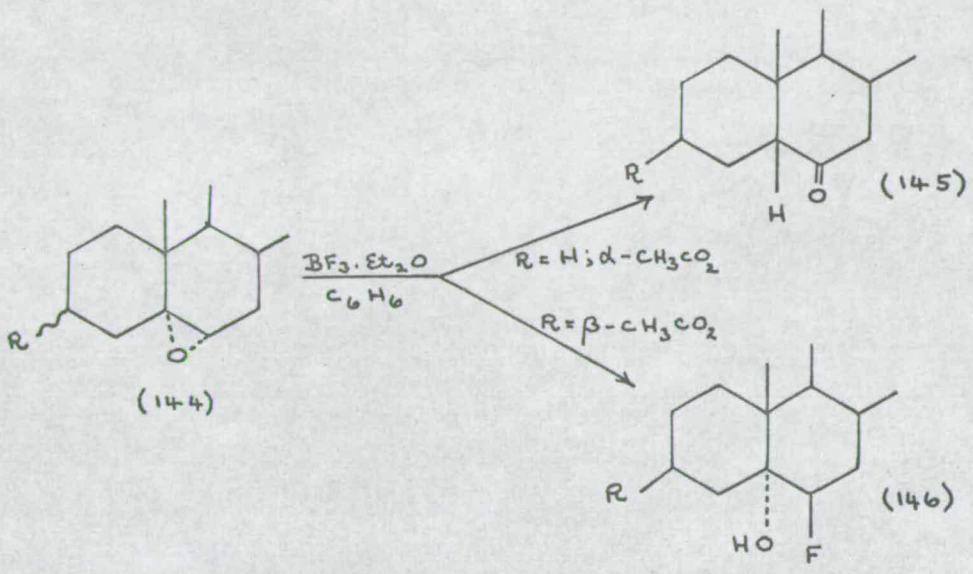
These principles were then applied to the results from the rearrangement of 4,5-epoxy-4-methyl-[57,58] and 5,6-epoxy-6-methyl-steroids.[59] Skeletal rearrangements are involved in the BF_3-catalysed rearrangements of 4α,5-epoxy-4β-methyl-5α-cholestane (135a)[58] and 5,6α-epoxy-6β-methyl-5α-cholestane (136a)[59] giving (137) and (138) respectively. Both can be explained as proceeding via axial cleavage to give the C-4 or C-6 carbonium ion with rotation about the appropriate bond to allow concerted trans-attack by the 10,5-bond. Equatorial cleavage would afford a C-5 carbonium ion for each of these epoxides, rotation about C-4 or C-6 placing the 4β- or 6β-methyl group in position for trans-attack upon C-5.[56] This results in 5β-methyl ketones (139) and (140) which are in fact the ultimate ketonic products of thermodynically controlled rearrangements from either the α-epoxides or the homo-nor ketones.[58,59]

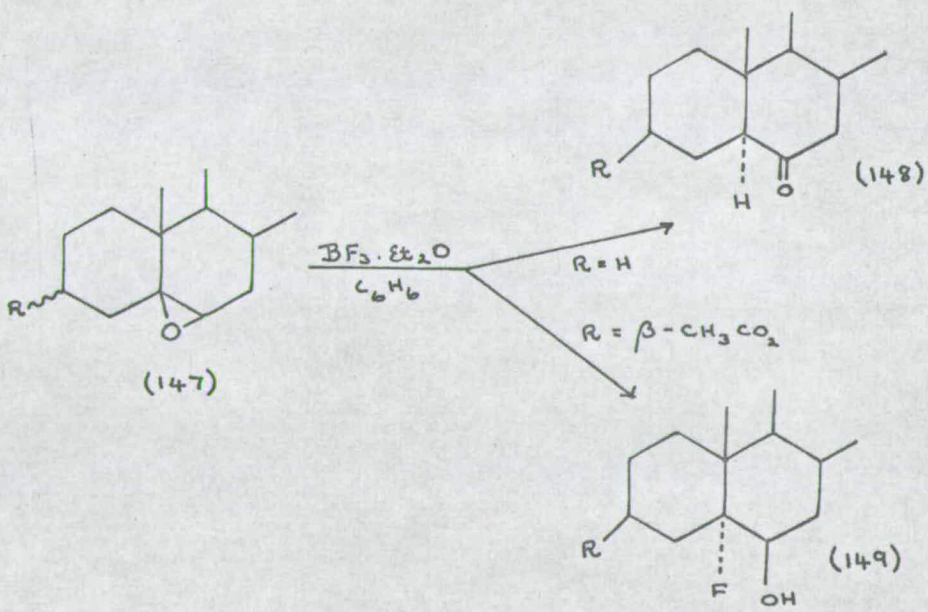
4β,5-Epoxy-4α-methyl-5α-cholestane (135b) gives the 5α-methyl-4-ketone (141) as the main product, the result of methyl group migration,[58] while the 5β,6β-epoxide (136b) gives as the major ketonic product 5β-acetyl-B-nor-cholestane (142), a ring contraction product.[59] In both cases epoxide cleavage at C-5 is involved.[56]

The reactions for the two epoxides proceed through similar transition states and the marked difference in products is attributed to the two extreme conformations for the C-5 carbonium ions (135c) and (135d). (135c) permits ring B to exist in a strain-free conformation while (135d) involves unfavourable interactions which include a partial eclipsing about the 7,8-bond, and twisting of the 9,10-bond, which forces the C-19 angular methyl group towards C-11. In structure (135c) the 6,5-bond is suitably placed for ring contraction in the case of the 5β,6β-epoxide (136b), while the same structure for the 4β,5β-epoxide (135b) places the methyl group in a suitable position for trans-attack on the C-5 carbonium ion.

Both epoxides give minor ketonic products. With the 5β,6β-epoxide (136b)[59] a 5α-methyl-6-ketone (143a) is formed and with the 4β,5β-epoxide (135b)[58] ring contraction to (143b) takes place. Both require structure (135d) for suitable arrangement of the migrating substituents.[56]

So far apart from fluorohydrin formation this review of epoxide rearrangement reactions has only dealt with ketonic product formation. However in many instances polar and non-polar material has been isolated from BF_3-catalysed epoxide rearrangement reactions, in some cases in large yields. In most cases such products have not been fully identified. One exception, however, exists in the case of the 4β,5β-epoxide (135b) where 4-methyl-cholesta-3,5-diene (143c) is formed in large yield.[58] In fact this is only one of several examples of elimination reactions

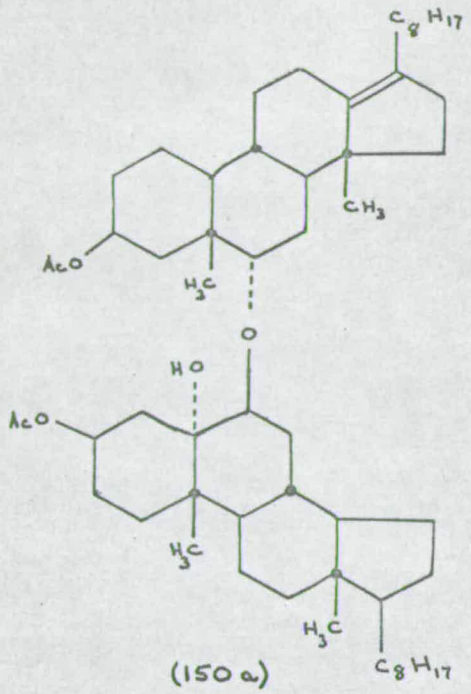

R
O
(144)
BF3.Et2O
C6H6
R = H; α-CH3CO2
R = β-CH3CO2
R
H
O
(145)
R
HO
F
(146)


R
O
(147)
BF3.Et2O
C6H6
R = H
R = β-CH3CO2
R
H
O
(148)
R
F
OH
(149)

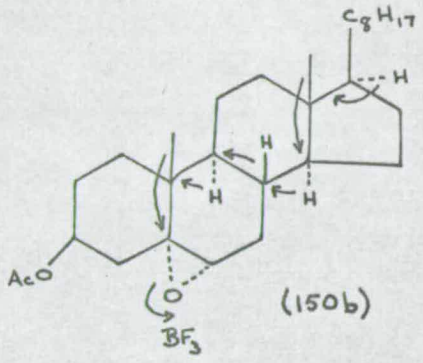
in 4β,5β-epoxide systems.[56,57]

Epoxide substituents which carry a polar group have a marked effect on the rearrangement of the epoxides. Rearrangements of epoxides in which the polar group is α or β to one of the epoxide carbon atoms will be considered. For example, whereas it was found that 5α,6α-epoxy- and 5β,6β-epoxy-cholestanes (144, R = H) and (147, R = H) isomerise to 6-keto-steroids (145, R = H) and (148) on treatment with boron trifluoride, the 3β-acetoxy derivatives (144, R = β-CH_3CO_2) and (147, R = β-CH_3CO_2) give the 6β-fluoro-5α-hydroxy-, (146), and 5α-fluoro-6β-hydroxy-, (149), -compounds instead of the expected ketones.[10,44] In the case of the α-epoxide (144, R = β-CH_3CO_2) this has been attributed[44] to a reduction of the partial ionisation of the C-5-oxygen bond by the long-range inductive (-I) effect of the BF_3 co-ordinated C-3 acetoxy group together with the unfavoured interactions that the acetate group would suffer in the A/B-cis product. Thus the alternative diaxial opening with F^- takes place in preference. With the 5β,6β-epoxide (147, R = β-CH_3CO_2) both fluorohydrin formation and hydride shift to an A/B-trans ketone would be expected to derive assistance from change of acetate conformation from axial to equatorial and hence it is suggested that the difficulty in C-5-oxygen bond ionisation necessary for ketone production is the decisive effect.

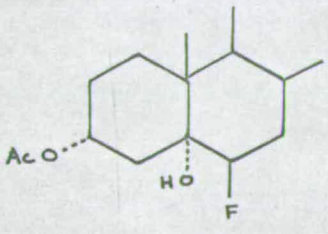
The same workers[44] found that 3α-acetoxy-5α,6α-epoxy-cholestane (144, R = α-CH_3CO_2) gives the ketone (145, R = α-CH_3CO_2) as the main product; since the electronic and conformational factors are in opposition it is assumed that the gain in energy resulting from



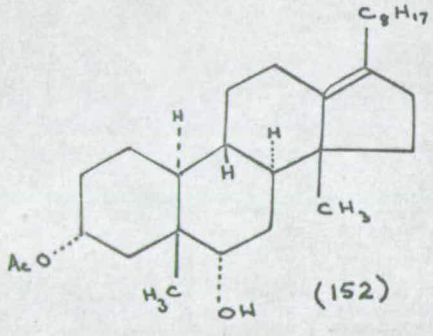
(150a)



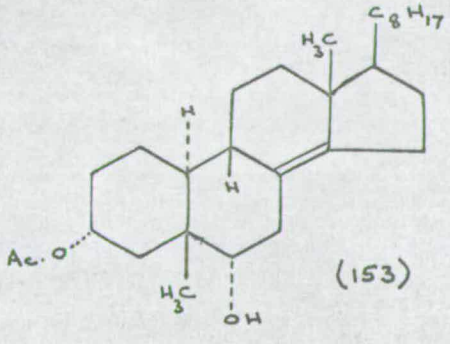
(150b)



(151)



(152)

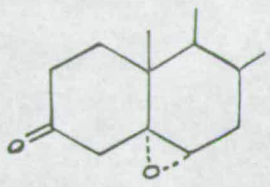


(153)

the axial acetate group assuming an equatorial conformation on ketone formation, and the unfavourable 1,3 (3α,5α)-diaxial interaction which would result if fluorohydrin formation occurred are more important than the -I effect of the acetoxy group.

Very recently reinvestigations of the BF_3 catalysed reactions of 3β-acetoxy-5,6α-epoxy-5α-cholestane (144, R = β-CH_3CO_2) and 3α-acetoxy-5,6α-epoxy-5α-cholestane (144, R = α-CH_3CO_2) have been carried out.[60,61] With the α-epoxide (144, R = β-CH_3CO_2) fluorohydrin formation again takes place along with a minor hydroxy compound mentioned by the first group of workers[44] which is now shown to be the dimer (150a) resulting from a 'backbone' rearrangement (150b) with C-19 attack on the C-5 carbonium ion.[60] Larger yields of this dimer are produced when the reaction is carried out with carefully purified BF_3. "Backbone" rearrangements have been shown to occur frequently with 4,5- and 5,6-epoxycholestanes where cleavage to a C-5 carbonium ion can take place.[61,65,69]

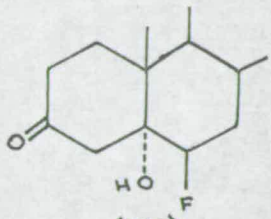
The re-examination of the reaction of the 3α-acetoxy-5α,6α-epoxide (144, R = α-CH_3CO_2) with BF_3 was carried out to see if an intermediate fluorohydrin was involved in final product formation.[61] With a reaction time of 25 seconds, in comparison with the 14 hrs., and 5 minutes of the first workers,[44] a crude product containing at least six compounds is obtained. This consisted of small yields of the fluorohydrin (151) and 6-ketone (145, R = α-CH_3CO_2), the bulk of the remainder being backbone rearranged compounds (152) and (153). A transition state involving C-5-oxygen bond cleavage accompanied by conformational changes leading to a carbonium ion



(154)

$BF_3 \cdot Et_2O$

C_6H_6



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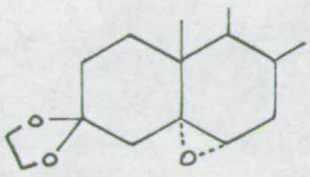

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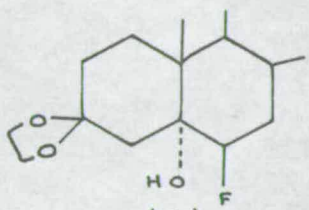

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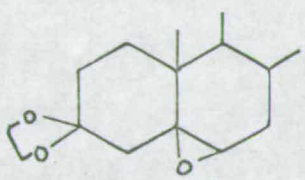

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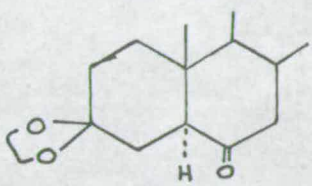

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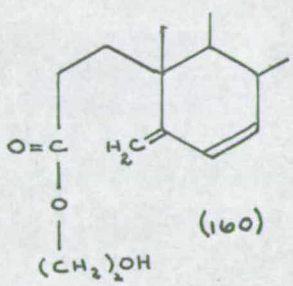

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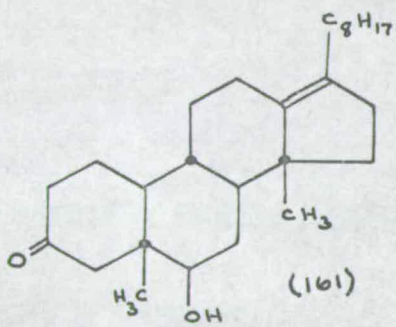

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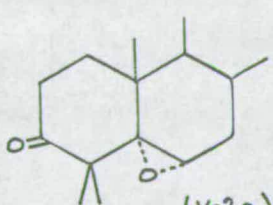
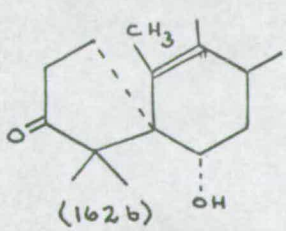
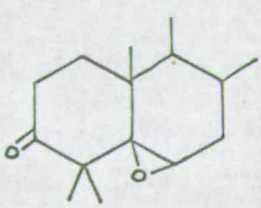


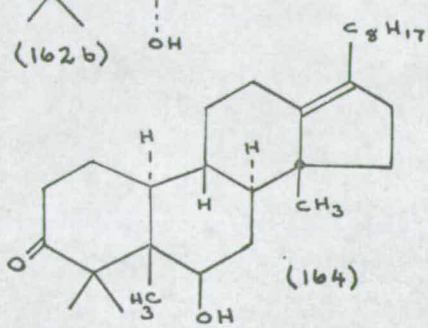
(162a)



(162b)



(163)



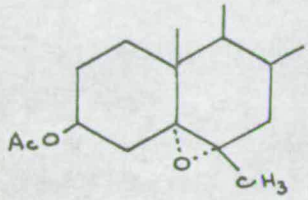
(164)

in which ring B adopts a skew form is suggested for this rearrangement.[61]

With 3-keto-5α,6α-epoxy-compounds (154) the conformational effects present with 3-acetates are absent, and the electron-withdrawing influence of the carbonyl causes the C-5-O bond to be firm and fluorohydrin (155) formation takes place.[62]

Interesting results have been obtained in the boron trifluoride catalysed reactions of 3,3-ethylenedioxy-5,6-epoxides. The 5α,6α-epoxide (156) undergoes C_6-O cleavage with formation of the 5α-hydroxy-6β-fluoro-derivative (157), the -I effect stabilizing the C_5-O epoxide bond.[62] In the reaction of the 5β,6β-epoxide (158) with boron trifluoride in benzene as solvent five compounds were isolated by chromatography.[63] The major product is the ketal-ketone (159) and its formation can be ascribed to the shielding of the α-face of the molecule by the ketal group preventing attack by F^- at C-5 even though the -I effect of the ketal opposes ketone formation. Minor products are due to removal of the ketal group giving the 3,6-dione, cleavage of ring A (160), backbone rearrangement (161),[60] and diene formation.

Two other 5,6-steroid epoxides with keto-groups at C-3 have been treated with boron trifluoride. 5α,6α-Epoxy-4,4-dimethylcholestan-3-one (162a) gives as the sole product the spiro-steroid (162b)[64,65] whilst the β-epoxide (163) gives a backbone rearrangement compound as the major product (164).[65] In neither case is a concerted migration involved.[64,65] The reaction of BF_3 with 3β-acetoxy-5α,6α-epoxy-4,4-dimethylcholestane also gives three



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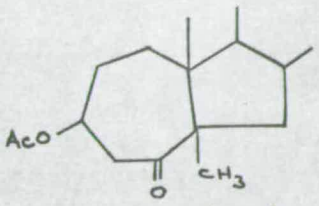

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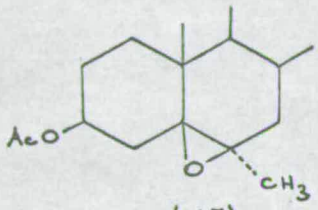

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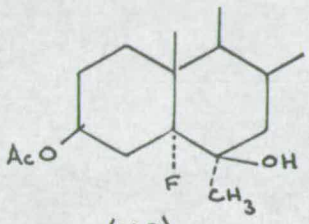

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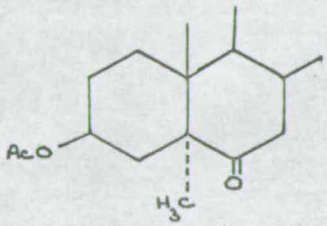

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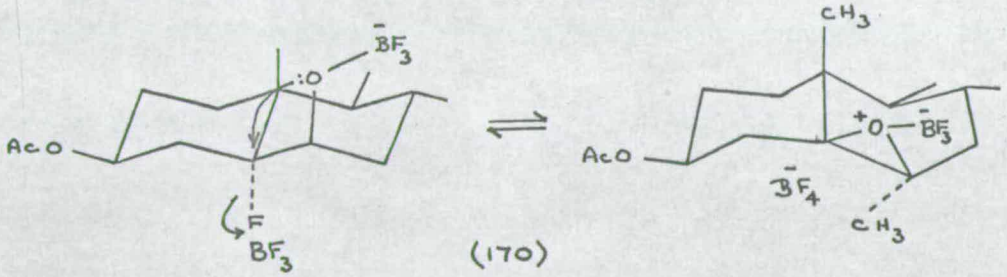
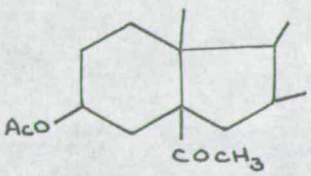


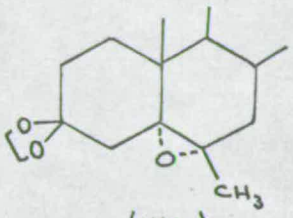
(170)



(171)

"backbone" rearrangement products.[65]

Rearrangements with boron trifluoride of 5,6-epoxy-6-methyl-cholestanes substituted at C-3 have been carried out.[59,63] 3β-Acetoxy-5,6α-epoxy-6β-methyl-5α-cholestane (165) gives an 85% yield of 3β-acetoxy-5-methyl-A-homo-B-nor-5β-cholestan-4a-one (166) on treatment with BF_3 in benzene for 25 minutes.[59] The corresponding 5,6β-epoxy-6α-methyl-compound (167)[59] gives the fluorohydrin (168) after 2 minutes in benzene, but the same reaction for 20 minutes gives a mixture of compounds which contains the fluorohydrin (168) and 3β-acetoxy-5-methyl-A-homo-B-nor-5β-cholestan-4a-one (166) and 3β-acetoxy-5-methyl-5α-cholestan-6-one (169). After 1 hr. in benzene the same ketonic products are produced along with a trace of fluorohydrin, and when (168) itself is treated with boron trifluoride-etherate in benzene the compounds (166) and (169) are produced. This tends to suggest that the fluorohydrin (168) could be an intermediate in the reaction to ketonic products. As has already been mentioned this type of secondary transformation is very common and clearly in some cases cannot involve simply rearrangement of the fluorohydrin or elimination of hydrogen fluoride.[10,42,44,45,59] In this example[59] an explanation is given to account for this type of reaction; abstraction of the 5α-fluoride ion with a molecule of boron trifluoride to give a BF_4^- ion is assisted by participation of the 6β-hydroxy group (possibly as $-OBF_2$) as shown (170) giving a structure equivalent to the original epoxide-boron trifluoride complex which then undergoes rearrangement to ketonic products by



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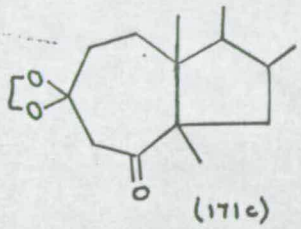
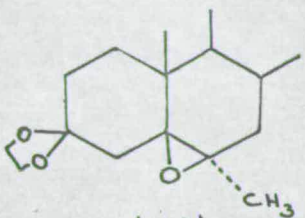
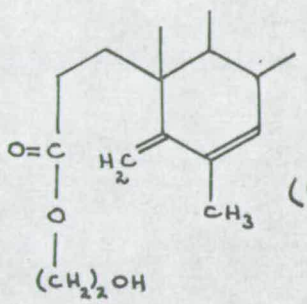


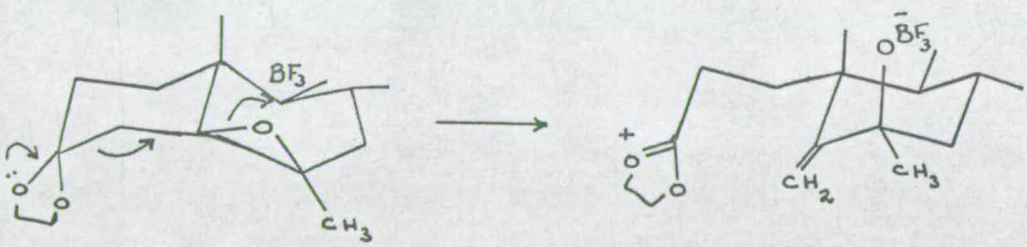
(171c)



(171b)



(171d)

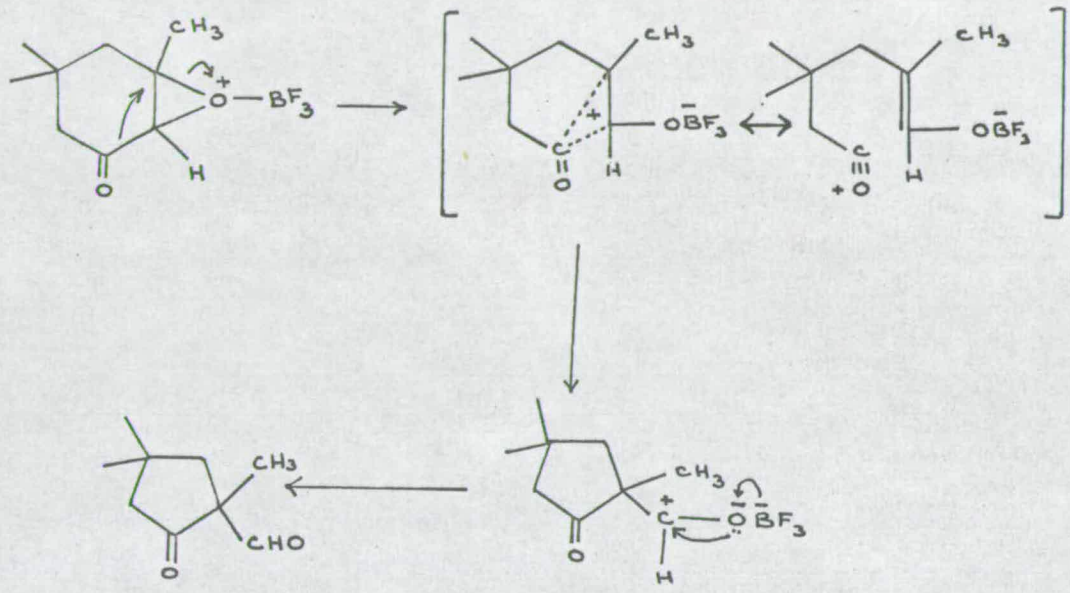


(171e)

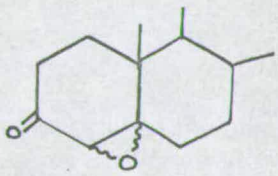
C_5-O or C_6-O cleavage.

Normal C-6 cleavage of the 5α,6α-epoxide (165) is not opposed by the -I substituent at C-3. In the case of the 5β,6β-epoxide (167), however, the -I effect of the acetate opposes the normal C_5-O cleavage thus explaining the initial fluorohydrin formation. The ketonic products are formed by equitorial cleavage (166) and axial cleavage (169). With equatorial cleavage both electronic and conformational factors make cis-bond migration the only possible migration with the A-homo-B-nor product resulting. The small yield of 3β-acetoxy-5-methyl-5α-cholestan-6-one results from axial cleavage. It was later found on re-examination[56] that some 5β-acetyl-B-nor compound (171) was also produced from this epoxide (167) but in low yield. This type of compound is also formed from the corresponding 3-deoxy-5β,6β-epoxide (136b) where of the two ketonic products the acetyl-compound (142) is the major. This reversal of ratios is thought to be due to conformational effects of the acetate group.[56]

It has been shown[63] that the reaction of 3,3-ethylenedioxy-6β-methyl-5,6α-epoxy-5α-cholestane (171a) with BF_3 gives as the main product the ketal ketone (171c), formed by the expected C_6-O cleavage and rearrangement, with other minor products derived from it. The 3,3-ethylenedioxy-6α-methyl-5β,6β-epoxide (171b) on the other hand[63] gives 6-methylcholesta-4,6-dien-3-one along with the diene-ester (171d). Formation of the diene-3-ketone is one of several examples of such rearrangements from β-epoxides,[56,57,58] while formation of the diene-ester (171b) can be attributed to a



(172)



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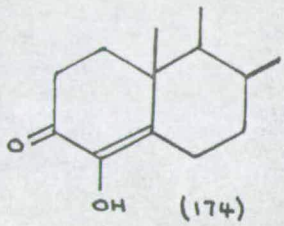
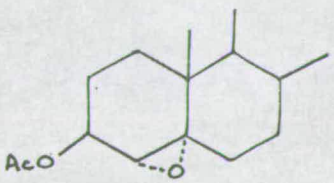


(174)



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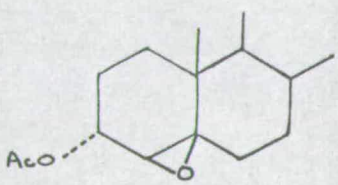
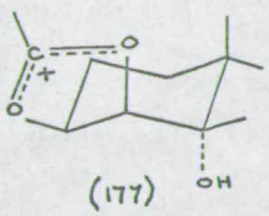


(176)

reaction which involves participation of the ketal group as shown (171e).

Polar groups α to one epoxide carbon have a very direct effect on epoxide rearrangement reactions. Electron releasing substituents such as aryl or alkoxy groups facilitate bond breaking, the bond which breaks being the one between the epoxide oxygen and the carbon carrying the electron releasing group.[24] Electron withdrawing groups have the opposite effect, opposing cleavage at the carbon carrying the electron attracting group.[24] In steroid examples, however, conformational factors as well as electronic factors can be of importance.

In α-keto-epoxides as well as a tendency for cleavage at the adjacent carbon not to take place there is one other important factor, for it has been shown that with these epoxides acyl-group migration is preferred to hydride or alkyl-migration when other steric complications are absent.[43] Thus 3-methyl-2,3-epoxycyclohexanone predominantly undergoes ring contraction (172) when treated with boron trifluoride. This has been explained[43] in terms of sharing of the positive charge by the carbonyl group in the transition state which can be resonance stabilized as shown (172). Acyl migration also leads to localisation of the positive charge on a carbon β to the original ketone which should be preferred to localisation of positive charge α to the ketone. 3-Alkyl-2,3-epoxycyclohexanones frequently rearrange to α-diketones on Lewis acid treatment. Here elimination of the C-2 proton from the initial C-3 carbonium ion gives the enol of the α-diketone.



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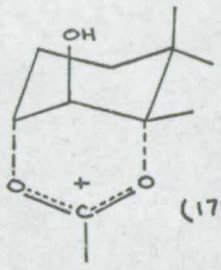

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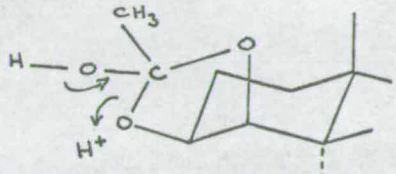

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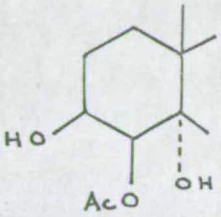

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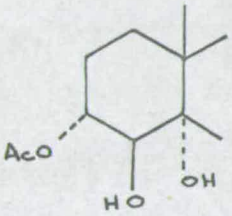
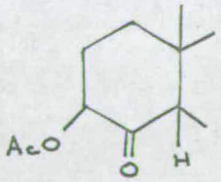
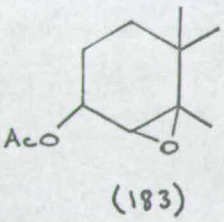


(181)



(182)



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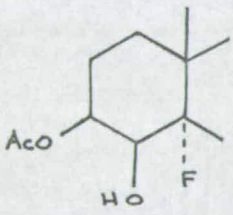

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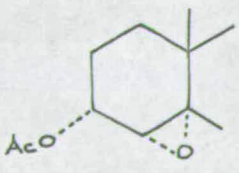

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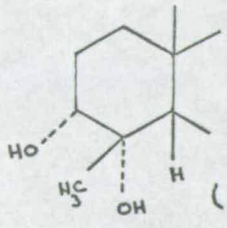
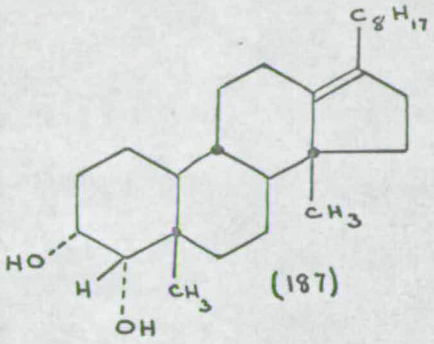


(186)

A good example of this is found in the BF_3-treatment of 4,5-epoxy-3-keto-steroids (173) where preferential formation of 4-hydroxy-Δ^4-steroid-3-ketones (174) is observed.[66] With α-acetoxy-epoxides the -I effect of the acetate carbonyl group opposes participation of the p-electrons on the other acetate oxygen in the type of resonance hybrid required for ring contraction. Here the -I effect of the acetate group and its conformation in starting material and possible products are the important influences in the rearrangement reactions. Some steroid examples of the influence of various electron withdrawing groups, and the part conformation plays will be given.

Reactions over a short time of 3β-acetoxy-4α,5-epoxy-5α-cholestane (175) and 3α-acetoxy-4β,5-epoxy-5β-cholestane (176) with BF_3 both involve attack of the acetate carbonyl to give the bridged structures (177) and (178). The orthoesters (e.g.179) then open giving the products (180) and (181).[67,68] Longer reaction for (175) with BF_3 gives as the major product 3β-acetoxy-5β-cholestan-4-one (182), the normal product from a 4α,5α-epoxide, together with a little 3β-acetoxy-5α-cholestan-4-one derived from the A/B-cis ketone (182) on alumina chromatography, and some 4β-acetoxy-3β,5α-diol.[68] Here formation of the ketone involves cleavage at C-5 in contrast to the diol where formation requires that the C-4-oxygen bond breaks. Thus formation of the 3β,4β-bridged structure (177) must be a reversible process since there is evidence that there is initial formation of it in the longer reaction. Longer reaction times for the BF_3 reaction of epoxide (176) gives only the diol (181).[68]



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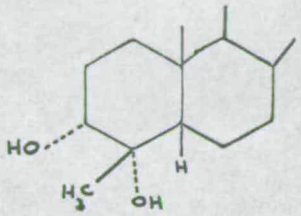

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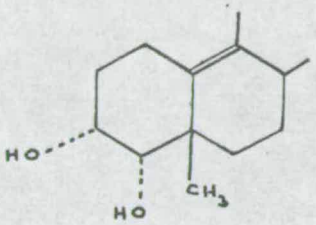

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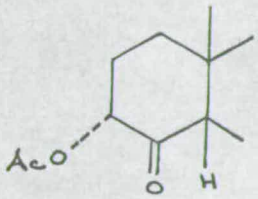

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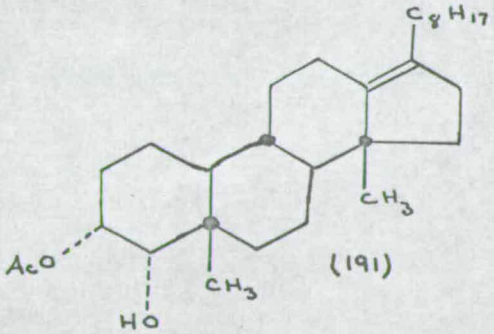

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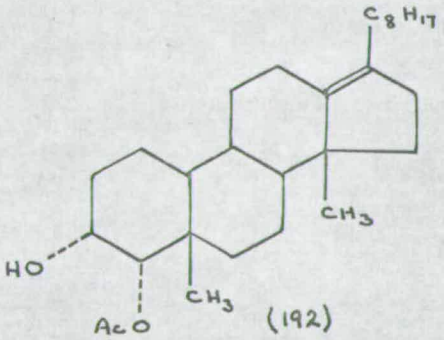
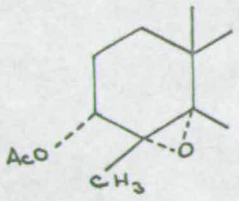


(192)

A bridged intermediate is, however, not possible for 3β-acetoxy-4β,5-epoxy-5β-cholestane (183). BF_3 treatment gives the fluorohydrin (184) as the only recognizable product irrespective of the length of the reaction time.[68]

The reaction of 3α-acetoxy-4α,5-epoxy-5α-cholestane (185) with BF_3 was not part of this original investigation[68] but has recently been carried out by the same group;[69] when a re-examination of the reaction of this epoxide (185) with methyl magnesium iodide showed that the diol (186) and the backbone rearranged product (187) are formed and not as previously reported[70] the compounds (188) and (189). With BF_3, epoxide (185) gives the expected ketone (190), 25%, together with backbone rearranged products (191), 58%, and (192).[69] There is evidence that (192) is formed from (191) on alumina chromatography.[69]

The BF_3-catalysed reactions of 3-acetoxy-tetrasubstituted epoxides of this type give products whose formation depends on the -I effect of the acetate and on the conformational preferences of the acetoxy group and ring A when cleavage to a C-5 carbonium ion takes place.[56] The length of the reaction is also important. If the reaction is very short diols and fluorohydrins as well as starting materials are the only products from these epoxides.[57] Except for epoxide (193)[69] longer reaction times give product mixtures containing ketonic products although in all cases these ketones account for relatively little of the product, being at best 36%. With the 3α-acetoxy-4α,5α-epoxide (193) an unsaturated hydroxy-acetate shown to be the backbone rearranged product (194)



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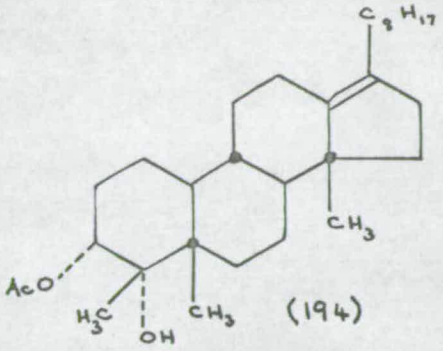

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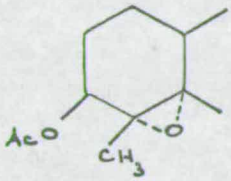

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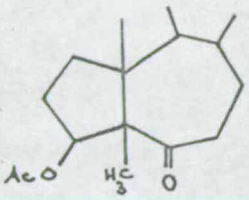

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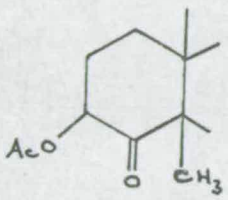

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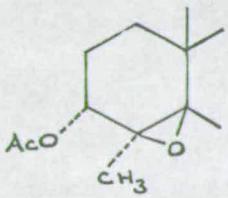
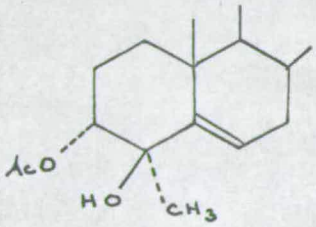


(198)



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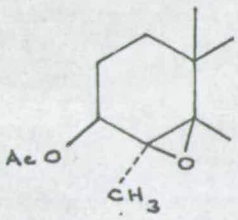

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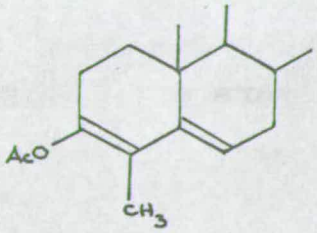

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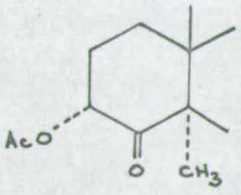
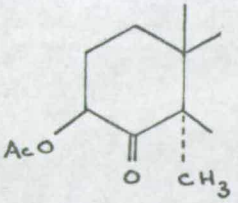


(202)

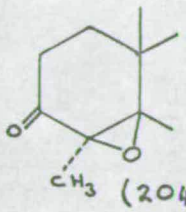


(203)

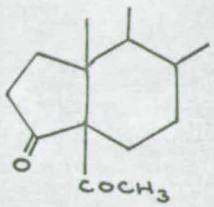
is formed, all routes to ketones being opposed by a combination of conformational and inductive effects.[56,69] The corresponding 3β-acetoxy-4α,5α-epoxide (195) gives two ketones.[57] One of these ketones, the A-nor-B-homo-5β-methyl-6-ketone (196), involves "normal" axial cleavage even although this is opposed by the -I effect of the acetate.[56] The other ketone, 3β-acetoxy-5-methyl-5β-cholestan-4-one (197), is a result of equatorial cleavage and migration of the C-4 methyl group.[56] With the two 4β,5β-epoxides elimination reactions take place to a large extent the 3α-epimer (198) giving the Δ^5-4β-alcohol (199) and the 3β-epimer (200) the $\Delta^{3,5}$-enol acetate of 4-methylcholest-4-en-3-one (201).[56,57] With both these epoxides ketone formation results from methyl migration, (202) from the 3α-acetate (198) and (203) from epoxide (200). The yield of (202) is 29% while that of the ketone from the 3β-acetoxy-compound is only 10%.[57] This difference in yields is attributed to the conformational effects of the two acetoxy-groups.[56]

Ring contraction (205) is observed in the boron trifluoride-catalysed rearrangement of 4β,5-epoxy-4α-methyl-5β-cholestan-3-one (204)[57] but is not dominant since conformational factors are somewhat against it,[56] formation of the transition state for carbonyl migration bringing about eclipsing of the 4-methyl and C_6-methylene groups and the close approach of the 4β-oxygen atom to the C-19 angular methyl group. 5α-Methylcholestane-3,4-dione (206) is, therefore, also formed, presumably, from a conformation with a strain free B-ring which allows 4-methyl migration.

Due to the -I effect of the carbonyl group 4α,5-epoxy-4β-



(204)



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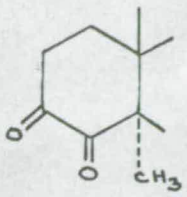

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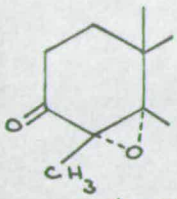

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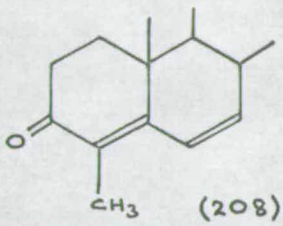

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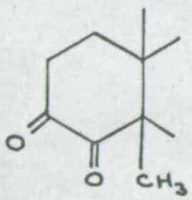

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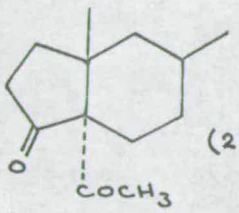

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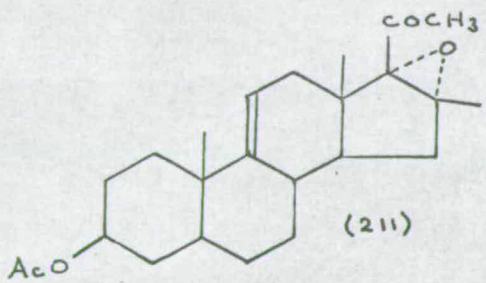

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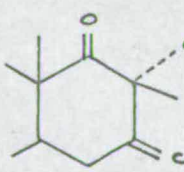

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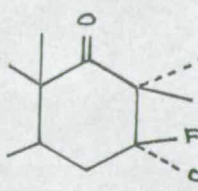

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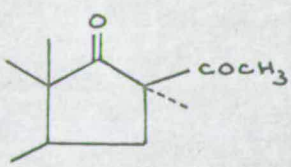

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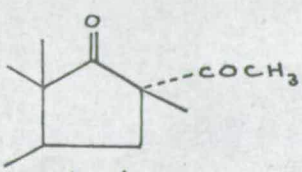
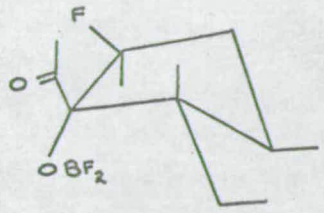


(215)

methyl-5α-cholestan-3-one (207) undergoes abnormal C-5 cleavage with the 4,6-dienone (208) as the major product. The two ketones (209) and (210) are formed as minor products.[57] Possible explanations for this is that acyl group migration to C-5 needs the near eclipsing of the 4-methyl group with C-6 and also gives a strained trans junction between a 5-membered A ring and 6-membered B ring, while 4-methyl migration leads to a strained cis-product with an unfavourable skew interaction between the 5β- and 19-methyl groups.[56]

Solvent and reaction time are shown to be important in the BF_3-catalysed reactions of some 16α,17α-epoxy-16β-methyl-5α-pregnan-20-ones.[71] In dioxan treatment of 3β-acetoxy-16α,17α-epoxy-16β-methyl-5α-pregn-9-en-20-one (211) with BF_3 gives mainly 3β-acetoxy-17α-hydroxy-17β-methyl-16-methylene-D-homo-5α-androst-9-en-17a-one (212), whereas with benzene as solvent a D-homo-fluorohydrin is formed, probably the 16β-fluoride (213). Longer reaction of (211) with BF_3 in drier benzene gives a mixture of the epimeric 3β-acetoxy-16-acetyl-16-methyl-5α-androst-9-en-17-ones (214) and (215). The fluorohydrin (213) when treated with boron trifluoride gives one of the 16-acetyl compounds, (214).

Formation of the D-homo-fluorohydrin (213) is thought to proceed via the 16β-fluoro-16α-methyl compound (216). Interaction of the 17α-OBF_2 group with the adjacent 20-carbonyl group creates a positive charge at C-20 (217) followed by migration of the 16,17-bond (218). Hydrolysis of the complex (218) will then produce the fluorohydrin (213). Ring contraction (219) of the fluorohydrin is thought to involve formation of a tetrafluoroborate intermediate



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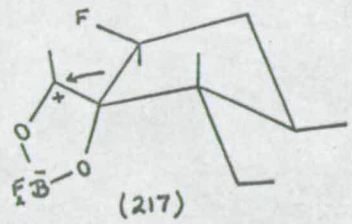

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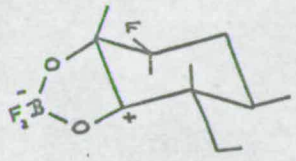

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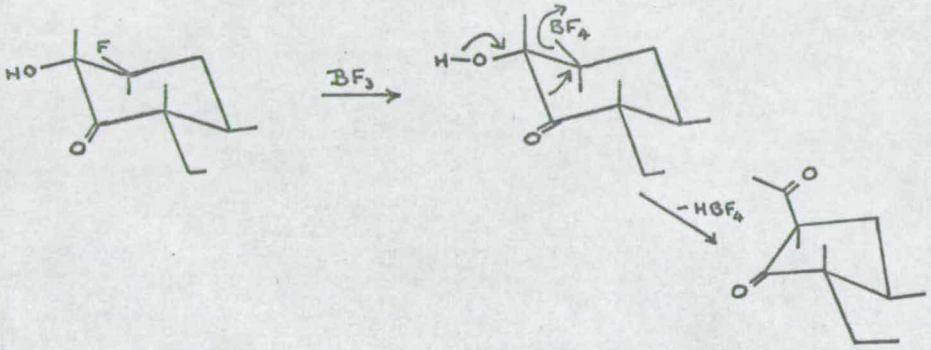

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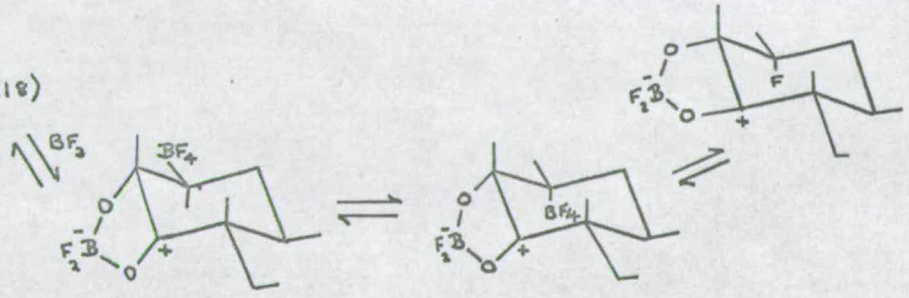

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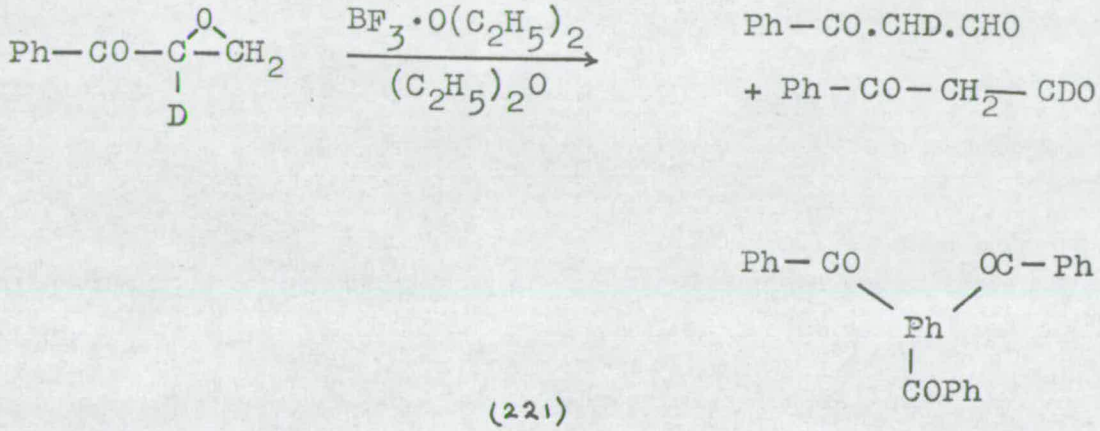

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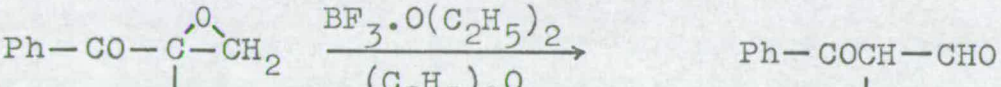


R=C_2H_5, C_6H_5.

(222)

with trans 17,17a-bond migration to the resulting positive charge at C-16 to give the 16β-acetyl compound (214). Isolation of epimers (214) and (215) when dry benzene is used is thought to involve equilibrium at C-16 (220) by reversible ionisation of the 16-tetrafluoroborates to give a mixture of the two fluorohydrins and hence the two acetylcyclopentanones.[71]

Finally there is one example of the rearrangement of an α-keto-terminal epoxide. Isotopically it has been shown that acrylophenone epoxide undergoes both benzoyl migration and 1,2-hydride transfer when treated with boron trifluoride (221).[72] The related α-ethyl- and α-phenylacrylophenone epoxides undergo isomerisation exclusively by a 1,2-hydride shift (222).[72]

Object of Research

Examples of work described in this thesis were chosen to show what influences if any were present in the epoxidation of an unhindered steroid ketone and its alkylidene derivatives (5α-cholestan-3-one, 3-methylene-5α-cholestane, 3-ethylidene-5α-cholestane, and 3-isopropylidene-5α-cholestane), two methylated derivatives of 5α-cholestan-3-one and 3-methylene-5α-cholestane (2α-methyl-5α-cholestan-3-one and its 3-methylene-derivative and 2,2-dimethyl-5α-cholestan-3-one and its 3-methylene derivative), and the hindered 5α-cholestan-2-one and its 2-methylene derivative. Although the epoxidation of several steroid-17-ketones and 17-alkylidene steroids has been reported it was felt desirable to carry out a study of the epoxidation of one such pair of 17-substituted steroids with dimethyloxosulphonium methylide, dimethylsulphonium methylide, peracid, and the alkaline hydrogen peroxide-benzonitrile system. To avoid the possibility of long range effects 5α-androstan-17-one and its 17-methylene derivative were chosen for this study.

The ring opening reactions of the derived A-ring methylene epoxides under acidic and basic or neutral conditions were carried out. In particular it was hoped that opening of the 3-methylene epoxides with a suitable reagent would give the amino-alcohol intermediates found in Tiffenean ring expansion reactions and thereby give information about the stereochemistry of the addition of CN^- to the original ketones.

The rearrangement reactions of the epoxides derived from the 3-alkylidenes and 2-methylene-5α-cholestane were carried out with

boron trifluoride. It was planned to prepare methylene epoxides with polar groups adjacent to the epoxide ring and to study the effect of these polar groups on subsequent ring opening reactions.

Finally the study of rearrangement reactions of tetrasubstituted epoxides was extended to include examples which did not possess a ring junction as one substituent. The examples chosen here were the two 2,3-epoxy-2,3-dimethyl-5α-cholestanes.

EXPERIMENTAL RESULTS AND DISCUSSION

The Preparation and Reactions of Methylene-Epoxides.

(1) Epoxides not adjacent to a polar group.

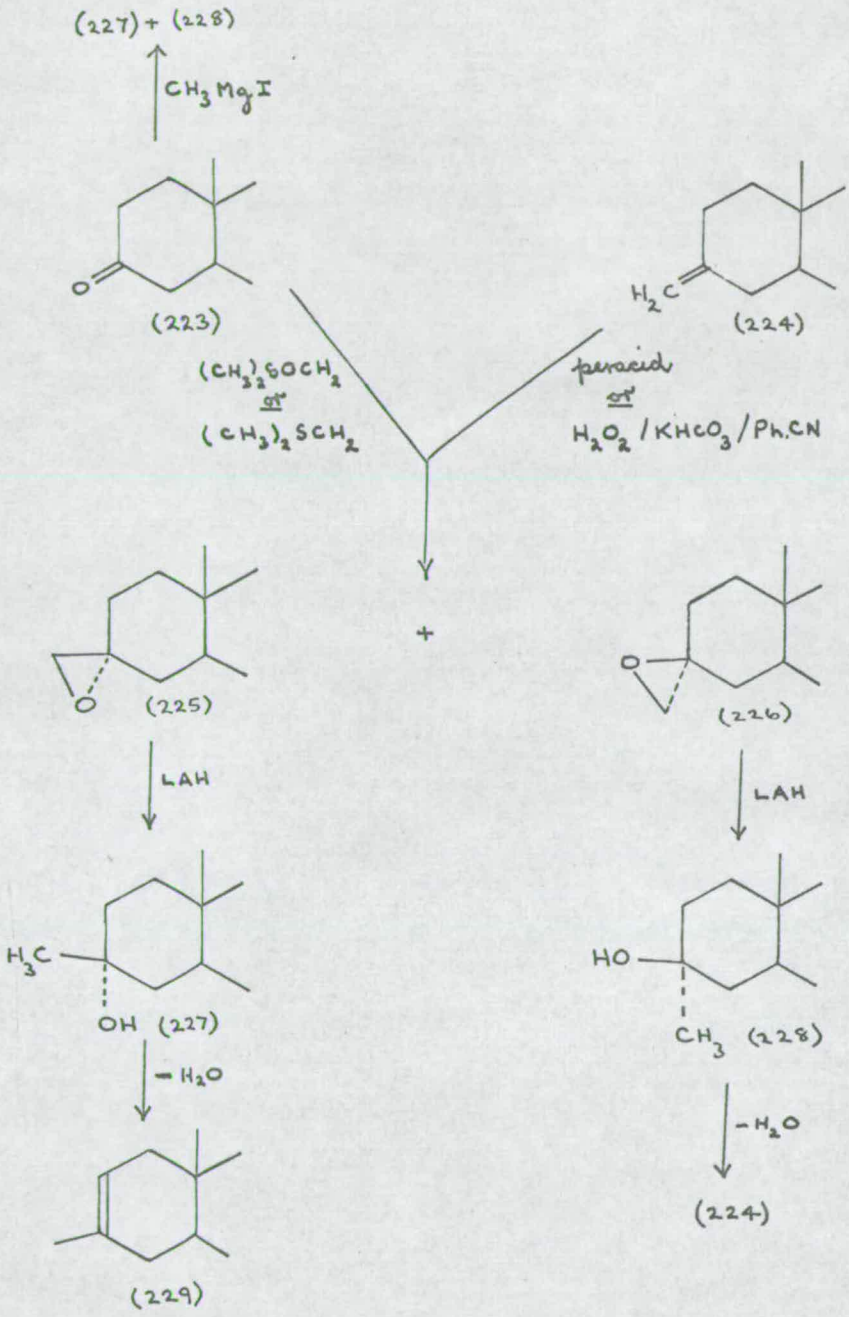
Starting materials

5α-Cholestan-3-one,[73,74] 2α-methyl-5α-cholestan-3-one,[75] and 2,2-dimethyl-5α-cholestan-3-one[76,77] were prepared by the standard procedures, and 5α-androstan-17-one was already available. 5α-Cholestan-2-one was obtained from 5α-cholest-2-ene by the addition of hypobromous acid to give 3α-bromo-5α-cholestan-2β-ol[19] which on treatment with alumina gave 2β,3β-epoxy-5α-cholestane. Reduction of this epoxide with lithium aluminium hydride in ether gave 5α-cholestan-2β-ol which was oxidised with Jones' reagent to the 2-ketone.[78]

Synthesis of the corresponding methylene derivatives of these five ketones was carried out with methylenetriphenylphosphorane prepared by the method of Corey et al.[79] In all cases crude products were obtained which from their i.r. spectra contained aromatic by-products. The pure exo-methylene-steroids were obtained by chromatography on alumina. All the olefins exhibited characteristic absorptions in the i.r. at ca.1650 and 890 $cm.^{-1}$,[80] and likewise characteristic n.m.r. peaks at ca.5.4τ.[81]

Epoxidations of 5α-cholestan-3-one and 3-methylene-5α-cholestane.

Dimethyloxosulphonium methylide was prepared by stirring together trimethyloxosulphonium iodide and sodium hydride in dry dimethyl sulphoxide under nitrogen until evolution of hydrogen ceased.[4] The ketone (223) in dimethyl sulphoxide and tetrahydrofuran was added to the ylide solution and stirring was continued


(227) + (228)
CH3MgI
(223)
(224)
(CH3)2SOCH2
or
(CH3)2SCH2
peracid
or
H2O2 / KHCO3 / Ph.CN
Y
+
(225)
(226)
LAH
LAH
H3C
OH (227)
HO
CH3 (228)
- H2O
- H2O
(224)
(229)

for 1 hour at room temperature and 1 hour at 50°. Crystalline 3β-methyl-3α,3'-epoxy-5α-cholestane (225) was obtained with a melting point of 131-2 (from acetone), with i.r. peaks at 925 (s), 790 (m), and 698 (w) cm. and a peak corresponding to 2 protons at 7.38 τ in the n.m.r. (half band width 0.012 ppm). Chromatography on alumina of the crude product from a second reaction of the oxosulphonium ylide with the 3-ketone (223) gave two compounds. The first (eluted with petrol) was the α-epoxide (225), 97%, and the second (also eluted with petrol) was 3α-methyl-3β,3'-epoxy-5α-cholestane (226), 3%. The β-epoxide (226) has a melting point of 170-1° and i.r. peaks at 935 (m), 840 (s, broad), and 723 (w) cm.$^{-1}$ with a two proton n.m.r. peak at 7.44 τ (half band with 0.030 ppm).

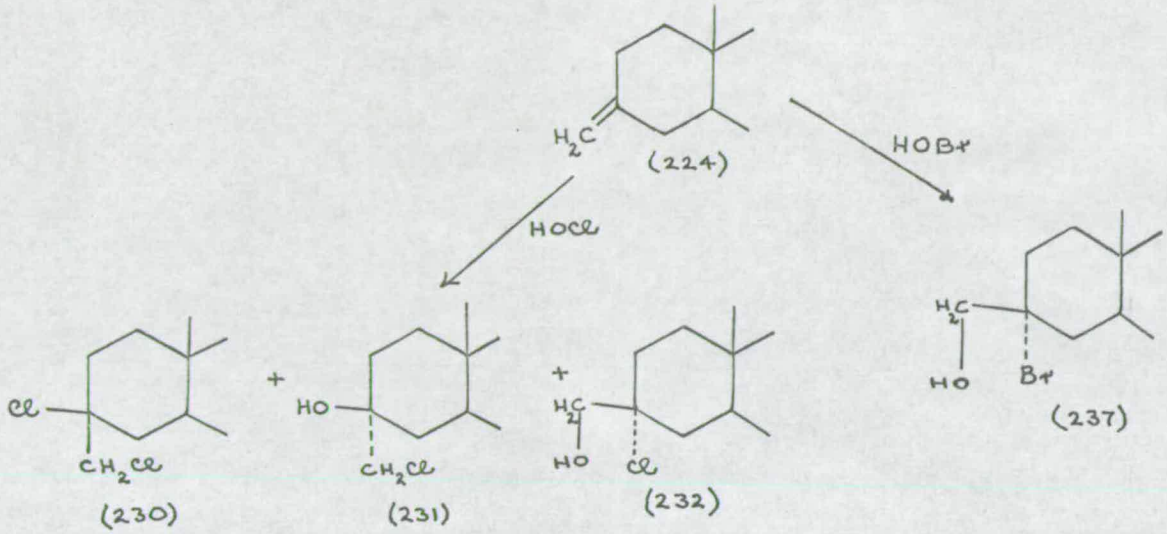
The stereochemical identity of these epoxides was deduced by the reduction of each to its corresponding tertiary alcohol,[26] followed by dehydration with phosphoryl chloride in pyridine.[82] Lithium aluminium hydride reduction of the α-epoxide (225) gave a product shown to be 3β-methyl-5α-cholestan-3α-ol (227)[83] by its dehydration to 3-methyl-5α-cholest-2-ene (229)[82] and by a mixed melting point and i.r. spectrum comparison with an authentic sample of the 3α-ol (229) prepared by the action of methyl magnesium iodide on 5α-cholestan-3-one.[82] These experiments show that the epoxide (225) must have a pseudoaxial C-3-oxygen bond. In a similar way the β-epoxide (226) was reduced to 3α-methyl-5α-cholestan-3β-ol (228), identified by its dehydration to 3-methylene-5α-cholestane (224) and by a mixed melting point and spectral comparison with a sample of the 3β-ol (228), also prepared by treatment of 5α-cholestan-3-one with methyl magnesium iodide.[82] Here the

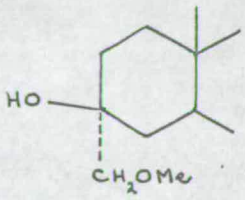
reduction indicates that the epoxide (226) has a pseudo-equatorial C-3-oxygen bond.

Additional evidence of the stereochemistry of the two epoxides is given by a comparison of the n.m.r. half band width of the epoxides ($C\underline{H}_2$-O). The α-epoxide (225) has a half band width of 0.012 ppm while the β-epoxide (226) has a half band width of 0.030 ppm. These results are in agreement with the findings of Carlson and Behn.[3]

Solutions of dimethylsulphonium methylide were prepared by addition of powdered trimethylsulphonium iodide to a stirred solution of methylsulphinyl carbanion in dimethyl sulphoxide and tetrahydrofuran under nitrogen at a temperature of ca.-10°.[4] After stirring for ten seconds the steroid ketone (223) in dimethyl sulphoxide and tetrahydrofuran was added with stirring and stirring was continued for ten minutes at ca.-10° and for 1 hour while the temperature of the reaction was allowed to reach room temperature. A mixture of products was obtained which on chromatography on alumina gave the α-epoxide (225), 31%, and the β-epoxide (226), 69%.

Epoxidation of 3-methylene-5α-cholestane (224) with p-nitroperbenzoic acid[85] in ether as solvent gave on chromatography the α-epoxide (225), 85%, and the β-epoxide (226), 15%. Replacing the p-nitroperbenzoic acid by m-chloroperbenzoic acid gave the same ratio of α- to β-epoxide. When the epoxidation with m-chloroperbenzoic acid was carried out in methylene chloride the α- to β-epoxide ratio was 64 to 36.





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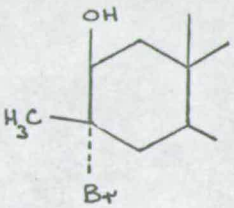

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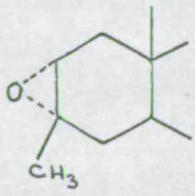

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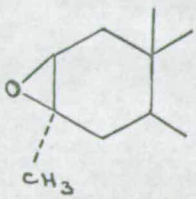


(236)

The 3-methylene-compound (224) in chloroform was added to a stirred mixture of benzonitrile, 30% hydrogen peroxide and potassium bicarbonate in methanol.[3] After stirring overnight a crude product was obtained which on chromatography on alumina gave 3-methylene-5α-cholestane, 16%, the α-epoxide (225), 22%, and the β-epoxide (226), 62%. The ratio of β- to α-epoxide is ca.3 to 1.

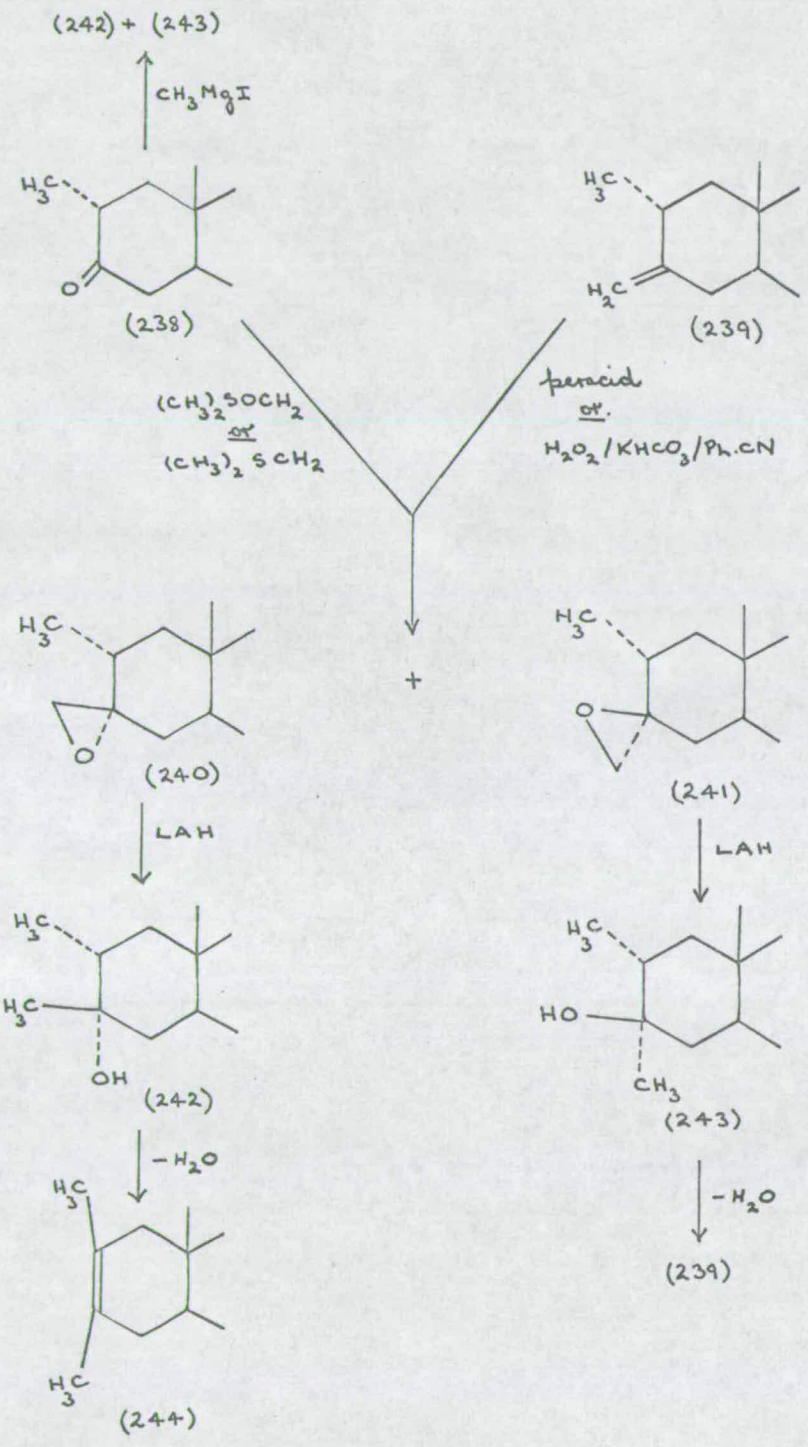
3-Methylene-5α-cholestane was stirred rapidly for five minutes at room temperature with bleaching powder in ether and water, and acetic acid was added with stirring continuing for half-hour.[87] A crude product was obtained which was chromatographed on florisil giving three main fractions, two of which were crystalline solids with the third a semi-solid. Analysis indicated that they all contained chlorine. The first product (eluted with petrol) showed i.r. bands at 770 and 730 $cm.^{-1}$ The n.m.r. spectrum indicated the absence of olefinic protons but had a strong two proton peak at 6.26 τ probably due to an exo-methylene group ($-C\underline{H}_2X$).[81] Elemental analysis showed it to be the dichloride (230). The second product (231) (eluted with petrol-benzene) could not be recrystallised, its i.r. spectrum had a band at 3560 $cm.^{-1}$(-OH) but no strong absorption in the region 1000-1100 $cm.^{-1}$ which would indicate that the alcohol was tertiary.[80] In fact treatment of this alcohol with acetic anhydride and pyridine did not give an acetate. The last product (232) (eluted with ether) was a crystalline solid which from its i.r. spectrum was an alcohol (3550 $cm.^{-1}$). A strong peak at 1050 $cm.^{-1}$ indicated that the alcohol was primary or secondary.[80] Acetylation of this compound with acetic anhydride

in pyridine gave a product containing an acetate (i.r. 1735 cm.$^{-1}$) and starting material even after a reaction time of two days. However this is sufficient to classify the alcohol as a primary or secondary alcohol since a tertiary alcohol would be even less reactive with these reagents.[88] The same chloro-compound (232) was obtained by the cleavage of 3α-methyl-3β,3'-epoxy-5α-cholestane with hydrogen chloride. Since it is known that addition of hypochlorous acid to methylenecycloalkanes gives mixtures of 1-chloro-cycloalkane-methanols and chloromethylcycloalkanols[23] while the corresponding exocyclic methylene epoxides are cleaved by hydrogen chloride to give only the 1-chloro-compounds[23] it would appear that compound (231) is probably a 3-chloromethyl-3-ol and compound (232) is a 3-hydroxymethyl-3-chloride. Here the "primary" alcohol is the major compound; "primary":"tertiary" = ca.7:4. This is in agreement with the similar work on methylenecyclohexanes.[23]

Treatment of either alcohol, (231) or (232), with sodium hydroxide in methanol gave a product (233) with i.r. bands at 3540 and 1118 cm.$^{-1}$ This later absorption can be attributed to an ether.[80] The n.m.r. showed peaks at 6.75 and 6.66 τ. The peak at 6.66 τ accounting for three protons can be attributed to the hydrogens on the methyl group of the ether grouping -O-C$\underline{H}_3$, while the other peak had approximately a two proton intensity and is probably due to the methylene protons -C$\underline{H}_2$-OCH$_3$. Treatment of the ether (223) with acetic anhydride in pyridine did not give an acetate indicating that the hydroxy-group was attached to C-3. The same compound (223) was obtained by cleavage of 3α-methyl-3β,3'-epoxy-5α-cholestane with

sodium hydroxide in methanol. Since basic or neutral substitution of epoxides of this kind are known to involve attack at the exocyclic carbon with retention of the epoxide oxygen configuration[24] this ether (233) would be expected to be 3α-methoxymethyl-5α-cholestan-3β-ol (233) and this is confirmed by the tertiary nature of the hydroxy-group. The formation of this compound from both chlorides can only be explained by prior formation from them of the β-epoxide (226), i.e. in both cases attack of the Cl^+ ion was from the α-side giving 3α-chloromethyl-5α-cholestan-3β-ol (231) and 3β-hydroxymethyl-3α-chloro-5α-cholestane (232). In fact when either chloride was treated with potassium t-butoxide each gave the β-epoxide (226) in good yield.

Treatment of 3-methylene-5α-cholestane with HOBr generated from N-bromosuccinimide and perchloric acid[19] gave a gum which was chromatographed on florisil. There were no early non-polar compounds and elution with benzene gave a product the i.r. of which indicated the presence of a hydroxy-group (3550 $cm.^{-1}$) and exhibited a medium-strong band at 1035 $cm.^{-1}$ A second gum was eluted with ether and had a very similar i.r. spectrum to that of the first. Both compounds contained bromine. Chromatography of the first product on alumina gave on elution with petrol an oil with no strong peaks in the i.r. There was a moderate band at 925 $cm.^{-1}$ and a strong peak at 8.76 τ was present in the n.m.r. Both these spectra are similar to the corresponding spectra of 2α,3α-epoxy-3β-methyl-5α-cholestane (234). This observation can be explained by assuming that the first fraction from the florisil column contained 3α-bromo-


(242) + (243)
CH_3MgI
(238)
(239)
$(CH_3)_2SOCH_2$
or
$(CH_3)_2SCH_2$
peracid
or
$H_2O_2/KHCO_3/PhCN$
+
(240)
(241)
LAH
LAH
OH
(242)
HO
CH_3
(243)
$-H_2O$
$-H_2O$
(239)
(244)

3β-methyl-5α-cholestan-2β-ol (235) which would give 2β,3β-epoxy-3α-methyl-5α-cholestane (236) on treatment with alumina. The methyl steroid (229) could result from a perchloric acid catalysed isomerisation[89] of the methylene steroid (224) and subsequent addition of HOBr to this compound leads to the product (235) in an analogous fashion to the HOBr addition to $\Delta^{9,11}$-steroids.[21] The second fraction from the florisil column was further chromatographed on alumina to give 3α-methyl-3β,3'-epoxy-5α-cholestane.

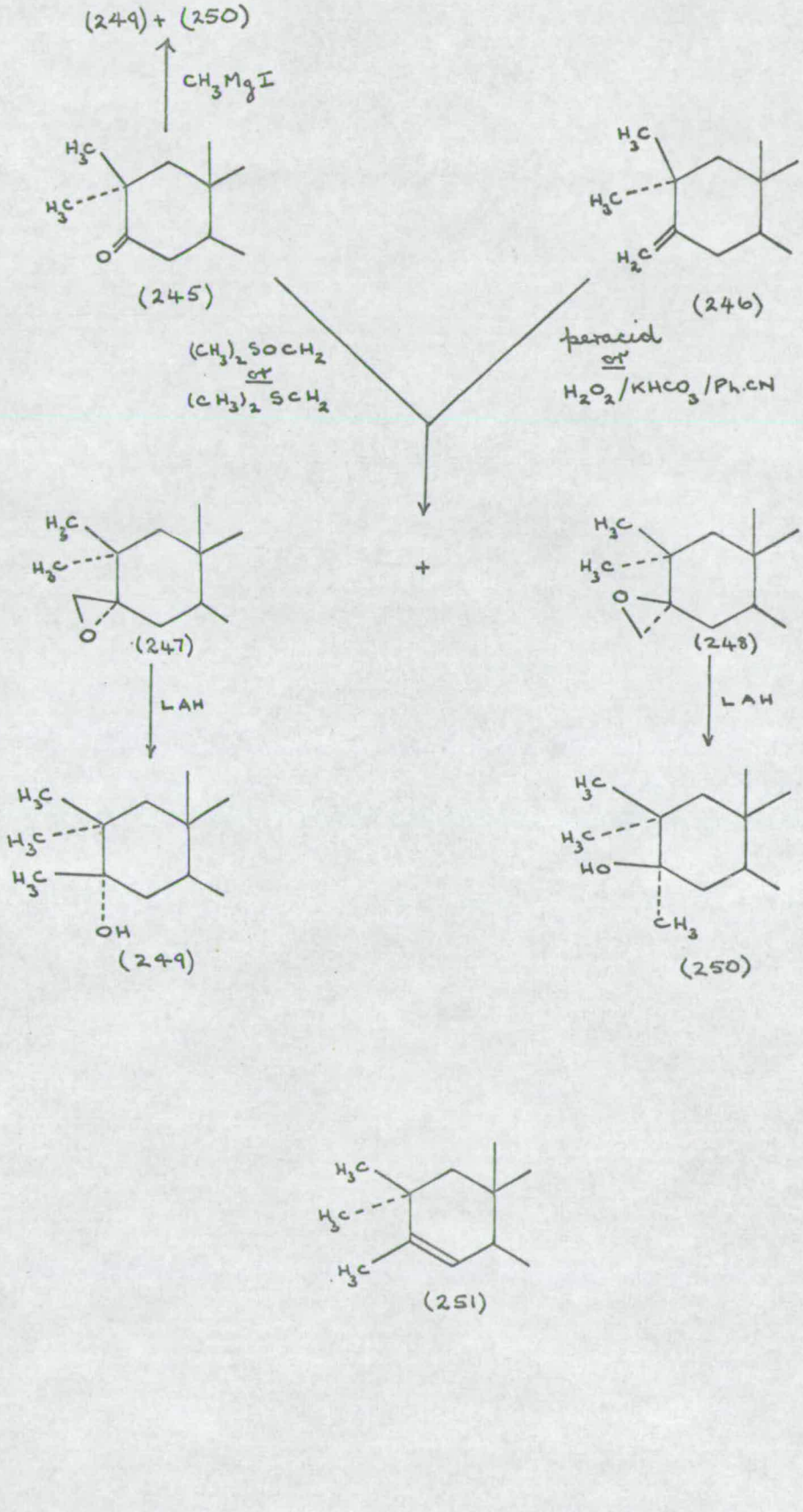
The addition of HOBr to the 3-methylene-compound (224) was repeated using less drastic conditions. The reaction was carried out in aqueous acetone with N-bromosuccinimide and acetic acid. Florisil chromatography of the reaction product gave two components, 3-methylene-5α-cholestane and an alcohol (i.r. 3540 and 1035 $cm.^{-1}$). This alcohol (237) also contained bromine and with acetic anhydride in pyridine gave after two days a mixture of starting material and acetate, indicating that the compound was a primary or secondary alcohol. Chromatography of this bromo-alcohol on alumina gave 3α-methyl-3β,3'-epoxy-5α-cholestane in good yield, from which it could be regenerated by cleavage with hydrobromic acid. This indicates that the product (237) is 3β-hydroxymethyl-3α-bromo-5α-cholestane.

Epoxidation of 2α-methyl-5α-cholestan-3-one and 3-methylene-2α-methyl-5α-cholestane.

Treatment of 2α-methyl-5α-cholestan-3-one (238) with dimethyloxosulphonium methylide gave two products which were separated by chromatography on alumina. The first compound (eluted with petrol) was 3β-methyl-3α,3'-epoxy-2α-methyl-5α-cholestane (240), 97%, while

the second (also eluted with petrol) was 3α-methyl-3β,3'-epoxy-2α-methyl-5α-cholestane (241), 3%. Marked similarities were found between the i.r. spectra of the α-epoxide (240) and the corresponding epoxide (225). This was also true for the two β-epoxides (241) and (226). The principle similarity was in the intensity of absorption rather than in band position. The α-epoxide (240) for example showed a strong absorption at 942 and a medium one at 788 $cm.^{-1}$ while the α-epoxide (225) has a strong peak at 925 with a medium intensity band at 795, both also had weak peaks at 691 and 698 $cm.^{-1}$ respectively. On the other hand the β-epoxide (241) exhibited a medium band at 939 with a weak one at 690 along with a strong broad peak at 839 $cm.^{-1}$ The β-epoxide (226) has corresponding absorptions at 840 (broad and strong) and at 935 and 723 $cm.^{-1}$(both weak). In the case of the two epoxides (240) and (241) the n.m.r. spectra could not be used as a means of identification by half band width determinations since the α-epoxide (240) exhibited epoxide peaks at 7.15; 7.22; 7.52; 7.59τ and the β-epoxide (241) at 7.18; 7.26; 7.58; 7.66τ.

Identification of the two epoxides of the 2α-methyl series was established using the lithium aluminium hydride reduction-phosphoryl chloride in pyridine dehydration technique. The α-epoxide (240) gave an alcohol (242) which lost a molecule of water to give an olefin. This olefin had no significant peaks in the i.r. but the n.m.r. exhibited a strong six proton peak at 8.43τ. This can be attributed to two methyl groups attached to a double bond, which in this case can only be accounted for by assuming that the olefin is 2,3-dimethyl-5α-cholest-2-ene (244), and in fact the n.m.r. of this compound has been shown to have a six proton peak at 8.46τ.[90]


(249) + (250)
CH_3MgI
(245)
(246)
$(CH_3)_2SOCH_2$
or
$(CH_3)_2SCH_2$
peracid
or
$H_2O_2/KHCO_3/Ph.CN$
+
(247)
(248)
LAH
LAH
(249)
(250)
(251)

The melting point of the compound here also corresponds to that reported for 2,3-dimethyl-5α-cholest-2-ene.[90,91] The alcohol (242) was also obtained by treatment of 2α-methyl-5α-cholestan-3-one with methyl magnesium iodide where it accounted for 79% of the mixture of the two C-3 tertiary alcohols (242) and (243). The second alcohol (243) was as expected identical ~~to~~ with the compound produced by lithium aluminium hydride reduction of 3α-methyl-3β,3'-epoxy-2α-methyl-5α-cholestane, and on dehydration gave 3-methylene-2α-methyl-5α-cholestane (239).

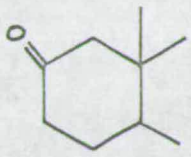
The reaction of 2α-methyl-5α-cholestan-3-one (238) with the sulphonium ylide gave a low yield of products. Chromatography on alumina gave the α-epoxide (240), 75%, and the β-epoxide (241), 25%. The yield of α-epoxide (240) from the reaction of 3-methylene-2α-methyl-5α-cholestane with m-chloroperbenzoic acid in ether was 63% with the remainder β-epoxide (241). Treatment of the olefin (239) with the alkaline hydrogen peroxide-benzonitrile system produced 3-methylene-5α-cholestane, 16%, the α-epoxide (240), 6%, and the β-epoxide (241), 78%.

Epoxidation of 2,2-dimethyl-5α-cholestan-3-one and 3-methylene-2,2-dimethyl-5α-cholestane.

When the epoxidation of the ketone (245) with dimethyloxosulphonium methylide was carried out the α-epoxide (247), 94%, was obtained with the remainder of the product the β-epoxide (248). The α-epoxide (247) was identified from its i.r. spectrum which had a strong peak at 930 and a medium intensity band at 780 $cm.^{-1}$ which was a very similar spectrum to those of the other two

α-epoxides (225) and (240) previously mentioned. The i.r. spectrum of the β-epoxide (248) had a strong and broad peak at 851 (with a shoulder at 840) and a medium peak at 918 cm.$^{-1}$ again similar to the spectra of the β-epoxides (226) and (241). Supplementary structural evidence comes from the polarity on alumina of the two epoxides, the epoxide with a pseudoaxial C-3-O bond would be expected to be and is less polar. Also by now it was apparent that the expected major product from treatment of a cyclohexanone with the oxosulphonium ylide would involve equatorial attack.[3,4,5] The n.m.r. spectrum of the α-epoxide (247) showed -C$\underline{H}_2$-O (epoxide) peaks at 7.20; 7.28; 7.53; 7.60 while the corresponding spectrum of the β-epoxide (248) had similar bands at 7.10; 7.18; 7.55; 7.63 .

Lithium aluminium hydride treatment of the α-epoxide (247) gave an alcohol (249) identical with the less polar of the two tertiary alcohols produced in a 1:1 mixture from the reaction of methyl magnesium iodide with 2,2-dimethyl-5α-cholestan-3-one. The less polar alcohol must be 2,2,3β-trimethyl-5α-cholestan-3α-ol (249) and further indication that this was so was expected to follow from its dehydration with phosphoryl chloride in pyridine. However when this was carried out a product was obtained whose i.r. and n.m.r. spectra were identical to those of 3-methylene-2,2-dimethyl-5α-cholestane, except that the i.r. spectrum had one additional small peak at 830 cm.$^{-1}$ which could be attributed to an endocyclic olefin. However the n.m.r. spectrum showed no absorptions in the endo-olefinic region. That the exocyclic olefin was not the more



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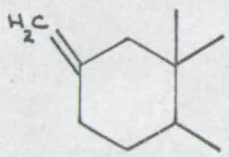

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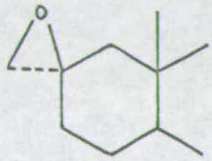

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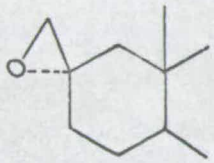

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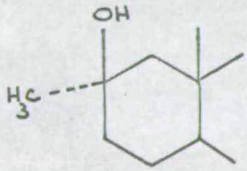


(256)

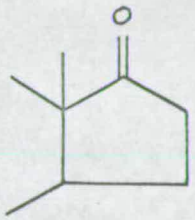
stable of the two possible dehydration products[92] was seen by the conversion of the 3α-ol (249) into an endocyclic olefin (i.r. 840 cm.$^{-1}$) by treatment at 90° with acetic acid containing a few drops of perchloric acid. The endocyclic olefin is 2,2,3-trimethyl-5α-cholest-3-ene (251) since its n.m.r. spectrum displays a three proton peak at 8.38 τ ($C\underline{H}_3$-Ċ=Ċ) and a one proton peak at 4.5 τ ($\underline{H}$-Ċ=Ċ-). Dehydration of the 3β-alcohol (250) gave almost entirely 3-methylene-2,2,-dimethyl-5α-cholestane.

The 2,2-dimethyl group is known to distort the normal chair conformation of the A-ring[93] and this destroys the geometry for the trans-coplanar dehydrations into the A-ring observed with the simpler systems (227) and (242). Elimination of the equatorial hydroxy-group of (250) with loss of a trans-coplanar proton of the C-3-methyl group to give the exocyclic methylene derivative is, however, still possible, and clearly such a mechanism could also operate for the 3α-hydroxy-group of compound (249).

Treatment of the dimethyl-3-ketone (245) with the sulphonium methylide produced a mixture of the same two epoxides in which the β-epoxide (248) was the major product, 60%. Treatment of 3-methylene-2,2-dimethyl-5α-cholestane (246) with m-chloroperbenzoic acid in ether gave the α-epoxide (247), 82%, while the corresponding reaction with the alkaline hydrogen peroxide-benzonitrile system gave the β-epoxide (248), 65%.

Epoxidation of 5α-cholestan-2-one and 2-methylene-5α-cholestane.

A high yield of the β-epoxide (254), 99%, was obtained by methylene transfer to the carbonyl group of 5α-cholestan-2-one (252)



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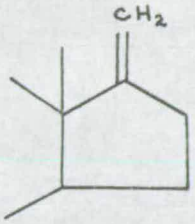

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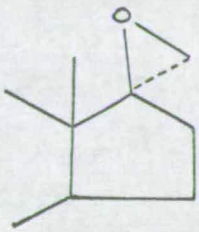

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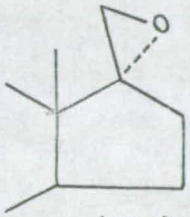


(260)

with dimethyloxosulphonium methylide, the α-epoxide (255) was also isolated, 1%. It was again possible to determine the stereochemistry of these two epoxides on a spectral basis. The material with a pseudoaxial C-2-O bond had a similar i.r. spectrum to those of the corresponding C-3 series (225, 240, and 247) with a strong peak at 912 and a medium one at 795 cm.$^{-1}$ It also had a peak in the n.m.r. at 7.54 τ with a half band width of 0.015 ppm. The α-epoxide (255) showed now characteristic pseudoequatorial carbon-oxygen epoxide absorptions; i.r. broad strong peak at 822 with a medium one at 942 cm.$^{-1}$ and an n.m.r. absorption at 7.37 τ with a half band width of 0.033 ppm. Cleavage of the β-epoxide (254) with lithium aluminium hydride gave 2α-methyl-5α-cholestan-2β-ol (256), identified by a mixed melting point and spectral comparison with an authentic sample of the 2β-ol (256).[50]

Slightly less of the β-epoxide (254) was formed on reaction of the 2-ketone (252) with the sulphonium ylide, 75.5%. Epoxidation of the 2-methylene-compound (253) with m-chloroperbenzoic acid in ether gave a similar result with 82% of the product mixture being the α-epoxide (255), while with the alkaline hydrogen peroxide-benzonitrile system a 100% yield of the α-epoxide (255) was produced.

Epoxidation of 5α-androstan-17-one and 17-methylene-5α-androstane.

5α-Androstan-17-one (257) with the oxosulphonium ylide gave the β-epoxide (259), 83%, while only β-epoxide (259) was formed when the corresponding reaction was carried out with dimethylsulphonium methylide. The separation of the two epoxides from the oxosulphonium ylide reaction was carried out on alumina the α-

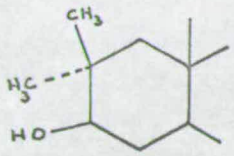
epoxide being eluted first, as expected. Here identification of the two epoxides apart from polarity differences was based upon results from similar reactions on other steroid-17-ketones. In all known cases the β-epoxide is the major (or only) product from these methylene transfer reactions[5a,b,c,d,e] and thus the major product here was assigned the 17β,20-configuration (259), which was confirmed by the epoxidations of the 17-methylene compound (258). Treatment with m-chloroperbenzoic acid in ether gave the α-epoxide (260), 85%, which was identical to the minor product isolated from the oxosulphonium ylide reaction. This result is in line with epoxidations of other 17,20-olefins.[94,95] The reaction with the alkaline hydrogen peroxide-benzonitrile system gave an even larger yield of the α-epoxide (260), 98%.

The same i.r. identification procedure adopted with the A-ring exocyclic epoxides was not possible here. The α-epoxide had medium intensity peaks at 939, 835, and 760 while the β-epoxide had i.r. bands (all medium intensity) at 919, 861, and 786 $cm.^{-1}$ In the same way the determination of the stereochemistry of these epoxides from n.m.r. half band widths was not possible with the epoxide proton absorptions not appearing as single signals.

Finally two partial studies of the epoxidation of other steroid systems to exocyclic methylene epoxides can be reported.

Epoxidation of A-nor-5α-cholestan-2-one and 2-methylene-A-nor-5α-cholestane.

The two epoxides from 2-methylene-A-nor-5α-cholestane were compounds required for the determination of the stereochemistry of



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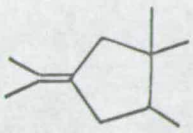

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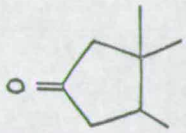

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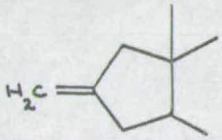

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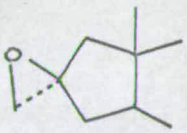

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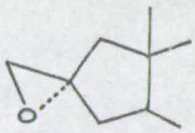

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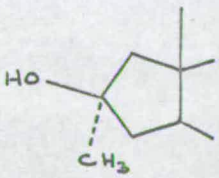

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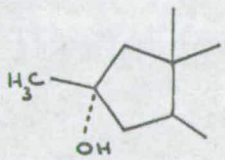

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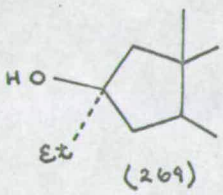
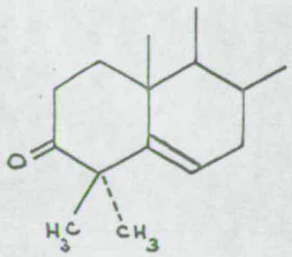


(269)

the products from the BF_3-catalysed isomerisation of the two 2,3-epoxy-2,3-dimethyl-5α-cholestanes. A-nor-5α-cholestan-2-one was prepared from 2,2-dimethyl-5α-cholestan-3β-ol (261) by its conversion to 2-isopropylidene-A-nor-5α-cholestane (262) with phosphorus pentachloride followed by treatment of this olefin (262) with ozone.[90] The 2-methylene-compound (264) was prepared from the A-nor-2-ketone (263) by treatment with methylenetriphenylphosphorane.

The A-nor-2-ketone (263) with dimethyloxosulphonium methylide gave a product which was recrystallised from acetone to give the β-epoxide (265), ca.100%. while reaction of the 2-methylene-compound (264) with m-chloroperbenzoic acid in ether gave after recrystallisation from acetone the α-epoxide (266), ca.80%. Identification of the two epoxides came from their reduction to the pair of epimeric alcohols (267) and (268). Compound (267) was also obtained from A-nor-5α-cholestan-2-one on treatment with methyl magnesium iodide. Since ethyl magnesium iodide has been shown to attack the carbonyl group of the A-nor-5α-cholestan-2-one to give the 2β-alcohol (269)[96] it was assumed that a similar stereochemistry of addition would apply for the methyl magnesium iodide reaction giving 2α-methyl-A-nor-5α-cholestan-2β-ol (267). This would mean that the epoxide from the ylide treatment of the A-nor-ketone (263) is 2α-methyl-2β,2'-epoxy-A-nor-5α-cholestane (265) while the compound from the attack by peracid must be the corresponding α-epoxide (266). In fact very recently Levisalles and Tkatchenko[97] have carried out and reported the same epoxidations with similar results.



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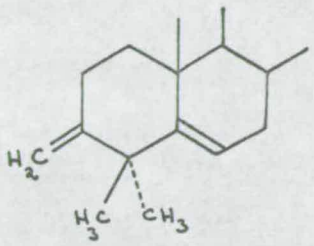

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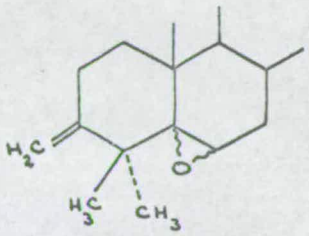

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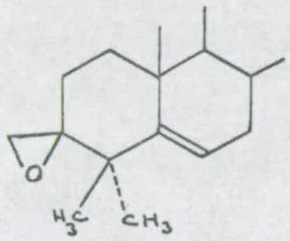

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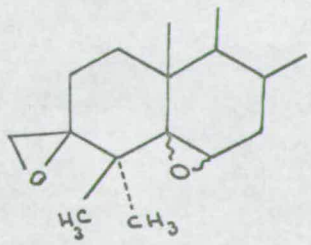


(274)

Epoxidations of 4,4-dimethyl-cholest-5-en-3-one and 3-methylene-4,4-dimethyl-cholest-5-ene.

Synthesis of 4,4-dimethyl-cholest-5-en-3-one[99] from cholest-4-en-3-one[98] was carried out and the 3-methylene derivative (271) was prepared by the reaction of the ketone (250) with methylene-triphenylphosphorane. The i.r. spectrum of the diene (271) showed strong bands at 1630 and 880 $cm.^{-1}$, while the n.m.r. spectrum exhibited olefinic peaks centred at 5.25 ($\underline{H_2}C=C<$) and 4.45 τ ($-\dot{C}=\dot{C}\underline{H}$).

When the 4,4-dimethyl-5-en-3-one (270) was treated with dimethylsulphonium methylide a product was obtained which from its i.r. spectrum seemed to consist only of the 3-ketone (270). However chromatography on alumina gave initial fractions (less than 1% of the total product) with no carbonyl peak in the i.r., the remainder being the dimethyl-ketone (270). A similar result was observed when the ketone (270) was added to a solution of the oxosulphonium methylide. In this case the ketone was extremely insoluble under the reaction conditions and this remained true even on the addition of considerable quantities of organic solvents. Since most of the cholestanes dealt with here have been observed to be very insoluble in dimethyl sulphoxide the reaction was repeated using dimethylformamide as the solvent for the generation of the ylide. However, the ketone again appeared to come out of solution and the resulting product consisted of starting material with only trace quantities of material less polar than the ketone (270) being isolated by chromatography. Although these initial fractions

were probably epoxides no verification of this was possible because of the lack of material.

Treatment of the diene (271) with one equivalent of m-chloroperbenzoic acid in ether gave a crude product which was chromatographed on alumina. The first compound (eluted with petrol) was the diene (271) and this was quickly followed by a compound with an i.r. spectrum similar to that of the diene (271). The n.m.r. spectrum of this material indicated the presence of the C-3 methylene group (5.21τ) as well as an electronegative-group at C-6; protons at 7.68; 7.77τ which are attributed to the C-7 protons, along with a set of absorptions centred about 6.9/7.0 τ which are attributed to a 5,6-epoxide. The elemental analysis also supported this type of compound.

Epoxidation of 4,4-dimethyl-5-en-3-ones with peracids has been shown[64] to give mixtures of 5α,6α- and 5β,6β-epoxides (α:β = 3:2) and on the face of it a similar result would be expected here, for purely steric reasons the C-3 methylene group probably having the same effect as the 3-ketone. The configurations of the epoxides from the 3-keto-steroids were partly determined on n.m.r. evidence. It has been shown[100] that α- and β-epoxides at C_5-C_6 can be distinguished by the value of the C-19 proton frequency, on the magnitude of the coupling constant between the C-6 and C-7 protons, or on the difference in chemical shifts of the C-6 protons for each type of epoxide. In this case the C-19 proton frequency could not be distinguished from other methyl absorptions in the 9.0 τ region caused by the methyl groups at

C-4. Using the coupling constant and chemical shift differences in this case would have required spectra of both the 5α,6α- and 5β,6β-epoxides for an obvious distinction to be made. Thus the stereochemistry of this epoxide (272) remains unknown.

The next compound on elution from the column did not contain a methylene group but from its n.m.r. spectrum could be seen to contain an endocyclic double bond 4.48 τ (1 proton H-C=C), i.e. probably the 5,6-double bond. Peaks which could be assigned to protons on an epoxy group where also present (7.05; 7.14; 7.49; 7.58 τ) and the compound was assumed to be a 3-methylene epoxide (273), and in fact this type of structure was confirmed by elemental analysis. Identification from its i.r. spectrum in a similar way to that used to determine the stereochemistry of the other A-ring methylene epoxides was not possible in this case and lack of material did not permit a chemical investigation of its structure.

The last compound from the column was a gum (ca.0.5% of the total product). The n.m.r. spectrum indicated that it did not contain any protons attached to double bonds while a multitude of peaks about 7.0 τ led to the assumption that it was a bi-epoxide (274).

Thus in this case only the positions of peracid attack of the diene (271) are known with both the 5,6-epoxide(s) and 3-methylene epoxide(s) being produced. The ratio of the two sets of epoxides was almost exactly 1:1.

Table I Epoxide formation

a.

Ketone	Percent axial attack $(CH_3)_2SOCH_2$	Percent axial attack $(CH_3)_2SCH_2$
5α-cholestan-3-one	3	69
2α-methyl-5α-cholestan-3-one	3	25
2,2-dimethyl-5α-cholestan-3-one	6	60
5α-cholestan-2-one	1	24.5
5α-androstan-17-one	83	100
A-nor-5α-cholestan-2-one	ca.100	-

b.

Olefin	Percent axial attack Peracid	Percent axial attack PhCN, H_2O_2, $KHCO_3$
3-methylene-5α-cholestane	85	26
3-methylene-2α-methyl-5α-cholestane	63	7
3-methylene-2,2-dimethyl-5α-cholestane	82	35
2-methylene-5α-cholestane	18	0
17-methylene-5α-androstane	85	98
2-methylene-A-nor-5α-cholestane	ca.100	-

Discussion

The results of the various epoxidations of the ketones and methylene-compounds are listed in Table I in terms of percentage axial attack. Table II consists of results from the addition of Grignard reagents to steroid ketones.

In order to discuss the significance of the epoxidations carried out here it is necessary first to establish three points; the mechanism by which each epoxidation takes place, the size and shape of the attacking species, and the spacial geometry of the steroids at the moment of attack.

The mechanism at present in favour for the non-acid catalysed peracid epoxidation of a double bond is that devised by Bartlett (1) in which the electrophilic peracid oxygen attacks the double bond rather than one of the olefinic carbons. Markownikov's rule would then lead to greater bond development to the exocyclic carbon of the double bond in the rate determining stage. Since this last stage is unlikely to involve any great steric influences it is the approach of the peracid to the olefin which must be the stereochemically important step. The Bartlett mechanism has also been proposed for double bond attack by peroxybenzimidic acid.[3] This type of peroxy acid has been shown to be different from other peracids in its attack of substituted olefins, for while 2-methyl-2-butene is epoxidised by peracetic acid at a rate 290 times that of 1-hexene, the rate of disappearance of hydrogen peroxide in a mixture of acetonitrile, hydrogen peroxide and olefins is essentially independent of olefin structure. Thus formation of the peroxy

Table II Addition of Grignard reagents

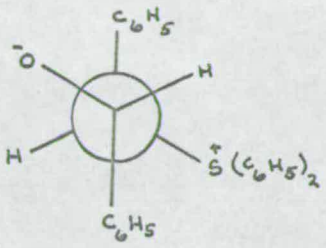
Ketone	Percent axial attack
5α-cholestan-3-one	43 - 40[82,83]
2α-methyl-5α-cholestan-3-one	20
4α-methyl-5α-cholestan-3-one	30[101]
4β-methyl-5α-cholestan-3-one	50[101]
2,2-dimethyl-5α-cholestan-3-one	49
5α-cholestan-2-one	0[50,144]
Steroid-17-ketones	100[52]
A-nor-5α-cholestan-2-one	ca.100[96]

carboximidic acid intermediate is the slow step in these reactions with rapid reaction with any available reducing agent then taking place.[2a]

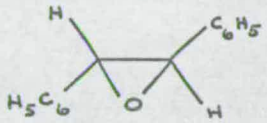
The mechanism for the ylide reactions is likely to involve attack by the ylide carbanion on the carbon of the carbonyl group in a similar way to that of addition of Wittig reagents to carbonyl groups. With the sulphonium ylides the second step will involve attack of oxyanion on the carbon of the sulphonium group (see pp.9, 10).[5f] The first stage is also thought to be reversible.[5f] A similar mechanism has been proposed by Johnson[6a,b] for the reaction of the butylide (275) with benzaldehydes. In these reactions it was noted that only one stereoisomer, the trans-stilbene oxides, was produced, and since it was found that cis-stilbene oxide was stable to the reaction and work-up conditions it was concluded that the reactions between the ylide (275) and the benzaldehydes were stereospecific. This stereochemistry was accounted for by assuming that the step involving ylide attack is reversible and could result in formation of both the erythro- and threo-betaines. The necessary transition states for epoxide formation would then require conformations (276) and (277) and clearly for (277) this is an unfavourable conformation involving the three bulkiest groups being gauche to one another. Thus with the first step reversible mainly the erythro form is converted into the epoxide the threo form reverting to ylide and carbonyl compound.

If betaine formation were not reversible the stereochemistry of the reaction would be determined in the first step and this

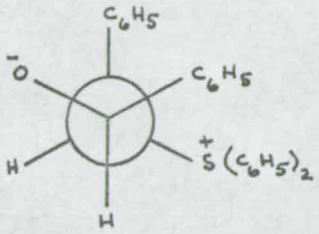
$(C_6H_5)_2\overset{+}{S}-\overset{-}{C}HC_6H_5$ (275)



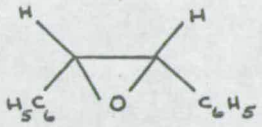
(erythro) (276)



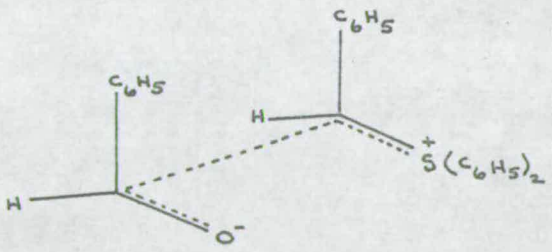
(trans)



(threo) (277)

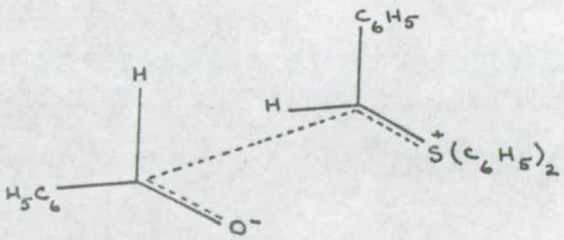


(cis)



(erythro) (278)

trans epoxide



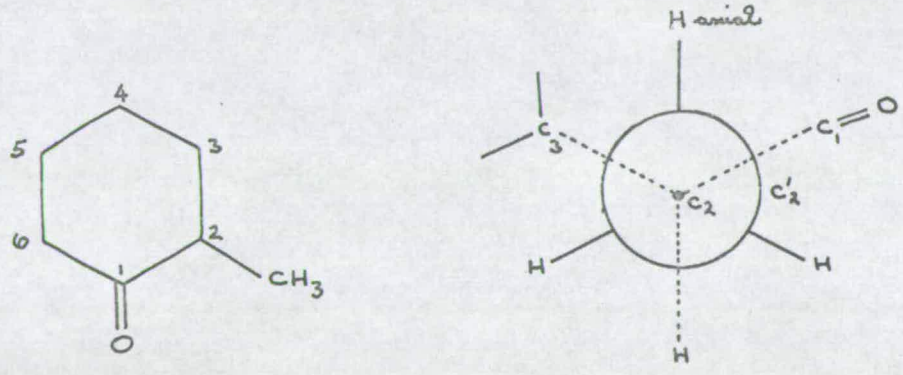
(threo) (279)

cis epoxide

would mean that there must be a considerable energy difference between the two transition states for betaine formation. The most likely transition states for ylide addition are thought to be (278) and (279) due to ion-dipole interactions between the carbonyl compound and the ylide grouping. In this case the threo form has the lower energy which would imply ultimate formation of the cis-epoxide in preference to epoxide formation from the erythro form in which the two phenyl groups are eclipsed. However this is in complete disagreement with the observed results.

The influence that the size and shape of the attacking species can have on the stereochemistry of nucleophilic attack of cyclic ketones is well documented.[52] As has been indicated the reduction of unhindered cyclohexanones usually involves axial attack by the hydride ion while similar results are observed with the addition of CN^- or acetylene to the same type of ketones. Here the attacking species is either quite small (H^-) or has a rod-like shape (CN^-, $HC \equiv CH$) so that axial attack will give transition states in which there is little non-bonded 1,3-interaction with the axial substituents. Equatorial attack as has been pointed out can be explained as unlikely either on the basis of product development control or because of steric interference with the axial alpha substituents. Attack by Grignard reagents to unhindered ketones takes place to a large extent with equatorial methyl attack and this can be attributed to the severe interactions that the hydrogens on the methyl group in the axial position will have with the beta axial substituents.

(280)



(281)

These observations on the effect of small nucleophiles with unhindered cyclohexanones also depend on the shapes of the cyclic ketones. While the A-ring of most A-ring steroid-cyclohexanones can be regarded as existing to a major extent in the chair form, the A-ring of 2,2- and 4,4-dimethyl-3-keto-steroids has been shown to exist as a flattened chair (280).[93]

The results from the epoxidation of 5α-cholestan-3-one with dimethyloxosulphonium methylide and dimethylsulphonium methylide can be compared with those obtained from the similar epoxidations of dihydrotestosterone. With the oxosulphonium ylide both the 3-ketones give overwhelmingly α-epoxides, the result of equatorial attack. Clearly the mechanism proposed by Cook et al. (pp.9,10) involving reversibility of oxosulphonium ylide attack can also be used to explain the result from 5α-cholestan-3-one. The non-reversibility of attack by the labile dimethylsulphonium methylide which was used as an explanationfor the stereospecificity of the reaction of that ylide with dihydrotestosterone cannot on the face of it be used with 5α-cholestan-3-one. However, since the sulphonium ylide is indeed very reactive and because of the good yields of epoxides obtained from its reaction with 5α-cholestan-3-one it is difficult to imagine that the ylide is not "locked" into position after attack of the carbonyl group carbon. This would then mean that attack of the ylide did not take place only from the α-side initially but that some equatorial attack did occur. In fact other examples of attack by dimethylsulphonium methylide of cyclohexanones to give a fair amount of equatorial attack have been reported. For example reaction of trans-2-

decalone with this ylide gives a mixture of epoxides with that resulting from axial attack accounting for 55% of the mixture.[3] Such a stereochemical situation has been observed for the addition of Grignard reagents to 5α-cholestan-3-one (Table II). Since the ylide carbanion differs from the methyl group from the Grignard reagent in that it has one much larger grouping attached to the attacking carbon atom it is difficult to see why the sulphonium ylide should not initially attack to a greater degree from the equitorial side. This could be due to shielding by the axial hydrogens at C-2 and C-4 if the reagent has to closely approach the carbonyl group in the transition state, or to shielding due to the C-19 angular methyl group.

The results for the peracid epoxidation of 3-methylene-5α-cholestane can be explained in terms of the different shielding properties of the α and β faces of the molecule. If the transition states for epoxidation by peracid are taken as at the critical point resembling the final epoxides with the only difference being that the bulk of the peracid is still attached to the electrophilic oxygen atom then the epoxide oxygen can be taken as a reference point from which to measure the shielding to reagent approach from both sides of the molecule. It can be seen that the axial hydrogens on C-2 and C-4 are nearer the epoxide oxygen than are those on C-1, and C-5. Thus the attack by peracid of the 3-methylene compound from the α-side on steric grounds seems reasonable. The reduction in axial attack with methylene chloride as solvent is likely to be due to an increase in the reagent bulk due to tighter solvation of

the transition state,[12,17] the differences in shielding of the α and β faces now being less important.

It is difficult to see why peroxybenzimidic acid should be so different from the other peracids if it operates by the Bartlett mechanism. On the face of it it is difficult to believe that its size is so great that equatorial attack becomes preferred to such a great degree. (+)-Peroxycamphoric acid for example gives high yields of the epoxide resulting from axial attack of 4-t-butyl-1-methylenecyclohexane.[12] Another mechanism for this reaction seems a more likely answer. The observed preference for axial attack is observed with hypochlorous and hypobromous acid attack of 3-methylene-5α-cholestane.

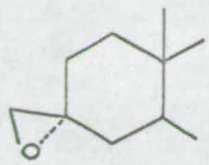
The presence of a methyl group alpha to the 3-ketone can be seen to alter in a marked way all the epoxidation reactions of the 2α-methyl-steroids as well as the addition of Grignard reagent to 2α-methyl-5α-cholestan-3-one (and 4α-methyl-5α-cholestan-3-one[101]). In all cases there is a reduction in axial attack compared with the same reactions on the parent 3-ketone (223) or 3-methylene compound (224). Such observations have also been reported for simple α-methyl-cyclohexanones.[52] The Grignard reaction with 2-methyl-cyclohexanones takes place with 75 percent of equitorial attack. Examination of the molecular model of 2-methylcyclohexanone showed that the methyl group in the equatorial position will be more stable in the case where the hydrogen atoms are in a skew position with respect to the substituents at C-2 (281).[52] In this case the distance of one of the hydrogens on the methyl group from the C-1

carbon will be the same as that for the axial beta hydrogen atoms, i.e. there are now three axial beta hydrogens causing additional steric hindrance. Applying this observation to the 2α-methyl-steroids would therefore mean that the three interactions with axial beta hydrogens will push the reaction in each case towards more equatorial attack taking place.

The epoxidations of the 2,2-dimethyl-steroids and the addition of Grignard reagent to the dimethyl-ketone (245) show results similar in the main to those of the parent series (223) and (224). These results will depend on the shapes of the A-ring of the dimethyl-ketone (245) and its methylene derivative (246). Examination of the molecular models of the two dimethyl compounds in the half-chair A-ring form in fact indicates that the β-face is now quite heavily shielded by axial substituents and even with several axial or pseudoaxial hydrogens bringing about non bonded interactions with reagent approach from the α-side this direction of approach is now favoured over top-side approach.

Axial attack of 5α-cholestan-2-one and its methylene derivative involves a 1,3-interaction with the C-10 methyl group and thus all the reagents tend to attack in the main from the equatorial side. Attack to some extent from the equatorial side has in fact also been observed for small nucleophiles such as hydride.[52]

The reactions of the two sets of cyclopentane-steroids indicate in all cases high shielding of the β-face of the molecules. This is doubtless due to the relative nearness of the angular methyl groups.



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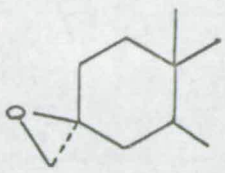

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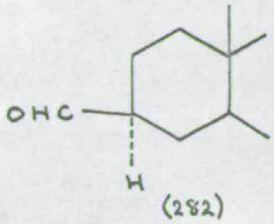

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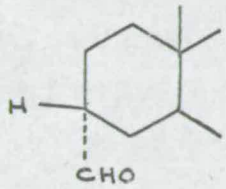

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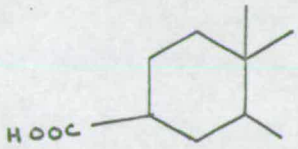

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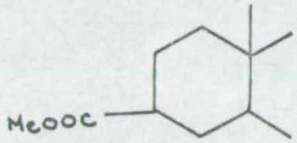

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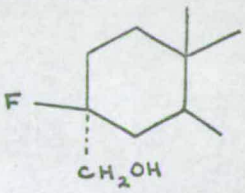

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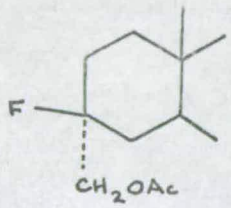

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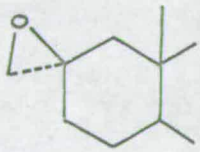

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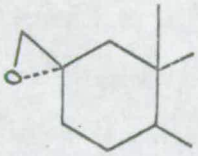

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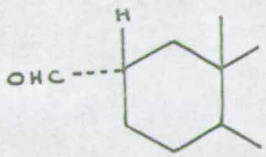

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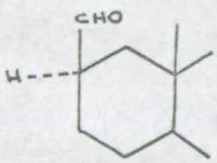

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Reactions

Boron trifluoride

Boron trifluoride-etherate (1 drop per 100 mg. steroid) was added to a solution of 3β-methyl-3α,3'-epoxy-5α-cholestane in dry benzene. The reaction was terminated after 2 minutes and a crude product was obtained which on chromatography on alumina gave the α-epoxide (225), 20%, followed by an aldehyde, 26%, (i.r. bands at 2715 and 1725 cm.$^{-1}$) and an alcohol, 54%, (i.r. bands at 3350 and 1057 cm.$^{-1}$). The aldehyde was also characterised by its n.m.r. spectrum which had present a one proton peak at 0.39τ. Attempts to recrystallise the aldehyde from petrol led to a crystalline product whose i.r. spectrum was different from that of the aldehyde with bands at 3400 to 2450 (broad) and 1695 (s) cm.$^{-1}$ characteristic of a carboxylic acid.[80] This acid reacted with ethereal diazomethane to give a product identifiable as a methyl ester by its i.r. spectrum which had present peaks at 1730 and 1160 cm.$^{-1}$[80] The melting points of these two compounds were similar to those reported for 5α-cholestan-3β-carboxylic acid (284) and its methyl ester (285)[102] and from this evidence the petrol-recrystallised material was assigned the 3β-carboxylic acid structure (284).

The n.m.r. spectrum of the alcohol from the BF_3 reaction of the α-epoxide (225) had peaks at 6.62 and 6.3τ probably attributable to a deshielded methylene group. It was found to contain fluorine and on treatment with acetic anhydride in pyridine it gave a monoacetate (i.r. bands at 1740, 1242, and 1052 cm.$^{-1}$ and a three proton absorption at 7.9τ in the n.m.r. with other downfield peaks at

6.09 and 5.76τ). Assuming epoxide oxygen co-ordination with BF_3 prior to ring opening to the fluorohydrin an analogous reaction to those observed with the β-epoxide (226) and hydrogen chloride and hydrogen bromide (pp.42-45) would be expected, i.e. opening to the 3α-hydroxymethyl-3β-fluoro-compound (286), and this is justified by the acetate formation (287).

When the fluoro-alcohol (286) was treated with a further quantity of boron trifluoride-etherate in benzene conversion to the 3-aldehyde took place, and this was also the observed result when excess boron trifluoride-etherate was added to the α-epoxide (225) in benzene. The n.m.r. spectrum of the crude product from this last reaction had present two aldehydic proton absorptions. The major, 0.39τ, corresponded to that observed for the 3-aldehyde isolated by alumina chromatography with the other at 0.29τ. It has been shown that pairs of epimeric aldehydes can be distinguished by differences in chemical shifts.[103] Equatorial aldehydes show a peak at a slightly higher field. Applying this concept here would imply that the aldehyde corresponding to the band at 0.39 had an equatorial configuration and this is borne out by the fact that the aldehyde mixture when run through a column of alumina or when treated with base epimerises to a single aldehyde with a peak in the n.m.r. at 0.39τ, i.e. the more stable equatorial form.

When the reaction was carried out in ether as solvent it was found that little or no reaction occurred with reaction times of 2 to 60 minutes. Therefore the reaction was allowed to continue for 2 hours before being terminated. When this was done a crude product was obtained the n.m.r. spectrum of which showed the

presence of fluorohydrin (6.62, 6.3 τ) and the two aldehydes (0.39 and 0.28 τ). On this occasion the intensities of the two aldehydic signals were approximately equal. Chromatography of the crude product on alumina gave the 3β-aldehyde and the fluorohydrin.

The same reactions were carried out with the β-epoxide (226). Here with benzene as solvent the n.m.r. of the crude product showed the two aldehydic protons with that of the equatorial aldehyde again the major. Fluorohydrin formation was not observed in this case. With ether as solvent and a reaction time of 2 hours the only absorption band present in the n.m.r. of the crude reaction product was that of the 3β-aldehyde proton (0.39 τ). Again only 3β-aldehyde could be isolated for both crude products by alumina chromatography.

When the reaction between 2α-methyl-2β,2'-epoxy-5α-cholestane (254) and excess boron trifluoride-etherate was carried out in benzene as solvent a product was obtained which again had two aldehyde peaks, 0.41 and 0.24 τ, in the n.m.r. By using the chemical shift distinction method the band at 0.41 must belong to the hydrogen of the 2α-aldehyde (288), and in fact chromatography on alumina of the crude product gave a single aldehyde with a peak in the n.m.r. at 0.41 τ which must be due to an aldehyde in the stable equatorial configuration. No fluorohydrin formation was observed with this reaction. With ether as the solvent and a reaction time of 2 hours the crude product could be seen to contain only the two aldehydes from its n.m.r. spectrum, with the two peaks having approximately equal intensities. The single 2α-aldehyde was isolated by chromatography on alumina. It was found that the

2α-aldehyde could be recrystallised from petrol with apparently no conversion to a carboxylic acid.

The reactions of 2β-methyl-2α,2'-epoxy-5α-cholestane (255) with boron trifluoride-ethorate were carried out in a similar way to those of the α-epoxide (254). With benzene as a solvent almost equal amounts of the two aldehydes were formed (n.m.r. 0.41 and 0.24 τ) while the use of ether as solvent gave principally the 2α-aldehyde. Again alumina chromatography allowed for the isolation of only the 2α-aldehyde.

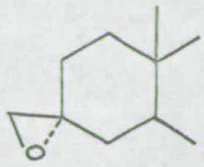
By using these n.m.r. techniques it was hoped that some information about the use of ether and benzene as solvents in boron trifluoride epoxide isomerisations could be obtained. As has been already mentioned in the Introduction (p.18) the work of Goldsmith[42] indicated a greater tendency to these types of reactions taking place by a carbonium ion mechanism with benzene as a solvent than with ether as solvent.

In all cases the use of benzene as a solvent led to mixtures of aldehydes and this can only be explained by the reactions to some extent going through a two step carbonium ion mechanism. The equatorial aldehydes would result by a concerted process only for epoxides (226) and (255). From the observation that the stable equatorial aldehydes are in all cases the major products (for epoxide (255) ca.1:1) it could be assumed that reaction pathways involving carbonium ion intermediates are more important than concerted mechanisms for epoxides (225) and (254). However it is equally likely that both concerted and carbonium ion mechanisms

are favoured for the BF_3-catalysed reactions, the fast reactions in benzene allowing for sufficient time for partial epimerisation of the axial aldehydes to the more stable equatorial ones under the reaction conditions.

On the other hand there does seem to be a difference between the epoxide isomerisations with ether as the solvent. The two axial-oxygen epoxides give almost equal amounts of the two aldehydes which must mean at least 50 percent of the reactions go by concerted processes. The observation of almost complete conversion of the equatorial-oxygen epoxides to the equitorial aldehydes could also be explained by a greater degree of concerted epoxide rearrangement with ether as a solvent.

The reactions of the two α-epoxides of 3-methylene-2α-methyl- and 3-methylene-2,2-dimethyl-5α-cholestane with boron trifluoride-etherate in benzene were also studied. The i.r. spectra of the products from both reactions with excess BF_3 and a reaction time of 2 minutes had present no readily identifiable absorption bands and the n.m.r. spectra of both crude reaction products indicated that aldehydic protons were not present. Neither crude product could be fractionated on alumina. A second reaction with the α-epoxide of the 2,2-dimethyl-series in benzene with a small amount of boron trifluoride-etherate (1 drop/150 mg. steroid) for half-minute also gave unrecognisable material.



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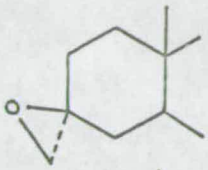

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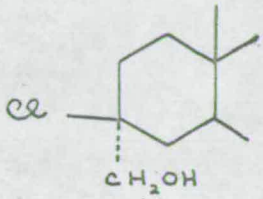

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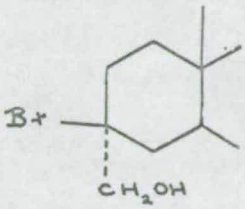

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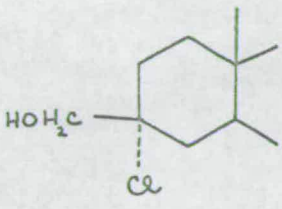

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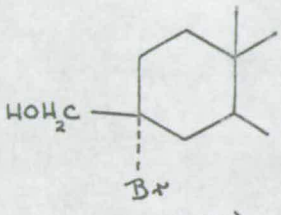

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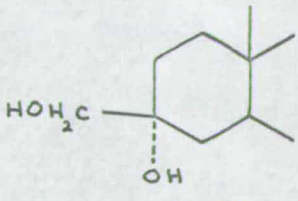

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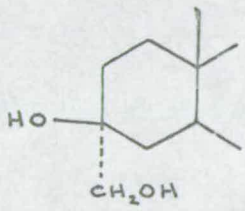

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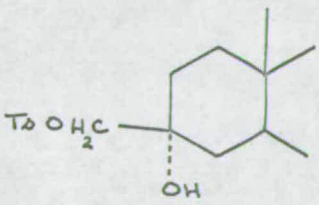

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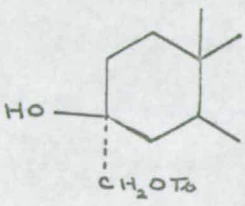

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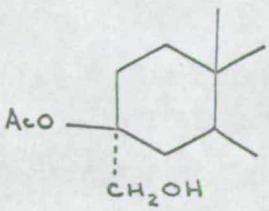

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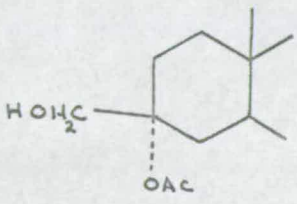


(297)

Hydrogen chloride and hydrogen bromide

The corresponding reactions to those already mentioned for the β-epoxide (226), (pp.44,45), were carried out for the α-epoxide (225) with hydrogen chloride in chloroform and with hydrobromic acid. In both cases products were obtained with similar i.r. spectra to the α-halo-compounds (232) and (237). The product from the α-epoxide with HCl had peaks at 3560 and 1075 while the product from the same epoxide with HBr showed absorption bands at 3540 and 1010 $cm.^{-1}$ These products on the basis of the results from the β-epoxide would be expected to be 3α-hydroxymethyl-3β-chloro-5α-cholestane (290) and 3α-hydroxymethyl-3β-bromo-5α-cholestane (291), and in fact both were converted into mixtures of acetates and starting materials on treatment with acetic anhydride in pyridine overnight. Also the α-epoxide (225) was regenerated from both the compounds (290) and (291) on treatment with base (potassium t-butoxide in the case of the 3β-chloro-compound (290) and chromatography on alumina for the 3β-bromide (291)).

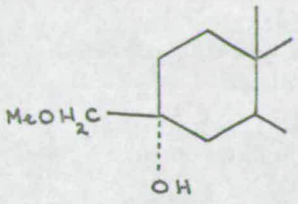
Alumina (Activity II)

Cleavage of epoxides to 1,2-diols is usually accomplished under acidic conditions.[130] However it has recently been shown that treatment of 3β-methyl-3α,3'-epoxy-5α-cholestane with 60% perchloric acid gives a complicated mixture of products.[105] Thus in this case a suitable method for cleavage to hydroxy-hydroxymethyl compounds under basic conditions was investigated. The best method for attacks of this nature is by treatment with base in a high boiling solvent such as dimethyl sulphoxide.[131] However the methylene-

epoxides were all very insoluble in that solvent, but cleavage to diols was accomplished by treatment of the epoxy-compounds with alumina of activity II. The α- and β-epoxides (225) and (226) when treated in this way overnight gave on elution with chloroform the required diols. The material from the α-epoxide gave a mono-tosylate (293) with toluene-p-sulphonyl chloride in pyridine. The i.r. spectrum had peaks at 3600 (hydroxyl) and 1180, 1190 cm.$^{-1}$ (characteristic of a tosylate[104]), while the n.m.r. showed a peak at τ 7.54 (3 protons, aryl methyl group). Treatment of this tosylate with base regenerated the α-epoxide (225) while with lithium aluminium hydride 3β-methyl-5α-cholestan-3α-ol was produced (mixed melting point and i.r. spectra comparison). This indicates that the diol is 3β-hydroxymethyl-5α-cholestan-3α-ol (292) formed by nucleophilic attack at C-3'. The tosylate of the diol from the β-epoxide was also prepared (295) (i.r. 3580, 1190, and 1180 cm.$^{-1}$) and was treated with potassium t-butoxide to give the β-epoxide, thus also showing that epoxide cleavage had occurred with nucleophilic attack at the exocyclic carbon atom.

Acetic acid

The acetolysis of 3β-methyl-3α,3'-epoxy-5α-cholestane has been shown to give a mixture of diacetate and α-acetoxy-alcohols.[105] However when this reaction was repeated using dried and redistilled acetic acid a single compound was obtained whose i.r. spectrum indicated that both acetate and hydroxy groups were present. The n.m.r. spectrum had a three proton absorption band at τ 7.87 (acetate) with peaks corresponding to two protons at τ 5.86 and



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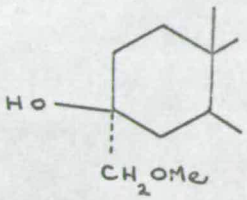

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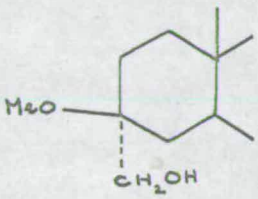

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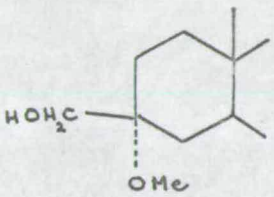

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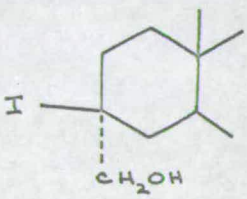

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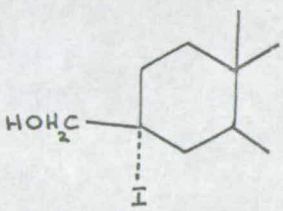

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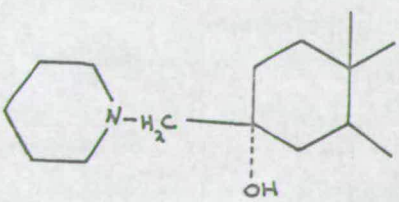

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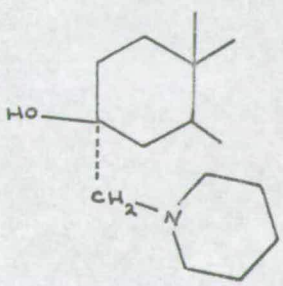


(304)

6.07, which can be attributed to the methylene group $-C\underline{H}_2-OH$. Treatment of this compound with lithium aluminium hydride gave the 3α-hydroxymethyl-3β-ol (294), while a diacetate was formed with acetic anhydride in pyridine thus showing the acetolysis product to be 3α-hydroxymethyl-3β-acetoxy-5α-cholestane (296).

The β-epoxide (226) with purified acetic acid gave after heating at 90° for 2 hours a product which contained both acetoxy and hydroxy groups (i.r.) and whose n.m.r. spectrum was very similar to that of the acetolysis compound (296). With lithium aluminium hydride it was converted into the 3β-hydroxymethyl-3α-ol compound (292) and thus it was assigned the 3β-hydroxylmethyl-3α-acetate structure (297).

Methanolic potassium hydroxide and acid catalysed addition of methanol

The α-epoxide (225) was cleaved with potassium hydroxide in methanol to give a crystalline product (298) with an i.r. spectrum (3560 and 1118 $cm.^{-1}$) similar to that of the 3α-methoxymethyl-compound (233) formed by cleavage of the β-epoxide (226) under the same conditions (p.44). The n.m.r. spectrum of the compound (298) had a three proton peak at τ 6.62 ($-O-C\underline{H}_3$) and a peak at τ 6.84 corresponding to two protons ($-C\underline{H}_2-OCH_3$). As expected no acetate was formed when the compound was treated with acetic anhydride in pyridine, and it is, therefore, 3β-methoxymethyl-5α-cholestan-3α-ol (298).

When either of the 3-methoxymethyl-3-ols were treated with acetic anhydride in the presence of boron trifluoride,[132] crude products,

showing acetoxy signals in the i.r., were obtained which after treatment with lithium aluminium hydride gave on chromatography from alumina the 3-hydroxymethyl-3-ols in moderate yields (the 3α-ol from the β-methoxymethyl-compound and the 3β-ol from the α-methoxymethyl-compound).

The α-epoxide (225) on treatment with methanol in the presence of either perchloric or toluene-p-sulphonic acid gave a crystalline product which from its i.r. spectrum appeared to be an alcohol. A mono-acetate was formed on treatment with acetic anhydride in pyridine and the n.m.r. spectrum of the alcohol had absorptions at τ 6.75, 3 protons, (-O-C$\underline{H}_3$) and τ 6.37, 2 protons, (-C$\underline{H}_2$-OH). The compound must therefore be 3α-hydroxymethyl-3β-methoxy-5α-cholestane (299). Similar reactions for the β-epoxide with methanol in the presence of perchloric or toluene-p-sulphonic acid gave a crystalline product which from spectra could be seen to be a methoxy-alcohol (i.r. 3550 and 1075 cm.$^{-1}$ n.m.r.τ 6.82, 3 protons, (-O-C$\underline{H}_3$) and τ 6.58, 2 protons (-C$\underline{H}_2$-OH)). On the basis of the cleavage of the α-epoxide this later compound must be 3β-hydroxymethyl-3α-methoxy-5α-cholestane (300).

Methyl Magnesium Iodide

The α-epoxide (225) in ether was added to an ethereal solution of methyl magnesium iodide and the mixture was refluxed for 5 hours to give a product containing a hydroxy-group (i.r.) with a strong peak at 1010 cm.$^{-1}$ suggesting a primary or secondary alcohol. When this product was chromatographed on alumina 100 percent conversion to the α-epoxide took place unless the chromatogram was completed

within minutes of its start when a pure sample of the alcohol could be obtained. This would suggest that the reaction product was 3α-hydroxymethyl-3β-iodo-5α-cholestane (301) and in fact elemental analysis consistant with this structure were obtained. The same product was obtained when the α-epoxide was cleaved with hydriodic acid.

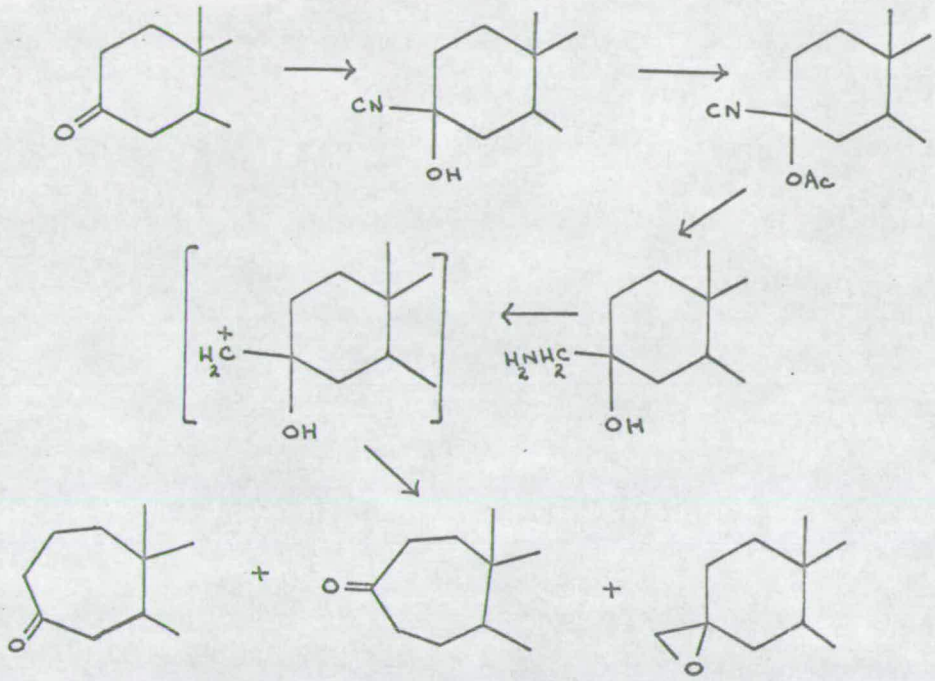
The β-epoxide (226) likewise gave an alcohol (302) with methyl magnesium iodide which on alumina gave back the β-epoxide. The i.r. spectrum indicated a primary or secondary alcohol (3550, 1030 $cm.^{-1}$), and on standing for several weeks the product started to brown around the edges of the crystals and after a longer period of time a purple gum was obtained which did not give interpretable spectral evidence as to its structure. The product from the β-epoxide with HI was also non-crystalline and again spectral information did not lead to a conclusion as to its structure. The observed instability of the product from the β-epoxide is almost certainly due to a 3α-axial iodine in the molecule, with iodine both large and a good leaving group it will be easily eliminated and thus the structure of the alcohol from the Grignard reaction is 3β-hydroxymethyl-3α-iodo-5α-cholestane (302).

Piperidine

Both epoxides (225) and (226) when refluxed with piperidine gave nitrogen containing products. The i.r. spectra had bands in the region about 3500 (-OH) but neither had primary or secondary alcohol peaks in the region 1100-1000 $cm.^{-1}$ as would be expected with epoxide-cleavage under basic conditions. The elemental

analysis indicated that the products were the 3β-piperidinomethyl-3α-ol (303) (from the α-epoxide) and the 3α-piperidinomethyl-3β-ol (304) (from the β-epoxide).

It can be concluded, therefore, that the expected attack at C-3' took place with nucleophilic substitution reactions of the two 3-methylene epoxides under basis conditions. With acids or reagents involving co-ordination to the epoxide oxygen as the first stage (BF_3, MeMgI) attack took place at the more heavily substituted C-3.



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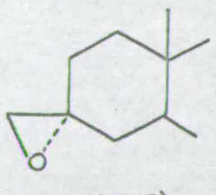

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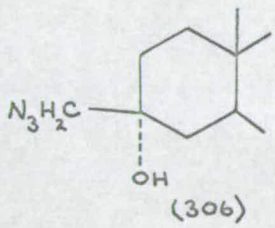

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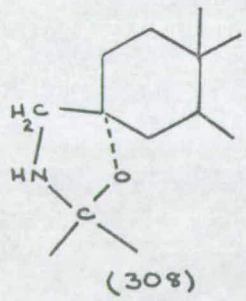

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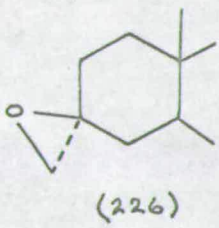

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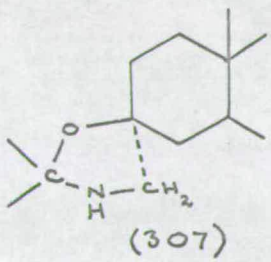

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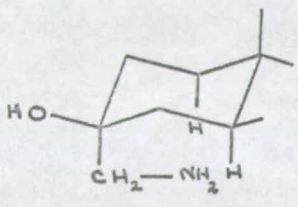


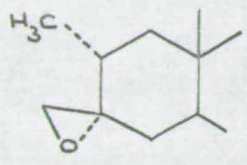
(309)

The Stereochemistry of Tiffeneau Reactions

The homologation of several A-ring steroid ketones including 5α-cholestan-3-one, 2α-methyl-5α-cholestan-3-one and 2,2-dimethyl-5α-cholestan-3-one has recently been carried out using the Tiffeneau ring enlargement technique[105] (305, with 5α-cholestan-3-one as an example). The preparation of the intermediate amino-alcohols was achieved by addition of CN^- to the 3-ketones followed by reduction of the cyanohydrin acetates to the required compounds. On treatment with nitrous acid A-homo-ketones were obtained along with in each case a 3-methylene-epoxide as a bi-product. It was recognised that these epoxides presented a clue as to the stereochemistry of the addition of CN^- to the original ketones since from that stage onwards the exocyclic carbon atom remains in the same configuration. The two epoxides from 5α-cholestan-3-one and 2,2-dimethyl-5α-cholestan-3-one were identified[105] as α-epoxides, which was taken to mean that attack by CN^- on the carbonyl groups of these 3-ketones was equatorial. The epoxide from 2α-methyl-5α-cholestan-3-one was assumed to be also an α-epoxide on the basis that the 2α-methyl group would be sterically neutral.[105] Comparison now of this epoxide with the two known 2α-methyl-3-methylene epoxides showed it, however, to be 3α-methyl-3β,3'-epoxy-2α-methyl-5α-cholestane. It is interesting also to note that the epoxide bi-product from 4α-methyl-5α-cholestan-3-one in the Tiffeneau reaction can now be shown to be a β-epoxide from its i.r. spectrum which has a broad absorption band at 830 with a medium one at 930 $cm.^{-1}$ On this basis it would seem that attack by CN^- to the carbonyl group of these α-monomethyl-3-ketones is axial.

The stereochemistry of the Tiffeneau intermediates can also be determined by a comparison of the amino-alcohols produced on reduction of the cyanohydrin acetates with each of the epimeric pair of such amino-alcohols produced by an unambiguous route. The cleavage of the α-epoxide (225) directly with lithamide, sodamide and potassamide has been shown not to be possible[105] and therefore a less direct route involving reactions of known stereochemistry on the pairs of methylene epoxides seemed a reasonable proposition. The method chosen was nucleophilic attack of the epoxides by N_3^- followed by reduction of the azido-alcohols to the amino-alcohols. In fact such a route has been described[13] for the mixture of epoxides derived from peracid attack of 4-t-butyl-methylenecyclohexane, with as expected attack by N_3^- taking place at the exocyclic carbon atom. The conditions used on applying this technique to the series of steroid methylene epoxides was cleavage by refluxing with lithium azide in methanol overnight, followed by reduction with either lithium aluminium hydride or Raney nickel/hydrazine hydrate.[106] When this technique was applied to the α-epoxide (225) a crystalline product was obtained with very strong azide bands in the i.r. at 2200-2050 $cm.^{-1}$[106] along with a peak at 3560 $cm.^{-1}$ (-OH), there were no strong peaks in the region 1100-1000 $cm.^{-1}$, and the n.m.r. showed peaks at τ 6.83 and 6.78 ($-CH_2N_3$). The product was homogeneous on alumina chromatography. Reduction of this azido-alcohol (306) gave with either reducing agent a white solid which could be recognised as an amino-alcohol from its i.r. spectrum 3600 (hydroxyl) and 3200 (amino) $cm.^{-1}$ The direct comparison of this compound with the amino-alcohol from the Tiffeneau reactions

of the 3-ketone[105] was not possible as the 3-aminomethyl-3-ol in the later case was not isolatable in a pure form. It was noted there, however, that purification of this amino-alcohol could be accomplished by conversion into its acetonide (307) and this was attempted here by refluxing the amino-alcohol with acetone followed by slow distillation of the acetone. In this case, however, a crystalline product could not be obtained, nevertheless the i.r. of this crude compound (308) was not the same as that of the acetonide from the 3-ketone. The whole process was then repeated for the β-epoxide (226) with crystalline products formed at every stage, and in this case the acetonide was identical to that produced from the 3-ketone (307), (mixed m.p., i.r. and n.m.r.). On the face of it this would seem an impossible situation as the α-epoxide cannot be formed from 3α-aminomethyl-5α-cholestan-3β-ol. However it was noticed that α-epoxide formation was only observed[105] when nitrous acid treatment of the crude amino-alcohol mixture was carried out, the acetonide (307) in a similar reaction giving a 90% yield of A-homo-4-one with no epoxide-bi-product. Thus it would appear that the α-epoxide was only formed from a mixture of the two epimeric C-3 aminomethyl-alcohols with only the 3β-aminomethyl-3α-ol going to the epoxide and in the case of the acetonide reaction preliminary purification to the β-alcohol was achieved by its selective reaction with acetone. Such a conclusion is justifiable from the work of Favre and Gravel[13] who found that while the trans 4-t-butyl-aminomethyl-cyclohexanol gave ca.20% of an epoxide bi-product the cis amino-alcohol gave a very small yield of epoxide. Obviously a



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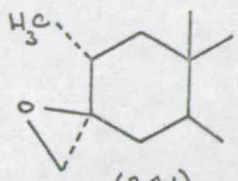

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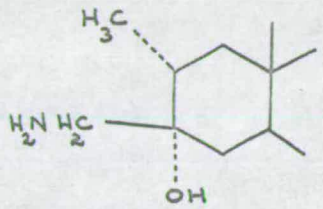

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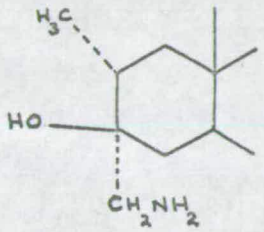

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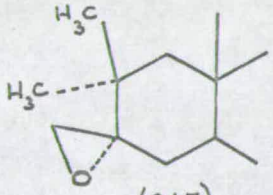

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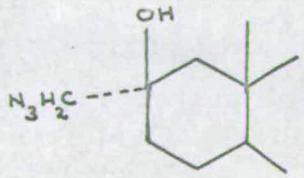

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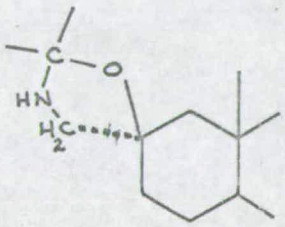


(313)

trans-coplanar deamination of the 3α-aminomethyl-3β-ol (309) to the β-epoxide would involve strong interactions with the C-1 and C-5 axial hydrogens. Since the acetonide (307) from the 3-ketone was formed in 60% yield this must mean that axial attack occurred to a greater extent than equatorial attack.

Reduction of the azido-alcohols (identified by i.r.) formed from the 3-methylene epoxides of the 2α-methyl series (240) and (241) gave white solids identifiable as amino-alcohols from their i.r. spectra. The 3β-aminomethyl-3α-ol (310) on heating with acetone gave a crystalline acetonide different from that produced via CN^- attack of 2α-methyl-5α-cholestan-3-one. The acetonide from the 3α-aminomethyl-3β-ol (311) could not unfortunately be isolated in a crystalline form. Nevertheless its spectra (i.r. and n.m.r.) were identical with those of the acetonide for the Tiffeneau reactions. Thus again it would appear that attack by CN^- on the ketone was to some extent equatorial (in fact the yield of acetonide from the cyanohydrin acetate was 67%).

There was insufficient 3α-methyl-3β,3'-epoxy-2,2-dimethyl-5α-cholestane to carry out a cleavage with N_3^- and thus only the α-epoxide (247) was subjected to that reaction. The azido-alcohol (i.r. 3560 and 2250-2100 $cm.^{-1}$) so produced was reduced to give a white solid which on refluxing with acetone gave after removal of the solvent a glass with peaks in the n.m.r. which could be attributed to an acetonide (τ 8.55 [geminal methyl protons], C-3' methylene protons centred at ca. τ 7.0). The i.r. spectrum was different from that of the crude acetonide formed in the Tiffeneau reactionm thus

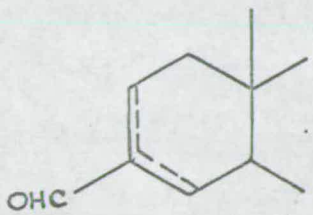
giving "negative" evidence indicating again equatorial attack by CN^- on the dimethyl-ketone.

The epoxides from 2-methylene-5α-cholestane were also cleaved with N_3^- to give crystalline azido-alcohols (i.r. and n.m.r.). The 2α-azidomethyl-2β-ol (312) was reduced to give the aminomethyl-alcohol (i.r. 3600 and 3200 $cm.^{-1}$) which with acetone again gave a crude product, identifiable as the acetonide (313) (i.r. 820 $cm.^{-1}$). Treatment of this acetonide with nitrous acid gave a product the i.r. spectrum of which indicated only partial conversion to products. Chromagography on alumina and elution with petrol-benzene (1:1) yielded a ketonic product which from g.l.c. evidence could be seen to be a mixture of 5α-cholestan-2-one and an A-homo-ketone. This identification was based on the retention times found for a series of A-homo-ketones[105,107] (and for 5α-cholestanones). The retention time for the A-homo-ketone in this case was different from that for A-homo-5α-cholestan-3-one and thus formation of the ring enlargement product here must have resulted from 2,3-bond migration. Separation of the two products by rechromatography on alumina or crystallisation was not possible.

(2) Epoxides adjacent to a polar group

The epoxidation of cholest-4-en-3-one with dimethylsulphonium methylide.

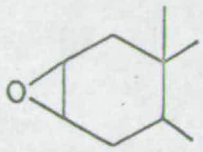
The isolation of epoxides from the reaction of cholest-4-en-3-one with dimethylsulphonium methylide has been reported[4] with one of the epoxides obtained from the mixture of methylene epoxides by repeated recrystallisation. However when this epoxidation was repeated, a crude product was obtained which showed similar i.r. absorptions to those reported for the recrystallised epoxide (1720(w), 1685(w), 940(s), 880(w), lit.[4] 1724(w), 1689(m) cm.$^{-1}$). The n.m.r. spectrum was also consistent with an epoxide product (τ 7.23, hydrogens on C-3'). However it was not found possible to recrystallise the material and in most cases evaporation of the solvent gave gums whose i.r. spectra had lost most of the epoxide absorption bands with broad hydroxyl peaks now present. This would indicate partial epoxide cleavage on recrystallisation. The methylene transfer to the enone was therefore repeated and the crude product was chromatographed on alumina. The first fractions were eluted with petrol-benzene and their i.r. spectra corresponded to a single α,β-unsaturated aldehyde (i.r. 2680, 1680 and 1660 cm.$^{-1}$, u.v. max. 235 mμ (ϵ 13,100)[109]). A second non-crystalline α,β-unsaturated aldehyde was next eluted. Here only the fingerpoint region of the i.r. was different from the corresponding spectrum of the first aldehyde. Treatment with base did not lead to its epimerisation. Several minor fractions were next eluted whose i.r. spectra all contained carbonyl groups. Identification of



(314)

these minor products was not possible. Finally elution with chloroform-methanol (95:5) gave the bulk of the product which could not be recrystallised. The i.r. spectrum indicated the presence of a hydroxy group. Other attempts at separation of the methylene epoxides from cholest-4-en-3-one were all equally unsuccessful. Chromatography on deactivated neutral alumina again gave mainly hydroxy-material while no separation was observed with Florisil or silica gel.

It is obvious from the above that these epoxy-derivatives of cholest-4-en-3-one are readily cleaved. The crystalline aldehyde indicates that epoxide isomerisation takes place to some extent with hydrogen migration. The double bond must then move to either C_2-C_3 or C_3-C_4 (314). The position of the double bond has not been determined.



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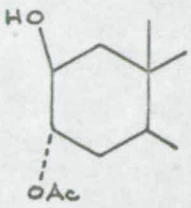

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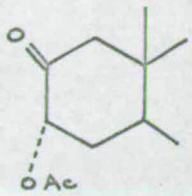

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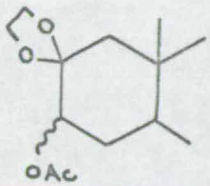

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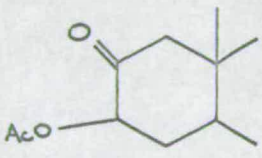

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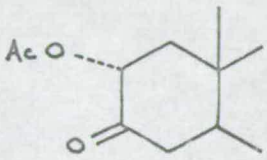

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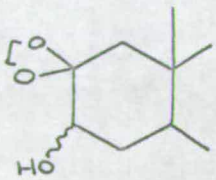

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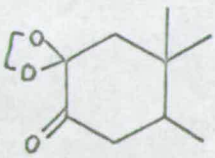

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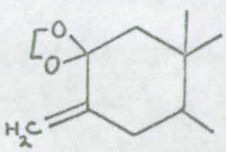

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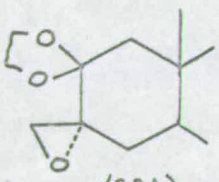

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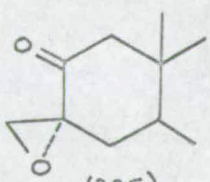


(325).

Synthesis of the epoxides of 3-methylene-5α-cholestan-2-one

The obvious method for the synthesis of the 3-methylene epoxide derivatives of 5α-cholestan-2-one would be alkaline hydrogen peroxide oxidation of 3-methylene-5α-cholestan-2-one, however such a route seemed impracticable since α-keto-methylene compounds (without an adjacent endocyclic double bond) appear to be somewhat labile. For example oxidation of 2-methylene-17α-methylandrostan-3β,17β-ol with chromium trioxide-pyridine gives a dimer which is presumed to result from original formation of the 2-methylene-3-one,[122] and other experiments involving the 2-methylene-5α-3-one system have also indicated its easy conversion into dimeric compounds.[110] A possible alternative route to α-keto-methylene-epoxides through ylide treatment (sulphonium methylide or methylenetriphenylphosphorane followed by peracid) of an α-acetoxy-ketone is also not practicable since the basic ylide reaction conditions would undoubtedly lead to α-hydroxy-ketones which can rearrange to other α-hydroxy-ketones or mixtures of α-hydroxy-ketones.[111]

For epoxide synthesis in this case, therefore, an indirect synthetic route was followed. 2β,3β-Epoxy-5α-cholestane (315) was cleaved with redistilled and dried acetic acid to give a high yield of 3α-acetoxy-5α-cholestan-2β-ol (316) which was converted into the 3α-acetoxy-2-one (317) on treatment with Jones' reagent.[112,113] The next step was the protection of the 2-ketone by formation of the 2-ketal (318). However, the usual ketalisation procedure of ethylene glycol, triethyl orthoformate and toluene-p-sulphonic acid[114] gave only starting material and so a second method for

ketalisation was examined. The use of ethylene glycol and boron trifluoride in acetic acid with α-acetoxy-ketones has been shown[115] to produce high yields of α-acetoxy-ketals and this method was tried here. The α-acetoxy-ketone (317) in dry acetic acid at 60° was treated with ethylene glycol and cooled to 40°, boron trifluoride-etherate was added and the mixture was allowed to stand for 9 hours, during which time a solid precipitated out. Recrystallisation of this product gave a compound which from spectra could be identified as an acetoxy-ketal (i.r. 1738, 1247, 1053 cm.$^{-1}$ n.m.r. τ 7.92 (acetate) and 6.06 (-O-$\underline{CH_2}$-$\underline{CH_2}$-O-)[133]). The ketal group was assumed to be at C-2 on the basis of the following observations. It has been shown that the α-acetoxy-ketones (317) and (320) on treatment with HBr or alumina[112,113] give 3β-acetoxy-5α-cholestan-2-one (319) and so it would seem reasonable to assume that (317) under the ketalisation conditions reacted as the 2-ketone. The configuration of the acetoxy group might also be expected to be equitorial but this has not been confirmed. The yield from the ketalisation was 48% and it is of interest to note that treatment of 3α-acetoxy-5α-cholestan-2-one with HBr does at best give a yield of 50% of the equatorial acetate (319).[113]

The 3-acetoxy-2-ketal (318) was refluxed with sodium hydroxide in methanol to give a product containing a hydroxy group (i.r.). This was assumed to be 2,2-ethylenedioxy-5α-cholestan-3-ol (321). Oxidation of this compound with chromium trioxide pyridine complex[116] gave the ketal-ketone (322) (i.r. 1720 cm.$^{-1}$ n.m.r. τ 6.03 (ethylene ketal hydrogens)), and conversion to the 3-methylene-2-ketal (323)

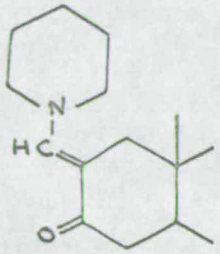
(i.r. 1650, 915, 910 cm.$^{-1}$ n.m.r. τ 6.09, 6.06 (ketal), 5.29, 5.01 (exocyclic methylene hydrogens)), was achieved with methylenetriphenylphosphorane.

The reaction of the ketal-ketone (322) with dimethyloxosulphonium methylide gave on recrystallisation from acetone a compound identical to that formed by m-chloroperbenzoic acid attack of (323) (after recrystallisation). The i.r. spectrum of this compound had bands at 1170, 1060, 982, 950, 838, 750 cm.$^{-1}$ while present in the n.m.r. were absorptions at τ 7.44, 7.37, 7.07, 6.99 (epoxide hydrogens at C-3'), 6.09, 6.00 (ethylene ketal hydrogens). On this basis the compound was assumed to be a 3-methylene epoxide and by analogy with oxosulphonium methylide epoxidation of 5α-cholestan-3-one and 2,2-dimethyl-5α-cholestan-3-one and the peracid attack of 3-methylene-5α-cholestane and 3-methylene-2,2-dimethyl-5α-cholestane it was also assumed to be the α-epoxide (324).

The last stage for the preparation of 3β-methyl-3α,3'-epoxy-5α-cholestan-2-one was the removal of the ketal group. This type of reaction is usually achieved by acid treatment[117] and in this case HBr was used since the reagent used for de-ketalisation would also have to in this case convert the acid labile epoxy-group into a compound(s) from which it could easily be regenerated at a later stage. HBr gas was bubbled through a solution of the epoxy-ketal (324) in chloroform and a gum was obtained with a carbonyl group (1715 cm.$^{-1}$) and a hydroxy group (3500 cm.$^{-1}$). The yield was low and indicated probably that the conditions of cleavage had been rather drastic. The product on chromatography on alumina gave on

elution with petrol a crystalline product with peaks in the i.r. at 3050, 1718, 940 and 835 cm.$^{-1}$ The n.m.r. showed an absorption band at τ 7.20 which can be attributed to epoxide protons ($C\underline{H}_2$-O). This product was therefore assumed to be 3β-methyl-3α,3'-epoxy-5α-cholestan-2-one (325).

From this first attempted synthesis it was obvious that apart from ketalisation and the final removal of the ketal group the route was a practical one each of the intermediate steps giving high yields of products. The main problem was the regeneration finally of the 2-ketone and doubtless the use of milder acidic conditions could improve the yields from this stage. However the report[121] of the preparation of 3-oxygenated-2-methylene-epoxy-steroids suggested that these types of epoxides would be easy to prepare, thus giving sufficient material for a study of the reactions of α-oxygenated-methylene epoxides.



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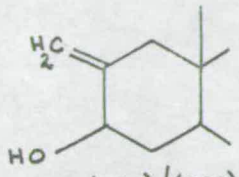

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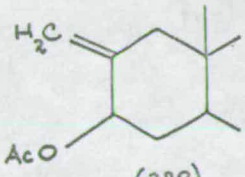

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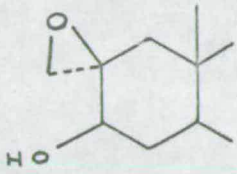

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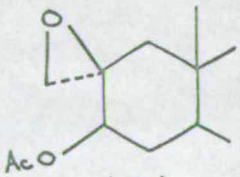

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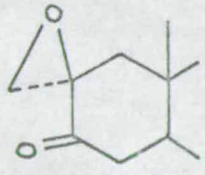

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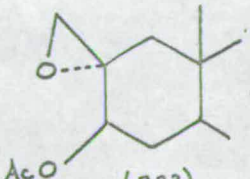

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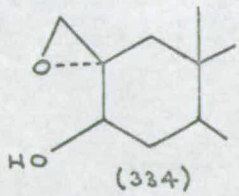

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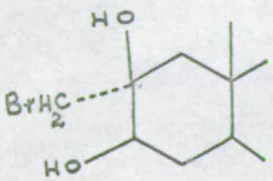

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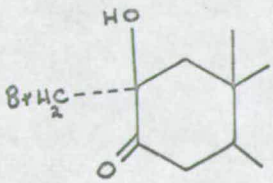

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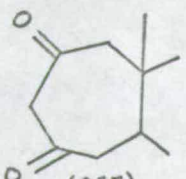


(337)

The synthesis and reactions of 3-oxygenated-2-methylene epoxides

The preparation of 2-methylene-5α-cholestan-3β-ol (326) was carried out in a similar way to that reported for the synthesis of a number of 2-methylene-3β-ols in other steroid systems.[122] Refluxing 2-hydroxymethylene-5α-cholestan-3-one[75] with piperidine in benzene[123] gave a product identifiable by elemental analysis and spectra[123] as 2-N-piperidinomethylene-5α-cholestan-3-one (327) (i.r. 1655 cm.$^{-1}$, u.v. 334 mμ (ϵ 22,800)). Treatment of this compound (327) with excess sodium borohydride in methanol at 0° gave a precipitate which was recrystallised from acetone. The i.r. spectrum of this compound exhibited absorption bands at 3560 (hydroxyl), 1645, 895 (CH_2=$\dot{C}$-) cm.$^{-1}$, while the n.m.r. spectrum had present peaks at τ 5.00 and 5.28 (CH_2=$\dot{C}$-). Treatment of this compound with acetic anhydride in pyridine gave a mono-acetate (329) (i.r. 1738, 1650, 1238, 1039, 895 cm.$^{-1}$, n.m.r. τ 7.89 (3 protons, acetate), 5.17 and 5.29 (2 protons, exocyclic methylene group)). All this indicates that the borohydride reduction product was 2-methylene-5α-cholestan-3β-ol (328).

The epoxidation of (328) and (329) and the subsequent alteration of the functional groups at C-3 were carried out in similar ways to those described by Klimstra.[121] There it was found that epoxidation of the 2-methylene compounds containing a 3β-hydroxy group gave epoxides in which the epoxide oxygen assumed a position on the same side of the steroid ring as the 3-substituent, i.e. 2β, while with the 3β-substituent an acetoxy group the epoxide oxygen on epoxidation assumed the 2α position.

Treatment of 2-methylene-5α-cholestan-3β-ol (328) with an excess of m-chloroperbenzoic acid in either ether or benzene-chloroform as solvent gave a product, m.p. 162-164°, i.r. bands at 940, 835, 700 cm.$^{-1}$ and n.m.r. peaks at τ 7.49, 7.41, 6.88, 6.80 (attributed to the C-2' protons of a 2,2'-epoxide). On the basis of Klimstra's work[121] and because in all cases[12,17,18,134] at least some cis-epoxide is formed on peracid attack of α,β-unsaturated-alcohols, this compound was assumed to be the 2β-epoxide (330). Treatment of this compound (330) with acetic anhydride in pyridine gave a compound; m.p. 153-155° with i.r. bands at 1640, 1230 (acetate), 942, 905, 835 cm.$^{-1}$ and n.m.r. peaks at τ 8.00 (3 protons, acetate); 7.53; 7.44; 6.99; 6.90 (C-2' hydrogens). This compound was assumed to be the 3β-acetate (331). Oxidation of 2α-methyl-2β,2'-epoxy-5α-cholestan-3β-ol (330) with Jones' reagent gave a ketone, assumed to be the 2β,2'-epoxy-3-ketone (332); m.p. 164-166°, i.r. bands at 1720 and 830 cm.$^{-1}$ n.m.r. peaks at τ 7.36, 7.26, 7.22, 7.12 (exocyclic epoxide protons).

When 2-methylene-5α-cholestan-3β-ol acetate (329) was treated with excess m-chloroperbenzoic acid in ether a product was obtained which after recrystallisation from acetone melted over a 10° range (120-130°). This melting point was not improved on after repeated recrystallisation. The i.r. spectrum was similar to that of the 2β,2'-epoxide (331); 1640, 1230, 905, 835 cm.$^{-1}$ with the peak at 905 cm.$^{-1}$ much broader in this case. The n.m.r. spectrum was also very similar; τ 8.00 (acetate), 7.54, 7.45, 7.10, 6.91 (epoxide).

There would seem, therefore, to be a difference between the result here and those patented[121] for the androstanes. It would seem very unlikely that peracid attack of the 2,2'-double bond should occur to a marked extent from the β-face (18% axial attack by peracid for 2-methylene-5α-cholestane, page 50). However steric and/or electronic effects of the 3β-acetate may give slightly more β-epoxide here and this coupled with a greater loss of the more polar 2α,2'-epoxide on crystallisation could well give a product containing a fair proportion of the β-epoxide (331) (total epoxide product was obtained in a 69% yield after crystallisation). Since the mixed m.p. of the product here with the 2β,2'-epoxy-3β-acetate (331) was 122-149° it was assumed that the product isolated from peracid attack of the 2-methylene-3-acetate (329) contained a substantial amount of the 2α,2'-epoxide (333). Removal of the acetate of this product with potassium carbonate in warm aqueous methanol gave an alcohol, m.p. 126-150° (mostly 127-134°), with an i.r. spectrum similar to that of the 2β,2'-epoxy-3β-ol (330) with the addition of a peak of medium intensity at 900 $cm.^{-1}$ and an n.m.r. spectrum identical to the β-epoxide (330). Oxidation of this compound, which was assumed to contain (330) and the 2α,2'-epoxy-3β-ol (334), with Jones' reagent gave a ketone which after crystallisation from acetone had a m.p. 164-166°. The i.r. and n.m.r. spectra of this ketone were similar to those of the 2β,2'-epoxy-3-ketone (332), and the mixed melting point of this oxidation product with the 2β,2'-epoxy-3-one (332) was 161-6°. Thus it would appear that progressive loss through recrystallisation of the 2α,2'-epoxides

on going from the 3β-acetate via the alcohol to the 3-ketone had given in the end 2α-methyl-2β,2'-epoxy-5α-cholestan-3-one.

The β-epoxide (330) when treated with HBr gave in high yield a crystalline product which contained bromine. Chromatography of this product on alumina gave back the epoxide (330), and when the bromohydrin was treated with acetic anhydride in pyridine it gave a product containing hydroxy and acetoxy groups (i.r.) and which from its n.m.r. spectrum appeared to be a mono-acetate (τ 7.94 ca.3 protons). This acetate was not wholly crystalline but attempts to further acetylate it with acetic anhydride in pyridine over 2 days did not alter its composition (n.m.r., i.r.), and thus the parent bromo-compound was assumed to have only one secondary alcohol group (at C-3) and was thus assigned the 2α-bromomethyl-2β,3β-diol structure (335).

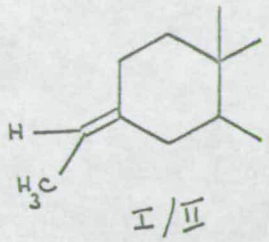
It is interesting that neither the n.m.r. spectrum of the bromohydrin (335) nor the corresponding spectrum of the crude acetate contained methyl signals downfield from τ 9.09. It has been noticed[124] with other 2β-substituted compounds that the position of the C-19 methyl group absorption is shifted downfield. However not all 2β-compounds dealt with in this work have shown downfield shifts. The diacetate of 5α-cholestan-2β,3α-diol, for example, showed only peaks attributable to the two acetates downfield from τ 9.1.

The α-keto-epoxide (332) was also treated with HBr and gave a bromohydrin (336) from which the parent epoxide (332) could be regenerated on alumina chromatography. This bromohydrin (336)

did not form an acetate on treatment with acetic anhydride in pyridine overnight and thus it was assumed to be the 2α-bromomethyl-compound (336). In this case the n.m.r. spectrum of (336) showed methyl signals at τ 9.34, 9.19, 9.09, and 8.87, the last of which can be attributed to the C-19 methyl group.

Treatment of 2α-methyl-2β,2'-epoxy-5α-cholestan-3-one with boron trifluoride-etherate in benzene gave after 5 minutes a crude product from which it was not possible to isolate crystalline material. Chromatography on alumina gave on elution with solvent systems from petrol to chloroform gums accounting for little of the product. The remaining bulk of the product could not be eluted using chloroform plus 10% methanol. The experiment was repeated using twice redistilled boron trifluoride-etherate and redistilled benzene and gave on work up after a reaction time of 5 minutes only starting material. With this purified boron trifluoride-etherate in fact no conversion of the epoxide was observed with reaction times up to 5 hours and so the reaction was allowed to proceed overnight after which time a crystalline product with a sharp m.p. was obtained which had strong peaks in the i.r. at 1658 and 1630 (enone) with a medium peak at 1710 $cm.^{-1}$ No information on other than the methyl signals was possible from the n.m.r. spectrum. The elemental analysis indicated the formation of a product isomeric with the starting epoxide. The obvious possible rearrangement products in this case would be 2-hydroxymethylene-5α-cholestan-3-one or A-homo-5α-cholestan-2,4-dione. The first could be ruled out by spectra and mixed melting point. The compound exhibited a peak at 279 mμ

in the u.v. (ethanol) which shifted to 318 mμ with 0.01N NaOH in ethanol-water (9:1) as solvent. This is characteristic of a β-diketone.[125] On treatment with ca.2 moles of bromine a crude product was obtained with no absorptions in the i.r. in the region 1690-1600 $cm.^{-1}$ but with peaks at 1700 and 1720 $cm.^{-1}$ There were no strong absorptions in the u.v. and thus it was assumed that the bromine atoms had attached themselves at C-3, between the two keto-groups of A-homo-5α-cholestan-2,4-dione (337).



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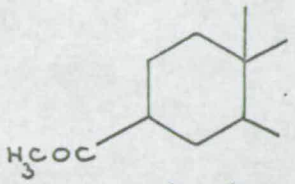

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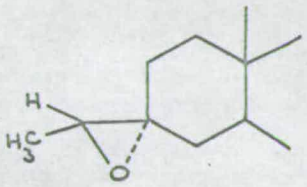
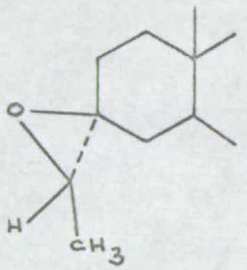
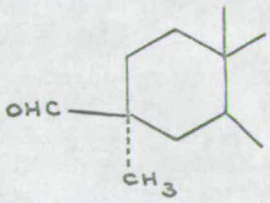


(339) or (341)



(340) or (342)



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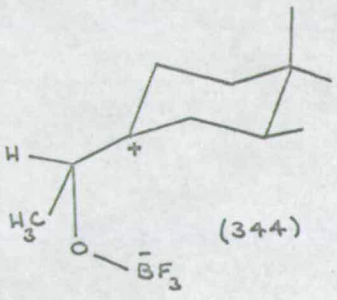


(344)

Ethylidene Epoxides

The synthesis and reactions of the epoxides of 3-ethylidene-5α-cholestane

The reaction of 5α-cholestan-3-one with ethylidenetriphenylphosphorane has been reported to give a product in which one of the 3-ethylidene-compounds predominates and from which this major olefin can be isolated by recrystallisation.[126] This was repeated here, using methylsulphinyl carbanion as the base,[79,127] and a product was obtained which could not be wholly purified by recrystallisation (m.p. 51-5°, lit. for the major olefin from the Wittig reaction[126] 56-7°). Hydration of the 3-ethylidene-compound isolated here (I) with diborane generated from sodium borohydride and boron trifluoride-etherate in tetrahydrofuran (a modification of the *in situ* diborane generation method of Sondheimer *et al.*[128]), followed by oxidation of the resulting organoborane with alkaline hydrogen peroxide[128] gave an alcohol which after chromatography and crystallisation from acetone melted over a 10° range. Oxidation of this compound with Jones' reagent gave a high yield of 3β-acetyl-5α-cholestane (338) (identified by a comparison of its melting point with that reported for 3β-acetyl-5α-cholestane[129] and from its i.r. and n.m.r. spectra). This indicates that hydration of the olefin had in fact produced a hydroxy group at C-3' (secondary). The wide melting point range for the hydration product probably indicates that the 3-ethylidene-5α-cholestane used in the hydroboration procedure consisted of the two geometrical isomers and/or that initial attack of diborane was not stereospecifically alpha. Dehydration of the alcohol with

phosphoryl chloride in pyridine gave a product (II) identical in spectra with the 3-ethylidene-5α-cholestane produced by the Wittig reaction (I). It was again difficult to recrystallise (m.p. 42-6°, mixed m.p. with (I) 42-52°). This would indicate that the 3-ethylidene derivative formed in the Wittig reaction was not the major product here and that a trans-coplanar dehydration had taken place. It also probably confirms that the product isolated from the Wittig reaction (I) (after recrystallisation) was not a single olefin.

The 3-ethylidene-5α-cholestane from the Wittig reaction (I) on treatment with excess m-chloroperbenzoic acid in ether gave a product which on chromatography on alumina and elution with petrol gave two fractions. The first fraction was the major product, 86%, and on recrystallisation from acetone had a sharp melting point (103-105°) probably signifying a single compound. The i.r. spectrum had peaks at 980, 879 and 687 $cm.^{-1}$ while the n.m.r. spectrum exhibited absorption intensities at τ 8.79, 8.70 (C-3' methyl group), 7.21, 7.12 (C-3' hydrogen). On the basis of polarity and from the results of the peracid epoxidation of the 3-methylene-cholestanes (pp. 41-49) this compound was assumed to be the α-epoxide (339). The second fraction, 14%, had a melting point 80-83° and absorptions in the i.r. at 1000, 928, 872, 770, 720, 710 $cm.^{-1}$ with peaks in the n.m.r. at τ 8.77, 8.67 (C-3' methyl group), 7.26, 7.16 (C-3' proton), and was assumed to be the β-epoxide (340). This epoxide (340) was the major product, 52%, resulting from the reaction of the 3-ethylidene compound (I) with the alkaline hydrogen peroxide-benzonitrile system.[3] The α-epoxide (339) was also isolated from

this reaction, 21%, as was a little starting material, 27%. The ratio of the β- to α-epoxide is 72:28.

These two epoxidation reactions were also carried out with the 3-ethylidene compound (II) resulting from the hydration-dehydration reaction sequence. m-Chloroperbenzoic acid in ether gave epoxides identical in their spectra to those formed in the peracid epoxidation of the Wittig 3-ethylidene-5α-cholestane (I). The major product (α-epoxide) was formed in 83% with 17% of the β-epoxide. Treatment of this 3-ethylidene-5α-cholestane (II) with the alkaline hydrogen peroxide-benzonitrile system also gave the α-epoxide, 23%, and the β-epoxide, 57%, along with some starting material 20%. The ratio of β- to α-epoxide is 71:29. The m.p. of the α-epoxide (341) from the hydration-dehydration olefin (II) was 98-107° (mixed m.p. of the two α-epoxides 94-105°) with that of the β-epoxide (342) 110-120° (mixed m.p. of the two β-epoxides 70-90°). This would indicate that the epoxides from the 3-ethylidene (II) were not single compounds with in both cases contamination by the corresponding epoxides of the other 3-ethylidene system (I).

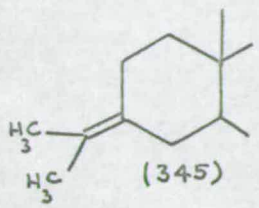
The α-epoxide (339) when treated with excess boron trifluoride in benzene gave a product which from spectra appeared to be an acetyl-compound (i.r. 1705 and 1355 cm.$^{-1}$, n.m.r. τ 9.34, 9.23, 9.20, 9.09 and 7.88 ($C\underline{H}_3$-C=O). Chromatography on alumina gave a single compound identified as 3β-acetyl-5α-cholestane by its spectra and by a mixed m.p. The n.m.r. here was identical to that for the crude product indicating that a high or total yield of the equatorial acetyl compound was isolated on work up. The rearrangement was repeated using ether as solvent, with a reaction time of 2 hours,

and again the n.m.r. spectra of the crude and alumina purified products were the same and indicated formation of 3β-acetyl-5α-cholestane. Thus there is in this case no information from spectra as to whether the reaction pathway involved a concerted mechanism or a carbonium ion intermediate.

The β-epoxide (340) was also treated with excess boron trifluoride in benzene and the n.m.r. spectrum of the crude product was run. This showed a three proton peak at τ 7.88 ($C\underline{H}_3$-C-) and a one proton peak at τ 0.61 (-C$\underline{H}$O). The crude product was chromatographed on alumina to give two fractions. The first, 24%, was the aldehyde (i.r. 2670, 1720 cm.$^{-1}$). Its n.m.r. spectrum showed the one proton peak at τ 0.61 and there were also peaks present at τ 8.73 and 8.87 which could be attributed to a methyl group adjacent to the aldehyde function (OHC-$\dot{C}$-$C\underline{H}_3$). The product was assigned the 3α-methyl-3β-aldehyde (343) structure from the spectral evidence and because this is the aldehyde which would be formed from the β-epoxide (340) by a concerted process. A concerted mechanism for the formation of the aldehyde was thought to be a reasonable assumption since the transition state for a carbonium ion mechanism for both the α- and β-epoxides would be expected to be the same (344) and thus formation of the aldehyde from both epoxides would be expected to result. It also seems reasonable to explain the non-formation of aldehyde from the α-epoxide on the basis of a concerted mechanism taking place with then an equatorial hydride shift being preferred for steric reasons to an equatorial methyl migration. The second fraction from the rearrangement of the β-epoxide (340) was 3β-acetyl-5α-cholestane, 76%. The reaction of the β-epoxide

(340) with boron trifluoride in ether also gave a mixture of aldehyde (343), 26% and 3β-acetyl-5α-cholestane, 74%. There is thus little difference in the yields of the aldehyde (343) with the two solvents and thus it is not possible to tell to what degree the reaction is concerted in ether or benzene.[42]

The rearrangement reactions were also carried out with the α- and β-epoxides from the hydration-dehydration 3-ethylidene-5α-cholestane (II). The α-epoxide (341) with boron trifluoride in either benzene or ether as solvent gave as the only recognisable product 3β-acetyl-5α-cholestane while the β-epoxide (342), again in either benzene or ether as solvent gave mixtures of the aldehyde (343) and 3β-acetyl-5α-cholestane; 25% aldehyde and 75% 3β-acetyl in benzene and 27% aldehyde and 73% 3β-acetyl in ether.



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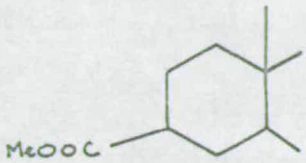

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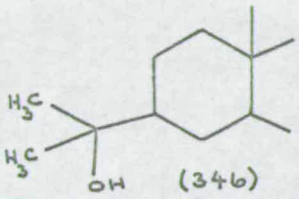

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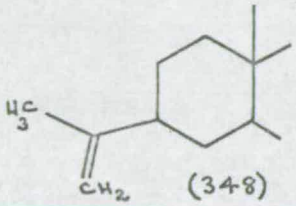

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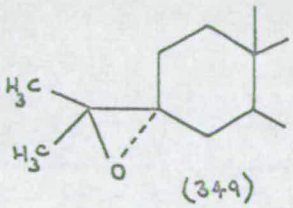

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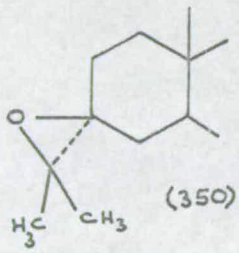

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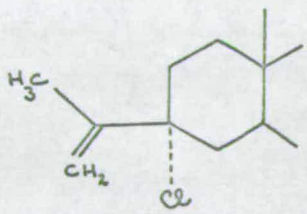

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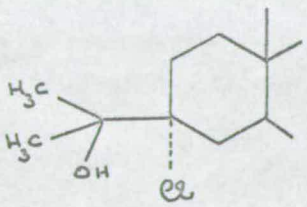

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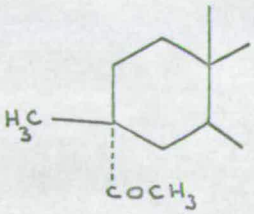

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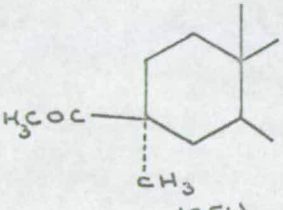


(354)

Isopropylidene Epoxides

The synthesis and reactions of the epoxides of 3-isopropylidene-5α-cholestane

The preparation of 3-isopropylidene-5α-cholestane (345) from 5α-cholestan-3-one and isopropylidenetriphenylphosphorane has been reported.[126] The reaction was repeated here with either potassium t-butoxide or methylsulphinyl carbanion[79] as base, with disappointing results. Only on a few occasions could ylide solutions be prepared, although no fault in the adopted procedures was obvious with all reagents being carefully purified and dried prior to their use. As a result only a limited amount of the 3-isopropylidene-compound (345) was available for subsequent reactions. An alternative route for the preparation of the isopropylidene steroid was unsuccessful, the dehydration with phosphoryl chloride in pyridine or thionyl chloride in pyridine of the tertiary alcohol (346) derived by the addition of excess methyl magnesium iodide to the 3β-methoxycarbonyl-compound (347) giving the 3-isopropenyl derivative (348) (i.r. 3050, 1640, 895 cm.$^{-1}$, n.m.r. τ 8.36, 8.30 (methyl group on the double bond), 5.34 ($C\underline{H}_2$=$\overset{|}{C}$-). This does in fact seem to be the usual route for the dehydration of such hydroxyisopropyl-derivatives of six-membered rings.[135]

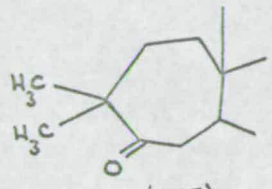
Treatment of the isopropylidene compound (345) with excess m-chloroperbenzoic acid in ether gave after alumina chromatography and elution with petrol two compounds. The first and major, 87%, product had peaks in the i.r. at 1215 and 870 cm.$^{-1}$ and a strong absorption at τ 8.71 in the n.m.r. which can be attributed to the

two methyl groups adjacent to the epoxide oxygen ($\underline{CH_3}>\dot{C}-O-$ / $\underline{CH_3}$). Thus on polarity, spectra, and from the observed preference for axial attack by peracid found in this work for other 3-alkylidene-5α-cholestanes the product here was assigned the α-epoxide structure (349). The second product, 13%, on similar reasoning was assumed to be the β-epoxide (350). It had i.r. peaks at 1235 and 875 $cm.^{-1}$ and a strong methyl group absorption in the n.m.r. at τ 8.67 ($\underline{CH_3}>\dot{C}-O-$ / $\underline{CH_3}$). The reaction of 3-isopropylidene-5α-cholestane with the alkaline hydrogen peroxide-benzonitrile system[3] gave the same two epoxides (349) and (350). On this occasion the β-epoxide (350) was only just the major of the two epoxides, 54%. An alternative attempt at synthesis of the β-epoxide (350) from the olefin (345) was not successful. Addition of HOCl generated from bleaching powder and acetic acid gave a single product showing no hydroxy absorptions in the i.r. There was however a strong peak at 908 with a medium one at 1635 $cm.^{-1}$ ($CH_2=\dot{C}-$) and the n.m.r. showed peaks at τ 4.94, 5.12 ($\underline{CH_2}=\dot{C}-$) and at τ 8.06 ($\underline{CH_3}-\dot{C}=CH_2$). The compound also contained chlorine and with the assumption of initial attack by Cl^+ from the α-face this product was assigned the 3β-isopropenyl-3α-chloro-structure (351), and probably results from acid dehydration of the initially formed 3β-hydroxyisopropyl compound (352).

The α-epoxide (349) with boron trifluoride in benzene gave after alumina chromatography two rearrangements products. The first product, eluted with petrol-benzene (95:5), was a ketone showing methyl signals in the n.m.r. at τ 8.97 and 8.93. The second and minor, 7%, product (eluted with petrol-benzene (9:1)) was also a

ketone and from its spectra appeared to be an acetyl-compound (i.r. 1699 and 1350 cm.$^{-1}$ n.m.r. τ 8.84 ($C\underline{H}_3$-C-C-) and τ 7.87 (three protons, $C\underline{H}_3$-C-). The β-epoxide (350) with BF_3 in benzene gave a single product identifiable as a methyl ketone by its spectra (i.r. 1699, 1350 cm.$^{-1}$ n.m.r. τ 8.83 ($C\underline{H}_3$-C-C-) and τ 7.89 (three protons, $C\underline{H}_3$-C-). The methyl-ketones from the α- and β-epoxides were different and on assuming concerted processes for their formation from the epoxides then the one from the α-epoxide should be the 3β-methyl compound (353) with the 3α-methyl product (354) resulting from the rearrangement of the β-epoxide. Because of the limited amount of the ketone from the α-epoxide a proof of the stereochemistry of the two acetyl compounds on a chemical basis was only possible from the ketone from the β-epoxide. Here the methyl ketone (354) was treated with excess m-chloroperbenzoic acid in chloroform and left at room temperature for eight days. On work up a crude product was obtained which appeared to be a mixture of acetoxy and ketonic products (i.r.). Chromatography on alumina gave starting material and acetate, lithium aluminium hydride treatment of the acetate giving 3α-methyl-5α-cholestan-3β-ol showing that a concerted mechanism for rearrangement of the β-epoxide had taken place.

The major ketonic product from the rearrangement of the α-epoxide (349) was thought to be an A-homo-ketone, this being the only other obvious rearrangement product for the epoxide. The methyl signals at τ 8.97 and 8.93 in the n.m.r. for this compound can be attributed to methyl groups adjacent to a carbonyl group. The g.l.c. retention time with respect to A-homo-5α-cholestan-4-one was 1.11 which is similar in magnitude to the retention times found for



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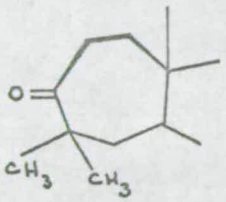

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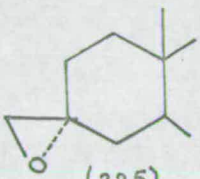

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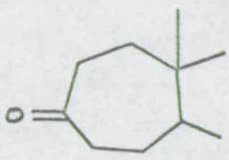

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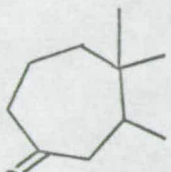

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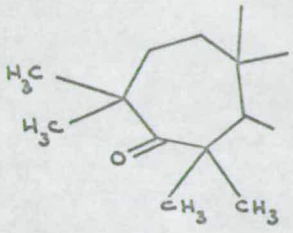

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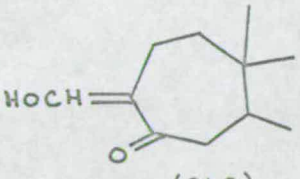

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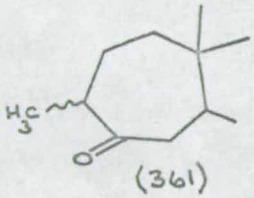

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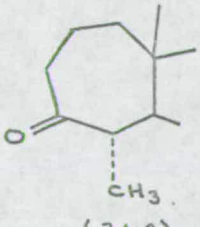

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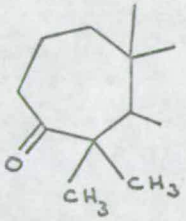


(363)

a number of β-methylated-A-homo-ketones.[105] The rearrangement of (349) can result in formation of either 3,3-dimethyl-A-homo-5α-cholestan-4-one (355) from a 2,3-bond shift to the exocyclic carbonium ion or 4,4-dimethyl-A-homo-5α-cholestan-3-one (356), the result of 3,4-bond migration. In order to prove which was in fact the product formed, the rearrangement product was treated with 1.05 moles of bromine to give a product $\nu_{max.}$ 1718 and 1699 $cm.^{-1}$ Silica gel chromatography afforded a crystalline compound, $\nu_{max.}$ 1718 $cm.^{-1}$, and an oil, $\nu_{max.}$ 1699 $cm.^{-1}$, which appeared from the "fingerprint" region of its i.r. spectrum to be mainly starting material. Attempted dehydrobromination of either fraction with lithium bromide and lithium carbonate in refluxing dimethylformamide gave crude products which could not be fractionated on alumina. It was not entirely clear from the u.v. spectra of these crude products as to whether enone formation had or had not taken place, although the product from the ketone with $\nu_{max.}$ 1718 $cm.^{-1}$ did show a shoulder at ca.230 mμ.

Thus, owing to a limited amount of the rearrangement product, a less direct proof of its structure was required. Addition of diazomethane in the presence of potassium hydroxide to 5α-cholestan-3-one was carried out as described,[107,136] and a crude product was obtained which was adsorbed onto alumina. Elution with petrol gave 3β-methyl-3α,3'-epoxy-5α-cholestane (225), 4%, which was followed, on elution with petrol-benzene (8:2), by A-homo-5α-cholestan-3-one (357), 6%. Finally elution with petrol-benzene (8:2) and benzene gave A-homo-5α-cholestan-4-one (358), 90%. The A-homo-ketones were identified from their melting points,[107,136] i.r. spectra,[136] and

g.l.c. retention times.[107] The isolation of the 3α,3'-epoxide (225) from this reaction has not hitherto been reported and must imply some equatorial attack by the nucleophile[107] on the carbonyl group at C-3.

Since the purpose of these experiments was the preparation of α-dimethyl-A-homo-ketones, the methylation of A-homo-5α-cholestan-4-one was carried out with methyl iodide and potassium t-butoxide under similar conditions to those reported for the synthesis of 2,2-dimethyl-5α-cholestan-3-one from 5α-cholestan-3-one.[76,77] Under these reaction conditions the A-homo-ketone (358) gave a crude product which was adsorbed onto alumina (activity II). Elution with petrol-benzene mixtures ranging from 1% to 30% benzene gave a series of fractions most of which were non-crystalline while elution with petrol-benzene (6:4) and benzene gave A-homo-5α-cholestan-4-one, 35%. These first fractions were assumed to contain methylated A-homo-4-ketones. An indication of the degree of methylation of each fraction from their g.l.c. retention times by comparison with the retention times reported for a number of methylated-A-homo-ketones was not successful, all the fractions here giving broad peaks at ca.1.1 with respect to A-homo-5α-cholestan-4-one. This nevertheless indicates the formation of material with higher molecular weights to A-homo-5α-cholestan-4-one.

The presence of at least one unsubstituted methylene group at C-2 or C-4 in steroid 3-ketones has been shown[137] to be associated with an i.r. absorption at ca.1420 $cm.^{-1}$, which is attributed to the bending vibration of the α-methylene groups perturbed from 1450 $cm.^{-1}$ the normal position for a six-membered ring, by the effect of the

carbonyl group. In a similar way 5α-androstan-17-one shows a peak at 1410 $cm.^{-1}$ It was therefore thought worthwhile to see whether this effect was also observable for the seven-membered ring ketones from the methylation reaction. The i.r. spectra of a representative number of the fractions from the alumina (activity II) column were therefore run in carbon tetrachloride solutions. The early fractions from the column showed no absorptions in the region 1450-1380 $cm.^{-1}$ while the later fractions showed peaks at 1412 $cm.^{-1}$, as did A-homo-5α-cholestan-4-one and A-homo-5α-cholestan-3-one. It would therefore seem probable that monomethyl- and/or dimethyl-A-homo-4-ones had been isolated from this methylation experiment. It was also apparent however that further methylation of these types of compounds was quite readily achieved under the strong conditions used. The experiment was therefore repeated using methyl chloride in the presence of potassium t-butoxide.[138] With these conditions a crude product, found to consist mainly of starting material, 56%, was isolated, with fractionation of the remainder of the product on alumina (activity II) not wholly successful. When the methylation of A-homo-5α-cholestan-4-one was carried out using methyl iodide and 3 equivalents of potassium t-butoxide a product was obtained which was somewhat easier to fractionate on alumina (activity II). As well as a high proportion of non-crystalline material, three crystalline fractions, the last being A-homo-5α-cholestan-4-one, 40%, were eluted. The first, eluted with petrol-benzene (9:1) was assumed from its i.r. spectrum to be a tri- or tetra-methyl-A-homo-4-one and with isopropenyl acetate and concentrated sulphuric acid[107] gave a product containing both acetate and ketone absorptions in the i.r.

The ketone was the major product and was mostly separated from the acetate on silica gel chromatography. This ketone had an i.r. spectrum very similar to that of the ketone prior to the enol-acetylation, and was recovered unchanged when similarly treated with isopropenyl acetate and concentrated sulphuric acid. The acetate and ketone mixed fraction showed peaks in the n.m.r. at τ 7.86 (acetate) and 8.36 (methyl group on the double bond). Thus this first crystalline fraction must contain 3,3,4a,4a-tetramethyl-A-homo-5a-cholestan-4-one (359) slightly contaminated by trimethylated material. The second crystalline fraction, eluted with petrol-benzene (7:3), had a peak in the i.r. at 1412 $cm.^{-1}$ and a g.l.c. retention time with respect to A-homo-5a-cholestan-4-one of 1.12. It gave, after treatment with isopropenyl acetate and concentrated sulphuric acid, an enol-acetate with a peak at τ 7.86 (acetate) in the n.m.r. but with no other methyl peaks downfield from τ 8.70, thus showing, in confirmation to the i.r. evidence, the presence of an unsubstituted methylene group alpha to the carbonyl group.

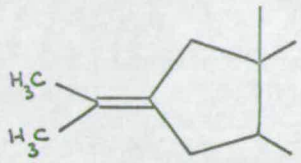
An attempt at the formation of 3-methyl-A-homo-5a-cholestan-4-one from 3-hydroxymethylene-A-homo-5a-cholestan-4-one (360),[136] by hydrogenolysis with palladium on charcoal catalyst[75] gave after chromatography on alumina (activity II) and elution with petrol-benzene (1:1) a moderate yield of ketonic material with a retention time of 1.11 with respect to A-homo-5a-cholestan-4-one, which would indicate that formation of the 3-methyl-A-homo-4-one (361) had taken place. The second crystalline fraction from the last methylation of A-homo-5a-cholestan-4-one was different from this monomethyl-

compound (361) and was also different from the known 4aα-methyl-A-homo-5α-cholestan-4-one (362)[105] which left only two possibilities for its structure; 3,3-dimethyl-A-homo-5α-cholestan-4-one (355) or 4a,4a-dimethyl-A-homo-5α-cholestan-4-one (363). In order to find out which the methylation material was treated with approximately 1 mole of bromine to give a crude bromo-ketone which on treatment with lithium bromide and lithium carbonate in boiling dimethylformamide gave an oil with a λ_{max} at 237 mμ (ε ca.8000) which can be taken as indicating the presence of a ring junction double bond in the molecule[139] (A-homo-5α-cholest-2-en-4-one has been shown[107] to have a $\lambda_{max.}$ at 229 mμ). The methylation product must therefore be the 3,3-dimethyl-compound (355) and because it is different from the ring expansion product formed by the action of BF_3 on the α-epoxide (349) this must imply formation of the 4,4-dimethyl-A-homo-3-ketone (356) in the later case.

The BF_3-catalysed rearrangements of the α- and β-epoxides of 3-isopropylidene-5α-cholestane therefore show real differences in their reaction pathways. The β-epoxide (350) cleaves the C-3-O bond with a concerted shift of the methyl group to the partially formed carbonium ion at C-3 from the relatively unhindered α-side. The corresponding reaction for the α-epoxide takes place only to a small extent and doubtless this is due to the fact that the methyl shift here would involve equatorial attack which would be expected for steric reasons to be an unfavoured process. Thus a ring expansion rearrangement is preferred for the α-epoxide. It is not altogether clear why a similar reaction does not occur at all for the β-epoxide, since one might expect a positive charge or partial

positive charge to be better accommodated on the exocyclic carbon than on the six-membered ring,[140] but this may be due to the nature of the possible products formed or the avoidance of having two bulky groups attached at C-3 in the transition state. It is also not clear why the ring expansion of the α-epoxide involves a 3,4-bond shift since the comparable diazomethane and Tiffereau ring expansions of 5α-cholestan-3-one involve overwhelmingly formation of A-homo-5α-cholestan-4-one, due to a 2,3-bond migration. Again it can only be assumed that it is the nature of the final possible products which is the directive force in the BF_3-catalysed re-arrangement.

The methylation of the A-homo-ketone (358) seems to be a somewhat complicated reaction. Since it has been shown that base catalysed condensations occur at position 3 for the A-homo-ketone (358) it is probably safe to assume that monomethylation also occurs at this position. Further methylation, however, takes place rapidly and it is not possible to judge from the major methylation products which are the favoured positions of attack. It is interesting to note in fact that enol-acetylation of 3-methyl-A-homo-5α-cholestan-4-one with isopropenyl acetate and concentrated sulphuric acid gives a product in which double-bond formation towards C-4a takes place, there being no downfield methyl signals in the n.m.r. of this compound attributable to a methyl group attached to a double-bond.



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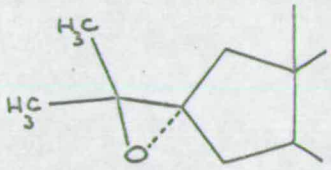

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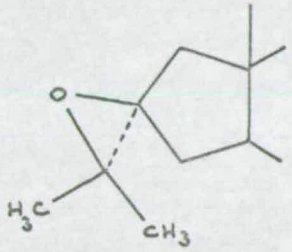

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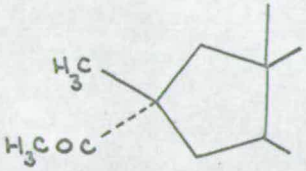
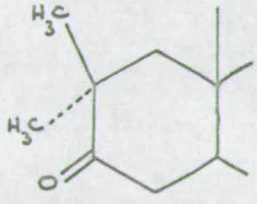
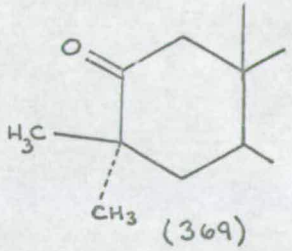


(367)



(368)



(369)

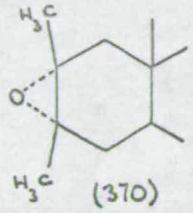
Synthesis and reactions of the epoxides of 3-isopropylidene-A-nor-5α-cholestane

3-Isopropylidene-A-nor-5α-cholestane was treated with m-chloroperbenzoic acid in ether to give a product which was crystallised from acetone. The i.r. spectrum of this compound had bands at 920, 850 $cm.^{-1}$ while the n.m.r. spectrum possessed a strong peak at τ 8.74 ($\underline{CH_3}\diagdown \dot{C}-O$, epoxide). This compound was assumed to be $\underline{CH_3}\diagup$ the epoxide resulting from α-attack, (365), by analogy with the epoxidations carried out on the other steroid alkylidene-cyclopentane (pp.50-52). HOBr, generated from N-bromosuccinimide and acetic acid, was added to the isopropylidene steroid (364) to give a crude alcohol which was adsorbed onto alumina. Elution with petrol gave a product with peaks in the i.r. at 1700 (carbonyl) and 850 $cm.^{-1}$ Repeated chromatography on alumina failed to fractionate what was obviously a mixture of ketone and epoxide. By using neutral alumina (activity III) a little epoxide (850 $cm.^{-1}$) was isolated free from the ketone. This was assumed to be the β-epoxide (366), resulting from initial attack by Br^+ on the double bond from the α-side. The mixed fraction of epoxide and ketone on gas liquid chromatography showed retention times with respect to 5α-cholestane at 2.21 and 1.38. The first is exactly the same as was found for 2,2-dimethyl-5α-cholestan-3-one, and with the absence of methyl ketone absorptions in the i.r. it was assumed that addition of HOBr to the 2,2'-double bond involved attack by OH^- on C-2 with some ring expansion to a dimethyl-ketone then taking place on treatment with alkali.

The α-epoxide (365) was treated with boron trifluoride in

benzene to give a ketonic product. This product showed g.l.c. retention time with respect to 5α-cholestane at 2.21, 2.03 (small peak), and 1.85. Alumina chromatography and crystallisation from acetone allowed for the isolation of two of these compounds. The first compound from the column had a retention time with respect to 5α-cholestane at 1.85 on g.l.c. and possessed peaks in the i.r. at 1700 and 1355 $cm.^{-1}$ (methyl ketone). The n.m.r. spectrum showed peaks at τ 8.67 ($C\underline{H}_3$-$\dot{C}$-$\dot{C}$=O), 7.86 ($C\underline{H}_3$-$\dot{C}$=O), and it was therefore assumed to be a 2-methyl-2-acetyl-A-nor-compound (367), resulting probably from a concerted mechanism for the rearrangement. The second compound from the column, after crystallisation, had a g.l.c. retention time with respect to 5α-cholestane at 2.21. Since it did not have a sharp melting point, it was assumed to be a mixture of the two dimethyl ketones (368) and (369) resulting from a 1,2- and 2,3-bond shift.

A small amount (50 mg.) of the β-epoxide (366) was treated with boron trifluoride in benzene to give a product which contained a methyl ketone (i.r. 1700, 1355 $cm.^{-1}$). On g.l.c. two peaks were obtained, the major having a retention time with respect to 5α-cholestane at 1.85, which, being identical to the retention time for the 2α-acetyl compound (367), was assumed to be due to the methyl-ketone. The minor g.l.c. peak had a retention time with respect to 5α-cholestane at 2.06 (ca.10% of the product). Alumina chromatography by not bringing about a separation of these compounds and repeated crystallisation from acetone gave a compound which melted over 10^{o} ($83-93^{o}$).



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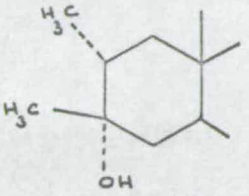

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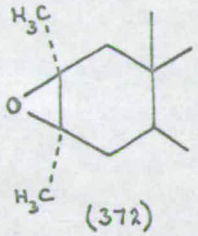

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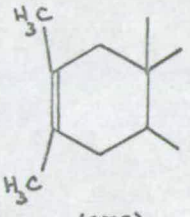
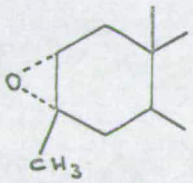
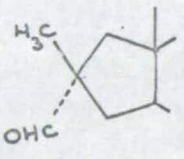


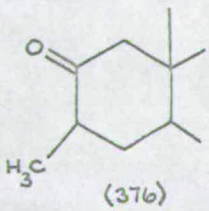
(373)



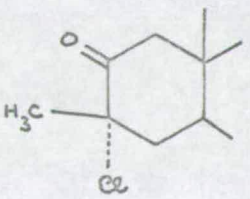
(374)



(375)



(376)



(377)

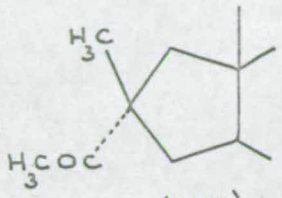
The Synthesis and Reactions of 2,3-Epoxy-5α-Cholestanes

The synthesis and reactions of 2,3-dimethyl-2,3-epoxy-5α-cholestanes

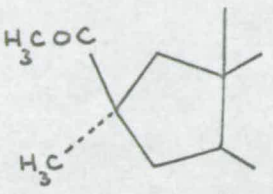
2,3-Dimethyl-5α-cholest-2-ene was prepared by the addition of methyl magnesium iodide to 2α-methyl-5α-cholestan-3-one, followed by dehydration of the mixture of tertiary alcohols with acetic acid containing a few drops of perchloric acid. Treatment of this olefin with excess m-chloroperbenzoic acid in ether gave a single compound identified as the α-epoxide (370). The i.r. spectrum of the epoxide had bands at 1162, 870, 850 $cm.^{-1}$ while the n.m.r. spectrum exhibited a strong methyl signal at τ 8.71, corresponding to the methyl groups at C-2 and C-3 in (370). Cleavage of the epoxide with lithium aluminium hydride gave the known 2α,3β-dimethyl-5α-cholestan-3α-ol (371). Two routes were employed to synthesise the β-epoxide (372). The first was the most direct and consisted of the addition of HOBr generated from N-bromosuccinimide and acetic acid to the dimethyl-2-ene (373). A gum was obtained which contained bromine and a hydroxy-group (i.r.). Treatment of this product with alumina gave, on elution with petrol, in moderate yield, a non-polar compound identified as the β-epoxide (372). The i.r. spectrum contained absorptions at 1130 and 855 $cm.^{-1}$, while strong methyl signals at τ 8.76 and 8.73 were present in the n.m.r. which can doubtless be attributed to the methyl groups at C-2 and C-3 of the epoxide (372). Cleavage with lithium aluminium hydride gave an alcohol identical to that formed by addition of methyl magnesium iodide to 3β-methyl-5α-cholestan-2-one (see below), which is most likely to involve equatorial methyl attack by analogy with

Grignard reagent additions to 5α-cholestan-2-one?[50,144] The first step in the second route to the β-epoxide (372) was the synthesis of 3β-methyl-5α-cholestan-2-one. The preparation of this compound from the BF_3-catalysed rearrangement of 3β-methyl-2α,3α-epoxy-5α-cholestane (374) has been described[145] and this was repeated here. Epoxidation of 3-methyl-5α-cholest-2-ene with m-chloroperbenzoic acid gave the α-epoxide (374) (m.p. 131-132°, lit.[145] 135°) which was then treated with boron trifluoride-etherate in benzene. A crude product was obtained which showed aldehyde and ketone peaks in the i.r. (2670, 1715 and 1705 $cm.^{-1}$). Chromatography on alumina gave first the aldehyde, 28%; i.r. 2670 and 1715 $cm.^{-1}$; n.m.r. τ 8.77 ($C\underline{H}_3-\dot{C}-\dot{C}=O$); τ 0.59 (aldehyde). This would indicate formation of a 2-methyl-A-nor-2-aldehyde and in fact later work showed it to be 2β-methyl-A-nor-5α-cholestan-2α-aldehyde (375). The second fraction on chromatography consisted of 3β-methyl-5α-cholestan-2-one, 72%, (m.p. 145-148°, lit.[145] 147-149°). Thus formation of both rearrangement products involves epoxide cleavage to the tertiary carbonium ion (or partially formed carbonium ion) at C-3, with then competition between hydride and 1,2-bond shift.

The 3β-methyl-2-ketone (376) was treated with approximately 1 equivalent of t-butyl hypochlorite[146] in warm acetic acid. When this was carried out on a small scale a high melting crystalline solid was precipitated from the reaction mixture. This product contained chlorine and analysed for a 3-methyl-3-chloro-5α-cholestan-2-one. It possessed a $\nu_{max.}$ at 1715 $cm.^{-1}$ and a $\lambda_{max.}$ (O.R.D.) at 308 mμ. These figures indicate the formation of an axial



(378)



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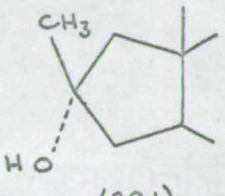

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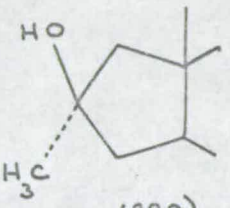

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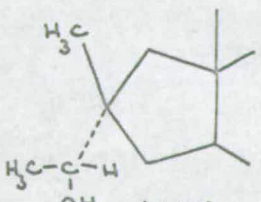


(382)

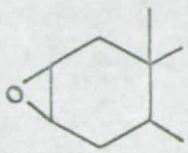
chloride, the shifts relative to the parent 3-ketone (376) ($\nu_{max.}$ 1705 $cm.^{-1}$, λ_{max}(O.R.D.) 291 mμ) being within the observed limits for an axial halogen adjacent to a carbonyl group.[147,148] Treatment of the chloro-compound with HBr in acetic acid did not bring about epimerisation. Thus formation of 3α-chloro-3β-methyl-5α-cholestan-2-one (377) had taken place. When the 3β-methyl-2-ketone (376) was treated with t-butyl hypochlorite in acetic acid on a larger scale a mixture of starting material and the 3α-chloride (377) precipitated out. Chromatography on silica gel led to the separation of the two compounds, the 3α-chloride (377) being eluted first. This chloro-compound (377) was then treated with an ethereal solution of methyl lithium[149] and the crude product so obtained was filtered through alumina with petrol to give the β-epoxide (372).

When 2β,3β-dimethyl-2α,3α-epoxy-5α-cholestane (370) was treated with boron trifluoride a single compound (378), identical to the major product isolated by alumina chromatography from the reaction of the α-epoxide of 3-isopropylidene-A-nor-5α-cholestane (365) with BF_3, was obtained. The β-epoxide (372) likewise gave an acetyl-compound (379) on treatment with boron trifluoride in benzene (i.r. 1699, 1355 $cm.^{-1}$, n.m.r. τ 7.87 ($C\underline{H}_3$-$\dot{C}$=O). These two acetyl-compounds (378) and (379) were then treated with an excess of m-chloroperbenzoic acid and after 8 days both were worked up to give mixtures of starting material and acetate, separated by chromatography on silica gel. In neither case was the crude acetate purified, but was immediately treated with base to give hydroxy-compounds. The alcohol resulting from these reactions on (379) was found to be identical (mixed melting point and i.r. spectra

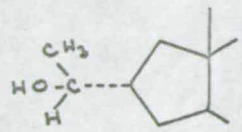
examination) with 2α-methyl-A-nor-5α-cholestan-2β-ol (380) while the alcohol formed from (378) was similarly found to be 2β-methyl-A-nor-5α-cholestan-2α-ol (381). This means that the product formed by boron trifluoride treatment of (370) and (365) must be 2β-methyl-2α-acetyl-A-nor-5α-cholestane (378) and that the product from the rearrangement of (372) must similarly be 2α-methyl-2β-acetyl-A-nor-5α-cholestane (379).

The aldehyde (375) was treated with methyl magnesium iodide to give a product identifiable as the two secondary alcohols (382) by i.r. and n.m.r. spectra (i.r. 3650, 1110, 1090 $cm.^{-1}$; n.m.r. τ methyl groups at 8.80, 8.86, 8.96). Treatment of this product with Jones' reagent then gave 2β-methyl-2α-acetyl-A-nor-5α-cholestane, showing that formation of the 2α-aldehyde had in fact taken place.

The rearrangement of the α- and β-epoxides (370) and (372) therefore both involve "axial" cleavage with concerted bond migration to the electron-deficient centre, and are thus uncomplicated examples of the tetrasubstituted-epoxide hypothesis of Hartshorn and Kirk.[56]



(383)



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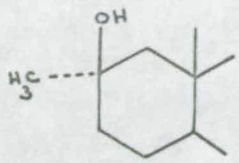

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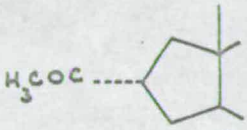

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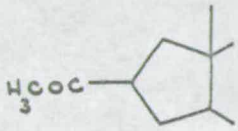

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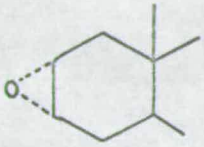

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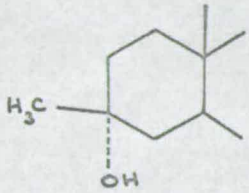

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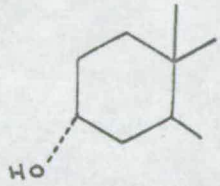

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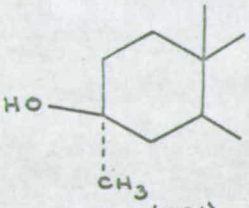

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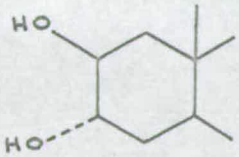

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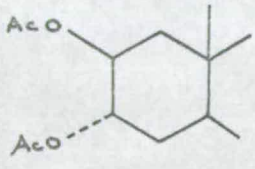

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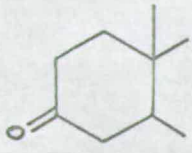

(394)

The reaction of 2α,3α-epoxy-5α-cholestane with methyl magnesium iodide

2β,3β-Epoxy-5α-cholestane (383) has been shown[50] to react with methyl magnesium iodide to give, as the main product, 2α-(1'-hydroxyethyl)-A-nor-5α-cholestane (384) (isolated as the two epimeric alcohols) along with a little 2α-methyl-2β-hydroxy-5α-cholestane (385). This was repeated here with similar results and the mixture of hydroxyethyl-A-nor-compounds (384) was oxidised with Jones' reagent to 2α-acetyl-A-nor-5α-cholestane (386) to give a comparison compound for the two 2-acetyl-A-nor-compounds (378) and (379) derived from the BF_3 reactions on the two 2,3-dimethyl-2,3-epoxy-5α-cholestanes (370) and (372). That only the 2α-acetyl-compound (386) had been isolated from the oxidation of (384), and not an equilibrium mixture of the 2α, (386), and 2β-, (387), -acetyl-compounds,[151] was confirmed by the melting point of the oxidation product, 78-80°, (lit.[151] m.p. for (386) 77-78°, and for the equilibrium mixture 67°[50,151]), and from its n.m.r. spectrum, τ 9.33, 9.27, 9.18, 9.09 (C-18, C-19 and side chain methyl groups) (lit.[151] value for the C-19 methyl group for (386) τ 9.27 and for (387) τ 9.42).

The reaction of methyl magnesium iodide with (383) doubtless involves epoxide rearrangement under the influence of magnesium iodide[150] to give a mixture of aldehyde and ketone which then reacts in the normal way with methyl magnesium iodide. It was therefore decided to carry out a similar reaction with 2α,3α-epoxy-5α-cholestane (388). Accordingly the α-epoxide (388) was prepared from 5α-cholest-2-ene on reaction with m-chloroperbenzoic acid in ether

and was treated with methyl magnesium iodide in ether. A crude product was obtained which was chromatographed on alumina. Elution with petrol-benzene (1:1) gave 3β-methyl-5α-cholestan-3β-ol (389), 37%, identified by a mixed melting point, i.r. spectrum and dehydration with phosphoryl chloride in pyridine to 3-methyl-5α-cholest-2-ene. Further elution with the same solvent gave 5α-cholestan-3α-ol (390), 11%, identified by a mixed melting point, i.r. spectrum and oxidation with Jones' reagent to 5α-cholestan-3-one. Elution with benzene-ether (9:1) gave 3α-methyl-5α-cholestan-3β-ol (391), 34%, identified by a mixed melting point, i.r. spectrum and dehydration with phosphoryl chloride in pyridine to 3-methylene-5α-cholestane. The last product from the column, eluted with chloroform, was shown to be 5α-cholestan-2β,3α-diol (392), 17%, by a comparison with a sample of that compound (392) formed by the treatment of the α-epoxide (388) with dilute sulphuric acid;[152] and by the formation, from both samples of the diol (392), of the 2β,3α-diol diacetate (393) by treatment with acetic anhydride in pyridine.

The 3α-alcohol (390) and 2β,3α-diol (392) can be assumed to be derived directly from the epoxide by cleavage; the alcohol (390) by reduction, since a little magnesium[153] remained after the formation of the Grignard reagent, and the diol (392) by hydrolysis, indicating the presence of a trace of moisture in the reaction mixture. The two tertiary alcohols, however, must result from magnesium iodide rearrangement of the 2α,3α-epoxide (388) to give 5α-cholestan-3-one (394), and this will involve C-2-O cleavage, i.e. "axial" cleavage[56] and a hydride shift to C-2. The remaining step in the reaction will then involve addition of methyl magnesium iodide to the 3-ketone (394).

EXPERIMENTAL

General Notes on Experimental Section

Melting points were determined on a Kofler block and are corrected. Optical rotations at 589 mμ were measured at room temperature on a Perkin Elmer 141 Polarimeter, for chloroform solutions in a 1 dm. cell. The concentration value quoted in brackets after each rotation is in g./100 ml. Infra-red spectra were recorded for carbon disulphide (unless otherwise stated) on either a Unicam SP200 spectrophotometer or a Perkin Elmer 237 spectrophotometer. Ultra violet spectra were recorded for ethanol solutions on a Unicam SP800 spectrophotometer. Nuclear magnetic resonance spectra were recorded for deuterochloroform solutions using tetramethylsilane as an internal standard on a Perkin Elmer R10 (60 mc/s) spectrometer. Rotatory dispersion measurements were recorded for chloroform solutions (unless otherwise stated), of concentration 1mg./ml., on a Bendix Ericsson Polarmatic 62 spectropolarimeter. G.L.C. analysis was carried out on either a Perkin Elmer model 801 gas chromatograph or a Perkin Elmer model F11 gas chromatograph (flame ionisation). For the Perkin Elmer 801 a column (6 ft. x 1/16 in.) of S.E. 30/Epon on A.W.-D.M.C.S. Chrom G (80-100 mesh) or E301 on A.W.-D.M.C.S. Chrom G (80-100 mesh) at temperatures of 240-255°, with an inlet heater at ca.270° and inlet pressures of nitrogen of 35 lb./sq.in., was used. For the Perkin Elmer F11 a column of E301 on A.W.-D.M.C.S. Chrom G (80-100 mesh) at a temperature of 250°, carrier gas N_2, was used.

Column chromatography was carried out by the method of Reichstein and Shoppee[84] and the activity of the alumina used was defined by the method of Brockmann and Schodder.[108] Alumina

(activity II) infers Peter Spence type 'H' alumina, activity II. 'Alumina' infers Spence type 'H' alumina treated with 5% (by volume) of 10% acetic acid, and was activity III.

m-Chloroperbenzoic acid was obtained as a gift from FMC International of New York. Epoxides rearrangements were carried out in dry benzene, using freshly distilled boron trifluoride-etherate. Quantities in brackets after 'sodium hydride' refer to the hydride free from mineral oil. Solutions were dried over magnesium sulphate. The petrol used had b.p. 60-80°.

Microanalyses were determined by Drs. Weiller and Strauss of Oxford.

The Preparation of Methylene-Epoxides

(1) Epoxides not adjacent to a polar group

5α-Cholestan-3β-ol[73]

Cholesterol (120 g.) in ethyl acetate, was reduced by catalytic hydrogenation over 10% palladium on charcoal catalyst, at 30° and 1 atmos. pressure. Perchloric acid (8 drops) was added as promoter. The acid was neutralised with sodium hydroxide, and the catalyst filtered off. The volume of solvent was reduced to give crystalline 5α-cholestan-3β-ol (91.2 g.) m.p. 141-2° (lit. 142°).

5α-Cholestan-3-one[74]

5α-Cholestan-3β-ol (30 g.) in acetone (2 l.) was oxidised with 8N chromic acid (Jones' reagent) (60 ml.). The reaction was allowed to proceed for 4 minutes and excess reagent was decomposed with methanol (200 ml.). Water (200 ml.) was added, the acetone removed under reduced pressure and the steroid extracted into ether. The ethereal solution was washed with dilute hydrochloric acid, with water, until the washings were neutral, and with saturated sodium chloride solution. The solution was dried and the solvent removed under reduced pressure to give 5α-cholestan-3-one, which was recrystallised from acetone (28.5 g.), m.p. 128-129° (lit. 129°), $[\alpha]_D$ + 44° (c 0.11) (lit. +43.5°).

2α-Methyl-5α-cholestan-3-one[75]

5α-Cholestan-3-one (8.2 g.) in dry benzene (100 ml.) was added over 1 hour to a stirred suspension of sodium methoxide (1.5 g.) in

dry benzene (80 ml.) and ethyl formate (11 ml.). After adding additional sodium methoxide (0.5 g.) and stirring for four hours the mixture was filtered and the solid washed with benzene and dried. The bright yellow salt so obtained was stirred 1 hour with a mixture of concentrated hydrochloric acid (8.5 ml.), water (65 ml.) and ethanol (20 ml.), filtered and washed with water until the washings were neutral to give 2-hydroxymethylene-5α-cholestan-3-one (7.9 g.) m.p. 166-168° (lit. 164-166°).

2-Hydroxymethylene-5α-cholestan-3-one (4 g.) in benzene (50 ml.) was added to 10% palladium on charcoal catalyst (2 g.) in ethanol (50 ml.) and the mixture was shaken in an atmosphere of hydrogen for two days. The catalyst was removed and the solvent evaporated to give a product which was chromatographed on alumina (activity II) (150 g.) to give on elution with petrol-benzene (1:1) 2α-methyl-5α-cholestan-3-one (2.2 g.) m.p. 119-120° (lit. 121°).

2,2-Dimethyl-5α-cholestan-3-one[76,77]

Potassium (12 g.) in t-butanol (300 ml.) was added to a boiling solution of 5α-cholestan-3-one (12 g.) in dry benzene (300 ml.) and t-butanol (150 ml.). Methyl iodide (90 ml.) in dry benzene (300 ml.) was added and the mixture refluxed for 1 hour. Ice and water were added and the steroid was extracted into ether which was washed with water, dried and evaporated to give a mixture of methylated ketones. Chromatography on alumina (activity II) (1000 g.) and elution with petrol-benzene (7:3) gave 2,2-dimethyl-5α-cholestan-3-one (8.2 g.) m.p. 99-101° (lit. 111-113°).

5α-Cholestan-3β-ol Tosylate[104]

5α-Cholestan-3β-ol (20 g.) was dissolved in pyridine (250 ml.) and cooled to 0°. This solution was added to a solution, also at 0°, of toluene-p-sulphonyl chloride (20 g.) in pyridine (100 ml.), and the mixture was left at 0° for 48 hours. Water (500 ml.) was added and the steroid was filtered off and washed well with water, dried, and recrystallised from ethanol to give 5α-cholestan-3β-ol tosylate (21 g.) m.p. 140-142° (lit.135°), ν_{max} 1189 and 1176 cm.$^{-1}$

5α-Cholest-2-ene[104]

5α-Cholestan-3β-ol tosylate (20 g.) was dissolved in petrol (100 ml.) and adsorbed on alumina (activity II) (800 g.). After 48 hours elution with petrol (2 l.) gave on crystallisation from acetone 5α-cholest-2-ene (10.6 g.) m.p. 74-75°, (lit. 75°), $\nu_{max.}$ 3010, 1655, 785, and 675 cm.$^{-1}$, n.m.r. τ 9.33 (C-18 methyl), 9.23, 9.18, 9.09 (C-19 and side chain methyls), 4.34 (shoulder at 4.39) (H-C=C-H). Chloroform-methanol (99:1) afforded 5α-cholestan-3α-ol (0.3 g.) m.p. 185-6° (lit.182°).

2β,3β-Epoxy-5α-cholestane

N-Bromosuccinimide (13.5 g.) in dioxan (150 ml.) and N perchloric acid (13.5 ml.) were added in succession to a solution of 5α-cholest-2-ene (27 g.) in 5% - aq. t-butanol (600 ml.) and dioxan (300 ml.) at room temperature. After keeping at room temperature overnight, the solution was concentrated *in vacuo* below 45° to remove most of the solvent, water was added and the steroid extracted with ether. The ether extract was washed with water, potassium iodide

solution, sodium bisulphite solution, and water, dried and evaporated to give crude 3α-bromo-5α-cholestan-2β-ol (21.6 g.) which was chromatographed on alumina (500 g.) to give on elution with petrol 2β,3β-epoxy-5α-cholestane (16.2 g.) m.p. 90-91° (lit.[8] 89-91°), $\nu_{max.}$ 825 and 818 $cm.^{-1}$; n.m.r. τ 9.36 (C-18 methyl group), 9.18, 9.15, 9.09 (side chain and C-19 methyl groups) and 6.87 (center) (epoxide protons).

5α-Cholestan-2β-ol[78a]

2β,3β-Epoxy-5α-cholestane (5.0 g.) in dry ether (50 ml.) was added to lithium aluminium hydride (3 g.) in dry ether (100 ml.) and the solution refluxed for 2 hours. Ethyl acetate was added, followed by dilute hydrochloric acid. The ethereal solution was washed with water, dried and evaporated to give a white solid which on crystallisation from acetone gave 5α-cholestan-2β-ol (4.8 g.) m.p. 152-155° (lit. 153-5°) $\nu_{max.}$ 3560 and 1015 $cm.^{-1}$

5α-Cholestan-2-one[78b]

5α-Cholestan-2β-ol (10 g.) was dissolved in acetone (600 ml.) and 8N.chromic acid (20 ml.) added with stirring. Stirring was continued for 4 minutes and methanol (50 ml.) added, followed by water. The organic solvents were distilled off and the steroid was extracted into ether. The ether solution was washed with dilute hydrochloric acid and water until the washings were neutral, dried and evaporated to give on crystallisation from acetone 5α-cholestan-2-one (8.9 g.) m.p. 129-131° (lit. 131°), $\nu_{max.}$ 1710 $cm.^{-1}$

Methyltriphenylphosphonium bromide[118]

Triphenylphosphine (100 g.) in benzene (500 ml.) was cooled to ca.-10° with a salt-ice bath and methyl bromide (50 g.) was added. The mixture was allowed to stand at room temperature and after two days the precipitate was filtered off, washed with benzene and dried to give methyltriphenylphosphonium bromide (105 g.) m.p. 227-229° (lit. 227-229°).

General Method for the Methylenetriphenylphosphorane Reaction[79]

Sodium hydride (7.8 mmoles) (50% dispersion in oil) was washed three times with dry petrol and then blown dry with nitrogen. Dry dimethyl sulphoxide (20 ml.) was added and the mixture was heated with stirring under nitrogen at 70-75° until evolution of hydrogen ceased (ca.45 min.). The resulting solution of methylsulphinyl carbanion was cooled and equal volumes (10 ml.) of tetrahydrofuran (distilled from calcium hydride) and dry dimethyl sulphoxide were added. To this solution at 0° was added, under nitrogen, methyltriphenylphosphonium bromide (7.8 mmoles), rapid stirring producing a deep yellow solution of methylenetriphenylphosphorane. The appropriate steroid ketone (2.6 mmoles) in dry tetrahydrofuran (10 ml.) was added to the ylide solution and stirring was continued for 12 hours at 60°. Water was then added and the steroid was extracted with ether. The ether solution was washed with water, dried and evaporated to give a crude product which was chromatographed on alumina (activity II) (100 g.) to give on elution with petrol the methylene-steroid which was crystallised from acetone. By this method was prepared:

3-Methylene-5α-cholestane[119] from 5α-cholestan-3-one (10 g.)

(9.1 g.) m.p. 65-66°, $[\alpha]_D$ +22° (c.0.2) (lit., m.p. 64-65°, $[\alpha]_D$ +24°), $\nu_{max.}$ 3070, 1650, 888 cm.$^{-1}$ n.m.r. τ 9.34 (C-18 methyl), 9.18, 9.16, 9.1 (side chain and C-19 methyl groups), 5.43 ($CH_2=\overset{|}{C}-$)

3-Methylene-2α-methyl-5α-cholestane from 2α-methyl-5α-cholestan-3-one (1.0 g.).

Yield of 3-methylene-2α-methyl-5α-cholestane (0.86 g.) m.p. 68-70° $[\alpha]_D$ +17° (c. 0.23), $\nu_{max.}$ 3060, 1645, 890 cm.$^{-1}$ n.m.r. τ 9.33 (C-18 methyl group), 9.18, 9.10, 9.05, 8.93 (C-19, C-2, and side chain methyl groups), 5.36, 5.47 (exocyclic methylene group) (Found: C, 87.6; H, 12.5. $C_{29}H_{50}$ requires C, 87.4; H, 12.6%).

3-Methylene-2,2-dimethyl-5α-cholestane from 2,2-dimethyl-5α-cholestan-3-one (1.0 g.).

Yield of 3-methylene-2,2-dimethyl-5α-cholestane (0.79 g.) m.p. 79-80° $[\alpha]_D$ +53° (c.0.20), $\nu_{max.}$ 3060, 1640, 885 cm.$^{-1}$ n.m.r. τ 9.35 (C-18 methyl group), 9.18, 9.09 (side chain methyl groups), 9.04, 8.93, 8.90 (C-19 and C-2 methyl groups), 5.37 (exocyclic methylene group). (Found: C, 86.9; H, 12.3. $C_{30}H_{52}$ requires C, 87.3; H, 12.7%).

2-Methylene-5α-cholestane[120] from 5α-cholestan-2-one (1.0 g.).

(0.83 g.) m.p. 65-67° (lit. 65-67°), $\nu_{max.}$ 3040, 1645, 895 cm.$^{-1}$ n.m.r. τ 9.33 (shoulder 9.35), 9.19, 9.10, 8.76 (methyl signals), 5.41 (centre) (exocyclic methylene group).

17-Methylene-5α-androstane from 5α-androstan-17-one (1.0 g.)

(0.74 g.) m.p. 67-68°, $[\alpha]_D$ +8° (c.0.15), $\nu_{max.}$ 3060, 1650, 882 cm.$^{-1}$ n.m.r. τ 9.24, 9.21 (C-18 and C-19 methyl groups), 5.36

(center) (exocyclic methylene group). (Found: C, 88.2; H, 11.6. $C_{20}H_{32}$ requires C, 88.2; H, 11.8%).

Trimethyloxosulphonium iodide.[4]

A solution of dimethyl sulphoxide (32 g.) and methyl iodide (60 ml.) were refluxed for 3 days during which time a solid precipitated. The solid was filtered off, washed with chloroform and dried to give trimethyloxosulphonium iodide (50 g.), m.p. 237°.

Trimethylsulphonium iodide[4]

Dimethyl sulphide (30 g.) and methyl iodide (75 g.) were mixed together and allowed to stand at room temperature overnight. The resulting salt was washed well with chloroform and dried, yield (100 g.).

p-Nitroperbenzoic Acid[85]

A slurry of p-nitrobenzoic acid (40 g.) in methanesulphonic acid (116 g.) was stirred at 0° while hydrogen peroxide (87%, 35 ml.) was added over 10 minutes. The temperature rose to 35° during the addition, and the slurry was stirred at 40° for 3 hours. Ice was then added, and water before the mixture was filtered and the solid material washed with water. The peracid was dried over phosphorus pentoxide to constant weight, (40.2 g.).

The purity of this peracid was determined by reacting a known weight (0.25 g.) of acid with sodium iodide in acetic acid-chloroform (3:2). Water was added and the liberated iodine titrated with standard sodium thiosulphate solution (0.1N). The product was found to contain 97% peracid.

General Method for the Dimethyloxosulphonium Methylide Reaction[4]

Sodium hydride (6 mmoles) (50% dispersion in oil) was washed three times with dry petrol and then blown dry with nitrogen. Powdered trimethyloxosulphonium iodide (5.5 mmoles) and dry dimethyl sulphoxide (20 ml.) were then added and the mixture was stirred rapidly. Vigorous evolution of hydrogen ensued which ceased after ca.30 minutes to give a milky-white reaction mixture. The steroid ketone (2.6 mmoles) in dry tetrahydrofuran (10 ml.) and dry dimethyl sulphoxide (5 ml.) was added with stirring and stirring was continued for 1 hour at room temperature and for 1 hour at 50°. The reaction mixture was cooled, water added and the steroid extracted into ether. The ether solution was washed well with water, dried and evaporated to give the mixture of methylene epoxides which was then either recrystallised to give the major epoxide or chromatographed on alumina (50 g.) to give both epoxides followed by crystallisation of each epoxide from acetone.

Reaction with 5α-cholestan-3-one (1.0 g.)

a) The product was recrystallised from acetone to give 3β-methyl-3α,3'-epoxy-5α-cholestane (0.761 g.) m.p. 131-2° $[\alpha]_D$ +20° (c.0.21), $\nu_{max.}$ 3010 (w), 925 (s), 790 (m), 698 (w) $cm.^{-1}$ n.m.r. τ 9.33 (C-18 methyl group), 9.17, 9.16, 9.09 (C-19 and side chain methyl groups), and 7.38 (half band width 0.012 ppm.) (epoxide protons) (Found: C, 83.8; H, 11.8. $C_{28}H_{48}O$ requires C, 83.9; H, 12.1%).

b) The product on chromatography gave 3β-methyl-3α,3'-epoxy-5α-cholestane (0.760 g.) m.p. and m.m.p. 130-1°, followed by 3α-methyl-3β,3'-epoxy-5α-cholestane (0.027 g.) m.p. 170-1° $[\alpha]_D$ +20° (c.0.15)

$\nu_{max.}$ 3010 (w), 935 (m), 840 (s, broad), 723 (w) cm.$^{-1}$ n.m.r. τ 9.34 (C-18 methyl group), 9.20, 9.14, 9.09 (C-19 and side chain methyls), 7.44 (half band width 0.03 ppm.) (epoxide protons). (Found: C, 83.8; H, 11.9. $C_{28}H_{48}O$ requires C, 83.9; H, 12.1%).

Reaction with 2α-methyl-5α-cholestan-3-one (0.90 g.)

Chromatography gave 3β-methyl-3α,3'-epoxy-2α-methyl-5α-cholestane (0.736 g.) m.p. 111-112° $[\alpha]_D$ +27° (c.0.22) $\nu_{max.}$ 3020 (w), 942 (s), 788 (m), 698 (w) cm.$^{-1}$, n.m.r. τ 9.34 (C-18 methyl group), 9.38, 9.26, 9.18, 9.15, 9.10 (C-19, C-2, and side chain methyl groups), 7.59, 7.52, 7.22, 7.15 (epoxide protons). (Found: C, 83.9; H, 12.5. $C_{29}H_{50}O$ requires C, 84.0; H, 12.2%), and 3α-methyl-3β,3'-epoxy-2α-methyl-5α-cholestane (0.021 g.) m.p. 81-82° $[\alpha]_D$ +3° (c.0.20), $\nu_{max.}$ 3020 (w), 939 (m), 839 (s, broad), 690 (w) cm.$^{-1}$, n.m.r. τ 9.33 (C-18 methyl group), 9.38, 9.25, 9.18, 9.09 (C-19, C-2, and side chain methyl groups), 7.66, 7.58, 7.26, 7.18 (epoxide protons). (Found: C, 84.1; H, 12.0. $C_{29}H_{50}O$ requires C, 84.0; H, 12.2%).

Reaction with 2,2-dimethyl-5α-cholestan-3-one (0.80 g.)

The compounds eluted were 3β-methyl-3α,3'-epoxy-2,2-dimethyl-5α-cholestane (0.495 g.) m.p. 94-95° $[\alpha]_D$ +55° (c.0.17), $\nu_{max.}$ 3020 (w), 930 (s), 780 (m) cm.$^{-1}$, n.m.r. τ 9.34 (C-18 methyl group), 9.30, 9.18, 9.09, 9.07, 8.89 (C-19, C-2 and side chain methyls), 7.60, 7.53, 7.28, 7.20 (epoxide protons). (Found: C, 83.8; H, 12.0. $C_{30}H_{52}O$ requires C, 84.0; H, 12.2%), and 3α-methyl-3β,3'-epoxy-2,2-dimethyl-5α-cholestane (0.036 g.) m.p. 78-80° $[\alpha]_D$ +39° (c.0.21), $\nu_{max.}$ 3020 (w), 918 (m), 851 (s, broad, with a shoulder at 840) cm.$^{-1}$, n.m.r. τ 9.34 (C-18 methyl group), 9.31, 9.19, 9.09,

9.05, 8.89 (C-19, C-2, and side chain methyls), 7.63, 7.55, 7.18, 7.10 (epoxide protons). (Found: C, 84.0; H, 12.1. $C_{30}H_{52}O$ requires C, 84.0; H, 12.2%).

Reaction with 5α-cholestan-2-one (0.910 g.)

The product on chromatography gave 2α-methyl-2β,2'-epoxy-5α-cholestane (0.717 g.) m.p. 96-98° $[\alpha]_D$ +24° (c.0.19), $\nu_{max.}$ 3020 (w), 912 (s), 795 (m) $cm.^{-1}$ n.m.r. τ 9.35 (C-18 methyl group), 9.19, 9.09, 9.07 (C-19 and side chain methyl groups), 7.54 (half band width 0.015 ppm.) (epoxide protons). (Found: C, 84.1; H, 12.3. $C_{28}H_{48}O$ requires C, 83.9; H, 12.1%), and 2β-methyl-2α,2'-epoxy-5α-cholestane (0.010 g.) m.p. 105-106° $[\alpha]_D$ +20° (c,0.066), $\nu_{max.}$ 3015 (w), 942 (m), 822 (s, broad) $cm.^{-1}$ n.m.r. τ 9.35 (C-18 methyl group), 9.19, 9.14, 9.09 (C-19 and side chain methyl groups), 7.37 (half band width 0.033 ppm.) (epoxide protons). (Found: C, 83.9; H, 11.9. $C_{28}H_{48}O$ requires C, 83.9; H, 12.1%).

Reaction with 5α-androstan-17-one (0.770 g.)

Chromatography gave 17α,20-epoxy-5α-androstane (0.121 g.) m.p. 88-89° $[\alpha]_D$ -9° (c.0.06) $\nu_{max.}$ 3020, 939, 835, 760 $cm.^{-1}$ n.m.r. τ 9.19 (C-18 and C-19 methyl groups), 7.39, 7.30, 7.29, 7.20 (epoxide protons). (Found: C, 83.1; H, 11.0. $C_{20}H_{32}O$ requires C, 83.3; H, 11.2%), and 17β,20-epoxy-5α-androstane (0.585 g.) m.p. 160-4° $[\alpha]_D$ +5° (c.0.21), $\nu_{max.}$ 3010, 919, 861, 786 $cm.^{-1}$ n.m.r. τ 9.22, 9.14 (C-18 and C-19 methyl groups) 7.47, 7.38, 7.15, 7.06 (epoxide protons). (Found: C, 83.0; H, 11.1. $C_{20}H_{32}O$ requires C, 83.3, H, 11.2%).

General Method for the Dimethylsulphonium Methylide Reaction[4]

Sodium hydride (6 mmoles) (50% dispersion in oil) was washed three times with dry petrol and blown dry with nitrogen. Dry dimethyl sulphoxide (15 ml.) was added and the mixture was heated with stirring under nitrogen at ca.70° until evolution of hydrogen ceased (ca.45 min.). Dry tetrahydrofuran (15 ml.) was added and the mixture was cooled to ca.-10° (salt-ice bath) and powdered trimethylsulphonium iodide (5.8 mmoles) was added with stirring quickly and stirring was continued for 10 seconds and then the steroid ketone (2.6 mmoles) in dimethyl sulphoxide (5 ml.) and tetrahydrofuran (10 ml.) was added with stirring and stirring was continued for 10 minutes at -10° and for 1 hour with the salt-ice bath removed. Water was added and the steroid was extracted with ether. The ethereal solution was washed well with water, dried and the ether evaporated to give the methylene epoxides (except for 5α-androstan-17-one) which were separated by chromatography on alumina (50 g.) with petrol as solvent. The epoxides were then crystallised from acetone and identified by infrared examination and mixed m.p.

Reaction with 5α-cholestan-3-one (1.07 g.)

Eluted first was 3β-methyl-3α,3'-epoxy-5α-cholestane (0.311 g.), m.p. and mixed m.p. 129-131°, and this was followed by 3α-methyl-3β,3'-epoxy-5α-cholestane (0.686 g.), m.p. and mixed m.p. 170-1°.

Reaction with 2α-methyl-5α-cholestan-3-one (1.0 g.)

Isolated were 3β-methyl-3α,3'-epoxy-2α-methyl-5α-cholestane (0.31 g.) mixed m.p. 111-112°, and 3α-methyl-3β,3'-epoxy-2α-methyl-5α-cholestane (0.101 g.) mixed m.p. 80-2°.

Reaction with 2,2-dimethyl-5α-cholestan-3-one (1.01 g.)

The compounds in order of elution were 3β-methyl-3α,3'-epoxy-2,2-dimethyl-5α-cholestane (0.53 g.) mixed m.p. 91-4°, and 3α-methyl-3β,3'-epoxy-2,2-dimethyl-5α-cholestane (0.35 g.) mixed m.p. 78-80°.

Reaction with 5α-cholestan-2-one (0.9 g.)

Eluted were 2α-methyl-2β,2'-epoxy-5α-cholestane (0.514 g.) m.p. and mixed m.p. 96-98°, and 2β-methyl-2α,2'-epoxy-5α-cholestane (0.166 g.) m.p. and mixed m.p. 103-106°.

Reaction with 5α-androstan-17-one (0.22 g.)

Crystallised was 17β,20-epoxy-5α-androstane (0.178 g.) mixed m.p. 160-163°.

Epoxidation with p-Nitroperbenzoic Acid

To 3-methylene-5α-cholestane (1.0 g.) in dry ether (20 ml.) was added p-nitroperbenzoic acid (0.9 g.) in dry ether (20 ml.). The ethereal solution was allowed to stand overnight at room temperature and then excess peracid was destroyed with ferrous sulphate solution. The ether layer was then washed with water, sodium bicarbonate solution, and water, dried and the solvent evaporated to give the crude epoxides. Chromatography on alumina (50 g.) gave on elution with petrol 3β-methyl-3α,3'-epoxy-5α-cholestane (0.74 g.) mixed m.p. 130-1° (acetone) and 3α-methyl-3β,3'-epoxy-5α-cholestane (0.13 g.) mixed m.p. 169-171° (acetone).

Epoxidation with m-Chloroperbenzoic Acid

To the appropriate olefin (2.6 mmoles) in dry ether (20 ml.) was added m-chloroperbenzoic acid (5 mmoles) in dry ether (20 ml.).

After standing overnight at room temperature the reaction mixed was worked up with ferrous sulphate solution, water, and sodium bicarbonate solution as above. The mixtures of epoxides were chromatographed on alumina (60 g.) with petrol as solvent. The epoxides were crystallised from acetone and identified by mixed m.p. and i.r. examination.

A similar procedure was used for the epoxidation in methylene chloride.

Epoxidation of 3-methylene-5α-cholestane

a) In ether (4.5 g. steroid). Chromatography gave 3β-methyl-3α,3'-epoxy-5α-cholestane (3.41 g.) mixed m.p. 129-130° and 3α-methyl-3β,3'-epoxy-5α-cholestane (0.60 g.) mixed m.p. 170-3°.

b) In methylene chloride (1.0 g. steroid). Eluted first was 3β-methyl-3α,3'-epoxy-5α-cholestane (0.427 g.) mixed m.p. 129-131°, and this was followed by 3α-methyl-3β,3'-epoxy-5α-cholestane (0.241 g.) mixed m.p. 170-4°.

Epoxidation of 3-methylene-2α-methyl-5α-cholestane (0.25 g.)

The yield of 3β-methyl-3α,3'-epoxy-2α-methyl-5α-cholestane was (0.108 g.), mixed m.p. 110-112° and that of 3α-methyl-3β,3'-epoxy-2α-methyl-5α-cholestane (0.064 g.) mixed m.p. 80-82°.

Epoxidation of 3-methylene-2,2-dimethyl-5α-cholestane (0.70 g.)

Eluted were 3β-methyl-3α,3'-epoxy-2,2-dimethyl-5α-cholestane (0.40 g.) mixed m.p. 91-94°, a fraction consisting of both epoxides (i.r.) (0.026 g.) and 3α-methyl-3β,3'-epoxy-2,2-dimethyl-5α-cholestane (0.090 g.) mixed m.p. 78-80°.

Epoxidation of 2-methylene-5α-cholestane (0.70 g.)

Eluted were 2α-methyl-2β,2'-epoxy-5α-cholestane (0.104 g.) mixed m.p. 95-97°, and 2β-methyl-2α,2'-epoxy-5α-cholestane (0.461 g.) mixed m.p. 104-105°.

Epoxidation of 17-methylene-5α-androstane (0.24 g.)

Chromatography gave 17α,20-epoxy-5α-androstane (0.136 g.) mixed m.p. 88-89°, and 17β,20-epoxy-5α-androstane (0.024 g.) mixed m.p. 156-160°.

Epoxidation with Alkaline Hydrogen Peroxide-Benzonitrile[3]

The appropriate olefin (1.3 mmoles) in chloroform (5 ml.) was added to methanol (5 ml.), benzonitrile (0.35 g.), potassium bicarbonate (0.075 g.), and hydrogen peroxide (30%, 0.4 ml.) and the mixture was stirred at room temperature for 24 hours. Ether and water were then added and the ether solution was washed with ferrous sulphate solution, water, sodium bicarbonate solution, and water, dried and the ether removed to give a crude product which was chromatographed on alumina (40 g.) with petrol as solvent. The compounds so eluted were crystallised from acetone and identified from their i.r. spectra and by a mixed m.p.

Epoxidation of 3-methylene-5α-cholestane (0.9 g.)

Chromatography gave 3-methylene-5α-cholestane (0.103 g.) mixed m.p. 64-65°, 3β-methyl-3α,3'-epoxy-5α-cholestane (0.137 g.) mixed m.p. 129-130°, and 3α-methyl-3β,3'-epoxy-5α-cholestane (0.391 g.) mixed m.p. 170-174°.

Epoxidation of 3-methylene-2α-methyl-5α-cholestane (1.54 g.)

Elution gave 3-methylene-2α-methyl-5α-cholestane (0.218 g.) mixed m.p. 69-71°, 3β-methyl-3α,3'-epoxy-2α-methyl-5α-cholestane (0.086 g.) mixed m.p. 111-112°, 3α-methyl-3β,3'-epoxy-2α-methyl-5α-cholestane (1.09 g.) mixed m.p. 79-81°.

Epoxidation of 3-methylene-2,2-dimethyl-5α-cholestane (0.52 g.)

Chromatography produced 3-methylene-2,2-dimethyl-5α-cholestane (0.14 g.) mixed m.p. 79-80°, 3β-methyl-3α,3'-epoxy-2,2-dimethyl-5α-cholestane (0.088 g.) mixed m.p. 92-95° and 3α-methyl-3β,3-epoxy-2,2-dimethyl-5α-cholestane (0.163 g.) mixed m.p. 76-79°.

Epoxidation of 2-methylene-5α-cholestane (0.89 g.)

Elution gave 2-methylene-5α-cholestane (0.228 g.) mixed m.p. 65-67° and 2β-methyl-2α,2'-epoxy-5α-cholestane (0.322 g.) mixed m.p. 105-106°.

Epoxidation of 17-methylene-5α-androstane (0.23 g.)

Chromatography gave 17-methylene-5α-androstane (0.076 g.) mixed m.p. 67-68°, 17α,20-epoxy-5α-androstane (0.092 g.) mixed m.p. 88-89° and 17β,20-epoxy-5α-androstane (0.002 g.) mixed m.p. 160-4°.

General Method for Reaction with Methyl Magnesium Iodide

The steroid ketone (1 g.) in dry ether (50 ml.) was added to methyl magnesium iodide in ether (100 ml.) (from magnesium (2 g.)) and the mixture was heated under reflux for 4 hours. Excess reagent was decomposed with ammonium chloride solution and the steroid was extracted with ether. The ether solution was washed with water, dried and the ether evaporated to give a solid which was adsorbed

from petrol on alumina (60 g.). The alcohols were eluted with suitable solvents and were crystallised from acetone.

Reaction with 5α-cholestan-3-one (5 g.)[82]

Elution with petrol-benzene (1:1) and benzene gave 3β-methyl-5α-cholestan-3α-ol (2.75 g.) m.p. 125-126° (lit.126-127°). Elution with ether gave 3α-methyl-5α-cholestan-3β-ol (2.09 g.) m.p. 146-148° (lit.147-9°).

Reaction with 2α-methyl-5α-cholestan-3-one (0.9 g.)

Elution with petrol-benzene (1:1) and benzene gave 2α,3β-dimethyl-5α-cholestan-3α-ol (0.530 g.) m.p. 147-148° $[\alpha]_D$ +27.5° (c.0.25) $\nu_{max.}$ 3600, 940, 955 cm.$^{-1}$ (Found: C, 83.7; H, 12.4. $C_{29}H_{52}O$ requires C, 83.6; H, 12.6%). Elution with benzene-ether (99:1) gave 2α,3α-dimethyl-5α-cholestan-3β-ol (0.135 g.) m.p. 158-160° $[\alpha]_D$ +19° (c.0.11) $\nu_{max.}$ 3600, 938 cm.$^{-1}$ (Found: C, 83.4; H, 12.4. $C_{29}H_{52}O$ requires C, 83.6,; H, 12.6%).

Reaction with 2,2-dimethyl-5α-cholestan-3-one (2.0 g.)

Elution with benzene-ether (99:1) gave 2,2,3β-trimethyl-5α-cholestan-3α-ol (0.851 g.) m.p. 105-106° $[\alpha]_D$ +48° (c.0.19) $\nu_{max.}$ 3590, 940, 925, 918, and 845 cm.$^{-1}$ (Found: C, 83 8; H, 12.2. $C_{30}H_{54}O$ requires C, 83.7; H, 12.6%). Elution with ether-methanol (99:1) gave 2,2,3α-trimethyl-5α-cholestan-3β-ol (0.825 g.) m.p. 139-140° $[\alpha]_D$ +45.5° (c.0.21) $\nu_{max.}$ 3580, 935, and 920 cm.$^{-1}$ (Found: C, 83.7; H, 12.4. $C_{30}H_{54}O$ requires C, 83.7; H, 12.6%).

General Method for Lithium Aluminium Hydride Reduction of the Methylene Epoxides

The epoxide (0.1 g.) in dry ether (10 ml.) was added to lithium aluminium hydride (0.1 g.) in dry ether (10 ml.) and the solution refluxed for 2 hours. Ethyl acetate was added, followed by dilute hydrochloric acid. The ether solution was washed with water, dried and evaporated to give the alcohol which was crystallised from acetone and identified by i.r. and a mixed m.p.

Reduction of 3β-methyl-3α,3'-epoxy-5α-cholestane (0.1 g.)

Produced 3β-methyl-5α-cholestan-3α-ol (0.08 g.) m.p. and mixed m.p. 126-127°.

Reduction of 3α-methyl-3β,3'-epoxy-5α-cholestane (0.1 g.)

Produced 3α-methyl-5α-cholestan-3β-ol (0.091 g.) m.p. and mixed m.p. 146-149°.

Reduction of 3β-methyl-3α,3'-epoxy-2α-methyl-5α-cholestane (0.11 g.)

Gave 2α,3β-dimethyl-5α-cholestan-3α-ol (0.073 g.) m.p. and mixed m.p. 147-148°.

Reduction of 3α-methyl-3β,3'-epoxy-2α-methyl-5α-cholestane (0.07 g.)

Gave 2α,3α-dimethyl-5α-cholestan-3β-ol (0.063 g.) m.p. and mixed m.p. 158-160°.

Reduction of 3β-methyl-3α,3'-epoxy-2,2-dimethyl-5α-cholestane (0.067 g

Produced 2,2,3β-trimethyl-5α-cholestan-3α-ol (0.054 g.) m.p. and mixed m.p. 104-106°.

Reduction of 2α-methyl-2β,2'-epoxy-5α-cholestane (0.324 g.)

Gave 2α-methyl-5α-cholestan-2β-ol (0.297 g.) m.p. and mixed m.p. 147-148°.

General method for Dehydration with Phosphoryl Chloride in Pyridine

The steroid alcohol (0.08 g.) in pyridine (4 ml.) was heated under reflux with phosphoryl chloride (0.8 ml.) for 30 minutes. Decomposition of the excess reagent with water and extraction with ether gave, after washing the ether solution with water and drying, a solid which was adsorbed from petrol on alumina (activity II) (20 g.). Elution with petrol gave the olefin which was crystallised from acetone.

Dehydration of 3β-methyl-5α-cholestan-3α-ol (0.08 g.)

Gave 3-methyl-5α-cholest-2-ene (0.051 g.) m.p. 82-83° (lit.[82] 82-83°), $\nu_{max.}$ 790 cm.$^{-1}$ (double bond).

Dehydration of 3α-methyl-5α-cholestan-3β-ol (0.08 g.)

Gave 3-methylene-5α-cholestane (0.048 g.) m.p. and mixed m.p. 64-65°.

Dehydration of 2α,3β-dimethyl-5α-cholestan-3α-ol (1.0 g.)

Gave 2,3-dimethyl-5α-cholest-2-ene (0.823 g.) m.p. 83-85° (lit.[90] 86.5-88°) n.m.r. τ 9.34 (C-18 methyl group), 9.32, 9.18, 9.1 (C-19 and side chain methyl groups), 8.43 (C-2 and C-3 methyls).

Dehydration of 2α,3α-dimethyl-5α-cholestan-3β-ol (0.15 g.)

Gave 3-methylene-2α-methyl-5α-cholestane (0.098 g.) m.p. and mixed m.p. 68-71°.

Dehydration of 2,2,3β-trimethyl-5α-cholestan-3α-ol (0.2 g.)

Gave a product $\nu_{max.}$ 1640, 885, 830 cm.$^{-1}$ n.m.r. 9.34 (C-18 methyl group), 9.20, 9.1, 9.05, 9.01, 8.95, 8.90 (methyl signals), 5.46 (exocyclic methylene group). The melting point on repeated crystallisation from acetone, 60-75°.

Dehydration of 2,2,3α-trimethyl-5α-cholestan-3β-ol (0.2 g.)

Gave 3-methylene-2,2-dimethyl-5α-cholestane (0.154 g.) m.p. and mixed m.p. 78-80°.

2,2,3-Trimethyl-5α-cholest-3-ene.

2,2,3β-Trimethyl-5α-cholestan-3α-ol (0.2 g.) in acetic acid (30 ml.) plus perchloric acid (3 drops) was heated at 90° for 2 hours. Most of the solvent was removed under reduced pressure and water was added. The steroid was extracted with ether and the ether solution was washed with water, dried and the ether removed to give 2,2,3-trimethyl-5α-cholest-3-ene (0.133 g.) m.p. 99-102° (acetone) $[\alpha]_D$ +15° (c.0.16) $\nu_{max.}$ 840 (broad) cm.$^{-1}$ n.m.r. τ 9.33 (C-18 methyl group), 9.21, 9.18, 9.09, 9.05, 8.98 (methyls at C-19, C-2, and in the side chain), 8.38 (C-3 methyl), 4.5 (C-4 proton). (Found: C, 87.2; H, 13.0. $C_{30}H_{52}$ requires C, 87.3; H, 12.7%).

Addition of hypochlorous acid to 3-methylene-5α-cholestane[87]

3-Methylene-5α-cholestane (1 g.) in ether (50 ml.) and water (60 ml.) was stirred strongly at room temperature with bleaching powder (1 g.) for 5 minutes. Then acetic acid (0.7 ml.) was added and the mixture was stirred for a further 25 minutes. Ether (200 ml.) was added and the ether layer was washed with water, potassium

iodide solution, sodium bisulphite solution and water, dried and the ether removed to give the product which was adsorbed from petrol on florisil (100 g.). Elution with petrol gave 3-chloromethyl-3-chloro-5α-cholestone (0.31 g.) m.p. 108-9° (acetone) $[\alpha]_D$ +27° (c.0.16), ν_{max} 770 and 730 cm.$^{-1}$ n.m.r. τ 9.33 (C-18 methyl group), 9.22, 9.18, 9.15, 9.09 (C-19 and side chain methyls), 6.26 (-C$\underline{H}_2$.Cl). (Found: C, 74.1; H, 10.3; Cl, 15.4. $C_{28}H_{48}Cl_2$ requires C, 73.8; H, 10.6; Cl, 15.6%). Elution with petrol-benzene (1:1) gave 3α-chloromethyl-5α-cholestan-3β-ol (semi-solid) (0.17 g.) $\nu_{max.}$ 3560, 759, 740 cm.$^{-1}$ and elution with ether gave 3β-hydroxymethyl-3α-chloro-5α-cholestane (0.300 g.) m.p. 128-131° $[\alpha]_D$ +26° (c.0.16) $\nu_{max.}$ 3560, 1050, 770, 740 cm.$^{-1}$ (Found: C, 76.6; H, 11.0; Cl, 8.4. $C_{28}H_{49}OCl$ requires C, 77.0; H, 11.3; Cl, 8.1%).

3α-Chloromethyl-5α-cholestan-3β-ol (0.05 g.) was treated with acetic anhydride (0.3 ml.) in pyridine (5 ml.) and allowed to stand at room temperature for 24 hours. The solution was poured into water and the steroid extracted into ether. The ether solution was washed well with water and the solution dried and evaporated to give 3α-chloromethyl-5α-cholestan-3β-ol (0.046 g.), identified by i.r. spectra examination.

3β-Hydroxymethyl-3α-chloro-5α-cholestane (0.05 g.) was treated with acetic anhydride (0.3 ml.) in pyridine (5 ml.) and allowed to stand at room temperature for 2 days before being worked up as above to give a product consisting of an acetate $\nu_{max.}$ 1740 and 1235 cm.$^{-1}$ and starting material (not fully separated by chromato-

graphy on silica gel and elution with benzene).

Cleavage of 3α-methyl-3β,3'-epoxy-5α-cholestane with hydrogen chloride

3α-Methyl-3β,3'-epoxy-5α-cholestane (0.08 g.) in dry chloroform (25 ml.) was treated with a stream of hydrogen chloride gas at room temperature for 5 minutes, and allowed to stand for 10 minutes. The chloroform solution was washed with water, sodium carbonate solution and water, dried and evaporated to give 3β-hydroxymethyl-3α-chloro-5α-cholestane (0.06 g.), m.p. and mixed m.p. 128-130° (acetone).

Reactions of the chloro-compounds with sodium hydroxide in methanol

3α-Chloromethyl-5α-cholestan-3β-ol (0.05 g.) was refluxed for six hours with sodium hydroxide (0.1 g.) in methanol (25 ml.). The solution was poured into water and the suspension obtained extracted into ether. The ether layer was washed with water, dried and the solvent removed to give on crystallisation from acetone 3α-methoxymethyl-5α-cholestan-3β-ol (0.03 g.) m.p. 96-97° $[\alpha]_D$ +27° (c.0.07) $\nu_{max.}$ 3540 and 1118 cm.$^{-1}$ n.m.r. τ 9.38 (C-18 methyl group), 9.21, 9.09 (C-19 and side chain methyl groups), 6.75 (2 protons, $C\underline{H}_2OMe$) and 6.66 (3 protons, methoxy methyl group). (Found: C, 80.2; H, 12.0. $C_{29}H_{52}O_2$ requires C, 80.5; H, 12.1%). When 3β-hydroxymethyl-3α-chloro-5α-cholestane (0.1 g.) was similarly treated with sodium hydroxide (0.5 g.) in methanol (100 ml.) it gave 3α-methoxymethyl-5α-cholestan-3β-ol (0.073 g.) m.p. and mixed m.p. 96-97° (acetone). Attempted acetylation of 3α-methoxymethyl-

5α-cholestan-3β-ol with pyridine-acetic anhydride at room temperature overnight gave back 3α-methoxymethyl-5α-cholestan-3β-ol, identified by an i.r. spectra examination.

Cleavage of 3α-methyl-3β,3'-epoxy-5α-cholestane with sodium hydroxide in methanol

3α-Methyl-3β,3'-epoxy-5α-cholestane (0.5 g.) with sodium hydroxide (2 g.) in methanol (100 ml.) was refluxed for 5 hours. The solution was poured into water and worked up as above to give 3α-methoxymethyl-5α-cholestan-3β-ol (0.464 g.) m.p. and mixed m.p. 96-96.5° (acetone).

Treatment of the chloro-compounds with potassium t-butoxide

3α-Chloromethyl-5α-cholestan-3β-ol (0.015 g.) in t-butanol (5 ml.) was added to potassium t-butoxide (0.02 g.) in t-butanol (5 ml.) and the mixture was heated at 60° for 2 hours and left overnight at room temperature. Water was added and the steroid extracted into ether. The ether layer was washed with water till neutral, dried and evaporated to give 3α-methyl-3β,3'-epoxy-5α-cholestane (0.01 g.) identified by i.r. spectra. A similar reaction with 3β-hydroxymethyl-3α-chloro-5α-cholestane (0.02 g.) also gave 3α-methyl-3β,3'-epoxy-5α-cholestane (0.01 g.), again identified by i.r. spectra examination.

Treatment of 3-methylene-5α-cholestane with N-bromosuccinimide and perchloric acid

3-Methylene-5α-cholestane (1.0 g.) in 5% aq. t-butanol (40 ml.) and dioxan (10 ml.) was treated with N-bromosuccinimide (1.0 g.) in

dioxan (20 ml.) and N perchloric acid (0.4 ml.) at room temperature and after keeping at room temperature overnight the solution was concentrated in vacuo below 45°, water was added and the steroid extracted with ether. The ether extract was washed with water, potassium iodide solution, sodium bisulphite solution, and water, dried and the ether evaporated to give the product which was adsorbed on florisil (100 g.). Elution with benzene gave a gum, (0.41 g.), $\nu_{max.}$ 3550 and 1035 $cm.^{-1}$ which was adsorbed from petrol on alumina (50 g.), and gave on elution with petrol an oil with $\nu_{max.}$ 925 $cm.^{-1}$; n.m.r. τ 9.34 (C-18 methyl group), 9.18, 9.16, 9.09 (C-19 and side chain methyl groups), 8.76 ($C\underline{H}_3$-$\dot{C}$-O, epoxide), 6.7 (C-2). Elution from the florisil column with ether gave a gum (0.21 g.) $\nu_{max.}$ 3550 and 1035 $cm.^{-1}$ which was adsorbed from petrol on alumina (50 g.) to give on elution with petrol 3α-methyl-3β,3'-epoxy-5α-cholestane identified by i.r. spectra examination.

Treatment of 3-methylene-5α-cholestane with N-bromosuccinimide and acetic acid

3-Methylene-5α-cholestane (1 g.) in acetone (15 ml.) was added to a solution of N-bromosuccinimide (1 g.) and acetic acid (0.8 ml.) in acetone (30 ml.) and water (10 ml.). After leaving at room temperature for 8 hours ether and water were added and the ether layer was washed with water, potassium iodide solution, sodium bisulphite solution and water, dried and the solvent removed to give a product which was adsorbed on to florisil (50 g.). Elution with petrol gave 3-methylene-5α-cholestane (0.231 g.) m.p. and mixed m.p. 64-65°, while elution with ether gave 3β-hydroxymethyl-3α-bromo-5α-

cholestane (0.444 g.) m.p. 110-113° $[\alpha]_D$ +24° (c.0.16) $\nu_{max.}$ 3540 and 1035 $cm.^{-1}$ (Found: C, 69.6; H, 9.8; Br, 16.5. $C_{28}H_{49}OBr$ requires C, 69.8; H, 10.2; Br, 16.8%). Acetylation of this compound (0.1 g.) with pyridine-acetic anhydride at room temperature for 2 days gave a mixture of acetate (1740 and 1230 $cm.^{-1}$) and alcohol (3560 $cm.^{-1}$). Separation on silica gel (10 g.) on elution with petrol-benzene mixtures was not possible.

Adsorption of 3β-hydroxymethyl-3α-bromo-5α-cholestane (0.09 g.) on alumina (10 g.) and elution with petrol gave 3α-methyl-3β,3'-epoxy-5α-cholestane (0.05 g.) m.p. and mixed m.p. 172-3° (acetone).

Cleavage of 3α-methyl-3β,3'-epoxy-5α-cholestane with hydrobromic acid

3α-Methyl-3β,3'-epoxy-5α-cholestane (0.2 g.) in acetone (50 ml.) was treated with 48% hydrobromic acid (10 drops) and the solution was left at room temperature for 2 hours. Water was added and the steroid extracted with ether to give after washing well with water, drying and solvent evaporation 3β-hydroxymethyl-3α-bromo-5α-cholestane (0.171 g.) mixed m.p. 110-112° (acetone).

2,2-Dimethyl-5α-cholestan-3β-ol[90]

2,2-Dimethyl-5α-cholestan-3-one (3 g.) in dry ether (50 ml.) was added to lithium aluminium hydride (2 g.) in dry ether (100 ml.) and the mixture was refluxed for 2 hours. Ethyl acetate and dilute hydrochloric acid were added and the steroid was extracted into ether. The ether layer was washed with water till neutral dried and the solvent removed to give a product which on crystallisation from

acetone afforded 2,2-dimethyl-5α-cholestan-3β-ol (2.9 g.) m.p. 145-146°, $[\alpha]_D$ +27° (c.0.76) (lit.[90] m.p. 146-7°, $[\alpha]_D$ +28°).

2-Isopropylidene-A-nor-5α-cholestane[90]

2,2-Dimethyl-5α-cholestan-3β-ol (1.0 g.) in dry petrol (500 ml.) at 0° was treated with freshly prepared phosphorus pentachloride (2 g.) and the mixture was stirred at 0° for 30 minutes and for 1 hour, while warming up to room temperature. Water was added and the organic layer was washed with sodium carbonate solution and water, dried and evaporated to give an oil which was filtered through alumina (activity II) with petrol as solvent to give after crystallisation from acetone 2-isopropylidene-A-nor-5α-cholestane (0.79 g.) m.p. 70-72° $[\alpha]_D$ +38° (c.0.18) (lit.[90] m.p. 71.5-73°, $[\alpha]_D$ +46° (c.0.9)); n.m.r. τ 9.36 (C-18 methyl group), 9.19, 9.12, 9.09 (C-19 and side chain methyl groups), 8.40 (C-2' methyl groups).

A-nor-5α-cholestan-2-one[90]

2-Isopropylidene-A-nor-5α-cholestane (2.6 g.) in methylene chloride (40 ml.) and methanol (40 ml.) was treated at ca.-70° (dry ice-acetone bath) with a stream of ozone for 1 hour (solution developed a blue colour), and then at a temperature of ca.0° acetic acid (10 ml.) and zinc (2.5 g.) were added and the mixture was stirred for 1 hour. The reaction mixture was then filtered and the filtrate washed well with water, sodium carbonate solution and water, dried and the solvent removed to give a gum which was dissolved in benzene and passed through a column of alumina (100 g.) with more benzene to give after crystallisation from acetone A-nor-5α-

cholestan-2-one (1.5 g.) m.p. 103-4°, $[\alpha]_D$ +149° (c.0.09) (lit.[90] m.p. 103-4°, $[\alpha]_D$ +143°[141]), $\nu_{max.}$ 1740 $cm.^{-1}$

2-Methylene-A-nor-5α-cholestane

Sodium hydride (0.5 g.) (50% dispersion in oil) was washed three times with dry petrol and then blown dry with nitrogen. Dry dimethyl sulphoxide (25 ml.) was added and the mixture was heated with stirring under nitrogen at 70-75° until evolution of hydrogen ceased (ca.30 minutes). The resulting solution of methylsulphinyl carbanion was cooled and tetrahydrofuran (15 ml.) was added. To this solution at 0° was added, under nitrogen, methyltriphenylphosphonium bromide (5 g.) rapid stirring giving the yellow ylide solution. A-nor-5α-cholestan-2-one (1.0 g.) in tetrahydrofuran (10 ml.) was added and the mixture was stirred at 55° overnight. Water was added and the steroid was extracted with ether. Work up in the usual manner gave a crude product which was filtered through alumina (activity II) (150 g.) with petrol to give 2-methylene-A-nor-5α-cholestane (0.68 g.) m.p. 62-64° $[\alpha]_D$ +64° (c.0.2), $\nu_{max.}$ 3020, 1650, 885 $cm.^{-1}$ n.m.r. τ 9.33, 9.29, 9.19, 9.09, 9.07 (C-18, C-19 and side chain methyl groups), 5.12 (C-2' hydrogens). (Found: C, 87.3; H, 12.3. $C_{27}H_{46}$ requires C, 87.5; H, 12.5%!.

2α-Methyl-2β,2'-epoxy-A-nor-5α-cholestane

A-nor-5α-cholestan-2-one (0.2 g.) in tetrahydrofuran (10 ml.) was added to a solution of dimethyloxosulphonium methylide in dimethyl sulphoxide (15 ml.), prepared from trimethyloxosulphonium iodide (0.6 g.) in the usual manner (p.122). Work up with ether and water gave a product which was crystallised from acetone to give 2α-methyl-

2β,2'-epoxy-A-nor-5α-cholestane (0.14 g.) m.p. 71-72°; $\nu_{max.}$ 3020 921 cm.$^{-1}$ n.m.r. τ 9.34 (C-18 methyl group), 9.19, 9.18, 9.10, 9.09 (C-19 and side chain methyl groups), 7.3, 7.25 (C-2' hydrogens).

2β-Methyl-2α,2'-epoxy-A-nor-5α-cholestane

2-Methylene-A-nor-5α-cholestane (0.4 g.) in ether (20 ml.) was treated with m-chloroperbenzoic acid (80%, 0.4 g.). After standing overnight at room temperature the mixture was worked up as usual (p.127) to give on crystallisation from acetone 2β-methyl-2α,2'-epoxy-A-nor-5α-cholestane (0.29 g.) m.p. 81-84°; $[\alpha]_D$ +16° (c.0.085); $\nu_{max.}$ 3020, 940, 925 cm.$^{-1}$ n.m.r. τ 9.34 (C-18 methyl group), 9.19, 9.18, 9.09, 9.07 (C-19 and side chain methyl groups), 7.20 (C-2' hydrogens). (Found: C, 83.4; H, 11.9. $C_{27}H_{46}O$ requires C, 83.9; H, 12.0%).

Cleavage of 2α-methyl-2β,2'-epoxy-A-nor-5α-cholestane with lithium aluminium hydride

2α-Methyl-2β,2'-epoxy-A-nor-5α-cholestane (0.067 g.) in dry ether (10 ml.) was treated with lithium aluminium hydride (0.05 g.) in dry ether (10 ml.) and the mixture was refluxed for 2 hours. After work up in the usual manner (p131), crystallisation from acetone gave 2α-methyl-A-nor-5α-cholestan-2β-ol (0.06 g.), m.p. 138-139°, $[\alpha]_D$ +27° (c.0.1); $\nu_{max.}$ 3560, 932 cm.$^{-1}$ (Found: C, 83.0; H, 12.4. $C_{27}H_{48}O$ requires C, 83.4; H, 12.4%).

Cleavage of 2β-methyl-2α,2'-epoxy-A-nor-5α-cholestane with lithium aluminium hydride

2β-Methyl-2α,2'-epoxy-A-nor-5α-cholestane (0.05 g.) in dry ether

(10 ml.) was treated with lithium aluminium hydride (0.05 g.) in dry ether (10 ml.) under the conditions outlined above and worked up to give 2β-methyl-A-nor-5α-cholestan-2α-ol (0.05 g.), m.p. 115-116°; $[\alpha]_D$ +20° (c.0.23); $\nu_{max.}$ 3570, 920 $cm.^{-1}$ (Found: C, 83.8; H, 12.3. $C_{27}H_{48}O$ requires C, 83.4; H, 12.4%).

2α-Methyl-A-nor-5α-cholestan-2β-ol

A-Nor-5α-cholestan-2-one (0.1 g.) in dry ether (25 ml.) was added to methyl magnesium iodide (from magnesium (0.1 g.)) in dry ether (25 ml.) and the mixture was refluxed for five hours. On cooling dilute ammonium chloride solution was added and the ether layer was washed well with water, dried and the solvent removed to give on crystallisation from acetone 2α-methyl-A-nor-5α-cholestan-2β-ol (0.099 g.) m.p. and mixed m.p. 137-139°.

Cholest-4-en-3-one[98]

Cholest-4-en-3-one was prepared from cholesterol (150 g.) using the procedure described in "Organic Synthesis." This yield was (99 g.) with m.p. 80-81° $[\alpha]_D$ +88° (c.0.20), $\lambda_{max.}$ 244 mu (ϵ 16,400), (lit.[98] m.p. 81-82°, $[\alpha]_D$ +88°).

4,4-Dimethyl-cholest-5-en-3-one[99]

Cholest-4-en-3-one (12 g.) was methylated with methyl iodide (12 ml.) in the presence of potassium t-butoxide (from potassium (4 g.)) to give on crystallisation from acetone 4,4-dimethyl-cholest-5-en-3-one (5.7 g.) m.p. 176-178° (lit.[99] 177°); $\nu_{max.}$ 1705 $cm.^{-1}$

3-Methylene-4,4-dimethyl-cholest-5-ene

Methylenetriphenylphosphorane (from methyltriphenylphosphonium bromide (6 g.)) was prepared as described on page 119 and to it was added 4,4-dimethyl-cholest-5-en-3-one (1.5 g.) in tetrahedrofuran (35 ml.) and the mixture was refluxed overnight under N_2. After work up in the usual manner a crude product was obtained which was adsorbed on alumina (activity II) (200 g.), elution with petrol and crystallisation from acetone giving 3-methylene-4,4-dimethyl-cholest-5-ene (1.32 g.) m.p. 92-93°; $[\alpha]_D$ -28° (c.0.21); ν max. 3040, 1630, 890 cm.$^{-1}$ n.m.r. τ 9.32 (C-18 methyl group), 9.18, 9.09, 9.07, 8.97, 8.78, 8.72 (C-19, C-4 and side chain methyl groups), 7.6 (broad, centre), 5.25 (centre) (C-3' hydrogens), 4.45 (centre) (C-6 hydrogen). (Found: C, 87.8; H, 12.2. $C_{30}H_{50}$ requires C, 87.7; H, 12.3%).

Reaction of 4,4-dimethyl-cholest-5-en-3-one with dimethylsulphonium methylide

A solution of dimethylsulphonium methylide in dimethyl sulphoxide (15 ml.) was prepared in the usual way (methylsulphinyl carbanion from sodium hydride (0.3 g.) and trimethylsulphonium iodide (1.6 g.)) and to it at ca.-10° was added 4,4-dimethyl-cholest-5-en-3-one (1.0 g.) in tetrahydrofuran (15 ml.). The mixture was stirred at ca.-10° for 10 minutes and for 1 hour while the temperature of the reaction rose to room temperature. The mixture was worked up with ether to give a crude product, ν max. 1705 cm.$^{-1}$ which was adsorbed on alumina (100 g.). Elution with petrol gave a product (0.025 g.), ν max. 3020, 985, 965, 925, 890, 865 cm.$^{-1}$ Elution with benzene gave

4,4-dimethyl-cholest-5-en-3-one (0.79 g.) m.p. and mixed m.p. 176-178° (acetone).

Reaction of 4,4-dimethyl-cholest-5-en-3-one with dimethyloxosulphonium methylide in dimethyl sulphoxide

Dimethyloxosulphonium methylide (from trimethyloxosulphonium iodide (5 g.)) was prepared in the usual manner (p.122) and to it, in tetrahedrofuran (30 ml.), was added 4,4-dimethyl-cholest-5-en-3-one (1.1 g.). A white precipitate was immediately formed which would not go into solution on adding tetrahedrofuran (25 ml.) and stirring. The mixture was thus heated at 60° under nitrogen for 2 hours and worked up as usual to give a product ($\nu_{max.}$ 1705 cm.$^{-1}$) which was adsorbed on alumina (180 g.). Elution with petrol gave a product (0.07 g.), $\nu_{max.}$ 960, 920, 885, 850 cm.$^{-1}$ (all weak to medium). Elution with benzene gave 4,4-dimethyl-cholest-5-en-3-one (0.91 g.) m.p. and mixed m.p. 176-178° (acetone).

Reaction of 4,4-dimethyl-cholest-5-en-3-one with dimethyloxosulphonium methylide in dimethylformamide

Dimethyloxosulphonium methylide was prepared from trimethyloxosulphonium iodide (5 g.) in dimethylformamide (35 ml.) using the experimental conditions outlined on page 122. 4,4-Dimethyl-cholest-5-en-3-one (0.9 g.) in tetrahydrofuran (35 ml.) was added precipitating a white solid. Additional tetrahydrofuran (25 ml.) was added and the mixture was heated at 50° for 2 hours. The crude product. isolated by means of ether, had $\nu_{max.}$ 1705 cm.$^{-1}$ It was adsorbed onto alumina (200 g.). Elution with petrol gave a product (0.06 g.) identical in i.r. with the petrol eluted material of the previous

experiment; $\nu_{max.}$ 960, 920, 885, 850 cm.$^{-1}$ Elution with benzene gave 4,4-dimethyl-cholest-5-en-3-one (0.86 g.) m.p. and mixed m.p. 176-178° (acetone).

Reaction of 3-methylene-4,4-dimethyl-cholest-5-ene with m-chloroperbenzoic acid

3-Methylene-4,4-dimethyl-cholest-5-ene (1.0 g.) in dry ether (100 ml.) was added to m-chloroperbenzoic acid (80%) (0.53 g.) in dry ether (100 ml.) and the mixture was allowed to stand overnight at room temperature before being worked up as described on page 127 The crude product was adsorbed onto alumina (100 g.) and elution with petrol gave 3-methylene-4,4-dimethyl-cholest-5-ene (0.252 g.) m.p. and mixed m.p. 92-93° (acetone). Further elution with petrol and crystallisation from acetone gave 5,6-epoxy-3-methylene-4,4-dimethyl-cholestane (0.267 g.) m.p. 89-92°, $[\alpha]_D$ +21° (c.0.11), $\nu_{max.}$ 3050, 1640, 938, 889, 765 cm.$^{-1}$ n.m.r. τ 9.39, 9.38, 9.29, 9.27, 9.10, 9.07, 8.91, 8.89, 8.73 (C-18, C-19, C-4 and side chain methyl groups), 7.77, 7.68 (C-7 protons), 7.02, 6.90 (C-6 protons). (Found: C, 83.9; H, 12.2. $C_{30}H_{52}O$ requires C, 84.0; H, 12.2%). Elution with petrol-benzene (99:1) and crystallisation from acetone gave 3-methyl-3,3'-epoxy-4,4-dimethyl-cholest-5-ene (0.254 g.), m.p. 90-94° $[\alpha]_D$ -36° (c.0.12); $\nu_{max.}$ 3040, 965, 930, 922 cm.$^{-1}$ n.m.r. τ 9.31, 9.18, 9.08, 9.01, 8.86 (C-18, C-19, C-4 and side chain methyl groups), 7.58, 7.49, 7.14, 7.05 (C-3' hydrogens), 4.48 (C-6 hydrogen). (Found: C, 84.1; H, 12.0. $C_{30}H_{52}O$ requires C, 84.0; H, 12.2%). Finally elution with petrol-benzene (98:2) gave the diepoxide (gum, 0.020 g.) $\nu_{max.}$ 3040, 970, 930 cm.$^{-1}$ n.m.r.

τ 9.36 (C-18 methyl group), 9.26, 9.18, 9.09, 8.96, 8.85, 8.77 (C-19, C-4 and side chain methyl groups), hydrogens (C-7, C-6, and C-3') at 7.56, 7.51, 7.46, 7.38, 7.32, 7.10, 7.03, 6.92.

Reactions of Methylene-Epoxides

(1) Epoxides not adjacent to a polar group

Reaction of 3β-methyl-3α,3'-epoxy-5α-cholestane with BF_3-etherate in benzene

3β-Methyl-3α,3'-epoxy-5α-cholestane (1.0 g.) in dry benzene (100 ml.) was treated with boron trifluoride-etherate (10 drops). After two minutes the solution was poured into a solution of sodium acetate and ether was added. The ether solution was washed with water, dried and the ether evaporated to give a product which was chromatographed on alumina (60 g.). Elution with petrol gave starting material (0.158 g.) identified by i.r. spectra examination. Elution with petrol-benzene (9:1) gave 5α-cholestan-3β-aldehyde (0.205 g.) m.p. mostly at 94-6° (not recrystallised); $[\alpha]_D$ +28.5° (c.0.22); $\nu_{max.}$ 2715, 1725 $cm.^{-1}$; n.m.r. τ 9.35 (C-18 methyl group), 9.21, 9.18, 9.09 (C-19 and side chain methyl groups), 0.39 (aldehyde), Recrystallisation from petrol of this aldehyde (0.2 g.) gave 5α-cholestan-3β-carboxylic acid (0.191 g.) m.p. 206-208° (lit.[102] 206-208°), $\nu_{max.}$ 3400-2450, 1695 $cm.^{-1}$ Treatment of the 3β-carboxylic acid (0.911 g.) with ethereal diazomethane (prepared from potassium hydroxide treatment of nitrosomethylurea[142] (1.0 g.) in ether (100 ml.)) gave after allowing to stand 4 hours at 18° and isolation with ether 3β-methoxycarbonyl-5α-cholestane (0.862 g.) m.p. 66-68° (acetone) (lit.[102] 54-56°/69°) $\nu_{max.}$ 1730, 1160 $cm.^{-1}$ Elution with ether gave after crystallisation from acetone 3α-hydroxymethyl-3β-fluoro-5α-cholestane (0.427 g.) m.p. 163-164°; $[\alpha]_D$ +29° (c.0.11); $\nu_{max.}$ 3550, 1057 $cm.^{-1}$; n.m.r. τ 9.33 (C-18 methyl group), 9.23, 9.18

9.09 (C-19 and side chain methyl groups), 6.62, 6.30 (C-3' hydrogens). (Found: C, 80.1; H, 11.5. $C_{28}H_{49}OF$ requires C, 79.7; H, 11.7%).

A solution of the fluoro-alcohol (0.05 g.) in pyridine (6 ml.) and acetic anhydride (0.3 ml.) were kept at room temperature for 16 hours. Isolation with ether and crystallisation from acetone gave 3α-acetoxymethyl-3β-fluoro-5α-cholestane (0.041 g.) m.p. 98-100°, $\nu_{max.}$ 1740, 1242, 1052 $cm.^{-1}$; n.m.r. τ 9.33, 9.23, 9.18, 9.09 (C-18, C-19, and side chain methyl groups), 7.9 (acetate), 6.09, 5.76 (C-3' hydrogens). Both the hydroxymethyl and acetoxymethyl compounds gave positive tests for fluorine.

Qualitative test for Fluorine[143]

a. Alizarin fluorine blue (0.0385 g.) was dissolved in sodium hydroxide solution (0.5N; 20 ml.) and the solution diluted to 150 ml. with water. Sodium acetate (0.02 g.) was added and the solution brought to pH 5 with dilute hydrochloric acid. A solution of sodium acetate (2.5 g.) and acetic acid (2.5 ml.) in water (30 ml.) was then added and the whole solution made up to 200 ml.

b. Cerous nitrate (0.0217 g.) was dissolved in water (200 ml.) and dilute nitric acid (1 drop) and hydroxylamine hydrochloride (0.1 g.) added.

c. Tribenzylamine (0.1 g.) was dissolved in warm n-pentanol-sec-butanol mixture (3:1 ; 35 ml.), the solution cooled and diluted to 100 ml. with the same mixture.

A small amount of steroid (less than 1 mg.) was combusted in a flask filled with oxygen, and the residue dissolved in water (1 ml.). Five drops of this solution were placed in a small tube and the

alizarin fluorine blue solution (a) (2 drops) added and the contents mixed. Cerous nitrate solution (b) (2 drops) was then added and mixed. A change to blue within 1 minute indicated fluorine present. The extraction solution (c) (10 drops) was added and the blue colour was absorbed into the organic layer.

Reaction of 3α-hydroxymethyl-3β-fluoro-5α-cholestane with BF_3 in benzene

3α-Hydroxymethyl-3β-fluoro-5α-cholestane (0.1 g.) in dry benzene (10 ml.) was allowed to react with BF_3-etherate (0.1 ml.) for 90 minutes. The solution was then poured into sodium bicarbonate solution, ether was added and the ether layer was washed with water, dried and the ether evaporated to give a product which was filtered through alumina (10 g.), elution with petrol-benzene (95:5) giving 5α-cholestan-3β-aldehyde (0.081 g.), identified from its i.r. and n.m.r. spectra.

Reaction of 3β-methyl-3α,3'-epoxy-5α-cholestane with excess BF_3-etherate in benzene

3β-Methyl-3α,3'-epoxy-5α-cholestane (1 g.) in dry benzene (100 ml.) was treated with boron trifluoride-etherate (1 ml.). After 2 minutes the benzene solution was poured into water and ether was added. The ether layer was washed well with water, dried and evaporated to give a product, n.m.r. τ 0.39 (3β-C<u>H</u>O), 0.29 (3α-C<u>H</u>O) (β:α ca.4:1). Chromatography of this product on alumina (60 g.) and elution with petrol-benzene (9:1) gave the 3β-aldehyde (0.731 g.), identified by n.m.r. spectra, (τ 0.39).

The treatment of the mixture of 3-aldehydes with potassium hydroxide in ethanol

The reaction of 3β-methyl-3α,3'-epoxy-5α-cholestane (0.1 g.) with boron trifluoride-etherate (0.1 ml.) in dry benzene (10 ml.) was carried out exactly as in the previous experiment, and the crude product (n.m.r. τ 0.39, 0.29), (0.09 g.), was kept at room temperature with KOH (0.15 g.) in aqueous ethanol (90%, 20 ml.) for eight hours. Work up with ether and water gave a product, with only one aldehyde peak in the n.m.r. (τ 0.39), identifiable as 5α-cholestan-3β-aldehyde (0.065 g.).

Reaction of 3β-methyl-3α,3'-epoxy-5α-cholestane with BF_3-etherate in ether

A solution of the α-epoxide (0.5 g.) in dry ether (50 ml.) was treated with boron trifluoride-etherate (0.5 ml.) at room temperature for 2 hours and was then poured into water. Ether was added and the ether layer washed with water, dried and evaporated to give a product, n.m.r. τ 6.62, 6.3 (fluorohydrin), 0.39 (3β-C<u>H</u>O), 0.29 (3α-CHO) (ratio of aldehydes from the two bands, ca.1:1). Chromatography of this product on alumina (50 g.) gave on elution with petrol-benzene (9:1) the 3β-aldehyde (0.221 g.) again identified by n.m.r. spectra. Elution with ether gave 3α-hydroxymethyl-3β-fluoro-5α-cholestane (0.174 g.) m.p. and mixed m.p. 163-164° (acetone)

Reaction of 3α-methyl-3β,3'-epoxy-5α-cholestane with boron trifluoride in benzene

3α-Methyl-3β,3'-epoxy-5α-cholestane (0.5 g.) in dry benzene (30 ml.) was treated with boron trifluoride-etherate (0.5 ml.) at room

temperature for 5 minutes. The reaction was terminated by pouring the benzene solution into water and ether was added. The ether solution was washed with water, dried and the ether evaporated to give the crude aldehydes, n.m.r. τ 0.39, 0.29 (ratio of aldehydes from peaks; β:α ca.4:1). The aldehyde mixture (0.5 g.) was adsorbed onto alumina (35 g.) and elution with petrol-benzene gave the 3β-aldehyde, n.m.r. τ 0.39.

Reaction of 3α-methyl-3β,3'-epoxy-5α-cholestane with BF_3-etherate in ether

A solution of the β-epoxide (0.5 g.) in dry ether (60 ml.) was treated with boron trifluoride-etherate (0.5 ml.) at room temperature for 2 hours. Work up with ether and water gave a product with only one aldehyde band in the n.m.r. (τ 0.39, equitorial aldehyde). The product (0.49 g.) was then cleaved up by filtering through a column of alumina (40 g.) with petrol-benzene (9:1) giving a pure sample of the 3β-aldehyde (0.40 g.), n.m.r. τ 0.39.

Reaction of 2α-methyl-2β,2'-epoxy-5α-cholestane with boron trifluoride in benzene

2α-Methyl-2β,2'-epoxy-5α-cholestane (0.2 g.) in dry benzene (20 ml.) was treated for 5 minutes at room temperature with boron trifluoride-etherate (0.2 ml.). Work up with ether and water gave a product (0.191 g.) containing the 2α-aldehyde (n.m.r. τ 0.41) and 2β-aldehyde (n.m.r. τ 0.24), the ratio of the α-:β-aldehyde being ca.4:1. The crude product was adsorbed onto alumina (20 g.) and elution with petrol-benzene (9:1) gave 5α-cholestan-2α-aldehyde (0.183 g.), m.p. 95-96° (petrol), $[\alpha]_D$ +22° (c.0.12) $\nu_{max.}$ 2700,

1725 cm.$^{-1}$ n.m.r. τ 9.35 (C-18 methyl group), 9.19, 9.10 (C-19, side chain methyl groups), 0.41 (2α-CHO). (Found: C, 83.9; H, 11.9. $C_{28}H_{48}O$ requires C, 83.9; H, 12.1%).

Reaction of 2α-methyl-2β,2'-epoxy-5α-cholestane with boron trifluoride-etherate in ether

The β-epoxide (0.11 g.) in dry ether (10 ml.) was treated with boron trifluoride-etherate (0.11 ml.) and kept at room temperature for 2 hours. The crude product, isolated by means of ether, contained both aldehydes (n.m.r. τ 0.41 (2α-aldehyde), 0.24 (2β-aldehyde))in an approximately 1:1 ratio. Chromatography of the crude product (0.107 g.) on alumina (10 g.) gave on elution with petrol-benzene (9:1) the 2α-aldehyde (0.1 g.) m.p. and mixed m.p. 94-96° (petrol).

Reaction of 2β-methyl-2α,2'-epoxy-5α-cholestane with BF_3-etherate in benzene

A solution of 2β-methyl-2α,2'-epoxy-5α-cholestane (0.1 g.) in dry benzene (10 ml.) was treated with boron trifluoride-etherate (0.1 ml.) and kept at room temperature for 5 minutes. The crude product, isolated by means of ether, contained, in a ratio of ca.1:1, the two aldehydes (n.m.r.). Alumina (10 g.) chromatography with elution by petrol-benzene (9:1) gave 5α-cholestan-2α-aldehyde (0.073 g.) m.p. and mixed m.p. 94-96° (from petrol).

Reaction of 2β-methyl-2α,2'-epoxy-5α-cholestane with BF_3 in ether

A solution of the 2α,2'-epoxide (0.05 g.) in dry ether (10 ml.) was treated with boron trifluoride etherate (0.05 ml.) at room

temperature for 2 hours. The crude product, isolated by means of ether, contained, from n.m.r. evidence τ 0.41, 0.24 (approximate ratio of the signals 95:5), the two aldehydes. Chromatography on alumina (10 g.) gave on elution with petrol-benzene (9:1) and crystallisation from petrol 5α-cholestan-2α-aldehyde (0.041 g.) m.p. and mixed m.p. 94-96°.

Reaction of 3β-methyl-3α,3'-epoxy-2α-methyl-5α-cholestane with boron trifluoride in benzene

A solution of the 3α,3'-epoxy-2α-methylcholestane (0.5 g.) in dry benzene (40 ml.) was treated with boron trifluoride (0.5 ml.) and kept at room temperature for 2 minutes. The crude product, (0.471 g.), isolated by means of ether, showed no assignable absorptions in the i.r. or n.m.r. (τ 9 - -2). Fractionation on alumina (60 g.) was not possible.

Reaction of 3β-methyl-3α,3'-epoxy-2,2-dimethyl-5α-cholestane with BF_3 in benzene

a) The epoxide (0.50 g.) in dry benzene (40 ml.) was treated with boron trifluoride-etherate (0.5 ml.) at room temperature for 2 minutes. The crude product (0.411 g.), isolated by means of ether, was unidentifiable from its spectra (i.r., n.m.r.) and could not be fractionated by chromatography on alumina (60 g.).

b) The epoxide (0.404 g.) in dry benzene (10 ml.) was treated with boron trifluoride-etherate (2 drops) at room temperature for 0.5 minutes. The crude product (0.4 g.), isolated by means of ether, could not be identified from its i.r. or n.m.r. spectra. Product

separation on alumina (60 g.) was not possible.

Reaction of 3β-methyl-3α,3'-epoxy-5α-cholestane with hydrogen chloride

The α-epoxide (0.4 g.) in dry chloroform (25 ml.) was treated with a stream of hydrogen chloride gas at room temperature for 10 minutes and allowed to stand for 30 minutes. The chloroform solution was washed with water, sodium carbonate solution and water, dried and evaporated to give after crystallisation from acetone 3α-hydroxymethyl-3β-chloro-5α-cholestane (0.33 g.) m.p. 142-144°, $[\alpha]_D$ +26° (c.0.19), $\nu_{max.}$ 3560, 1075 cm.$^{-1}$ (Found: C, 77.1; H, 11.30. $C_{28}H_{49}OCl$ requires C, 77.0; H, 11.3%).

Treatment of this compound (0.07 g.) in pyridine (5 ml.) with acetic anhydride (0.5 ml.) gave after a reaction time of 20 hours a crude product containing a hydroxy-group ($\nu_{max.}$ 3560 cm.$^{-1}$) and an acetate ($\nu_{max.}$ 1740, 1235 cm.$^{-1}$). Chromatography of this product on silica gel (10 g.) with elution with petrol-benzene (7:3) gave a mixture of alcohol and acetate (i.r.) while elution with ether gave 3α-hydroxymethyl-3β-chloro-5α-cholestane (0.011 g.) (i.r.).

When 3α-hydroxymethyl-3β-chloro-5α-cholestane (0.102 g.) in t-butanol (15 ml.) was treated with potassium t-butoxide (0.1 g.) in t-butanol (5 ml.) and the mixture refluxed 1 hour and allowed to stand overnight at room temperature a product (0.051 g.) was obtained which could be identified as 3β-methyl-3α,3'-epoxy-5α-cholestane by i.r. spectra examination.

Reaction of 3β-methyl-3α,3'-epoxy-5α-cholestane with hydrogen bromide

A solution of 3β-methyl-3α,3'-epoxy-5α-cholestane (0.253 g.) in acetone (30 ml.) and tetrahydrofuran (10 ml.) was treated with 48% hydrobromic acid (12 drops) and was kept at room temperature for 2 hours. Water was added and the steroid extracted with ether. The ether layer was washed free of acid with water, dried and the ether evaporated to give on crystallisation from acetone 3α-hydroxymethyl-3β-bromo-5α-cholestane (0.223 g.) m.p. 122-124°, $[\alpha]_D$ +22° (c.0.14), $\nu_{max.}$ 3540, 1010 cm.$^{-1}$ (Found: C, 70.0; H, 10.3; Cl, 16.8. $C_{28}H_{49}OBr$ requires C, 69.8; H, 10.2; Cl.16.6%).

Treatment of this compound (0.104 g.) with acetic anhydride (2 ml.) in pyridine (8 ml.) for 18 hours at room temperature afforded a mixture of acetate (i.r. 1740, 1235 cm.$^{-1}$) and alcohol (3540 cm.$^{-1}$). Chromatography of this product on silica gel (25 g.) and elution with petrol-benzene mixtures gave fractions, all containing the acetate and alcohol, while elution with benzene-ether (9:1) gave 3α-hydroxymethyl-3β-bromo-5α-cholestane, (0.010 g.) identified by i.r. spectra.

3α-Hydroxylmethyl-3β-bromo-5α-cholestane (0.021 g.) was adsorbed onto alumina (10 g.) and left for 15 minutes. Elution with petrol gave 3β-methyl-3α,3'-epoxy-5α-cholestane (0.017 g.) identified by i.r. spectra comparison.

Cleavage of 3β-methyl-3α,3'-epoxy-5α-cholestane on alumina (activity II)

The α-epoxide (1.0 g.) was adsorbed from petrol onto alumina

(activity II) (150 g.) and the column stoppered and left overnight. Elution with petrol gave starting material (0.124 g.) and elution with chloroform gave 3β-hydroxymethyl-5α-cholestan-3α-ol (0.431 g.) m.p. 181-183° (acetone) $[\alpha]_D$ +22° (c.0.15) $\nu_{max.}(CHCl_3)$ 3550, 3500-3300 $cm.^{-1}$ (Found: C, 80.0; H, 11.8. $C_{28}H_{50}O_2$ requires C, 80.3; H, 12.0%).

The diol (0.210 g.) in pyridine (10 ml.) was treated at 0° with toluene p-sulphonyl chloride (0.18 g.) and the mixture was kept at 0° for 24 hours. Isolation with ether and water gave the crude tosylate (0.217 g.) ($\nu_{max.}$ 3600, 1190, 1180 $cm.^{-1}$) contaminated with a small amount of starting material (3500-3300 $cm.^{-1}$) Repeated recrystallisation from acetone gave a small sample (0.01 g.) m.p. 130-134°, $\nu_{max.}$ 3600, 1190, 1180 $cm.^{-1}$ The n.m.r. of the second crop (0.107 g., m.p. 126-131°) had peaks at τ 9.35 (C-18 methyl group), 9.29, 9.18, 9.17, 9.1 (side chain and C-19 methyl groups), 7.54 (aryl methyl group), absorptions at ca.6.5 (impurity), 6.21 (C-3' hydrogens), 2.72, 2.58, 2.26, 2.14 (aromatic protons).

Impure tosylate (m.p. 126-131°) (0.035 g.) was treated with potassium t-butoxide (0.035 g.) in t-butanol (25 ml.) and the mixture was refluxed for 1 hour and allowed to stand overnight at room temperature. The crude product, isolated by means of ether, was adsorbed on alumina (10 g.), elution with petrol giving 3β-methyl-3α,3'-epoxy-5α-cholestane (0.022 g.) identified from its i.r. spectrum.

The tosylate (m.p. 126-131°) (0.041 g.) in dry ether (20 ml.) was added to lithium aluminium hydride (0.05 g.) in dry ether (20 ml.) and the mixture was refluxed for 2 hours. Ethyl acetate and

dilute hydrochloric acid were added, and the crude product was isolated with ether. Crystallisation from acetone gave an impure sample of 3β-hydroxymethyl-5α-cholestan-3α-ol (0.012 g.), identified by its i.r. spectrum ($CHCl_3$). The second crop (acetone) was 3β-methyl-5α-cholestan-3α-ol (0.016 g.) m.p. and mixed m.p. 126-127°, $\nu_{max.}$ 3600, 965, 960, 900 $cm.^{-1}$

Cleavage of 3α-methyl-3β,3'-epoxy-5α-cholestane on alumina (activity II)

The β-epoxide (0.5 g.) was adsorbed from petrol onto alumina (activity II) (100 g.) and the column was stoppered and left overnight. Elution with chloroform gave 3α-hydroxymethyl-5α-cholestan-3β-ol (0.221 g.) m.p. 180-182° (acetone), mixed m.p. with 3β-hydroxymethyl-5α-cholestan-3α-ol 169-181°, $[\alpha]_D$ +32° (c.0.11); $\nu_{max.}$ ($CHCl_3$) 3560, 3500-3300 $cm.^{-1}$ (Found: C, 80 1; H, 12.3. $C_{28}H_{50}O_2$ requires C, 80.3; H, 12.0%).

The diol (0.140 g.) in pyridine (25 ml.) was treated at 0° with toluene p-sulphonyl chloride (0.10 g.) and the mixture was kept at 0° for 24 hours. Isolation with ether gave the crude tosylate (0.141 g.), m.p. 155-161°, $\nu_{max.}$ 3600, 1190, 1180 $cm.^{-1}$ A portion of this impure tosylate (0.110 g.) was treated with potassium t-butoxide (0.110 g.) in t-butanol (40 ml.) under the conditions described on page 156, and the crude product, isolated by means of ether, was adsorbed on alumina (5 g.). Elution with petrol gave 3α-methyl-3β,3'-epoxy-5α-cholestane (0.038 g.), identified by its i.r. spectrum and elution with chloroform gave the 3α-hydroxymethyl-3β-ol (0.022 g.), identified by its i.r. spectrum.

Treatment of 3β-methyl-3α,3'-epoxy-5α-cholestane with acetic acid

3β-Methyl-3α,3'-epoxy-5α-cholestane (1.0 g.) was heated at 90° with dried and redistilled acetic acid (14 ml.) for 2 hours. The acetic acid was removed under reduced pressure giving on crystallisation from acetone 3α-hydroxymethyl-3β-acetoxy-5α-cholestane (0.699 g.) m.p. 121-124°, $[\alpha]_D$ +26° (c.0.16) $\nu_{max.}$ 3570, 1740, 1235, 1050 cm.$^{-1}$ n.m.r. τ 9.34 (C-18 methyl group), 9.24, 9.18, 9.09 (C-19 and side chain methyl groups), 7.87 (acetate), 6.07, 5.86 (C-3' hydrogens) (Found: C, 78.3; H, 11.4. $C_{30}H_{52}O_3$ requires C, 78.2; H, 11.4%).

The 3α-hydroxymethyl-3β-acetate (0.2 g.) was treated in the usual way with acetic anhydriee (4 ml.) and pyridine (8 ml.) overnight at room temperature to give on crystallisation from acetone 3α-acetoxymethyl-3β-acetoxy-5α-cholestane (0.192 g.) m.p. 136-137°, $\nu_{max.}$ 1740, 1235, 1050 cm.$^{-1}$ n.m.r. τ 9.34 (C-18 methyl group), 9.24, 9.19, 9.08 (C-19 and side chain methyl groups), 7.94 (6 protons, acetates).

3β-Acetoxy-3α-hydroxymethyl-5α-cholestane (0.2 g.) and lithium aluminium hydride (0.2 g.) in dry ether (25 ml.) were refluxed for 2 hours. The excess lithium aluminium hydride was destroyed and the ether solution was washed with dilute hydrochloric acid and water, dried and the ether evaporated to give on crystallisation from acetone 3α-hydroxymethyl-5α-cholestan-3β-ol (0.132 g.) m.p. and mixed m.p. 180-183°.

Treatment of 3α-methyl-3β,3'-epoxy-5α-cholestane with acetic acid

3α-methyl-3β,3'-epoxy-5α-cholestane (0.5 g.) was heated with dried and redistilled acetic acid (9 ml.) for 2 hours at 90°. The acetic acid was removed under reduced pressure to give on crystallisation from acetone 3β-hydroxymethyl-3α-acetoxy-5α-cholestane (0.447 g.) m.p. 124-125° (mixed m.p. with 3α-hydroxymethyl-3β-acetoxy-5α-cholestane 117-125°). $[\alpha]_D$ +28° (c.0.1), $\nu_{max.}$ 3580, 1740, 1230, 1050 cm.$^{-1}$ n.m.r. τ 9.34 (C-18 methyl group), 9.24, 9.18, 9.16, 9.09 (C-19 and side chain methyl groups), 7.88 (acetate), 6.07, 5.85 (C-3' hydrogens). (Found: C, 78.0; H, 11.1 $C_{30}H_{52}O_3$ requires C, 78.2; H, 11.4%).

3α-Hydroxymethyl-3β-acetoxy-5α-cholestane (0.2 g.) and lithium aluminium hydride (0.2 g.) in dry ether (25 ml.) were refluxed for 2 hours. The excess lithium aluminium hydride was destroyed and the ether solution was washed with dilute hydrochloric acid and water, dried and the ether evaporated to give on crystallisation from acetone 3α-hydroxymethyl-5α-cholestan-3β-ol (0.126 g.) m.p. and mixed m.p. 181-183°.

Cleavage of 3β-methyl-3α,3'-epoxy-5α-cholestane with sodium hydroxide in methanol

The α-epoxide (0.52 g.) was refluxed with a mixture of sodium hydroxide (2 g.) and methanol (50 ml.) for 5 hours. The solution was poured into water and the steroid extracted with ether. The ether layer was washed with water, dried and the ether evaporated to give 3β-methoxymethyl-5α-cholestan-3α-ol (0.491 g.) m.p. 87-88°, $[\alpha]_D$ +25.5° (c.0.2) $\nu_{max.}$ 3560, 1118 cm.$^{-1}$ n.m.r. τ 9.35 (C-18

methyl group), 9.25, 9.18, 9.09 (C-19 and side chain methyl groups), 6.84 (C-3' hydrogens), 6.62 (methoxy methyl group). (Found: C, 80.8; H, 12.0. $C_{29}H_{52}O_2$ requires C, 80.5; H, 12.1%). Only starting material was isolated when this product (0.08 g.) was treated with acetic anhydride (1 ml.) and pyridine (4 ml.) overnight at room temperature.

Acetylation with acetic anhydride and BF_3-etherate [132]

The 3β-methoxymethyl-3α-ol (0.1 g.) in acetic anhydride (5 ml.), boron trifluoride etherate (0.6 ml.) and dry ether (10 ml.) at 0° was allowed to stand at this temperature for 20 hours. The solution was then poured into ice-water and after 3 hours ether was added and the mixture stirred. The ether layer was washed with potassium bicarbonate solution and water, dried and evaporated to give a gum (0.1g.) $\nu_{max.}$ 3600, 1740, 1235 $cm.^{-1}$ This gum (0.09 g.) in dry ether (20 ml.) was added to lithium aluminium hydride (0.1 g.) in dry ether (20 ml.) and the mixture was refluxed for 5 hours. After addition of ethyl acetate and dilute hydrochloric acid the steroid was extracted into ether which was washed well with water, dried and evaporated to give a product ($\nu_{max.}$ 3590 $cm.^{-1}$) which on chromatography on alumina and elution with chloroform-methanol (99:1) gave 3β-hydroxymethyl-5α-cholestan-3α-ol (0.037 g.) m.p. and mixed m.p. 179-182°.

A similar reaction with the 3α-methoxymethyl-3β-ol (0.05 g.), acetic anhydride (2 ml.), boron trifluoride etherate (0.2 ml.) in dry ether (5 ml.) at 0° for 20 hours gave on work up a non-crystalline product (0.03 g.) (3600, 1740, 1235 $cm.^{-1}$). Treatment of

this product with excess lithium aluminium hydride in dry ether in the usual manner gave 3α-hydroxymethyl-5α-cholestan-3β-ol (0.01 g.) m.p. and mixed m.p. 178-181°.

Epoxide cleavage with methanol in the presence of an acid

a) To a methanolic solution (0.50 ml.) of 3β-methyl-3α,3'-epoxy-5α-cholestane (50 ml.) was added perchloric acid (70%, 0.3 ml.) and the mixture was allowed to stand for four hours. Water and ether were added and the ether layer was washed with sodium bicarbonate solution and water, dried and the ether evaporated to give on crystallisation from acetone 3α-hydroxymethyl-3β-methoxy-5α-cholestane (0.427 g.) m.p. 124-125° $[\alpha]_D$ +26° (c.0.22) $\nu_{max.}$ 3550, 1050, 1062, 1085 $cm.^{-1}$ n.m.r. τ 9.34 (C-18 methyl group), 9.18, 9.09 (C-19 and side chain methyl groups), 6.75 (methoxy methyl group), 6.37 (C-3' hydrogens). (Found: C, 80.7; H, 12.0. $C_{29}H_{52}O_2$ requires C, 80.5; H, 12.1%).

b) A methanolic solution (50 ml.) of 3β-methyl-3α,3'-epoxy-5α-cholestane (0.51 g.) was heated under reflux for 1 hour in the presence of toluene-p-sulphonic acid (0.051 g.). The solution was cooled and excess acid neutralised with addition of sodium bicarbonate solution prior to solvent removal. The residue was extracted with ether which was washed with water, dried and evaporated to give on crystallisation from acetone 3α-hydroxymethyl-3β-methoxy-5α-cholestane (0.458 g.) m.p. and mixed m.p. 124-125°.

3α-Hydroxymethyl-3β-methoxy-5α-cholestane (0.100 g.) was treated with acetic anhydride (2 ml.) and pyridine (8 ml.) and the mixture was kept at room temperature overnight. Work up in the usual way

with ether gave the acetate, $\nu_{max.}$ 1738, 1235, 1105, 1045 $cm.^{-1}$ (homogeneous on chromatography on florisil (30 g.) and elution with petrol-benzene mixtures).

a) 3α-Methyl-3β,3'-epoxy-5α-cholestane (0.211 g.) was cleaved under the conditions outlined for a. to give a semi-solid (0.199 g.) which was filtered through alumina with ether to give on crystallisation from acetone 3β-hydroxymethyl-3α-methoxy-5α-cholestane (0.178 g.) m.p. 90-91° $[\alpha]_D$ +29.5° (c.0.09) $\nu_{max.}$ 3550, 1075 $cm.^{-1}$, n.m.r. τ 9.35 (C-18 methyl group), 9.25, 9.18, 9.09 (C-19 and side chain methyl groups), 6.82 (methoxy methyl), 6.66 (-OH), 6.58 (C-3' hydrogens). (Found: C, 80.9; H, 12.3. $C_{29}H_{52}O_2$ requires C, 80.5; H, 12.1%).

b) 3α-Methyl-3β,3'-epoxy-5α-cholestane (0.2 g.) was cleaved with methanol (25 ml.) and toluene-p-sulphonic acid (0.020 g.) under the reaction conditions outlined in b. The crude product isolated by means of ether, was crystallised from acetone to give 3β-hydroxymethyl-3α-methoxy-5α-cholestane (0.168 g.) m.p. and mixed m.p. 90-91°.

The reaction of 3β-methyl-3α,3'-epoxy-5α-cholestane with methyl magnesium iodide

The α-epoxide (1.0 g.) in dry ether (20 ml.) was added to an ethereal solution (50 ml.) of methyl magnesium iodide (from magnesium (1 g.)) and the mixture was refluxed for 5 hours. Ammonium chloride solution was added dropwise and the ether layer was then washed well with water, dried and the ether evaporated to give 3α-hydroxymethyl-3β-iodo-5α-cholestane (0.897 g.) m.p. 134-136° $[\alpha]_D$ +20° (c.0.14), $\nu_{max.}$ 3560, 1190, 1010 $cm.^{-1}$, n.m.r. τ 9.34 (C-18 methyl

group), 9.25, 9.18, 9.09 (C-19 and side chain methyl groups), 6.71 (C-3' hydrogens). (Found: C, 63.8; H, 9.3; I, 23.6. $C_{28}H_{49}OI$ requires C, 63.5; H, 9.3; I, 24.0%).

3α-Hydroxymethyl-3β-iodo-5α-cholestane (0.4 g.) was absorbed onto alumina (40 g.). Immediate elution with petrol-benzene (1:1) gave the 3β-iodide (0.389 g.) m.p. and mixed m.p. 134-136° (acetone).

The above experiment was repeated (α-epoxide (0.12 g.), alumina (20 g.)) except that 2 minutes were allowed to elapse before elution. Elution with petrol then gave 3β-methyl-3α,3'-epoxy-5α-cholestane (0.087 g.) identified by i.r. spectra examination.

Cleavage of 3β-methyl-3α,3'-epoxy-5α-cholestane with hydriodic acid

To 3β-methyl-3α,3'-epoxy-5α-cholestane (0.1 g.) in dry ether (30 ml.) was added hydriodic acid (sp.gr. 1.94, 2 ml.). After stirring at room temperature 2 hours the solution was poured into water and the ether layer was washed with water, sodium bisulphite solution, and water, dried and the ether evaporated to give a slightly impure sample of 3α-hydroxymethyl-3β-iodo-5α-cholestane (0.11 g.), identified by i.r. examination. Crystallisation from acetone gave a sample m.p. and mixed m.p. 132-135°.

The reaction of 3α-methyl-3β,3'-epoxy-5α-cholestane with methyl magnesium iodide

The β-epoxide (0.5 g.) in dry ether (20 ml.) was added to an ethereal solution (50 ml.) of methyl magnesium iodide (from magnesium (1 g.)) and the mixture was refluxed for 5 hours. Work up with ammonium chloride solution and water in the usual way gave after crystallisation from acetone 3β-hydroxymethyl-3α-iodo-5α-cholestane

(0.496 g.) m.p. 115-116°, $\nu_{max.}$ 3550, 1185, 1030 $cm.^{-1}$; n.m.r. τ 9.35 (C-18 methyl group), 9.18, 9.09 (C-19 and side chain methyl groups), 6.43 (C-3' hydrogens). After standing for several weeks the crystalline sample began to brown around the edges of the crystals and after six months a purple gum was obtained with no specific functional group absorptions in the i.r.

A pure sample of 3β-hydroxymethyl-3α-iodo-5α-cholestane (0.09 g.) was adsorbed onto alumina (20 g.). After 2 minutes elution with petrol gave 3α-methyl-3β,3'-epoxy-5α-cholestane (0.061 g.) identified by i.r. spectra examination.

The reaction of 3α-methyl-3β,3'-epoxy-5α-cholestane with hydriodic acid

The β-epoxide (0.1 g.) in dry ether (10 ml.) was treated with hydriodic acid (sp. gr. 1.94; 2 ml.) in the same way as for the α-epoxide. A crude product was isolated (0.095 g.) which could not be identified by spectra examination.

Epoxide cleavage with piperidine

3β-Methyl-3α,3'-epoxy-5α-cholestane (0.25 g.) was refluxed for 2 hours with piperidine (10 ml.). Water was added and the steroid extracted with ether. The ether layer was washed with water, dried and the solvent evaporated to give 3β-piperidinomethyl-5α-cholestan-3α-ol (0.241 g.) m.p. 140-141° (acetone) $[\alpha]_D$ +24.5° (c.0.21), $\nu_{max.}$ 3500, 3450-3300 $cm.^{-1}$ (Found: C, 81.7; H, 12.0; N, 3.0. $C_{33}H_{59}ON$ requires C, 81.6; H, 12.2; N, 2.9%).

3α-Methyl-3β,3'-epoxy-5α-cholestane (0.05 g.) in piperidine

(4 ml.) was refluxed for 2 hours and the mixture was worked up as above to give 3α-piperidinomethyl-5α-cholestan-3β-ol (0.047 g.) m.p. 171-174°, $[\alpha]_D$ +28° (c.0.05), $\nu_{max.}$ 3500, 3450-3300 $cm.^{-1}$ (Found: C, 82.0; H, 12.1. $C_{33}H_{59}ON$ requires C, 81.6; H, 12.2%).

The Stereochemistry of Tiffeneau Reactions

Lithium azide in methanol

Lithium chloride (8.5 g.) was dissolved in analar methanol (200 ml.) and powdered sodium azide (15 g.) was added. The mixture was heated under reflux for 5 hours, cooled and kept at 0° for 4 hours after which time it was filtered to give methanolic lithium azide solution.

General method for epoxide cleavage with methanolic lithium azide

The epoxide (1 g.) in chloroform (25 ml.) was added to lithium azide in methanol (100 ml.) and if necessary more methanol was added to obtain a homogeneous solution. This solution was then refluxed overnight (ca.20 hours) and then most of the solvent was removed before the addition of water and ether. The ether layer was washed with water, dried and evaporated to give either the crude azido-alcohol, which was crystallised from acetone, or a mixture of azide-alcohol and starting material, separation of the products being achieved by chromatography on alumina with subsequent crystallisation of the azido-alcohol from acetone.

3β-Azidomethyl-5α-cholestan-3α-ol

By the above method 3β-methyl-3α,3'-epoxy-5α-cholestane (1 g.) gave 3β-azidomethyl-5α-cholestan-3α-ol (0.923 g.) m.p. 120-121°, $[\alpha]_D$ +24° (c.0.11), $\nu_{max.}$ 3560, 2200-2050 (azide) $cm.^{-1}$ n.m.r.τ 9.35 (C-18 methyl group), 9.25, 9.18, 9.09 (C-19 and side chain methyl groups), 6.83, 6.78 (C-3' hydrogens). (Found: C, 75.6; H, 11.4; N, 9.1. $C_{28}H_{49}ON_3$ requires C, 75.8; H, 11.1; N, 9.5%). The

azide was homogeneous on chromatography on alumina (60 g.) with solvents ranging from benzene to ether.

3α-Azidomethyl-5α-cholestan-3β-ol

3α-Methyl-3β,3'-epoxy-5α-cholestane (1.1 g.) gave with these reaction conditions 3α-azidomethyl-5α-cholestan-3β-ol (0.936 g.) m.p. 102-5°, $[\alpha]_D$ +31° (c.0.17), $\nu_{max.}$ 3580, 2200-2050 $cm.^{-1}$; n.m.r. τ 9.34 (C-18 methyl group), 9.17, 9.09 (C-19 and side chain methyl groups), 6.56 (C-3' hydrogens). (Found: C, 75.8; H, 10.9; N, 9.3. $C_{28}H_{49}ON_3$ requires C, 75.8; H, 11.1; N, 9.5%).

3β-Azidomethyl-2α-methyl-5α-cholestan-3α-ol

3β-Methyl-3α,3'-epoxy-2α-methyl-5α-cholestane (0.25 g.) gave 3β-azidomethyl-2α-methyl-5α-cholestan-3α-ol (0.226 g.) m.p. 96-98°, $[\alpha]_D$ +19° (c.0.13), $\nu_{max.}$ 3570, 2200-2080 $cm.^{-1}$ (Found: C, 76.1; H, 11.3; N, 9.7. $C_{29}H_{51}ON_3$ requires C, 76.1; H, 11.2; N, 9.2%).

3α-Azidomethyl-2α-methyl-5α-cholestan-3β-ol

3α-Methyl-3β,3'-epoxy-2α-methyl-5α-cholestane (0.2 g.) gave 3α-azidomethyl-2α-methyl-5α-cholestan-3β-ol (0.188 g.) m.p. 97-99°, $[\alpha]_D$ +32° (c.0.23), $\nu_{max.}$ 3570, 2220-2080 $cm.^{-1}$ (Found: C, 76.2; H, 11.4; N, 8.8. $C_{29}H_{51}ON_3$ requires C, 76.1; H, 11.2; N, 9.2%).

3β-Azidomethyl-2,2-dimethyl-5α-cholestan-3α-ol

3β-Methyl-3α,3'-epoxy-2,2-dimethyl-5α-cholestane (0.5 g.) gave 3β-azidomethyl-2,2-dimethyl-5α-cholestan-3α-ol (0.474 g.) m.p. 112-115°, $[\alpha]_D$ +42° (c.0.21) $\nu_{max.}$ 3560, 2250-2100 $cm.^{-1}$ (Found: C, 76.7; H, 11.4. $C_{30}H_{53}ON_3$ requires C, 76.4; H, 11.3%).

2α-Azidomethyl-5α-cholestan-3β-ol

2α-Methyl-2β,2'-epoxy-5α-cholestane (0.5 g.) gave 2α-azidomethyl-5α-cholestan-2β-ol (0.420 g.) m.p. 125-126°, $[\alpha]_D$ +20° (c. 0.13), $\nu_{max.}$ 3550, 2200-2050 $cm.^{-1}$; n.m.r. τ 9.35 (C-18 methyl group), 9.18, 9.09 (side chain methyl groups), 8.99 (C-19 methyl group), 6.84 (C-3' hydrogens). (Found: C, 75.9; H, 10.8; N, 9.9. $C_{28}H_{49}ON_3$ requires C, 75.8; H, 11.1; N, 9.5%).

2β-Azidomethyl-5α-cholestan-2α-ol

2β-Methyl-2α,2'-epoxy-5α-cholestane (0.22 g.) gave after chromatography on alumina (30 g.) the 2α,2'-epoxide (0.103 g.) on elution with petrol, and a low melting product (0.071 g.) on elution with ether. This last compound could not be crystallised from acetone but was observed to be homogeneous by its rechromatography on alumina (20 g.) with careful elution with solvents ranging from benzene-ether (1:1) to chloroform. By its spectra it was identified as 2β-azidomethyl-5α-cholestan-2α-ol, $\nu_{max.}$ 3550, 2200-2080 (azide) $cm.^{-1}$; n.m.r. τ 9.34 (C-18 methyl group), 9.19, 9.09, 9.07 (C-19 and side chain methyl groups), 6.59 (C-3' hydrogens).

General methods for reduction of azido-alcohols

(a). The azido-alcohol (0.1 g.) in dry ether (10 ml.) was added to lithium aluminium hydride (0.1 g.) in dry ether (10 ml.) and the solution was refluxed for 2 hours. Ethyl acetate and 10% sodium hydroxide solution were added and the ether layer washed with water, dried and the ether was removed to give the α-amino-alcohol which was either crystallised from ethanol or was converted into its acetonide by dissolving it in acetone followed by slow distillation

of the acetone.

(b). The azido-alcohol (0.5 g.) in ethanol (20 ml.) was treated with hydrazine hydrate (1 ml.) and a spatula tip of Raney nickel, and the mixture was heated under reflux for 20 minutes. The catalyst was filtered off and water was added. The steroid was extracted with ether and the ether solution was washed with water, dried and the ether evaporated to give the α-amino-alcohol which was either crystallised or converted into its acetonide as detailed above.

3β-Aminomethyl-5α-cholestan-3α-ol

(a). Reduction of 3β-azidomethyl-5α-cholestan-3α-ol (0.5 g.) with lithium aluminium hydride gave 3β-aminomethyl-5α-cholestan-3α-ol (0.217 g.) m.p. 141-145°, $\nu_{max.}$ 3600, 3200 $cm.^{-1}$ n.m.r. τ 9.36 (C-18 methyl group), 9.26, 9.18, 9.09 (C-19, side chain methyl groups), there were no signals detectable in the region τ 7.0-6.0. (Found: C, 80.5; H, 12.1; N, 3.4. $C_{28}H_{51}ON$ requires C, 80.5; H, 12.3; N, 3.4%).

(b). Reduction of 3β-azidomethyl-5α-cholestan-3α-ol (0.5 g.) with hydrazine hydrate and Raney nickel gave 3β-aminomethyl-5α-cholestan-3α-ol (0.318 g.), identified from its i.r. spectrum.

3β-Aminomethyl-5α-cholestan-3α-ol (0.2 g.) was dissolved in acetone and the acetone slowly distilled off until only 5 ml. remained No material crystallised out and the remaining acetone was removed to give the crude acetonide (0.19 g.) $\nu_{max.}$ 825 $cm.^{-1}$, n.m.r. τ 9.34 (C-18 methyl group), 9.25, 9.19, 9.09 (C-19 and side chain methyl groups), 8.64 (geminal methyl groups of acetonide), 7.13 (C-3'

protons alpha to imino).

3α-Aminomethyl-5α-cholestan-3β-ol

(a). Reduction with lithium aluminium hydride of 3α-azidomethyl-5α-cholestan-3β-ol (0.5 g.) gave 3α-aminomethyl-5α-cholestan-3β-ol (0.263 g.) m.p. 199-202°, $\nu_{max.}$ 3600, 3200 $cm.^{-1}$; n.m.r. τ 9.34 (C-18 methyl group), 9.18, 9.17, 9.09 (side chain and C-19 methyl groups), no detectable signals downfield from τ 7.0.

(b). Reduction of the 3α-aminomethyl-3β-ol (0.1 g.) with hydrazine hydrate and Raney nickel gave 3α-aminomethyl-5α-cholestan-3β-ol (0.062 g.), identified from its i.r. spectrum.

3α-Aminomethyl-5α-cholestan-3β-ol (0.15 g.) was dissolved in acetone and the acetone slowly distilled off until ca.5 ml. remained. The acetonide crystallised out on cooling: m.p. 143-6° (mixed m.p. with the acetonide from the Tiffeneau reactions on 5α-cholestan-3-one,[105] 143-6°) (lit.[136] 145-6°), $\nu_{max.}$ 830, 810 $cm.^{-1}$; n.m.r. τ 9.35 (C-18 methyl group), 9.19, 9.09 (side chain and C-19 methyl group), 8.63 (geminal methyl groups of acetonide), 7.00 (C-3' hydrogens).

3β-Aminomethyl-2α-methyl-5α-cholestan-3α-ol

(a). Reduction with lithium aluminium hydride of 3β-azidomethyl-2α-methyl-5α-cholestan-3α-ol (0.114 g.) gave 3β-aminomethyl-2α-methyl-5α-cholestan-3α-ol (0.063 g.), $\nu_{max.}$ 3600-3200 $cm.^{-1}$ Treatment with acetone in the usual way gave the acetonide (0.041 g.) m.p. 95-97°, $\nu_{max.}$ 818 $cm.^{-1}$; n.m.r. τ 9.34 (C-18 methyl group), 9.19, 9.09 (C-19 and side chain methyl groups), 8.63 (geminal methyl groups), 6.80, 7.00, 7.19, 7.29 (C-3' protons).

3α-Aminomethyl-2α-methyl-5α-cholestan-3β-ol

(a). Reduction with lithium aluminium hydride of 3α-azidomethyl-2α-methyl-5α-cholestan-3β-ol (0.121 g.) gave 3α-aminomethyl-2α-methyl-5α-cholestan-3β-ol (0.059 g.) $\nu_{max.}$ 3600, 3400-3200 $cm.^{-1}$ Treatment with acetone in the usual way gave the acetonide (0.050 g.) (not crystalline - probably due to the presence of a little 3α-aminomethyl-3β-ol (i.r. slight absorption ca.3600-3200 $cm.^{-1}$)). $\nu_{max.}$ 825 $cm.^{-1}$; n.m.r. τ 9.34 (C-18 methyl group), 9.19, 9.09 (C-19 and side chain methyl groups). 8.63 (geminal methyl groups), protons attributable to C-3' hydrogens at 6.90, 7.10 but other peaks obscured, (lit.[105] τ 6.70, 6.90, 7.09, 7.29).

3β-Aminomethyl-2,2-dimethyl-5α-cholestan-3α-ol

(a). Reduction of 3β-azidomethyl-2,2-dimethyl-5α-cholestan-3α-ol (0.212 g.) with lithium aluminium hydride gave 3β-aminomethyl-2,2-dimethyl-5α-cholestan-3α-ol (0.108 g.) $\nu_{max.}$ 3600, 3200 $cm.^{-1}$ Acetonide formation in the usual manner gave a glass (0.093 g.), $\nu_{max.}$ 820 $cm.^{-1}$ n.m.r. τ 9.34 (C-18 methyl group), 9.19, 9.12, 9.09, 8.99, 8.92, 8.72 (C-19 and side chain methyl groups plus also possibly acetonide methyl groups), 8.55 (acetonide methyl groups), C-3' protons at ca.7.0 (pattern not clear).

2α-Aminomethyl-5α-cholestan-2β-ol

(a). Reduction of 2α-azidomethyl-5α-cholestan-2β-ol (0.25 g.) with lithium aluminium hydride gave 2α-aminomethyl-5α-cholestan-2β-ol (0.170 g.) $\nu_{max.}$ 3600, 3200 $cm.^{-1}$ Refluxing with acetone, followed by slow distillation off of the acetone gave a glass (0.146 g.) identifiable as the acetonide, $\nu_{max.}$ 820 $cm.^{-1}$

The crude acetonide from the 2α-aminomethyl-2β-ol (0.1 g.) was dissolved in glacial acetic acid (10 ml.) and ether (4 ml.) and cooled to ca.-10°. A solution of sodium nitrite (0.5 g.) in water (4 ml.) was added over 2½ hours, so that the temperature did not exceed -5° during this time. The solution was poured into water and the steroids extracted into ether. The ether layer was washed with sodium carbonate solution and water, dried and the ether evaporated to give a pale brown oil (0.08 g.) with i.r. absorptions at 3600, 3200, 1695 $cm.^{-1}$ The oil was adsorbed onto alumina (10 g.) and elution with petrol-benzene (1:1) gave a ketonic product (0.012 g.), $\nu_{max.}$ 1695 $cm.^{-1}$ which showed two peaks on g.l.c. (Perkin Elmer F11 - full details are given in the introduction to the Experimental Section). One had a retention time with respect to 5α-cholestan-3-one at 1.25, with the other having a retention time 1.40 with respect to 5α-cholestan-3-one. Since on the same instrument 5α-cholestan-2-one was found to have a retention time with respect to 5α-cholestan-3-one of 1.26 the first peak of the product was assumed to be 5α-cholestan-2-one. The second retention time of the nitrous acid experiment product was similar to that for A-homo-5α-cholestan-4-one (1.4 with respect to 5α-cholestan-3-one) but different from that of A-homo-5α-cholestan-3-one (1.35 with respect to 5α-cholestan-3-one) and thus the second peak was assumed to belong to A-homo-5α-cholestan-2-one. Separation of these two compounds by chromatography on alumina (10 g.) with elution with solvents from petrol-benzene (9:1) to benzene was not possible. Similarly no separation was possible on crystallisation from acetone (m.p. 85-103°).

The Preparation and Reactions of Methylene Epoxides

(2) Epoxides adjacent to a polar group

The epoxidation of cholest-4-en-3-one with dimethylsulphonium methylide[4]

Dimethylsulphonium methylide was prepared from trimethylsulphonium iodide (8 g.) and methylsulphinyl carbanion (from sodium hydride (1.5 g.)) in dimethyl sulphoxide (70 ml.) by the method outlined on page 125. Cholest-4-en-3-one (5.0 g.) in tetrahydrofuran (35 ml.) was quickly added and the mixture was stirred at ca.-10° for five minutes and for one hour as the reaction temperature rose to room temperature. The crude product (4.7 g.), isolated by means of ether, had i.r. absorptions at 3050, 1730 (m), 1695 (m), 940 (s), 880 $cm.^{-1}$, and n.m.r. peaks at τ 9.31 (C-18 methyl group), 9.19, 9.09, 9.07, 8.90 (C-19 and side chain methyl groups), 7.23 (C-3' hydrogens of methylene epoxide). Attempts to recrystallise the crude product from acetone failed, evaporation of the solvent giving an oil (i.r. 3500-3200 $cm.^{-1}$).

The experiment was then repeated with trimethylsulphonium iodide (8 g.) and cholest-4-en-3-one (5 g.) in the usual manner, isolation by means of ether, giving a crude product (4.42 g.) with an i.r. spectrum identical to that of the crude product from the first attempted epoxidation of cholest-4-en-3-one. This second crude epoxide mixture was adsorbed onto alumina (500 g.) and elution with petrol-benzene (99:1) gave, on crystallisation from acetone, an α,β-unsaturated-5α-cholestan-3-aldehyde (0.321 g.) m.p. 110-112°, $\lambda_{max.}$ 235 mμ (ϵ 13,100), $\nu_{max.}$ 2680, 1680, 1660 $cm.^{-1}$,

n.m.r. τ 9.33 (C-18 methyl group), 9.18, 9.09 (side chain methyl groups), 8.95 (C-19 methyl group), 3.43 (proton on β-carbon of the α,β-unsaturated aldehyde system), 0.49 (aldehyde). (Found: C, 84.1; H, 11.8. $C_{28}H_{48}O$ requires C, 83.9; H, 12.1%).

Elution with petrol-benzene (98:2) gave a second α,β-unsaturated-3-aldehyde, as a gum, (0.062 g.): $\lambda_{max.}$ 235 mμ., $\nu_{max.}$ 2680, 1680, 1660 $cm.^{-1}$; n.m.r. τ 9.32 (C-18 methyl group), 9.27, 9.18, 9.09, 8.73 (C-19 and side chain methyl groups), 3.56 (double bond hydrogen), 0.57 (aldehyde). This compound (0.020 g.) in aqueous ethanol (90%, 10 ml.) containing KOH (0.040 g.) was kept at room temperature for 18 hours. Work up with ether gave a crude aldehyde (0.013 g.), identical in spectra with the starting material.

Elution of the column with solvent systems varying from benzene to ether gave fractions, (total 0.911 g.), whose i.r. spectra contained ketonic absorptions, none of which could be recrystallised from acetone nor identified.

Elution with chloroform-methanol (95:5) gave hydroxy-material (2.871 g.) ($\nu_{max.}$ 3400-3200 $cm.^{-1}$), as an oil. Crystallisation from acetone or ethanol was not possible, and the material was not characterised.

The addition of dimethylsulphonium methylide (from trimethylsulphonium iodide (8 g.)) to cholest-4-en-3-one (5 g.) was repeated, in the usual way, giving the required crude epoxides (i.r.) (4.17 g.) on ether work up. This product was divided into three approximately equal portions. One portion (1.5 g.) was adsorbed onto neutral alumina (100 g.), deactivated by shaking with water to activity III. Elution with petrol-benzene mixtures gave the two

α,β-unsaturated aldehydes (0.037 g.) and (0.011 g.) respectively, and again unknown ketones (0.141 g.) were eluted with benzene-ether solvent mixtures. Non-crystallisable material (0.98 g.) was eluted with chloroform-methanol (95:5), $\nu_{max.}$ 3400-3200 $cm.^{-1}$ The other two portions of the epoxide mixture were chromatographed on florisil (100 g.) and silica gel (150 g.). In both cases neither epoxide separation nor alcohol formation was observed.

Synthesis of the epoxides of 3-methylene-5α-cholestan-2-one

2β-Hydroxy-3α-acetoxy-5α-cholestane[113]

2β,3β-Epoxy-5α-cholestane (4 g.) was heated on a water bath at ca.90° with redistilled and dried acetic acid (56 ml.) for 3 hours. The acetic acid was removed under reduced pressure, giving on crystallisation from acetone 2β-hydroxy-3α-acetoxy-5α-cholestane (2.67 g.) m.p. 137-139° (lit.[113] for analytical sample 138.7-139.2°).

3α-Acetoxy-5α-cholestan-2-one[112,113]

2β-Hydroxy-3α-acetoxy-5α-cholestane (3 g.) was dissolved in acetone (200 ml.) and oxidised with 8N chromic acid (Jones' reagent) (6 ml.). The reaction was allowed to proceed for 4 minutes and excess reagent was decomposed with methanol (25 ml.). Water was added, the acetone removed under reduced pressure and the steroid extracted into ether. The ether solution was washed with water until the washings were neutral, dried and the ether evaporated to give 3α-acetoxy-5α-cholestan-2-one (2.66 g.) m.p. 149-150° (lit.[113] 150.2-150.9°), $\nu_{max.}$ 1742, 1720, 1235, 1040 $cm.^{-1}$; n.m.r. τ 9.34 (C-18 methyl group), 9.22, 9.19, 9.09 (C-19 and side chain methyl groups), 8.89 (acetate).

Attempted ketalisation of 3α-acetoxy-5α-cholestan-2-one

3α-Acetoxy-5α-cholestan-2-one (1 g.) in triethyl orthoformate (8 ml.) and ethylene glycol (1 ml.) was treated with toluene-p-sulphonic acid (0.050 g.) and the mixture was refluxed for 10 minutes, followed by distillation. The mixture was then poured into sodium bicarbonate solution and the steroid extracted into ether. The

ether solution was washed with water, dried and the solvent was removed to give the 3α-acetoxy-2-one (0.86 g.) m.p. and mixed m.p. 147-149° (acetone).

3-Acetoxy-2,2-ethylenedioxy-5α-cholestane

3α-Acetoxy-5α-cholestan-2-one (1 g.) and ethylene glycol (5 ml.) were dissolved in hot acetic acid (25 ml.) and the solution was cooled to ca.40° and freshly distilled boron trifluoride etherate (4 ml.) was added. After allowing the mixture to stand at room temperature for 9 hours, the resultant precipitate was collected and crystallised from acetone to give 3-acetoxy-2,2-ethylenedioxy-5α-cholestane (0.528 g.), m.p. 122-124°, $\nu_{max.}$ 1738, 1247, 1053 cm^{-1}; n.m.r. τ 9.34 (C-18 methyl group), 9.18, 9.09 (C-19 and side chain methyl groups), 7.92 (acetate), 6.06 (-O-CH_2-CH_2-O-).[133] (Found: C, 76.1; H, 10.7. $C_{31}H_{52}O_4$ requires C, 76.2; H, 10.7%).

3-Hydroxy-2,2-ethylenedioxy-5α-cholestane

2,2-Ethylenedioxy-5α-cholestan-3-ol acetate (1.3 g.) was dissolved in methanol (200 ml.) and was added to a solution of potassium hydroxide (3 g.) in 5% aqueous methanol (100 ml.). The mixture was refluxed for 3 hours and then most of the methanol was removed under reduced pressure. Water was added and the steroid was extracted with ether. The ether solution was washed with water, dried and the ether evaporated to give 2,2-ethylenedioxy-5α-cholestan-3-ol (0.951 g.) m.p. 128-129° (acetone). $\nu_{max.}$ 3530, 1245, 1220, 1360, 1100, 1090, 1058, 975, 950 cm^{-1}

2,2-Ethylenedioxy-5α-cholestan-3-one

Chromium trioxide (2.5 g.) was added with vigorous stirring to pyridine (35 ml.) at 0°-5°.[116] A yellow slurry of chromium trioxide-pyridine complex was obtained and to it was added 2,2-ethylenedioxy-5α-cholestan-3-ol (2.0 g.) in pyridine (25 ml.). The mixture was stirred for 30 minutes and left at room temperature for 20 hours, before being poured into water. The steroid was extracted with ether and the ether solution was washed with water, dried and the ether evaporated to give, on crystallisation from acetone, 2,2-ethylenedioxy-5α-cholestan-3-one (1.747 g.), m.p. 149-152°, $[\alpha]_D$ +51° (c,0.13), $\nu_{max.}$ 1720 $cm.^{-1}$, n.m.r. τ 9.34 (C-18 methyl group), 9.19, 9.10, 8.92 (C-19, and side chain methyl groups), 6.03 (ethylene ketal). (Found: C, 78.0; H, 10.7. $C_{29}H_{48}O_3$ requires C, 78.3; H, 10.9%).

3-Methylene-2,2-ethylenedioxy-5α-cholestane

Methylsulphinyl carbanion in dimethyl sulphoxide (30 ml.)(from sodium hydride (0.2 g.)) was prepared in the usual way, and from it was prepared methylenetriphenylphosphorane by the addition of methyltriphenylphosphonium bromide (2.5 g.). 2,2-Ethylenedioxy-5α-cholestan-3-one (0.35 g.) in tetrahydrofuran (20 ml.) was added and the mixture was heated at 50° for 13 hours. Water was added and the steroid extracted with ether. The ether solution was washed with water, dried and the ether removed under reduced pressure to give a crude product which was adsorbed onto alumina (activity II) (60 g.). Elution with petrol-benzene (1:1) gave a crude product (aromatic biproducts) which was crystallised from ether-methanol to

give 3-methylene-2,2-ethylenedioxy-5α-cholestane (0.282 g.), m.p. 101-102°, $\nu_{max.}$ 1650, 1190, 1120, 1080, 915, 910, 840 $cm.^{-1}$; n.m.r. τ 9.34 (C-18 methyl group), 9.18, 9.09 (side chain methyl groups), 8.99 (C-19 methyl group), 6.09, 6.06 (ethylene ketal), 5.29, 5.01 (C-3' hydrogens). (Found: C, 81.9; H, 11.1. $C_{30}H_{50}O_2$ requires C, 81.4; H, 11.4%).

3β-Methyl-3α,3'-epoxy-2,2-ethylenedioxy-5α-cholestane

(a) Dimethyloxosulphonium methylide (from trimethyloxosulphonium iodide (0.4 g.)) was prepared as described on page 122, and to the ylide solution was added 2,2-ethylenedioxy-5α-cholestan-3-one (0.40 g.) in tetrahydrofuran (10 ml.). The mixture was stirred for 40 minutes at room temperature and then for 2 hours at 55°, cooled, and water added. The steroid was extracted into ether and the ether layer was washed with water, dried and the ether evaporated to give, after crystallisation from acetone, 3β-methyl-3α,3'-epoxy-2,2-ethylenedioxy-5α-cholestane (0.289 g.) m.p. 76-80°, $\nu_{max.}$ 1170, 1060, 982, 950, 838, 750 $cm.^{-1}$; n.m.r. τ 9.34 (C-18 methyl group), 9.18, 9.09, 9.00, 8.79, 8.76 (side chain and C-19 methyl groups), 7.44, 7.37, 7.07, 6.99 (C-3' hydrogens), 6.09, 6.00 (ethylene ketal).

(b) 3-Methylene-2-ethylenedioxy-5α-cholestane (0.20 g.) in dry ether (20 ml.) was added to m-chloroperbenzoic acid (80%, 0.20 g.) in dry ether (50 ml.) and the solution was allowed to stand at room temperature overnight. The ethereal solution was then washed with ferrous sulphate solution, water, sodium bicarbonate solution, and water, dried and the ether was removed to give on crystallisation from acetone 3β-methyl-3α,3'-epoxy-2,2-ethylenedioxy-5α-cholestane

(0.163 g.) m.p. and mixed m.p. 75-79°.

3β-Methyl-3α,3'-epoxy-5α-cholestan-2-one

Hydrogen bromide gas was passed through a chloroform solution (50 ml.) of 3β-methyl-3α,3'-epoxy-2-ethylenedioxy-5α-cholestane (0.170 g.) for 20 minutes at room temperature, and the solution was set aside for 90 minutes. The chloroform solution was washed with water, sodium carbonate solution and water dried and the chloroform evaporated to give a crude product (0.152 g.) $\nu_{max.}$ 3500, 1715, 938 $cm.^{-1}$, which was adsorbed on alumina (40 g.). Elution with petrol-benzene (1:1) gave a product (0.051 g.) which was crystallised from acetone with difficulty to give 3β-methyl-3α,3'-epoxy-5α-cholestan-2-one (0.008 g.), m.p. 144-148°, $\nu_{max.}$ 3050, 1718, 940, 835 $cm.^{-1}$, n.m.r. τ 9.34 (C-18 methyl group), 9.19, 9.09, 9.05, 8.73 (C-19 and side chain methyl groups), 7.20 (CH_2-O-, epoxide).

The synthesis and reactions of 3-oxygenated-2-methylene epoxides

2-N-Piperidinomethylene-5α-cholestan-3-one

2-Hydroxymethylene-5α-cholestan-3-one (10 g.) was dissolved in benzene (200 ml.) and piperidine (10 ml.) and heated under reflux for 15 minutes. Removal of the benzene, filtration and crystallisation from acetone gave 2-N-piperidinomethylene-5α-cholestan-3-one (10.1 g.) m.p. 127-130°, $[\alpha]_D$ -214° (c.0.22), $\nu_{max.}$ 1655 $cm.^{-1}$, $\lambda_{max.}$ 334 mμ (ϵ 22,800), n.m.r. τ 9.34 (C-18 methyl group), 9.19, 9.09 (side chain and C-19 methyl groups), 6.57 (ca. 4 protons - hydrogens adjacent to N in piperidine ring), 2,48 (C-2' hydrogen). (Found: C, 82.5; H, 11.3; N, 3.0. $C_{33}H_{55}ON$ requires C, 82.3; H, 11.5; N, 2.9%).

2-Methylene-5α-cholestan-3β-ol

Sodium borohydride (5 g.) was added to a solution of 2-N-piperidinomethylene-5α-cholestan-3-one (5 g.) in methanol (320 ml.) at 0° (ice bath) and the reaction was left at this temperature for 5 hours. During this time a precipitate formed which was collected and crystallised from acetone to give 2-methylene-5α-cholestan-3β-ol (3.371 g.), m.p. 129-131°, $[\alpha]_D$ -5° (c.0.14); $\nu_{max.}$ 3560, 3050, 1645, 895 $cm.^{-1}$; n.m.r. τ 9.34 (C-18 methyl group), 9.30, 9.19, 9.09 (C-19, and side chain methyl groups), 5.26, 5.00 (C-2' hydrogens) (Found: C, 83.8; H, 12.0. $C_{28}H_{48}O$ requires C, 83.9; H, 12.1%).

2-Methylene-5α-cholestan-3β-ol acetate

2-Methylene-5α-cholestan-3β-ol (2.0 g.) was acetylated with acetic anhydride (10 ml.) and pyridine (10 ml.) at room temperature

overnight. Work up in the usual way, (p.134), and crystallisation from acetone gave 2-methylene-5α-cholestan-3β-ol acetate (1.937 g.) m.p. 91-92°, $[\alpha]_D$ -3° (c.0.12), $\nu_{max.}$ 3050, 1738, 1650, 1238, 1039, 895 $cm.^{-1}$; n.m.r. τ 9.34 (C-18 methyl group), 9.29, 9.18, 9.09 (C-19, and side chain methyl groups), 7.89 (acetate), 5.29, 5.17 (C-2' hydrogens). (Found: C, 81.3; H, 11.4. $C_{30}H_{50}O_2$ requires C, 81.4; H, 11.4%).

2α-Methyl-2β,2'-epoxy-5α-cholestan-3β-ol

(a) 2-Methylene-5α-cholestan-3β-ol (2.5 g.) in dry ether (200 ml.) was added to an ether solution (100 ml.) of m-chloroperbenzoic acid (80%, 2.5 g.) and the mixture was allowed to stand at room temperature overnight. The ethereal solution was then washed with ferrous sulphate solution, water, sodium bicarbonate solution and water, dried and the ether evaporated to give on crystallisation from acetone 2α-methyl-2β,2'-epoxy-5α-cholestan-3β-ol (2.086 g.) m.p. 162-164°, $[\alpha]_D$ +13° (c.0.15) $\nu_{max.}$ 3550, 1095, 1080, 1065, 940, 835, 700 $cm.^{-1}$; n.m.r. τ 9.34 (C-18 methyl group), 9.19, 9.15, 9.09 (C-19 and side chain methyl groups), 7.49, 7.41, 6.80, (C-2' epoxide protons). (Found: C, 80.7; H, 11.6. $C_{28}H_{48}O_2$ requires C, 80.7; H, 11.6%).

(b) 2-Methylene-5α-cholestan-3β-ol (0.51 g.) in benzene-chloroform (1:1) (50 ml.) was added to m-chloroperbenzoic acid (80%, 0.5 g.) in benzene-chloroform (1:1) (50 ml.). The mixture was allowed to stand at room temperature overnight before being worked up as in the previous example to give 2α-methyl-2β,2'-epoxy-5α-cholestan-3β-ol (0.431 g.) m.p. and mixed m.p. 162-164° (acetone).

2α-Methyl-2β,2'-epoxy-5α-cholestan-3β-ol acetate

A mixture of 2α-methyl-2β,2'-epoxy-5α-cholestan-3β-ol (0.25 g.), pyridine (5 ml.) and acetic anhydride (2.5 ml.) was kept at room temperature overnight before being poured into water. The steroid was then extracted with ether and the ether solution was washed with water, dried and the ether evaporated to give on crystallisation from acetone 2α-methyl-2β,2'-epoxy-5α-cholestan-3β-ol acetate (0.264 g.) m.p. 153-155°, $[\alpha]_D$ -7° (c.0.11); $\nu_{max.}$ 1640, 1230, 942, 905, 835 $cm.^{-1}$; n.m.r. τ 9.34 (C-18 methyl group), 9.19, 9.12, 9.09 (C-19 and side chain methyl groups), 8.00 (acetate), 7.53, 7.44, 6.99, 6.90 (C-2', epoxide hydrogens). (Found: C, 78.7; H, 11.0. $C_{30}H_{50}O_3$ requires C, 78.6; H, 11.0%).

2α-Methyl-2β,2'-epoxy-5α-cholestan-3-one

2α-Methyl-2β,2'-epoxy-5α-cholestan-3β-ol (3.0 g.) in acetone (200 ml.) was oxidised with 8N chromic acid (Jones' reagent) (6 ml.). The reaction was allowed to proceed for 4 minutes and excess reagent was decomposed with methanol (20 ml.). Water was added, the acetone removed under reduced pressure and the steroid extracted into ether. The ethereal solution was washed with water, dried and the ether evaporated to give on crystallisation from acetone 2α-methyl-2β,2'-epoxy-5α-cholestan-3-one (2.699 g.) m.p. 164-166°, $[\alpha]_D$ +22° (c.0.20), $\nu_{max.}$ 1720, 830 $cm.^{-1}$; n.m.r. τ 9.33 (C-18 methyl group), 9.19, 9.09 (side chain methyl groups), 8.94 (C-19 methyl group), downfield protons (C-1, C-4) at 8.26, 8.14, 7.70, 7.58, and 7.36, 7.26, 7.22, 7.12 (exocyclic epoxide protons). (Found: C, 81.3; H, 10.9. $C_{28}H_{46}O_2$ requires C, 81.1; H, 11.2%).

The epoxidation of 2-methylene-5α-cholestan-3β-ol acetate and the subsequent alterations of the C-3 functional groups

2-Methylene-5α-cholestan-3β-ol (2.5 g.) in dry ether (50 ml.) was added to a solution of m-chloroperbenzoic acid (80%, 2.5 g.) in dry ether (50 ml.). The mixture was allowed to stand at room temperature overnight before being worked up in the usual way with ferrous sulphate solution, sodium bicarbonate solution, and water. The crude product so obtained was crystallised from acetone to give the mixture of 2,2'-epoxy-5α-cholestan-3β-ol acetates (1.783 g.), m.p. 120-130°. This material was recrystallised three times from acetone to give a m.p. 120-129°; $[\alpha]_D$ -6° (c.0.22); $\nu_{max.}$ 1640, 1230, 905 (broad), 835 $cm.^{-1}$; n.m.r. τ 9.35 (C-18 methyl group), 9.19, 9.12, 9.09 (C-19 and side chain methyl groups), 8.00 (acetate), 7.54, 7.45, 7.10, 6.91 (epoxide). (Found: C, 78.6; H, 11.3. $C_{30}H_{50}O_3$ requires C, 78.6; H, 11.0%).

To the 2,2'-epoxy-3-acetoxy-product (0.5 g.) in warm methanol (60 ml.) was added dropwise a solution of potassium carbonate (0.4 g.) in water (5 ml.). The resulting reaction mixture was allowed to stand for 1 hour during which time the temperature fell to room temperature. Most of the methanol was then removed under reduced pressure and water and ether were added. The ether solution was washed with water, dried and the ether evaporated to give the mixture of 2-methyl-2,2'-epoxy-5α-cholestan-3β-ols (0.359 g.) m.p. 126-150° (most melting 127-134°) (acetone), $[\alpha]_D$ +9° (c.0.18); $\nu_{max.}$ 3550, 1095, 1080, 1065, 940, 900, 835 $cm.^{-1}$; n.m.r. τ 9.34 (C-18 methyl group), 9.19, 9.15, 9.09 (C-19 and side chain methyl groups), 7.49, 7.41, 6.80, 6.88 (epoxide) (Found: C, 80.3; H, 11.7. $C_{28}H_{48}O_2$

requires C, 80.7; H, 11.6%).

The 2-methyl-2,2'-epoxy-5α-cholestan-3β-ol product (m.p. 126-150°) (0.30 g.) in acetone (30 ml.) was oxidised with 8N chromic acid (Jones' reagent) (0.70 ml.). The reaction was allowed to proceed for 4 minutes and excess reagent was decomposed with methanol (5 ml.). Water was added, the acetone removed under reduced pressure and the steroid extracted with ether. The ethereal solution was washed with water, dried and the ether evaporated to give on crystallisation from acetone 2α-methyl-2β,2'-epoxy-5α-cholestan-3-one (0.239 g.) m.p. 164-166°, mixed m.p. 161-166°, $[\alpha]_D$ +25° (c.0.21).

Treatment of 2α-methyl-2β,2'-epoxy-5α-cholestan-3β-ol with HBr

2α-Methyl-2β,2'-epoxy-5α-cholestan-3β-ol (0.418 g.) in acetone (40 ml.) and tetrahydrofuran (10 ml.) was treated with hydrobromic acid (48%, 25 drops). After standing at room temperature for 1 hour, the reaction mixture was poured into water and the steroid was extracted with ether. The ether solution was washed with water until the washing were neutral, dried and the ether evaporated to give on crystallisation from acetone 2α-bromomethyl-5α-cholestan-2β,3β-diol (0.446 g.) m.p. 202-204°, $[\alpha]_D$ -2° (c.0.11); ν max. 3580, 1100, 1075, 1050, 1020 $cm.^{-1}$; n.m.r. τ 9.34 (C-18 methyl group), 9.19, 9.09 (C-19 and side chain methyl groups), signals at 6.18, 6.08 belonging to $-C\underline{H}_2-Br$. (Found: C, 67.5; H, 10.2; Br, 16.2. $C_{28}H_{49}O_2Br$ requires C, 67.3; H, 9.9; Br, 16.0%).

2α-Bromomethyl-5α-cholestan-2β,3β-diol (0.112 g.) was adsorbed on alumina (25 g.). After 10 minutes elution with ether and crystallisation from acetone gave 2α-methyl-2β,2'-epoxy-5α-cholestan-

3β-ol (0.081 g.) m.p. and mixed m.p. 162-164°.

2α-Bromomethyl-5α-cholestan-2β,3β-diol (0.10 g.) was treated with acetic anhydride (2 ml.) in pyridine (4 ml.) and allowed to stand at room temperature overnight. The crude product (0.10 g.), isolated by means of ether, possessed $\nu_{max.}$ 3560, 1740, 1235, 1030 $cm.^{-1}$; n.m.r. τ 9.34 (C-18 methyl group), 9.19, 9.09 (side chain and C-19 methyl groups), 7.94 (3 protons, acetate), protons at 7.65, 7.41, 6.32 (-$C\underline{H}_2$Br). This crude product (0.090 g.) was treated with acetic anhydride (5 ml.) in pyridine (10 ml.) and allowed to stand at room temperature for 2 days. The product (0.079 g.), isolated by means of ether, could not be crystallised from acetone, and had spectra (i.r. and n.m.r.) identical to those of the starting material.

Treatment of 2α-methyl-2β,2'-epoxy-5α-cholestan-3-one with HBr

2α-Methyl-2β,2'-epoxy-5α-cholestan-3-one (0.45 g.) in dry ether (10 ml.) and acetic acid (30 ml.) was treated with hydrogen bromide in acetic acid (40%, 0.6 ml.) at room temperature for 1 hour. The reaction mixture was then poured into water and the steroid extracted with ether. The ether solution was washed with sodium carbonate solution and with water, dried, and the solvent evaporated to give, on crystallisation from acetone 2α-bromomethyl-2β-hydroxy-5α-cholestan-3-one (0.484 g.) m.p. 174-177°, $[\alpha]_D$ +80° (c.0.1); $\nu_{max.}$ 3480, 1715, 1265, 1235, 1185, 1035, 935 $cm.^{-1}$; n.m.r. τ 9.34 (C-18 methyl group), 9.19, 9.09 (side chain methyl groups), 8.87 (C-19 methyl group), protons at 7.55, 7.30, and 6.48, 6.30, 6.29, 6.00 ($C\underline{H}_2$-Br). (Found: C, 67.8; H, 9.7; Br, 16.9. $C_{28}H_{47}O_2Br$ requires C, 67.7; H, 9.5;

Br, 16.1%).

2α-Bromomethyl-2β-hydroxy-5α-cholestan-3-one (0.057 g.) was adsorbed on alumina (25 g.). After 15 minutes elution with ether gave 2α-methyl-2β,2'-epoxy-5α-cholestan-3-one (0.043 g.), identified by i.r. spectra examination.

2α-Bromomethyl-2β-hydroxy-5α-cholestan-3-one (0.1 g.) was treated with acetic anhydride (4 ml.) in pyridine (8 ml.), and allowed to stand at room temperature overnight. Work up in the usual manner with ether and water gave 2α-bromomethyl-2β-hydroxy-5α-cholestan-3-one (0.091 g.), identified from its i.r. spectrum.

Treatment of 2α-methyl-2β,2'-epoxy-5α-cholestan-3-one with BF_3 in benzene

a) 2α-Methyl-2β,2'-epoxy-5α-cholestan-3-one (0.5 g.) in dry benzene (50 ml.) was allowed to react with boron trifluoride-etherate (0.5 ml.) for 5 minutes. The product (0.5 g.), isolated by means of ether, could not be crystallised from acetone or methanol, and was adsorbed on alumina. Elution with solvent systems from petrol to chloroform gave gums (total 0.119 g.) which could not be characterised from their i.r. spectra. Elution with chloroform-10% methanol gave an unknown trace quantity of material (0.011 g.).

b) 2α-Methyl-2β,2'-epoxy-5α-cholestan-3-one (0.1 g.) in redistilled benzene (10 ml.) was treated with twice redistilled boron trifluoride-etherate (0.1 ml.) and allowed to stand at room temperature for 5 minutes. Work up with ether and water gave after crystallisation from acetone 2α-methyl-2β,2'-epoxy-5α-cholestan-3-one (0.080 g.) m.p. and mixed m.p. 161-165°.

c) The above experiment was repeated for the 2β,2'-epoxide (0.1 g.), in redistilled benzene (10 ml.), with twice redistilled boron trifluoride-etherate (0.1 ml.), and reaction times from 10 minutes to 5 hours. On ether-water work up, in each case only 2α-methyl-2β,2'-epoxy-5α-cholestan-3-one was isolated (yields all in the range 0.085-0.096 g.), the identification of the epoxide resulting from i.r. spectra.

d) 2α-Methyl-2β,2'-epoxy-5α-cholestan-3-one (0.253 g.) in redistilled benzene (25 ml.) was treated with twice redistilled boron trifluoride-etherate (0.25 ml.) and allowed to stand at room temperature overnight. The product, isolated by means of ether, was crystallised from acetone to give A-homo-5α-cholestan-2,4-dione (0.166 g.) m.p. 162-165°, $[\alpha]_D$ +52° (c.0.08); $\nu_{max.}$ 1710 (m), 1658 (s), 1630 (s) $cm.^{-1}$; $\lambda_{max.}$ 279 mμ (ϵ 6,700)(ethanol), 318 mμ (ϵ 11,100) (0.01 N NaOH in ethanol-water (9:1)); n.m.r. τ 9.34 (C-18 methyl group), 9.24, 9.19, 9.09 (C-19 and side chain methyl groups). (Found: C, 80.9; H, 11.0. $C_{28}H_{46}O_2$ requires C, 81.1; H, 11.2%).

Treatment of A-homo-5α-cholestan-2,4-dione with bromine

Pyridinium hydrobromide perbromide (0.17 g.) was added to a warm solution (ca.40°) of A-homo-5α-cholestan-2,4-dione (0.091 g.) in acetic acid (5 ml.). After 1 hr. the mixture was poured into water and the steroid was extracted with methylene chloride. The organic layer was washed well with water, dried and the solvent evaporated to give a gum (0.082 g.); $\nu_{max.}$ 1720, 1700 $cm.^{-1}$

Ethylidene Epoxides

The synthesis and reactions of the epoxides of 3-ethylidene-5α-cholestane

Ethyltriphenylphosphonium iodide[127]

A solution of triphenylphosphine (58 g.) in ethyl iodide (150 ml.) was heated under reflux for two days. The precipitate was filtered, washed with benzene and dried to give ethyltriphenylphosphonium iodide (94 g.) m.p. 163-165° (lit.[127] m.p. 163-164.5°).

Reaction of 5α-cholestan-3-one with ethylidenetriphenylphosphorane

Sodium hydride (1.5 g.), obtained from a 50% dispersion in oil by washing three times with dry petrol and then blowing dry with nitrogen, was stirred with dry dimethyl sulphoxide (50 ml.) at 70-75°, until evolution of hydrogen ceased (ca.45 min.). The resulting solution of methylsulphinyl carbanion was then cooled, and tetrahydrofuran (50 ml.) was added. To this solution at 0° was added, under nitrogen, ethyltriphenylphosphonium iodide (20 g.), rapid stirring producing the deep red solution of ethylidenetriphenylphosphorane. 5α-Cholestan-3-one (3 g.), in tetrahydrofuran (20 ml.), was added to the ylide solution and the mixture was stirred, under nitrogen at 55-60°, overnight. Water was then added and the steroid was extracted with ether. The ether solution was washed with water, dried and the ether evaporated to give a product which was chromatographed on alumina (activity II) (400 g.) to give, on elution with petrol, the ethylidene-compounds (2.564 g.). Crystallisation from methanol-ether gave 3-ethylidene-5α-cholestane (I) (1.973 g.) m.p. 51-55° (lit.[126] m.p. for the major olefin from the Wittig reaction

56-57°), $[\alpha]_D$ +23° (c.0.19) (lit.[126] for the major olefin from the Wittig reaction + 15°); $\nu_{max.}$ 818, 815 cm.$^{-1}$ n.m.r. τ 9.35 (C-18 methyl group), 9.19, 9.17, 9.09 (C-19 and side chain methyl groups), 8.53, 8.40 ($\underline{CH_3}$-$\underline{C}$=$\underline{C}$-), the C-3' hydrogen appeared at about 4.85, but the absorption pattern was not clear.

Hydration of 3-ethylidene-5α-cholestane (I)

3-Ethylidene-5α-cholestane (I) (0.7 g.) was dissolved in tetrahydrofuran (200 ml.) and powdered sodium borohydride (1 g.) was added. The mixture was cooled in an ice bath and boron trifluoride-etherate (5 ml.) in tetrahydrofuran (25 ml.) was added over 1 hour, and the mixture was stirred for a further hour at room temperature before the addition of water (25 ml.). Aqueous sodium hydroxide (50 ml., 10% solution) was then added and the solution was cooled in an ice-bath. Hydrogen peroxide (30%, 30 ml.) was added dropwise with stirring and continued cooling. The mixture was stirred for 1 hour at 0° and diluted with water and ether. The ether solution was washed with sodium bisulphite solution and water, dried and the solvent evaporated. The product was filtered through alumina (activity II) (150 g.) with ether and crystallised from acetone to give 3-(1'-hydroxyethyl)-5α-cholestane (0.517 g.), m.p. 106-116°, $\nu_{max.}$ 3600 cm.$^{-1}$ (Found: C, 83.4; H, 12.4. $C_{29}H_{52}O$ requires C, 83.6; H, 12.6%).

Oxidation of 3-(1'-hydroxyethyl)-5α-cholestane

3-(1'-Hydroxyethyl)-5α-cholestane (0.1 g.) in acetone (20 ml.) was oxidised with 8N chromic acid (Jones' reagent) (0.25 ml.). The

reaction was allowed to proceed for 4 minutes and excess reagent was decomposed with methanol (5 ml.). Water was added, the acetone removed under reduced pressure and the steroid extracted into ether. The ether solution was washed with dilute hydrochloric acid, with water, until the washings were neutral, dried and the ether evaporated to give, on crystallisation from acetone, 3β-acetyl-5α-cholestane (0.088 g.) m.p. 108-109° $[\alpha]_D$ +30° (c.0.10) (lit.[129] m.p. 110-111°; $[\alpha]_D$ +29.5°); $\nu_{max.}$ 1705, 1355 cm.$^{-1}$; R.D. $[\bar{\Phi}]_{455}$ +25°, $[\bar{\Phi}]_{304}$ +108°, $[\bar{\Phi}]_{267}$ +8°, $[\bar{\Phi}]_{256}$ +14°; n.m.r. τ 9.34 (C-18 methyl group), 9.23, 9.20, 9.10 (C-19 and side chain methyl groups), 7.88 (acetyl).

Dehydration of 3-(1'-hydroxyethyl)-5α-cholestane

3-(1'-Hydroxyethyl)-5α-cholestane (1.6 g.) in pyridine (80 ml.) was heated under reflux with phosphoryl chloride (16 ml.) for 0.5 hours. After cooling in ice-water, the excess reagent was destroyed by careful addition of water, and the steroid was extracted with ether. The ether solution was washed with water, dried and the ether evaporated to give a product, which was adsorbed onto alumina (activity II) (200 g.), elution with petrol followed by crystallisation from methanol-ether giving 3-ethylidene-5α-cholestane II (1.037 g.) m.p. 42-46° (mixed m.p. with 3-ethylidene-5α-cholestane I 42-52°), $[\alpha]_D$ +27° (c.0.22), $\nu_{max.}$ 818, 815 cm.$^{-1}$ n.m.r. τ 9.34 (C-18 methyl group), 9.19, 9.17, 9.10 (C-19 and side chain methyl groups), 8.52, 8.40 (CH_3-C=C-), the position of the C-3' hydrogen again is not clear, but is centred about ca. τ 4.85. (Found: C, 87.0; H, 12.3. $C_{29}H_{50}$ requires C, 87.4; H, 12.7%).

Epoxidation of 3-ethylidene-5α-cholestane I with m-chloroperbenzoic acid

3-Ethylidene-5α-cholestane I (1 g.) in dry ether (100 ml.) was added to an ethereal solution (100 ml.) of m-chloroperbenzoic acid (1 g.). The solution was allowed to stand at room temperature overnight and the excess peracid was destroyed with ferrous sulphate solution. The ether layer was then washed with water, sodium bicarbonate solution, and water, dried and the ether evaporated to give a product which was adsorbed onto alumina (240 g.). Elution with petrol and crystallisation from acetone gave 3β-ethyl-3α,3'-epoxy-5α-cholestane (339) (0.769 g.) m.p. 103-105°, $[\alpha]_D$ +19° (c. 0.19); $\nu_{max.}$ 980, 879 and 687 $cm.^{-1}$; n.m.r. τ 9.34 (C-18 methyl group), 9.18, 9.14, 9.09, 9.07 (C-19 and side chain methyl groups), 8.79, 8.70 (C-3' methyl group), 7.21, 7.12 (C-3' hydrogen). (Found: C, 84.3; H, 11.9 $C_{29}H_{50}O$ requires C, 84.0; H, 12.1%). Further elution with petrol and crystallisation from acetone gave 3α-ethyl-3β,3'-epoxy-5α-cholestane (340) (0.124 g.) m.p. 80-83°, $[\alpha]_D$ +22° (c.0.10); $\nu_{max.}$ 1000, 928, 872, 770, 720, 710 $cm.^{-1}$; n.m.r. τ 9.34 (C-18 methyl group), 9.19, 9.14, 9.09 (C-19 and side chain methyl groups), 8.77, 8.67 (C-3' methyl group), 7.26, 7.16 (C-3' hydrogen). (Found: C, 84.4; H, 12.2. $C_{29}H_{50}O$ requires C, 84.0; H, 12.1%).

Epoxidation of 3-ethylidene-5α-cholestane I with alkaline hydrogen peroxide-benzonitrile

3-Ethylidene-5α-cholestane I (2.5 g.) in chloroform (50 ml.) was added to methanol (55 ml.), benzonitrile (3.5 g.), potassium

bicarbonate (1.25 g.), and hydrogen peroxide (30%, 4 ml.) and the mixture was stirred at room temperature for 24 hours. Ether and water were then added and the ether solution was washed with ferrous sulphate solution, water, sodium bicarbonate solution, and water, dried and the ether removed to give a product which was adsorbed onto alumina (150 g.). Elution with petrol gave 3-ethylidene-5α-cholestane I (0.562 g.), identified by its i.r. spectrum, and further elution with the same solvent and crystallisation from acetone gave 3β-ethyl-3α,3'-epoxy-5α-cholestane (339) (0.437 g.) m.p. and mixed m.p. 102-105°. Elution with petrol and crystallisation from acetone then gave 3α-ethyl-3β,3'-epoxy-5α-cholestane (340) (1.105 g.) m.p. and mixed m.p. 80-83°.

Epoxidation of 3-ethylidene-5α-cholestane II with m-chloroperbenzoic acid

3-Ethylidene-5α-cholestane II (0.5 g.) in dry ether (25 ml.) was added to m-chloroperbenzoic acid (0.5 g.) in ether (40 ml.) and the solution was allowed to stand overnight at room temperature. Work up with ferrous sulphate solution, sodium bicarbonate solution, and water in the usual way gave a product which was adsorbed onto alumina (60 g.). Elution with petrol and crystallisation from acetone gave 3β-ethyl-3α,3'-epoxy-5α-cholestane (341) (0.357 g.) m.p. 98-107° (mixed m.p. with 3β-ethyl-3α,3'-epoxy-5α-cholestane (339) 94-105°), $[\alpha]_D$ +22° (c.0.20); $\nu_{max.}$ 980, 879, 687 cm.$^{-1}$ n.m.r. τ 9.34 (C-18 methyl group), 9.18, 9.14, 9.09, 9.07 (C-19 and side chain methyl groups), 8.80, 8.70 (C-3' methyl group), 7.21, 7.11 (C-3' hydrogen). Further elution with petrol and crystallisation

from acetone gave 3α-ethyl-3β,3'-epoxy-5α-cholestane (342) (0.073 g.) m.p. 110-120° (mixed m.p. with 3α-ethyl-3β,3'-epoxy-5α-cholestane (340) 70-90°), $[\alpha]_D$ +27° (c.0.21); $\nu_{max.}$ 1000, 928, 872, 770, 720, 710 cm.$^{-1}$; n.m.r. τ 9.33 (C-18 methyl group), 9.18, 9.14, 9.09 (C-19 and side chain methyl groups), 8.77, 8.67 (C-3' methyl group), 7.26, 7.15 (C-3' hydrogen).

Epoxidation of 3-ethylidene-5α-cholestane II with alkaline hydrogen peroxide-benzonitrile

3-Ethylidene-5α-cholestane II (0.450 g.) in chloroform (10 ml.) was added to methanol (15 ml.), benzonitrile (0.63 g.), potassium bicarbonate (0.22 g.), and hydrogen peroxide (30%, 0.75 ml.) and the mixture was stirred at room temperature for 24 hours. Work up with ether, ferrous sulphate solution, sodium bicarbonate solution, and water in the usual way gave a product which was adsorbed on alumina (40 g.). Elution with petrol gave 3-ethylidene-5α-cholestane II (0.082 g.), identified by its i.r. spectrum, and further elution with petrol gave on crystallisation from acetone 3β-ethyl-3α,3'-epoxy-5α-cholestane (341) (0.093 g.) m.p. and mixed m.p. 96-106°. Elution with petrol and crystallisation from acetone also gave 3α-ethyl-3β,3'-epoxy-5α-cholestane (342) (0.233 g.) m.p. and mixed m.p. 98-115°.

Reaction of 3β-ethyl-3α,3'-epoxy-5α-cholestane (339) with BF_3 in benzene

The α-epoxide (339) (0.120 g.) in dry benzene (15 ml.) was treated with boron trifluoride-etherate (0.12 ml.) at room temperature for 2 minutes. Isolation with ether gave a product; i.r.

1705 and 1355 cm.$^{-1}$ n.m.r. τ 9.34, 9.23, 9.20, 9.10 (C-18, C-19 and side chain methyl groups), 7.88 (CH_3-C=O). This product was adsorbed on alumina (10 g.), elution with petrol-benzene (1:1) and crystallisation from acetone giving 3β-acetyl-5α-cholestane (0.092 g.) m.p. and mixed m.p. 107-109° (n.m.r. τ 9.34 (C-18 methyl group), 9.23, 9.20, 9.10 (C-19 and side chain methyl groups), 7.88 (CH_3-C=O)).

Reaction of 3β-ethyl-3α,3'-epoxy-5α-cholestane (339) with BF_3 in ether

The α-epoxide (339) (0.136 g.) in dry ether (20 ml.) was treated with boron trifluoride-etherate (0.14 ml.) at room temperature for 2 hours. The crude product, isolated by means of ether, had n.m.r. peaks at τ 9.34, 9.23, 9.20, 9.10, and 7.88, and on chromatography on alumina (25 g.) and elution with petrol-benzene (1:1) gave 3β-acetyl-5α-cholestane (0.101 g.) m.p. and mixed m.p. 108-109° (acetone).

Reaction of 3α-ethyl-3β,3'-epoxy-5α-cholestane (340) with BF_3 in benzene

The β-epoxide (340) (0.5 g.) in dry benzene (50 ml.) was treated with boron trifluoride-etherate (0.5 ml.) and kept at room temperature for 2 minutes. The crude product, isolated by means of ether, showed n.m.r. peaks at τ 9.34, 9.22, 9.19, 9.09 (C-18, C-19, and side chain methyl groups), 7.88 (CH_3-C=O), and 0.61 (-CHO). The product was adsorbed on alumina (25 g.). Elution with petrol-benzene (8:2) gave 3α-methyl-5α-cholestan-3β-aldehyde (0.087 g.) m.p. 116-118° (petrol), $[\alpha]_D$ +26° (c.0.11); $\nu_{max.}$ 2670, 1720 cm.$^{-1}$ n.m.r. τ 9.34 (C-18 methyl group), 9.21, 9.19, 9.09 (C-19 and side chain methyl

groups), 8.87, 8.73 (CH_3-C(CHO)), 0.61 (-CHO). (Found: C, 84.1; H, 12.2. $C_{29}H_{50}O$ requires C, 84.0; H, 12.2%). Elution with petrol-benzene (1:1) gave 3β-acetyl-5α-cholestane (0.270 g.) m.p. and mixed m.p. 107-108° (acetone).

Reaction of 3α-ethyl-3β,3'-epoxy-5α-cholestane (340) with BF_3 in ether

The β-epoxide (340) (0.1 g.) in dry ether (10 ml.) was treated with boron trifluoride-etherate (0.1 ml.) and was kept at room temperature for 2 hours. The crude product, isolated by means of ether, was adsorbed on alumina (25 g.). Elution with petrol-benzene (8:2) gave 3α-methyl-5α-cholestan-3β-aldehyde (0.022 g.) m.p. and mixed m.p. 116-118° (petrol). Elution with petrol-benzene (1:1) then gave 3β-acetyl-5α-cholestane (0.064 g.) m.p. and mixed m.p. 108-109° (acetone).

Reaction of 3β-ethyl-3α,3'-epoxy-5α-cholestane (341) with BF_3 in benzene

The α-epoxide (341) (0.1 g.) in dry benzene (10 ml.) was treated with boron trifluoride-etherate (0.1 ml.) and kept at room temperature for 2 minutes. The crude product, isolated by means of ether, had peaks in the n.m.r. at τ 9.34, 9.23, 9.20, 9.10, and 7.88, and was adsorbed on alumina (25 g.). Elution with petrol-benzene (1:1) and crystallisation from acetone gave 3β-acetyl-5α-cholestane (0.068 g.) m.p. and mixed m.p. 108-109°.

Reaction of 3β-ethyl-3α,3'-epoxy-5α-cholestane (341) with BF_3 in ether

The α-epoxide (341) (0.1 g.) in dry ether (10 ml.) was treated with boron trifluoride-etherate (0.1 ml.) at room temperature for 2 hours. The crude product, isolated by means of ether, had n.m.r. peaks at τ 9.34, 9.23, 9.20, 9.10 and 7.88, and on chromatography on alumina (25 g.) and elution with petrol-benzene (1:1) gave 3β-acetyl-5α-cholestane (0.074 g.) m.p. and mixed m.p. 107-109° (acetone)

Reaction of 3α-ethyl-3β,3'-epoxy-5α-cholestane (342) with BF_3 in benzene

The β-epoxide (342) (0.1 g.) in dry benzene (10 ml.) was treated with boron trifluoride-etherate (0.1 ml.) and the solution was allowed to stand at room temperature for 2 minutes. The crude product, isolated by means of ether, was adsorbed on alumina (40 g.). Elution with petrol-benzene (9:1) gave 3α-methyl-5α-cholestan-3β-aldehyde (0.017 g.) m.p. and mixed m.p. 116-118° (petrol), while elution with petrol-benzene (1:1) gave 3β-acetyl-5α-cholestane (0.054 g.) m.p. and mixed m.p. 107-109° (acetone).

Reaction of 3α-ethyl-3β,3'-epoxy-5α-cholestane (342) with BF_3 in ether

The β-epoxide (342) (0.110 g.) in dry ether (10 ml.) was treated with boron trifluoride-etherate (0.11 ml.) and the solution was allowed to stand at room temperature for 2 hours. The crude product, isolated by means of ether, was chromatographed on alumina (40 g.). Elution with petrol-benzene (9:1) gave 3α-methyl-5α-cholestan-3β-

aldehyde (0.022 g.), m.p. and mixed m.p. 116-118° (petrol). Elution with petrol-benzene (1:1) gave 3β-acetyl-5α-cholestane (0.061 g.) m.p. and mixed m.p. 108-109° (acetone).

Isopropylidene Epoxides

The synthesis and reactions of the epoxides of 3-isopropylidene-5α-cholestane

Isopropyltriphenylphosphonium bromide [154]

Isopropyl bromide (12.4 g.) and triphenylphosphine (26.4 g.) were heated together in a Carius tube at 150° for 24 hours. The crystalline product so obtained was crystallised from ethanol-ether to give isopropyltriphenylphosphonium bromide (38 g.) m.p. 238-239° (lit.[154] 238-239°).

Reaction of 5α-cholestan-3-one with isopropyltriphenylphosphorane

a) Sodium hydride (0.19 g.), obtained from a 50% dispersion in oil, by washing three times with dry petrol and blowing dry with nitrogen, was stirred under nitrogen with dry dimethyl sulphoxide (20 ml.) at 70° until evolution of hydrogen ceased (ca. 45 minutes). Dry tetrahydrofuran (10 ml.) was added, followed by, at 0°, isopropyltriphenylphosphonium bromide (3 g.), and stirring under nitrogen gave the deep-red ylide solution. 5α-Cholestan-3-one (1 g.) in dry tetrahydrofuran (10 ml.) was then added and stirring under nitrogen was continued for 1 hour at 30° and for 12 hours at 60°. Water was added, and the steroid was extracted with ether. The ether solution was washed with water, dried and the ether evaporated to give a crude product which was chromatographed on alumina (activity II) (40 g.) to give, on elution with petrol, 3-isopropylidene-5α-cholestane (0.738 g.) m.p. 95-97° (acetone) (lit.[126] 95-97°), $[\alpha]_D$ +27° (c.0.15) (lit.[126] +14°); n.m.r. τ 9.38 (C-18 methyl group), 9.21, 9.11

(C-19 and side chain methyl groups), 8.42 (6 protons, $\underline{CH}_3\diagdown$ $\diagup\underline{CH}_3$ C=C-).

b)[126] Isopropyltriphenylphosphonium bromide (3 g.) was dissolved in dry dimethyl sulphoxide (20 ml.), under nitrogen, and to it was added potassium t-butoxide (0.9 g.) in dry dimethyl sulphoxide (10 ml.). Stirring gave the intense red ylide solution. 5α-Cholestan-3-one (1 g.) in dry tetrahydrofuran (20 ml.) was then added, and the mixture was heated at 60° with stirring for 1 hour, and kept overnight under nitrogen at 60°. Water was then added and the steroid extracted with ether. The ether solution was washed with water, dried and the ether evaporated to give a crude product which was adsorbed on alumina (activity II) (40 g.). Elution with petrol gave 3-isopropylidene-5α-cholestane (0.727 g.) m.p. and mixed m.p. 95-97° (acetone).

Reaction of 3β-methoxycarbonyl-5α-cholestane with methyl magnesium iodide

3β-Methoxycarbonyl-5α-cholestane (0.9 g.) in dry ether (25 ml.) was added to an ethereal solution (150 ml.) of methyl magnesium iodide (from magnesium (1 g.)) and the solution was heated under reflux for 4 hours. On cooling, dilute ammonium chloride solution was added with care, and the steroid was extracted with ether. The ether solution was washed with water, dried and the ether evaporated to give 3β-(1'-hydroxyisopropyl)-5α-cholestane (0.684 g.) m.p. 145-147° (lit.[129] 145-146°), $\nu_{max.}$ 3580 cm.$^{-1}$ n.m.r. τ 9.34 (C-18 methyl group), 9.24 (C-19 methyl group), 9.19, 9.09 (side chain methyl groups), 8.85 (methyl groups on C-3').

Dehydration of 3β-(1'-hydroxyisopropyl)-5α-cholestane

a) 3β-(1'-Hydroxyisopropyl)-5α-cholestane (0.402 g.) in pyridine (20 ml.) was heated under reflux with phosphoryl chloride (4 ml.) for 30 minutes. After cooling, the excess reagent was decomposed with water and the steroid was extracted with ether. The ether solution was washed with water, dried and the ether evaporated to give a crude product which was adsorbed on alumina (activity II) (40 g.). Elution with petrol gave 3β-isopropenyl-5α-cholestane (0.339 g.) m.p. 90-91° (acetone) $[\alpha]_D$ +26° (c.0.14); $\nu_{max.}$ 3050, 1640, 895 cm.$^{-1}$; n.m.r. τ 9.34 (C-18 methyl group), 9.21, 9.19, 9.17, 9.10 (side chain and C-19 methyl groups), 8.36, 8.30 (methyl group on the double bond), 5.34 ($C\underline{H}_2$=C-). (Found: C, 87.5; H, 12.3. $C_{30}H_{52}$ requires C, 87.3; H, 12.7%).

b) A solution of the hydroxyisopropyl-compound (0.080 g.) in pyridine (4 ml.) and thionyl chloride (0.2 ml.) was kept at ca.-20° for 3 minutes. Water was added and the steroid was extracted with ether. The ether solution was washed with water, dried and the ether evaporated to give a crude product which was adsorbed on alumina (activity II) (40 g.). Elution with petrol then gave 3β-isopropenyl-5α-cholestane (0.063 g.) m.p. and mixed m.p. 90-91° (acetone).

Treatment of 3-isopropylidene-5α-cholestane with m-chloroperbenzoic acid

3-Isopropylidene-5α-cholestane (1.517 g.) in dry ether (100 ml.) was added to m-chloroperbenzoic acid (80%, 1.52 g.) in dry ether (100 ml.) and the solution was left at room temperature overnight.

Excess peracid was destroyed with ferrous sulphate solution, and the ether layer was washed with water, sodium bicarbonate solution, and water, dried and the ether evaporated to give a product which was adsorbed on alumina (80 g.). Elution with petrol gave 3β-isopropyl-3α,3'-epoxy-5α-cholestane (1.183 g.) m.p. 131-132° (acetone), $[\alpha]_D$ +24° (c.0.13); $\nu_{max.}$ 1215, 870 cm.$^{-1}$; n.m.r. τ 9.34 (C-18 methyl group), 9.18, 9.09 (C-19 and side chain methyl groups), 8.71 (C-3' epoxide methyl groups). (Found: C, 83.8; H, 12.1. $C_{30}H_{52}O$ requires C, 84.0; H, 12.2%). Elution with petrol also gave 3α-isopropyl-3β,3'-epoxy-5α-cholestane (0.174 g.) m.p. 119-120° (acetone), $[\alpha]_D$ +22° (c.0.11); $\nu_{max.}$ 1235, 875 cm.$^{-1}$; n.m.r. τ 9.33 (C-18 methyl group), 9.17, 9.10, 9.09 (C-19 and side chain methyl groups), 8.67 (C-3' epoxide methyl groups). (Found: C, 83.7;; H, 12.1. $C_{30}H_{52}O$ requires C, 84.0; H, 12.2%).

Treatment of 3-isopropylidene-5α-cholestane with alkaline hydrogen peroxide-benzonitrile

3-Isopropylidene-5α-cholestane (1.0 g.) in chloroform (20 ml.) was added to methanol (25 ml.), benzonitrile (1.4 g.), potassium bicarbonate (0.5 g.), and hydrogen peroxide (30%, 1.6 ml.), and the mixture was stirred at room temperature for 24 hours. Ether and water were then added and the ether solution was washed with ferrous sulphate solution, water, sodium bicarbonate solution, and water, dried and the ether evaporated to give a product which was adsorbed on alumina (80 g.). Elution with petrol gave 3-isopropylidene-5α-cholestane (0.056 g.), m.p. and mixed m.p. 95-97° (acetone). Further elution with petrol gave 3β-isopropyl-3α,3'-epoxy-5α-cholestane

(0.328 g.) m.p. and mixed m.p. 131-132° (acetone). Lastly, elution with the same solvent gave 3α-isopropyl-3β,3'-epoxy-5α-cholestane (0.390 g.) m.p. and mixed m.p. 119-120° (acetone).

Treatment of 3-isopropylidene-5α-cholestane with bleaching powder and acetic acid

3-Isopropylidene-5α-cholestane (1.0 g.) in ether (250 ml.) and water (300 ml.) was stirred strongly at room temperature with bleaching powder (0.7 g.) for 5 minutes. Then acetic acid (0.5 ml.) was added and the mixture was stirred for a further 25 minutes. Ether (200 ml.) was added and the ether layer was washed with water, potassium iodide solution, sodium thiosulphate solution and water, dried and the ether evaporated to give 3β-isopropenyl-3α-chloro-5α-cholestane (0.774 g.) m.p. 126-129° (acetone) $[\alpha]_D$ +36° (c.0.12); $\nu_{max.}$ 1635, 908 cm.$^{-1}$ n.m.r. τ 9.34 (C-18 methyl group), 9.27, 9.19, 9.10, 9.08 (C-19 and side chain methyl groups), 8.38, 8.30, 8.06 (double bond methyl group), 5.12, 4.94 (CH_2=C-). (Found: C, 80.6; H, 11.5; Cl, 7.9. $C_{30}H_{51}Cl$ requires C, 80.5; H, 11.5; Cl, 7.9%).

Reaction of 3β-isopropyl-3α,3'-epoxy-5α-cholestane with BF_3 in benzene

The α-epoxide (349) (0.368 g.) in dry benzene (25 ml.) was treated with boron trifluoride-etherate (0.37 ml.) at room temperature for 2 minutes. The product, isolated by means of ether, was adsorbed on alumina (100 g.). Elution with petrol-benzene (95:5) gave 4,4-dimethyl-A-homo-5α-cholestan-3-one (0.251 g.) m.p. 169-170° (acetone); $\nu_{max.}$ 1699 cm.$^{-1}$ n.m.r. τ 9.35 (C-18 methyl group), 9.19, 9.10 (C-19 and side chain methyl groups), 8.97, 8.93 (methyl groups on C-4) (Found: C, 83.9; H, 12.2. $C_{30}H_{52}O$ requires C, 80.0; H, 12.2%).

The g.l.c. retention time with respect to A-homo-5α-cholestan-4-one was 1.11. Elution with petrol benzene (9:1) gave 3β-methyl-3α-acetyl-5α-cholestane (0.019 g.) m.p. 80-83° (acetone); $\nu_{max.}$ 1699 and 1350 $cm.^{-1}$; R.D. $[\bar{\Phi}]_{455}$ +17°, $[\bar{\Phi}]_{333}$ +36°, $[\bar{\Phi}]_{308}$ 0°, $[\bar{\Phi}]_{270}$ +98°; n.m.r. τ 9.35 (C-18 methyl group), 9.25, 9.19, 9.09 (C-19 and side chain methyl groups), 8.84 (3β-methyl group), 7.87 (acetyl). (Found: C, 83.8; H, 12.1. $C_{30}H_{52}O$ requires C, 84.0; H, 12.2%).

Reaction of 3α-isopropyl-3β,3'-epoxy-5α-cholestane with BF_3 in benzene

The β-epoxide (350) (0.15 g.) in dry benzene (15 ml.) was treated with boron trifluoride-etherate (0.15 ml.) at room temperature for 2 minutes. The product, isolated by means of ether, was crystallised from acetone to give 3α-methyl-3β-acetyl-5α-cholestane (0.107 g.) m.p. 94-95° (acetone); $\nu_{max.}$ 1699, 1350 $cm.^{-1}$ R.D. $[\bar{\Phi}]_{455}$ +30°, $[\bar{\Phi}]_{304}$ +94°, $[\bar{\Phi}]_{264}$ +49°, $[\bar{\Phi}]_{263}$ +53°; n.m.r. τ 9.34 (C-18 methyl group), 9.25, 9.18, 9.09 (C-19 and side chain methyl groups), 8.83 (CH_3-Ċ-Ċ=O), 7.89 (CH_3-Ċ-). (Found: C, 83.8; H, 12.0. $C_{30}H_{52}O$ requires C, 84.0; H, 12.2%).

Treatment of 3α-methyl-3β-acetyl-5α-cholestane with m-chloroperbenzoic acid

3α-Methyl-3β-acetyl-5α-cholestane (0.05 g.) in chloroform (30 ml.) was added to a solution of m-chloroperbenzoic acid (80%, 0.05 g.) in chloroform (20 ml.), and the solution was kept at room temperature for 8 days. Ferrous sulphate solution was added and the chloroform layer was washed with water, sodium bicarbonate

solution, and water, dried and the chloroform evaporated to give a product (0.051 g.), $\nu_{max.}$ 1725, 1699 $cm.^{-1}$, which was adsorbed on alumina (30 g.). Elution with petrol-benzene (9:1) gave 3α-methyl-3β-acetyl-5α-cholestane (0.011 g.), identified from its i.r. spectrum, and elution with petrol-benzene gave the acetate (0.028 g.) $\nu_{max.}$ 1725, 1250, 1240 $cm.^{-1}$ This acetate (0.02 g.) in dry ether (10 ml.) was heated under reflux with lithium aluminium hydride (0.02 g.) for 2 hours. On cooling, ethyl acetate and dilute hydrochloric acid were added and the ether layer was washed with water, dried and the ether evaporated to give 3α-methyl-5α-cholestan-3β-ol (0.013 g.) m.p. and mixed m.p. 146-149° (acetone) (lit.[82] 147-149°) ($\nu_{max.}$ 3580, 1010 (m), 945 (s), 930 (m), 920 (m), identical with the i.r. spectrum of the sample of 3α-methyl-5α-cholestan-3β-ol, produced by addition of methyl magnesium iodide to 5α-cholestan-3-one.[82] The corresponding spectrum of 3β-methyl-5α-cholestan-3α-ol has $\nu_{max.}$ 960 (m), 900 (s) $cm.^{-1}$

Treatment of 4,4-dimethyl-A-homo-5α-cholestan-3-one with bromine

4,4-Dimethyl-A-homo-5α-cholestan-3-one (0.12 g.) in acetic acid (5 ml.) containing hydrogen bromide in acetic acid (40%, 1 drop) was treated with bromine (0.052 g.) in acetic acid (2 ml.). After 4 hours at room temperature water was added and the steroid was extracted with methylene chloride. The organic layer was washed with water till neutral, dried and the solvent evaporated to give the crude product (0.117 g.), $\nu_{max.}$ 1718, 1699 $cm.^{-1}$, which was adsorbed on silica gel (50 g.). Elution with petrol-benzene (9:1) gave a crystalline compound (0.034 g.) m.p. 136-139° (acetone) $\nu_{max.}$

1718 cm.$^{-1}$ Elution with petrol-benzene (8:2) gave an oil (0.073 g.) $\nu_{max.}$ 1699 cm.$^{-1}$

The crystalline material ($\nu_{max.}$ 1718 cm.$^{-1}$) (0.025 g.) in dry dimethylformamide (5 ml.) was heated under reflux with lithium bromide (0.1 g.) and lithium carbonate (0.1 g.) for 5 hours. After cooling, the inorganic material was filtered off, and dilute hydrochloric acid was added. The steroid was extracted with ether and the ether layer was washed with water until the washings were neutral, dried and the ether evaporated to give an oil (0.013 g.) with no strong u.v. absorptions, but with a slight shoulder at ca. 230 mμ.

The oil from the bromination of 4,4-dimethyl-A-homo-5α-cholestan-3-one (0.070 g.) was similarly treated with lithium bromide (0.3 g.) and lithium carbonate (0.3 g.) in dimethylformamide (10 ml.), and gave on workup an oil (0.052 g.) with no strong absorptions in the u.v.

A-homo-5α-cholestan-4-one [107]

To 5α-cholestan-3-one (13.2 g.) in dry ether (500 ml.) and methanol (850 ml.) was added potassium hydroxide (28 g.). After the base had dissolved, the solution was cooled in ice-water to 0° and N-nitrosomethylurea (20 g.) was added over 20 minutes with stirring. Stirring was continued at 0° for an additional 5 hours and then cold dilute hydrochloric acid (300 ml.) was added. The insoluble salts were filtered and washed with ether, and the ether solution was washed with water till neutral, dried and the ether evaporated to give ketonic material (12.2 g.) which was adsorbed

on alumina (1000 g.). Elution with petrol gave 3β-methyl-3α,3'-epoxy-5α-cholestane (0.292 g.) m.p. and mixed m.p. 131-132° (acetone). Elution with petrol-benzene (8:2) gave A-homo-5α-cholestan-3-one (0.434 g.) m.p. 82-83° (acetone) (lit.[107] 82-83°); $\nu_{max.}$ 1705, 1412, 1334, 1315 cm.$^{-1}$ g.l.c. retention time with respect to 5α-cholestane 2.70 (lit.[105] 2.70 with respect to 5α-cholestane). Elution with petrol-benzene (8:2) and benzene gave A-homo-5α-cholestan-4-one (6.55 g.) m.p. 86-87° (acetone) (lit.[107] 87-88°); $\nu_{max.}$ 1705, 1412, 1334 cm.$^{-1}$; n.m.r. τ 9.33 (C-18 methyl group), 9.18, 9.12, 9.09 (C-19 and side chain methyl groups). The g.l.c. retention time with respect to 5α-cholestane was 2. 80, (lit.[105] value 2.80).

Methylation of A-homo-5α-cholestan-4-one

a) A solution of potassium (1 g.) in t-butanol (25 ml.) was added to a boiling solution of A-homo-5α-cholestan-4-one (1.1 g.) in dry benzene (25 ml.) and t-butanol (15 ml.). Methyl iodide (75 ml.) in dry benzene (25 ml.) was then added and the mixture was heated under reflux, cooled and ice added. The steroid was extracted with ether and the ether solution was washed with water, dried and the ether evaporated to give a crude product which was adsorbed on alumina (activity II) (100 g.). Elution with petrol-benzene mixtures ranging from 1% to 30% benzene gave 23 fractions (total weight 0.587 g.). Fractions 12, 13 and 19-23 were crystalline. All 23 fractions had $\nu_{max.}$ ca.1699 cm.$^{-1}$ with those from fraction 16 onwards also having a peak at 1412 cm.$^{-1}$ The g.l.c. retention times of fractions 15, 16, 20, 21 and 23 with respect to A-homo-5α-cholestan-4-one were, respectively, 1.12, 1.115, 1.12, 1.115, 1.113.

Elution from the column with petrol-benzene (6:4) and benzene gave A-homo-5α-cholestan-4-one (0.346 g.) m.p. and mixed m.p. 85-87° (acetone).

b) A-homo-5α-cholestan-4-one (1.5 g.) was stirred with potassium t-butoxide (from potassium (0.5 g.)) in t-butanol (30 ml.) and the solution was saturated with methyl chloride and allowed to stand for 2 hours. The solution was resaturated with methyl chloride for 1 hour, and left to stand overnight. Ice and water were then added, and the steroid was extracted with ether. The ether solution was washed with water, dried and the ether evaporated to give a crude product (1.39 g.) which was adsorbed on alumina (activity II) (400 g.). Elution with petrol-benzene mixtures ranging from 1% to 30% benzene gave 72 fractions. Fractions 46-50 and 57-68 were crystalline. The total weight of these early fractions was 0.411 g. Fractions 46-50 were combined and crystallised from acetone to give material m.p. 73-81°. Fractions 57-68 were similarly combined and crystallised to give material m.p. 80-87°. Elution with petrol-benzene (1:1) and benzene gave A-homo-5α-cholestan-4-one (0.840 g.) m.p. and mixed m.p. 85-87° (acetone).

c) A-homo-5α-cholestan-4-one (2.0 g.) was added to a solution of potassium (0.59 g.) in t-butanol (30 ml.) and the mixture was stirred until a solution was achieved (ca.0.5 hr.). Methyl iodide (1.84 ml.) was added dropwise, and the mixture was stirred for 4 hours. Water was added, and the steroid extracted with ether. The ether solution was washed with dilute hydrochloric acid, and with water until the washings were neutral, dried and the ether evaporated to give a crude product which was adsorbed on alumina (activity II)

(100 g.). Elution with solvents ranging from petrol to benzene gave 24 fractions of total weight 2.068 g.

Fractions 11 and 12, eluted with petrol-benzene (9:1) (combined weight 0.363 g.), were crystalline, $\nu_{max.}$ 1699 cm.$^{-1}$ in both cases. The fractions were combined and crystallised from acetone to give material with a m.p. 75-84°. This material (0.363 g.) in isopropenyl acetate (3 ml.) containing concentrated sulphuric acid (1 drop) was heated under reflux for 1 hour, and the solution was concentrated to ca.2 ml. The mixture was warmed with fused sodium acetate (0.09 g.) and chloroform (3 ml.), filtered, and evaporated under reduced pressure to give a semi solid (0.329 g.), $\nu_{max.}$ 1740, 1699, 1210, 1060, 1050 cm.$^{-1}$ This product was adsorbed on silica gel (60 g.). Elution with petrol-benzene (8:2) gave 3,3,4a,4a-tetramethyl-A-homo-5α-cholestan-4-one (0.291 g.), m.p. 84-88° (acetone); $\nu_{max.}$ 1699 cm.$^{-1}$; n.m.r. τ 9.33, 9.30, 9.19, 9.09, 8.89 (C-18, C-19, C-3, C-4a, and side chain methyl groups). (Found; C, 84.1; H, 12.1. $C_{32}H_{56}O$ requires C, 84.1; H, 12.4%). Treatment of this compound (0.108 g.) with isopropenyl acetate (2 ml.) and concentrated sulphuric acid (1 drop) in the usual way gave only starting material (0.094 g.) on work up. Elution with petrol-benzene (8:2), of the silica gel column, gave a mixed fraction of the tetramethyl-ketone (359) and enol-acetate (0.020 g.) $\nu_{max.}$ 1740, 1699, 1210, 1060, 1050 cm.$^{-1}$; n.m.r. τ 9.33, 9.30, 9.19, 9.09, 8.89 (C-18, C-19, C-3, C-4a, and side chain methyl groups), 8.36 (methyl group on double bond), 7.86 (acetate).

Fractions 20 and 21 (from the alumina (activity II) column) were also crystalline and were combined and crystallised from acetone to give 3,3-dimethyl-A-homo-5α-cholestan-4-one (0.374 g.) m.p. 87-91°;

$[\alpha]_D$ +49° (c.0.1); $\nu_{max.}$ 1699, 1412, 955, 940 $cm.^{-1}$; n.m.r. τ 9.35 (C-18 methyl group), 9.22, 9.19, 9.10, 9.04, 8.91 (C-19, C-3 and side chain methyl groups), downfield protons in a "hump" between 7.80 and 7.40. (Found: C, 83.8; H, 12.2. $C_{30}H_{52}O$ requires C, 84.0; H, 12.2%). The g.l.c. retention time with respect to A-homo-5α-cholestan-4-one was 1.12. The 3,3-dimethyl-compound (355) (0.08 g.) in isopropenyl acetate (6 ml.) containing concentrated sulphuric acid (1 drop) was heated under reflux for 1 hour, then concentrated to a volume of ca.3 ml. The mixture was warmed with fused sodium acetate (0.02 g.) and chloroform (4 ml.), filtered, evaporated under reduced pressure, and filtered through a column of silica gel (10 g.) with petrol-benzene (1:1) to give the enol-acetate (0.062 g.) (a semi-solid); $\nu_{max.}$ 1745, 1220 $cm.^{-1}$ n.m.r. τ 9.3 (C-18 methyl group), 9.16, 9.09, 9.07, 8.97, 8.70 (C-19, C-3, and side chain methyl groups), 7.86 (acetate).

Fractions 23 and 24 (from the alumina (activity II) column) were combined and crystallised from acetone to give A-homo-5α-cholestan-4-one (0.266 g.) m.p. and mixed m.p. 87-88°.

Treatment of 3,3-dimethyl-A-homo-5α-cholestan-4-one with bromine

3,3-Dimethyl-A-homo-5α-cholestan-4-one (0.120 g.) in acetic acid (5 ml.) containing hydrogen bromide in acetic acid (40%, 1 drop), was treated with bromine (0.050 g.) in acetic acid (1 ml.). After 4 hours at room temperature the mixture was worked up in the usual way to give a crude product which was adsorbed on silica gel (50 g.) and elution with petrol-benzene (1:1) gave an oil (0.07 g.), $\nu_{max.}$ 1705 $cm.^{-1}$

This oil (0.05 g.) in dry dimethylformamide (5 ml.) was heated under reflux with lithium bromide (0.12 g.) and lithium carbonate (0.12 g.), under nitrogen, for 5 hours. The inorganic material was filtered off, and dilute hydrochloric acid was added. The steroid was extracted with ether, and the ether solution was washed with water until the washings were neutral, dried and the ether evaporated to give an oil (0.033 g.); $\nu_{max.}$ 1699, 1670 $cm.^{-1}$; $\lambda_{max.}$ 237 mμ (ϵ ca.8000).

3-Hydroxymethylene-A-homo-5α-cholestan-4-one [107]

A-homo-5α-cholestan-4-one (3.15 g.) in dry benzene (38 ml.) was added over 1 hour to a stirred suspension of sodium methoxide (0.6 g.) in dry benzene (30 ml.) and ethyl formate (4.2 ml.). After adding additional sodium methoxide (0.3 g.) and stirring for four hours, the mixture was filtered and the solid washed with benzene and dried. The bright yellow salt so obtained was stirred 1 hour with a mixture of concentrated hydrochloric acid (4.2 ml.), water (54 ml.) and ethanol (27 ml.), filtered and washed with water until the washings were neutral to give 3-hydroxymethylene-A-homo-5α-cholestan-4-one (2.917 g.) m.p. 99-100° (ethanol) (lit.[107] 99-100°) $[\alpha]_D$ +18° (c.0.13) (lit.[107] +13°); $\nu_{max.}$ 1640 $cm.^{-1}$

3-Methyl-A-homo-5α-cholestan-4-one

3-Hydroxymethylene-A-homo-5α-cholestan-4-one (0.45 g.) in benzene (40 ml.) was added to 10% palladium on charcoal catalyst (0.2 g.) in ethanol (40 ml.) and the mixture was shaken in an atmosphere of hydrogen for 24 hours. The catalyst was removed and the solvent evaporated to give an oil which was adsorbed on alumina (activity II)

(60 g.) to give on elution with petrol-benzene (1:1) 3-methyl-A-homo-5α-cholestan-4-one (0.112 g.) m.p. 87-90° (acetone); $[\alpha]_D$ +25° (c.0.12); $\nu_{max.}$ 1699 $cm.^{-1}$; n.m.r. τ 9.34 (C-18 methyl group), 9.19, 9.09, 8.99, 8.89, 8.80 (C-19, C-3, and side chain methyl groups). (Found: C, 84.0; H, 11.9. $C_{29}H_{50}O$ requires C, 84.0; H, 12.1%). The g.l.c. retention time with respect to A-homo-5α-cholestan-4-one was 1.11.

A solution of the 3-methyl-A-homo-compound (361) (0.07 g.) in isopropenyl acetate (2 ml.) containing concentrated sulphuric acid (1 drop) was heated under reflux for 1 hour, then concentrated to a volume of ca.1 ml. The mixture was warmed with fused sodium acetate (0.1 g.) and chloroform (4 ml.), filtered, evaporated under reduced pressure, and the residue chromatographed on silica gel (15 g.). Petrol-benzene (1:1) elution gave the enol-acetate (semi-solid) (0.057 g.) $\nu_{max.}$ 1745, 1220 $cm.^{-1}$; n.m.r. τ 9.34 (C-18 methyl group), 9.19, 9.17, 9.09, 8.74 (C-19, C-3 and side chain methyl groups), 7.80 (acetate).

The synthesis and reactions of the epoxides of 3-isopropylidene-A-nor-5α-cholestane

3β-Isopropyl-3α,3'-epoxy-A-nor-5α-cholestane

3-Isopropylidene-A-nor-5α-cholestane (0.4 g.) in dry ether (20 ml.) was added to a dry ethereal solution (50 ml.) of m-chloroperbenzoic acid (0.4 g.). After standing at room temperature overnight, the excess peracid was destroyed with ferrous sulphate solution, and the ether layer was washed with water, sodium bicarbonate solution, and water, dried and the ether evaporated to give on crystallisation from acetone 3β-isopropyl-3α,3'-epoxy-A-nor-5α-cholestane (0.310 g.) m.p. 84.5-86°, $[\alpha]_D$ +22° (c.0.14); $\nu_{max.}$ 920, 850 $cm.^{-1}$; n.m.r. τ 9.34 (C-18 methyl group), 9.28, 9.19, 9.15, 9.09 (C-19 and side chain methyl groups), 8.74 (C-3' methyl groups). (Found: C, 83.7; H, 12.2. $C_{29}H_{50}O$ requires C, 84.0; H, 12.2%).

Treatment of 3-isopropylidene-A-nor-5α-cholestane with N-bromosuccinimide and acetic acid

3-Isopropylidene-A-nor-5α-cholestane (1 g.) in acetone (20 ml.) was added to 5% aqueous acetone (60 ml.) containing N-bromosuccinimide (2 g.). The mixture was stirred at room temperature to achieve solution, and acetic acid (0.8 ml.) was added with stirring. The mixture was stirred at room temperature for 3 hours, and part of the acetone was removed, under reduced pressure, at a temperature of ca.40°. Ether and water were then added, and the ether layer was washed with potassium iodide solution, water, sodium thiosulphate solution, and water, dried and the ether evaporated to give a gum (0.878 g.), $\nu_{max.}$ 3500 $cm.^{-1}$, which was adsorbed on alumina (80 g.).

After 0.5 hour elution with petrol gave a product, $\nu_{max.}$ 1700 and 850 $cm.^{-1}$; which was rechromatographed three times on columns of alumina (100 g.), elution with petrol on each occasion giving material with $\nu_{max.}$ 1700 and 850 $cm.^{-1}$ This material (0.716 g.) was then adsorbed on neutral alumina (activity III) (100 g.). Elution with petrol gave 3α-isopropyl-3β,3'-epoxy-A-nor-5α-cholestane (0.061 g.) m.p. 90-93° (acetone) (mixed m.p. with the α-epoxide (365) 80-93°), $\nu_{max.}$ 850 $cm.^{-1}$ Elution with the same solvent gave a semi-solid (0.51 g.), $\nu_{max.}$ 1700, 850 $cm.^{-1}$; with g.l.c. retention times with respect to 5α-cholestane at 1.38 and 2.21.

Reaction of 3β-isopropyl-3α,3'-epoxy-A-nor-5α-cholestane with boron trifluoride in benzene

The α-epoxide (365) (0.20 g.) in dry benzene (25 ml.) was treated with boron trifluoride-etherate (0.25 ml.), and the solution was kept at room temperature for 5 minutes. The crude product, isolated by means of ether, had a peak in the i.r. at 1700 $cm.^{-1}$; and possessed g.l.c. retention times with respect to 5α-cholestane at 2.21, 2.03, 1.85. The product was adsorbed on alumina (60 g.). Elution with petrol-benzene (99:1) gave, after crystallisation from acetone, 2β-methyl-2α-acetyl-A-nor-5α-cholestane (0.138 g.) m.p. 93-96°, $\nu_{max.}$ 1700 and 1355 $cm.^{-1}$; n.m.r. τ 9.34 (C-18 methyl group), 9.19, 9.16, 9.09 (C-19 and side chain methyl groups), 8.67 (C-3 methyl group), 7.86 (C-3' methyl group). The g.l.c. retention time with respect to 5α-cholestane is 1.85. (Other details are given on p.221). Elution with petrol-benzene (99:1) and petrol-benzene (9:1) gave a product (0.042 g.) m.p. 89-100° (acetone), $\nu_{max.}$ 1700 $cm.^{-1}$;

with a g.l.c. retention time with respect to 5α-cholestane at 2.21.

Treatment of 3α-isopropyl-3β,3'-epoxy-A-nor-5α-cholestane with BF_3 in benzene

The β-epoxide (366) (0.05 g.) in dry benzene (10 ml.) was treated with boron trifluoride-etherate (0.05 ml.), and the mixture was kept at room temperature for 5 minutes. The crude product (0.039 g.), isolated by means of ether, had $\nu_{max.}$ 1700 and 1355 $cm.^{-1}$, and g.l.c. retention times with respect to 5α-cholestane at 1.85 and 2.06. The crude product was adsorbed on alumina (20 g.), elution with petrol giving a compound (0.033 g.), with g.l.c. retention times at 1.85 and 2.06 with respect to 5α-cholestane. Crystallisation three times from acetone gave a compound with a m.p. 83-93°.

The synthesis and reactions of 2,3-epoxy-5α-cholestanes

The synthesis and reactions of 2,3-dimethyl-2,3-epoxy-5α-cholestanes

2,3-Dimethyl-5α-cholest-2-ene

2α-Methyl-5α-cholestan-3-one (5 g.) in dry ether (250 ml.) was added to an ethereal solution (200 ml.) of methyl magnesium iodide (from magnesium (5 g.)), and the mixture was refluxed for 5 hours. On cooling, dilute ammonium chloride solution was carefully added, and the mixture was worked up in the usual way to give the 2α,3-dimethyl-5α-cholestan-3-ols (4.98 g.), which were dissolved in acetic acid (500 ml.). Perchloric acid (14 drops) was added and the mixture was heated on a water bath (at ca.90°) for two hours. Most of the solvent was removed under reduced pressure, and water was added. The steroid was extracted with methylene chloride, and the organic layer was washed with water, till the washings were neutral, dried and the solvent evaporated to give an oil, which was adsorbed from petrol on alumina (activity II) (400 g.). Elution with petrol and crystallisation from acetone gave 2,3-dimethyl-5α-cholest-2-ene (3.81 g.) m.p. and mixed m.p. 83-85°.

2β,3β-Dimethyl-2α,3α-epoxy-5α-cholestane

2,3-Dimethyl-5α-cholest-2-ene (3 g.) in dry ether (250 ml.) was added to m-chloroperbenzoic acid (3 g.) in dry ether (100 ml.), and the solution was allowed to stand at room temperature overnight. Excess peracid was decomposed with ferrous sulphate solution, and the ether layer was washed with water, sodium bicarbonate solution, and water, dried and the ether evaporated to give 2β,3β-dimethyl-2α,3α-epoxy-5α-cholestane (2.61 g.) m.p. 121.5-123° (acetone)

$[\alpha]_D$ +38° (c.0.21); $\nu_{max.}$ 1162, 870, 850 cm.$^{-1}$; n.m.r. τ 9.36 (C-18 methyl group), 9.29, 9.17, 9.09 (C-19 and side chain methyl groups), 8.71 (C-2 and C-3 methyl groups). (Found: C, 83.9; H, 12.2. $C_{29}H_{50}O$ requires C, 84.0; H, 12.2%).

Treatment of 2β,3β-dimethyl-2α,3α-epoxy-5α-cholestane with lithium aluminium hydride

The α-epoxide (370) (0.5 g.) in dry ether (25 ml.) was added to an ethereal solution (50 ml.) of lithium aluminium hydride (0.5 g.), and the mixture was refluxed for 2 hours. After cooling, ethyl acetate and dilute hydrochloric acid were added, and the mixture was worked up in the usual way to give 2α,3β-dimethyl-5α-cholestan-3α-ol (0.471 g.) m.p. and mixed m.p. 147-148° (acetone).

Treatment of 2,3-dimethyl-5α-cholest-2-ene with N-bromosuccinimide and acetic acid

2,3-Dimethyl-5α-cholest-2-ene (0.25 g.) in acetone (20 ml.) was added to N-bromosuccinimide (0.5 g.) in 5% aqueous acetone (80 ml.). With stirring, acetic acid (0.4 ml.) was added, and the mixture was allowed to stand at room temperature for 3 hours. Work up with ether, potassium iodide solution, sodium thiosulphate solution, and water gave a gum (0.140 g.), $\nu_{max.}$ 3600 cm.$^{-1}$ which was adsorbed on alumina (40 g.). After 0.5 hour elution with petrol and crystallisation from acetone gave 2α,3α-dimethyl-2β,3β-epoxy-5α-cholestane (0.041 g.) m.p. 108-109° $[\alpha]_D$ +61° (c.0.09); $\nu_{max.}$ 1130, 855 cm.$^{-1}$; n.m.r. τ 9.35 (C-18 methyl group), 9.17, 9.09, 9.07 (side chain and C-19 methyl groups), 8.76, 8.73 (C-2 and C-3 methyl groups). (Found: C, 83.9; H, 11.9. $C_{29}H_{50}O$ requires C, 84.0; H, 12.2%).

Treatment of 2α,3α-dimethyl-2β,3β-epoxy-5α-cholestane with lithium aluminium hydride

The β-epoxide (372) (0.021 g.) in dry ether (20 ml.) was added to an ethereal solution (20 ml.) of lithium aluminium hydride (0.02 g.), and the mixture was refluxed for 2 hours. On cooling, ethyl acetate and dilute hydrochloric acid were added and the mixture was worked up in the usual fashion to give 2α,3β-dimethyl-5α-cholestan-2β-ol (0.019 g.) m.p. 158-159.5° (acetone), $[\alpha]_D$ +57° (c.0.1); $\nu_{max.}$ 3580, 945, 850 $cm.^{-1}$ (Found: C, 83.7; H, 12.2. $C_{29}H_{52}O$ requires C, 83.6; H, 12.6%).

3β-Methyl-2α,3α-epoxy-5α-cholestane

3-Methyl-5α-cholest-2-ene (13.9 g.) in dry ether (150 ml.) was added to an ethereal solution (200 ml.) of m-chloroperbenzoic acid (13.9 g.). The mixture was allowed to stand at room temperature overnight. Excess peracid was decomposed with ferrous sulphate solution, and the ether layer was washed with water, sodium bicarbonat solution, and water, dried and the ether evaporated to give 3β-methyl-2α,3α-epoxy-5α-cholestane (13.7 g.) m.p. 131-132° (acetone) (lit.[145] 135°); $\nu_{max.}$ 885, 820, 810, 705 $cm.^{-1}$; n.m.r. τ 9.37 (C-18 methyl group), 9.29, 9.19, 9.10 (C-19 and side chain methyl groups), 8.72 (C-3 methyl group), 7.13, 7.04 (C-2 proton).

Reaction of 3β-methyl-2α,3α-epoxy-5α-cholestane with boron trifluoride in benzene

3-Methyl-2α,3α-epoxy-5α-cholestane (4.5 g.) in dry benzene (200 ml.) was treated with boron trifluoride-etherate (4.5 ml.). After standing at room temperature for 5 minutes the mixture was poured

into water and ether was added. The ether layer was washed with water until the washings were neutral, dried and the ether and benzene evaporated to give a product (4.1 g.) ($\nu_{max.}$ 2670, 1715 and 1705 $cm.^{-1}$) which was adsorbed from petrol on alumina (600 g.). Elution with petrol-benzene (9:1) gave 2β-methyl-A-nor-5α-cholestan-2α-aldehyde (1.110 g.) m.p. 81-84° (petrol), $[\alpha]_D$ +24° (c.0.12); $\nu_{max.}$ 2670, 1715 $cm.^{-1}$; n.m.r. τ 9.34 (C-18 methyl group), 9.19, 9.15, 9.09 (C-19 and side chain methyl groups), 8.71 (C-2 methyl group), 0.59 (aldehyde). (Found: C, 83.7; H, 11.9. $C_{28}H_{48}O$ requires C, 83.9; H, 12.1%). Elution with petrol-benzene (8:2) gave 3β-methyl-5α-cholestan-2-one (2.859 g.) m.p. 145-148° (acetone) (lit.[145] 147-149°); $[\alpha]_D$ +47° (c.0.15); $\nu_{max.}$ 1705 $cm.^{-1}$; R.D. $[\Phi]_{435}$ +120°, $[\Phi]_{307.5}$ +540°, $[\Phi]_{269}$ -540°, $[\Phi]_{256}$ -470°; n.m.r. τ 9.34 (C-18 methyl group), 9.25, 9.17, 9.09 (C-19 and side chain methyl groups), 8.85, 8.74 (C-3 methyl group).

Treatment of 3β-methyl-5α-cholestan-2-one with methyl magnesium iodide

3β-Methyl-5α-cholestan-2-one (0.25 g.) in dry ether (100 ml.) was added to an ethereal solution (100 ml.) of methyl magnesium iodide (from magnesium (0.25 g.)), and the solution was heated under reflux for 5 hours. After cooling, dilute ammonium chloride solution was added and the ether layer was washed with water, dried and the ether evaporated to give, on crystallisation from acetone 2α,3β-dimethyl-5α-cholestan-2β-ol (0.202 g.) m.p. and mixed m.p. 158-159.5°.

t-Butyl hypochlorite[146]

Sodium hydroxide (8 g.) was dissolved in water (50 ml.), and

at 20° t-butanol (7.4 g.) and water (50 ml.) were added. A homogeneous solution was formed through which chlorine gas was passed, with stirring. The temperature was not allowed to exceed 20°. After 0.5 hour the upper layer was separated and was washed with sodium carbonate solution, till the washings were not acid to Congo-red, and with water, and dried over $CaCl_2$ to give t-butyl hypochlorite (7.9 g.).

Treatment of 3β-methyl-5α-cholestan-2-one with t-butyl hypochlorite

a) 3β-Methyl-5α-cholestan-2-one (0.15 g.) in acetic acid (8 ml.) at 65° was treated with t-butyl hypochlorite (0.05 ml.) and the mixture was warmed on a steam bath for 1 hour, and allowed to stand overnight at room temperature. The precipitate formed was filtered off and crystallised from acetone to give 3α-chloro-3β-methyl-5α-cholestan-2-one (0.098 g.) m.p. 195-197° $[\alpha]_D$ +152° (c.0.16); $\nu_{max.}$ 1715 $cm.^{-1}$; R.D. (dioxan) $[\bar{\Phi}]_{455}$ +170°, $[\bar{\Phi}]_{331}$ +1630°, $[\bar{\Phi}]_{284}$ -1588°, $[\bar{\Phi}]_{256}$ -1020°. (Found: C, 77.5; H, 10.7; Cl, 7.9. $C_{28}H_{47}OCl$ requires C, 77.3; H, 10.9; Cl, 8.1%).

Treatment of 3α-chloro-3β-methyl-5α-cholestan-2-one (0.020 g.) in acetic acid (5 ml.) with hydrogen bromide in acetic acid (40%, 1 drop) at room temperature for 39 hours gave on work up with methylene chloride and water 3α-chloro-3β-methyl-5α-cholestan-2-one (0.014 g.).

b) 3β-Methyl-5α-cholestan-2-one (1.56 g.) in acetic acid (18 ml.) at 65° was treated with t-butyl hypochlorite (0.48 ml.) and the mixture was warmed on a steam bath for 1 hour, and left to cool to room temperature overnight. The precipitate was filtered off and

washed with a little acetone and dried. Chromatography on silica gel (100 g.) and elution with petrol-benzene (8:2) gave 3α-chloro-3β-methyl-5α-cholestan-2-one (0.634 g.) m.p. and mixed m.p. 195-197° (acetone). Elution with petrol-benzene (3:2) gave 3β-methyl-5α-cholestan-2-one (0.882 g.) m.p. and mixed m.p. 145-147° (acetone).

Treatment of 3α-chloro-3β-methyl-5α-cholestan-2-one with ethereal methyl lithium

3α-Chloro-3β-methyl-5α-cholestan-2-one (0.5 g.) in dry ether (100 ml.) was added to an ethereal solution (100 ml.) of methyl lithium (from lithium (0.5 g.)) and the mixture was heated under reflux for 7 hours. After cooling, dilute ammonium chloride solution was added and the ether layer was washed with water, dried and the ether evaporated to give a sticky product (0.5 g.), $\nu_{max.}$ 3600 and 855 $cm.^{-1}$; which was adsorbed on alumina (100 g.). Elution with petrol gave 2α,3α-dimethyl-2β,3β-epoxy-5α-cholestane (0.212 g.) m.p. and mixed m.p. 108-109° (acetone).

Reaction of 2β,3β-dimethyl-2α,3α-epoxy-5α-cholestane with boron trifluoride in benzene

The α-epoxide (370) (0.4 g.) in dry benzene (25 ml.) was treated with boron trifluoride-etherate (0.4 ml.), and the mixture was kept at room temperature for 5 minutes. The product, isolated by means of ether, was crystallised from acetone to give 2β-methyl-2α-acetyl-A-nor-5α-cholestane (0.293 g.) m.p. 94-96.5°, $[\alpha]_D$ +17° (c.0.16); $\nu_{max.}$ 1700, 1355 $cm.^{-1}$; R.D. $[\Phi]_{455}$+8°, $[\Phi]_{333}$+12°, $[\Phi]_{305}$-12°, $[\Phi]_{278}$+74°, $[\Phi]_{256}$+103°; n.m.r. τ 9.34 (C-18 methyl group), 9.19, 9.16, 9.09 (C-19 and side chain methyl groups), 8.67 (C-3 methyl

group), 7.86 (C-3' methyl group). (Found: C, 83.7; H, 11.9. $C_{29}H_{50}O$ requires C, 84.0; H, 12.2%).

Reaction of 2α,3α-dimethyl-2β,3β-epoxy-5α-cholestane with boron trifluoride in benzene

The β-epoxide (372) (0.14 g.) in dry benzene (10 ml.) was treated with boron trifluoride-etherate (0.14 ml.), and the mixture was kept at room temperature for 5 minutes. The product, isolated by means of ether, was crystallised from acetone to give 2α-methyl-2β-acetyl-A-nor-5α-cholestane (0.118 g.) m.p. 114-117°, $[\alpha]_D$ +30° (c.0.15); $\nu_{max.}$ 1699, 1355 $cm.^{-1}$; R.D. $[\Phi]_{455}$+33°, $[\Phi]_{312}$+220°, $[\Phi]_{276}$-99°, $[\Phi]_{256}$-33°; n.m.r. τ 9.46 (C-19 methyl group), 9.35 (C-18 methyl group), 9.19, 9.09 (side chain methyl groups), 8.78 (C-2 methyl group), 7.87 (acetyl). (Found: C, 83.9; H, 12.0. $C_{29}H_{50}O$ requires C, 84.0; H, 12.2%).

Treatment of the 2-methyl-2-acetyl-A-nor-compounds with m-chloroperbenzoic acid

a) 2β-Methyl-2α-acetyl-A-nor-5α-cholestane (0.15 g.) in chloroform (35 ml.) was treated with m-chloroperbenzoic acid (0.15 g.) and the mixture was left at room temperature for 8 days. Work up in the usual way with ferrous sulphate solution, sodium bicarbonate solution, and water gave a product (0.136 g.), $\nu_{max.}$ 1730, 1700, 1260 and 1230 $cm.^{-1}$, which was adsorbed on silica gel (35 g.). Elution with petrol-benzene (9:1) gave 2β-methyl-2α-acetyl-A-nor-5α-cholestane (0.047 g.) m.p. and mixed m.p. 94-96° (acetone). Elution with petrol-benzene (3:2) gave the acetate (0.080 g.)

$\nu_{max.}$ 1730, 1260, 1230 $cm.^{-1}$ which was warmed with potassium hydroxide (0.2 g.) in 5% aqueous methanol (20 ml.) for 1 hour. Removal of the solvent and ether extraction gave after washing the ether layer with water until neutral, drying and ether evaporation 2β-methyl-A-nor-5α-cholestan-2α-ol (0.049 g.) m.p. and mixed m.p. 115-116° (acetone).

b) 2α-Methyl-2β-acetyl-A-nor-5α-cholestane (0.09 g.) in chloroform (20 ml.) was treated with m-chloroperbenzoic acid (0.09 g.) for 8 days. After the usual work up a product (0.079 g.) $\nu_{max.}$ 1730, 1700 $cm.^{-1}$ was obtained which was adsorbed on silica gel (25 g.). Elution with petrol-benzene (8:2) gave 2α-methyl-2β-acetyl-A-nor-5α-cholestane (0.022 g.) m.p. and mixed m.p. 114-116° (acetone). Elution with petrol-benzene (7:3) gave the acetate (0.040 g.) $\nu_{max.}$ 1730 $cm.^{-1}$ which on treatment with potassium hydroxide (0.1 g.) in 5% aqueous methanol (20 ml.) gave, on isolation by means of ether, 2α-methyl-A-nor-5α-cholestan-2β-ol (0.027 g.) m.p. and mixed m.p. 137-139° (acetone).

Treatment of 2β-methyl-A-nor-5α-cholestan-2α-aldehyde with methyl magnesium iodide

2β-Methyl-A-nor-5α-cholestan-2α-aldehyde (0.4 g.) in dry ether (50 ml.) was added to an ethereal solution (100 ml.) of methyl magnesium iodide (from magnesium (0.4 g.)). The solution was refluxed for 5 hours. On cooling ammonium chloride solution was added dropwise and the steroid was extracted with ether. The ether layer was washed with water, dried and the ether evaporated to give the 2α-(1'-hydroxyethyl)-2β-methyl-A-nor-5α-cholestanes (0.386 g.)

(semi-solid); $\nu_{max.}$ 3650, 1110, 1090 $cm.^{-1}$; n.m.r. τ 9.34 (C-18 methyl group), 9.19, 9.10 (C-19 and side chain methyl groups), 8.80, 8.86, 8.96 (C-2β methyl group and methyl group on C-2').

Oxidation of 2α-(1'-hydroxyethyl)-2β-methyl-A-nor-5α-cholestane

The alcohol mixture (382) (0.25 g.) in acetone (25 ml.) was oxidised with 8N chromic acid (Jones' reagent) (0.6 ml.). The reaction was allowed to proceed for 4 minutes and excess reagent was decomposed with methanol (5 ml.). Water was added, the acetone removed under reduced pressure and the steroid extracted with ether. The ether layer was washed with water, dried and the ether evaporated to give 2β-methyl-2α-acetyl-A-nor-5α-cholestane (0.212 g.) m.p. and mixed m.p. 93-96° (acetone).

The reaction of 2α,3α-epoxy-5α-cholestane with methyl magnesium iodide

Treatment of 2β,3β-epoxy-5α-cholestane with methyl magnesium iodide[50]

2β,3β-Epoxy-5α-cholestane (1 g.) in dry ether (50 ml.) was added to an ethereal solution (100 ml.) of methyl magnesium iodide (from magnesium (1 g.)), and the mixture was refluxed for 5 hours. On cooling dilute ammonium chloride solution was added, and the steroid was extracted with ether. The ether layer was washed with water, dried and the ether evaporated to give a product (1.002 g.) which was adsorbed on alumina (100 g.). Elution with petrol-benzene (1:1) gave 2α-methyl-2β-hydroxy-5α-cholestane (0.224 g.) m.p. 147-148° (acetone) (lit.[50] m.p. 148-149°) $[\alpha]_D$ +29° (c.0.13) (lit.[50] +48°); $\nu_{max.}$ 3580, 918, 855 $cm.^{-1}$ Elution with benzene and benzene-ether (98:2) gave 2α-(1'-hydroxyethyl)-A-nor-5α-cholestane (0.761 g.) (semi-solid); $\nu_{max.}$ 3570 $cm.^{-1}$

Oxidation of 2α-(1'-hydroxyethyl)-A-nor-5α-cholestane

The mixture of hydroxyethyl-compounds (384) (0.6 g.) in acetone (120 ml.) was oxidised with 8N-chromic acid (Jones' reagent) (1.2 ml.) in a manner similar to that described on page 115. The product, isolated by means of ether, was crystallised from acetone to give 2α-acetyl-A-nor-5α-cholestane (0.527 g.) m.p. 78-80° (lit.[151] m.p. 77-78°); $\nu_{max.}$ 1705, 1360 $cm.^{-1}$; R.D. $[\Phi]_{370}$ +64°, $[\Phi]_{304.5}$ +230°, $[\Phi]_{272}$ -100°, $[\Phi]_{256}$ -64°; n.m.r. τ 9.33 (C-18 methyl group), 9.27 (C-19 methyl group), 9.18, 9.09 (side chain methyl groups), 7.87 (acetyl methyl group).

2α,3α-Epoxy-5α-cholestane[8]

5α-Cholest-2-ene (3.8 g.) in dry ether (50 ml.) was added to an ethereal solution (50 ml.) of m-chloroperbenzoic acid (3.8 g.). After 36 hours the mixture was worked up with ferrous sulphate solution, sodium bicarbonate solution, and water to give 2α,3α-epoxy-5α-cholestane (3.296 g.) m.p. 102-104° (acetone) (lit.[8] m.p. 105°); $\nu_{max.}$ 820, 815 $cm.^{-1}$; n.m.r. τ 9.36 (C-18 methyl group), 9.24, 9.19, 9.09 (C-19 and side chain methyl groups), 6.92, 6.85 (C-2, C-3 protons).

Treatment of 2α,3α-epoxy-5α-cholestane with methyl magnesium iodide

The α-epoxide (388) (1.70 g.) in dry ether (100 ml.) was added to an ethereal solution (200 ml.) of methyl magnesium iodide (from magnesium (1.7 g.)) and the mixture was heated under reflux for 5 hours. On cooling, dilute ammonium chloride solution was added, and the steroid was extracted into ether. The ether layer was washed with water, dried and the ether evaporated to give a product (1.61 g.) which was adsorbed on alumina (250 g.). Elution with petrol-benzene (1:1) gave 3β-methyl-5α-cholestan-3α-ol (0.580 g.) m.p. and mixed m.p. 125-126° (acetone), $\nu_{max.}$ 3600, 965, 960, 900 $cm.^{-1}$ Dehydration with phosphoryl chloride in pyridine of this alcohol (0.1 g.) under the conditions outlined on page 132 gave 3-methyl-5α-cholest-2-ene (0.074 g.) m.p. and mixed m.p. 82-83° (acetone). Further elution with petrol-benzene (1:1) gave 5α-cholestan-3α-ol (0.178 g.) m.p. and mixed m.p. 185-186° (acetone), $\nu_{max.}$ 3570, 1010 $cm.^{-1}$ Oxidation of this alcohol (0.05 g.) with Jones' reagent (0.1 ml.) under conditions similar to those described on page 115

gave 5α-cholestan-3-one (0.044 g.), m.p. and mixed m.p. 128-129° (acetone). Elution with benzene-ether (9:1) gave 3α-methyl-5α-cholestan-3β-ol (0.541 g.) m.p. and mixed m.p. 146-148° (acetone); $\nu_{max.}$ 3580, 1010, 945, 930, 920 $cm.^{-1}$ Dehydration of this alcohol (0.1 g.) with phosphoryl chloride in pyridine under the conditions outlined on page 132 gave 3-methylene-5α-cholestane (0.079 g.) m.p. and mixed m.p. 65-66 (acetone). Elution with chloroform gave 5α-cholestan-2β,3α-diol (0.271 g.) m.p. 197-200° (mixed m.p. with an authentic sample[152] (see below) 197-200°) (ethanol). Treatment of 5α-cholestan-2β,3α-diol (0.1 g.) with acetic anhydride (10 ml.) in pyridine (20 ml.) at room temperature overnight gave 5α-cholestan-2β,3α-diol diacetate (0.098 g.) m.p. 131-134° (mixed m.p. with an authentic sample[152] (see below) 131-134°) (acetone).

5α-Cholestan-2β,3α-diol[152]

2α,3α-Epoxy-5α-cholestane (0.2 g.) in 5% aqueous acetone (50 ml.) was treated with dilute sulphuric acid (10 drops) at room temperature for 48 hours. Ether was added and the ether layer was washed with sodium carbonate solution and with water, dried and the ether evaporated to give 5α-cholestan-2β,3α-diol (0.193 g.) m.p. 199-201° (ethanol) (lit.[152] m.p. 200-202°). Acetylation with acetic anhydride in pyridine at room temperature overnight gave 5α-cholestan-2β,3α-diol diacetate, m.p. 131-134° (acetone) (lit.[152] m.p. 133-135°); $\nu_{max.}$ 1740, 1245, 1235, 1035 $cm.^{-1}$; n.m.r. τ 9.36 (C-18 methyl group), 9.19, 9.10 (C-19 and side chain methyl groups), 7.96, 7.92 (methyl groups of the acetates at C-2 and C-3).

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equatorial attack to take place. The epoxide derivatives of the 3-ethylidene-5α-cholestanes all gave 3β-acetyl-5α-cholestane on rearrangement with BF_3, the β-epoxides also giving some 3α-methyl-5α-cholestan-3β-aldehyde. The BF_3 catalysed rearrangements of the two 3-isopropylidene-epoxides have been carried out. The α-epoxide gave 4,4-dimethyl-A-homo-5α-cholestan-3-one and 3β-methyl-3α-acetyl-5α-cholestane, while the β-epoxide gave 3α-methyl-3β-acetyl-5α-cholestane. As part of the proof of the structure of the ring enlargement product from the α-epoxide, the methylation of A-homo-5α-cholestan-4-one was carried out.

The synthesis and the BF_3-catalysed rearrangements of the epoxide of 2-isopropylidene-A-nor-5α-cholestane have been carried out.

The α- and β-epoxides of 2,3-dimethyl-5α-cholestane have been prepared and treated with BF_3, the α-epoxide giving 2β-methyl-2α-acetyl-A-nor-5α-cholestane and the β-epoxide the corresponding 2α-methyl-2β-acetyl-compound.

Finally the reaction of 2α,3α-epoxy-5α-cholestane with methyl magnesium iodide was found to involve rearrangement to 5α-cholestan-3-one.