STUDIES IN THE SYNTHESIS AND THERMAL REARRANGEMENTS OF C-3 SUBSTITUTED 4-CHLORO-4,5-EPOXIDES IN RING-A OF STEROIDS

by

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A thesis submitted to the Faculty of Graduate Studies of the University of Manitoba in partial fulfillment of the requirements of the degree of

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ABSTRACT

The general objective of this work was the chemical synthesis of some hormonal steroid derivatives with the potential to act as specific steroid hormone inhibitors. In particular, the study of the thermal molecular rearrangement of C-3 substituted steroid 4-chloro-4,5-epoxides as intermediates in the synthesis of C-4 oxygenated derivatives was investigated. Thermal rearrangements of chloroepoxides with adjacent functional groups has not been reported previously. Thermal rearrangement of C-3 hydroxyl and carbonyl 4,5-epoxides derivatives of 17β-acetoxyandrostane is discussed. Further work on the novel rearrangement of the C-3 hydroxy-4-chloro-4,5-epoxides derivatives which lead to the 4-hydroxy-4-en-3-one diosphenol was carried out. This new diosphenol synthesis under neutral conditions is applicable to the synthesis of novel aromatase enzyme inhibitors.

The first thermal rearrangement of C-3 oxo-4-chloro-4,5-epoxides was carried out leading to 5-chloro-3-hydroxy-2-en-4-one diosphenol derivatives. These enolic compounds, at a higher temperature, gave the 4-hydroxy-4,6-dien-3-one system. Zinc-copper couple elimination of the 5-chloro-3-hydroxy-2-en-4-one derivatives or their acetates rearranged to the 4-hydroxy- and 4-acetoxy-4-en-3-one diosphenol derivatives.

The mechanism of the thermal rearrangement of chloroepoxides with a carbonyl and a hydroxyl function adjacent to the chlorine atom is discussed. Evidence is presented that the thermal molecular rearrangement of chloroepoxides may involve in some cases an oxiranyl cation-chloride ion pair which control the stereochemistry of chloride ion addition, rather than a planar carbocation intermediate.

Attempts to use the thermal rearrangement of the C-3 oxo-4-chloro-4,5-epoxides in the estrane series to synthesize the biologically interesting 3,4-catecholestrogens did not prove to be successful.

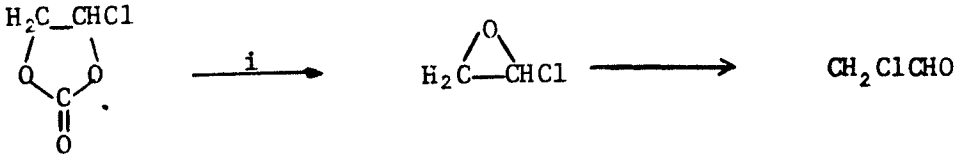
CONTENTS

INTRODUCTION

The molecular rearrangement of α-substituted epoxides has been reviewed[1,2] and they show that most attention from researchers has been given to the rearrangement of α-chloroepoxides. Only a few reports of studies on the rearrangement of α-bromoepoxides have been found in the literature[3-5]. Research involving α-fluoroepoxide rearrangements has been largely centered about tetrafluoroethylene oxide[6-10] and hexafluoropropylene oxide[10-14]. Only one report of a study on the rearrangement of an α-iodoepoxide has appeared in the literature[15]. The rearrangement of pseudohalo-epoxides (enol ester epoxides and cyanoepoxides) have also been reported[1].

A. α-Chloroepoxides

α-Chloroepoxides rearrangements have been thoroughly studied over the past fourty years. Zief and Schramm[16] have reported that by heating chloroethylene carbonate (1) with concentrated sulfuric acid to 230°C and removing the oxide (2) by distillation α-chloroethylene oxide (2) was formed. The oxide (2) was found to rearrange upon standing at room temperature to chloroacetaldehyde (Scheme 1).

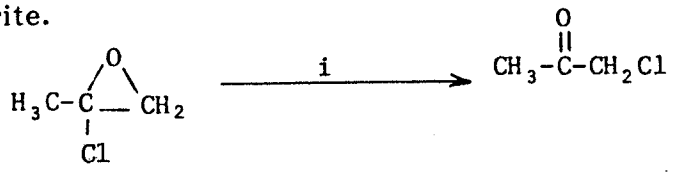


(1) (2)

SCHEME 1

i.H_2SO_4,

2-Chloropropylene oxide (3)[17,18] and 2-chloro-3-methyl-2-butene oxide[18] (4) have been prepared by chlorination of the corresponding epoxides with tert-butylhypochlorite.

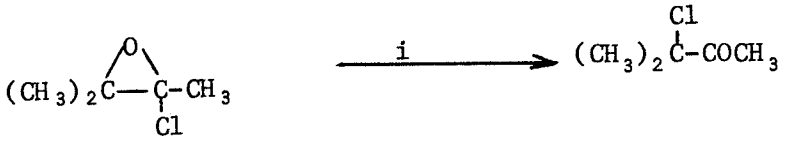


(3)

SCHEME 2

i. 2,4-Dinitrophenyl Hydrazine

Treatment of 2-chloropropylene oxide (3) with 2,4-dinitrophenylhydrazine gave the hydrazone of chloroacetone, while 2-chloro-3-methyl-2-butene oxide (4) when treated with acetic acid in ether, rearranged to 3-chloro-3-methyl-2-butanone (5). Both products are the result of chlorine migration (Scheme 2,3).



(4) (5)

SCHEME 3

i. HOAc,Et_2O

McDonald and Schwab[19] have investigated the peroxidations of α-chlorostilbenes (6,7) to establish whether the rearrangement of the epoxides is a result of chlorine or hydride migration. The authors found that in both cases the α-chloroketone isolated involved chlorine migration (Scheme 4).

TABLE 1

Certain Acyclic α–Chloro Epoxides and Their Rearrangement Products

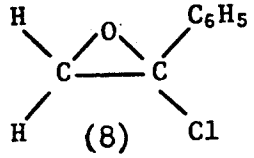
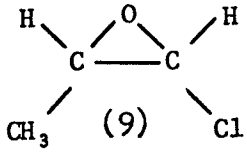
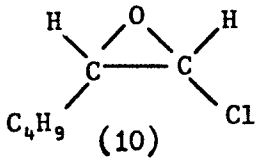
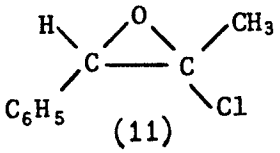
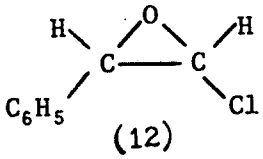
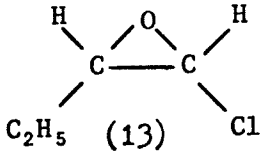
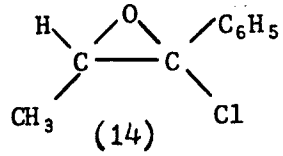
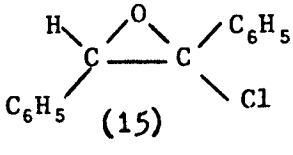
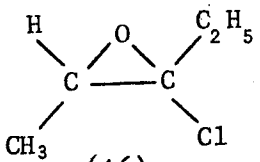
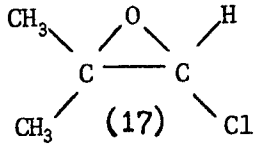
Epoxide	Product
 (8)	$C_6H_5COCH_2Cl$ + $C_6H_5CHClCHO$
 (9)	$CH_3CHClCHO$
 (10)	$C_4H_9CHClCHO$
 (11)	$C_6H_5CHClCOCH_3$
 (12)	$C_6H_5CHClCHO$
 (13)	$C_2H_5CHClCHO$
 (14)	$C_6H_5COCHClCH_3$ + $C_6H_5CHClCOCH_3$
 (15)	$C_6H_5CHClCOC_6H_5$

TABLE 1 (continued)



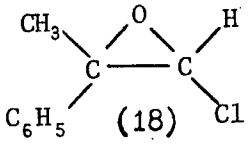
(16)

$CH_3CHClCOC_2H_5$



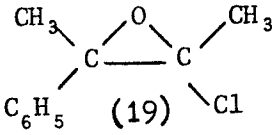
(17)

$(CH_3)_2CClCHO$ +
$CH_2 = C(CH_3)CHO$



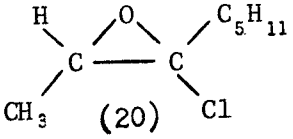
(18)

$C_6H_5CCl(CH_3)CHO$



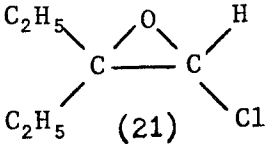
(19)

$C_6H_5CCl(CH_3)COCH_3$



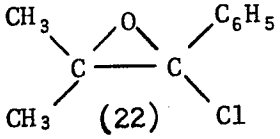
(20)

$CH_3CHClCOC_5H_{11}$



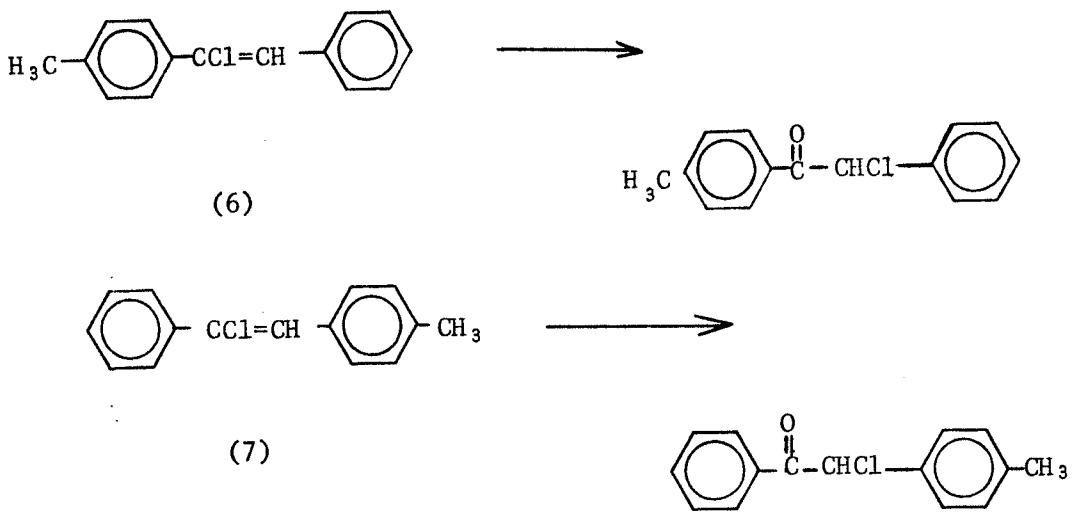
(21)

$(C_2H_5)_2CClCHO$ +
$CH_3CH = C(C_2H_5)CHO$



(22)

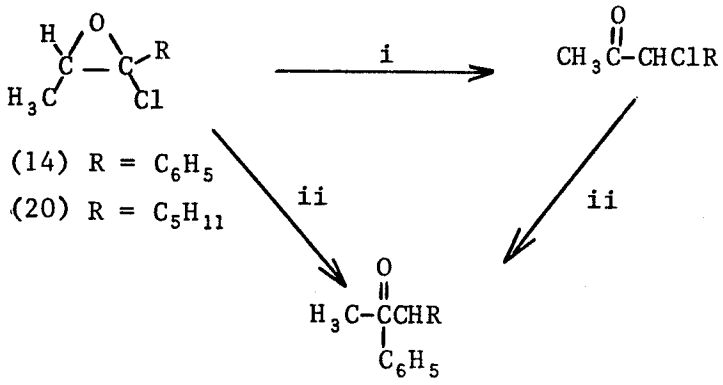
$C_6H_5COCCl(CH_3)_2$ +
$C_6H_5COC(CH_3) = CH_2$



SCHEME 4

Kirrmann and Nouri-Bimorghi[20] have published a study of the rearrangement reactions of a number of acylic α-chloroepoxides. These compounds, along with their products of thermal rearrangement, are listed in Table 1. It was noted that the products of chlorine and hydrogen migration occur when the phenyl ring is on the α-carbon (8,14) while their respective isomers (11,12), which have the phenyl ring attached to the β-carbon, only the product of chlorine migration was observed. In the α-chloroepoxide (22) it can be seen that by substituting the β-carbon with two methyl groups the rearrangement process proceeds completely through chlorine migration.

Kirmann and Nouri-Bimorghi[20] have studied the Lewis acid-catalyzed rearrangement of 1-phenyl-1-chloro-1,2-epoxypropane and 3-chloro-2,3-epoxyoctane (14,20) with both boron trifluoride in ether and aluminum chloride. The α-chloroketone product formed was that arising from hydride migration (Scheme 5).



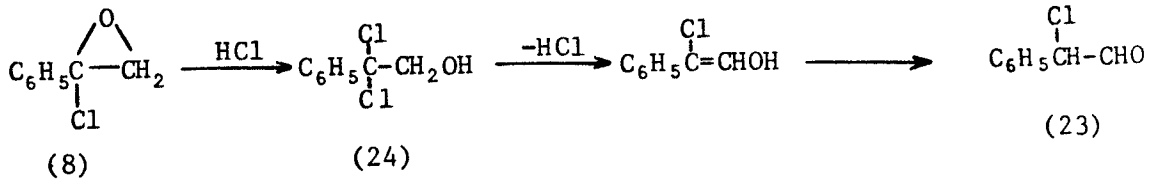
SCHEME 5

i. BF_3 or $AlCl_3$
ii. $AlCl_3$, C_6H_6

Lewis base catalysed rearrangement of α-chloro- α-phenylepoxides with pyridine yielded the α-chloroketone products of chlorine migration[20]. α-Chloroketones obtained from proton acid rearrangement were found to give the product of chlorine or hydrogen migration, depending on the acid used.

The products of the α-chloroepoxide rearrangement, using either hydrogen bromide or hydrogen fluoride were the corresponding α-bromo- or α-fluoroketone formed by chlorine migration. Hydrogen chloride, however, frequently leads to a compound that appears to be the product of hydrogen migration.

Nouri-Bimorghi[21] has studied the reaction of 1-phenyl- 1-chloro-1,2-epoxyethane (8) with hydrogen chloride. The product observed was α-chlorophenylacetaldehyde (23). In this study, the author has shown that the reaction proceeds only partially, if at all, by hydrogen migration. Rather, the reaction involves addition of hydrogen chloride to the α-chloroepoxide (8) to give the dichloroalcohol (24), which then eliminates hydrogen chloride in a reverse fashion to yield the enol form (23). This is the principal process in related reactions with hydrogen chloride which are discussed later.



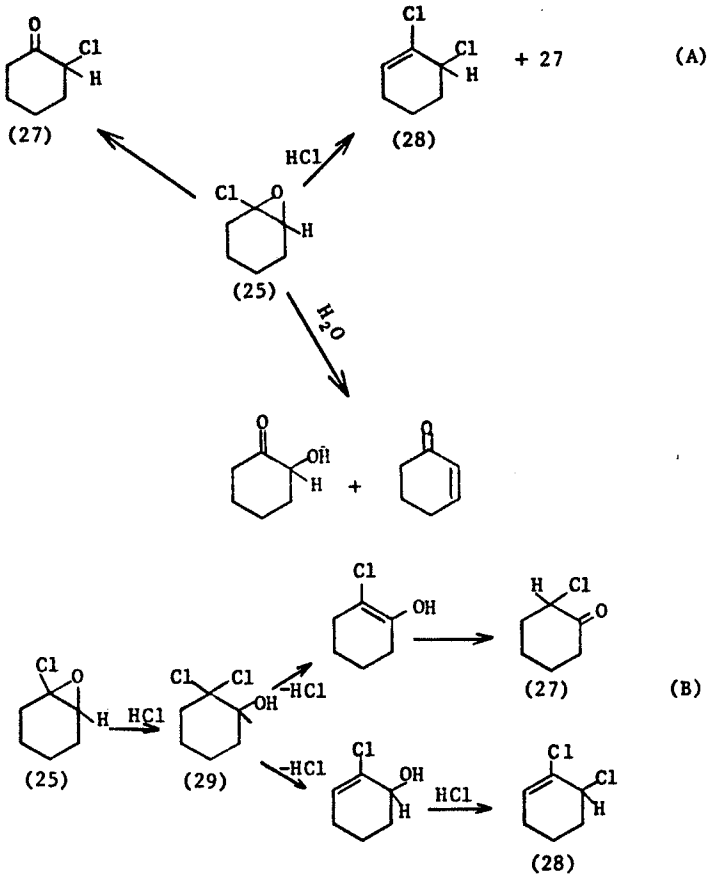
(8) (24) (23)

SCHEME 6

Mousseron and his co-workers[22-25] initiated research in the area of alicyclic α-chloroepoxides. They found that treatment of the corresponding vinyl chlorides with perbenzoic acid produced 1-chlorocyclohexene oxide[22-24] (25) and l-chloro-5-methyl-cyclohexene oxide (26)[22,24,25]. These α-chloroepoxides were reported to be relatively stable compounds.

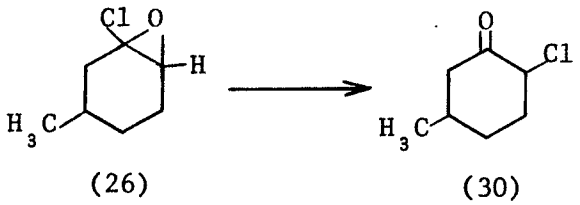
Upon standing in the atmosphere for a long time 1-chlorocyclohexene oxide (25) was reported to rearrange to 2-chlorocyclohexanone (27)[22]. Treatment of 1-chlorocyclohexene oxide (25) with hydrogen chloride at 0°C gave 27 and 2,3-dichlorocyclohexene (28).

The hydrolysis product of 1-chlorocyclohexene oxide (25) was found to give 2-hydroxycyclohexanone along with a small amount of 2-cyclohexenone[22]. The product (28) produced from the effect of hydrogen chloride on 1-chlorocyclohexene oxide (25) can be rationalized by the addition of hydrogen chloride to 25 to give 2,2-dichlorocyclohexanol (29), two different hydrogen chloride elimination might then proceed, as shown in Scheme 7(B), with subsequent ketonization to 27 on the one hand and conversion of the allylic alcohol to the allylic chloride (28) on the other. From Scheme 7(B) it seems possible that the amount of 27 produced is developed in the same reaction.



SCHEME 7(A,B)

Exposure of 1-chloro-5-methylcyclohexene oxide (26) to the atmosphere yielded 2-chloro-5-methylcyclohexanone (30), which is the product expected in chlorine migration rearrangement[22] (Scheme 8).

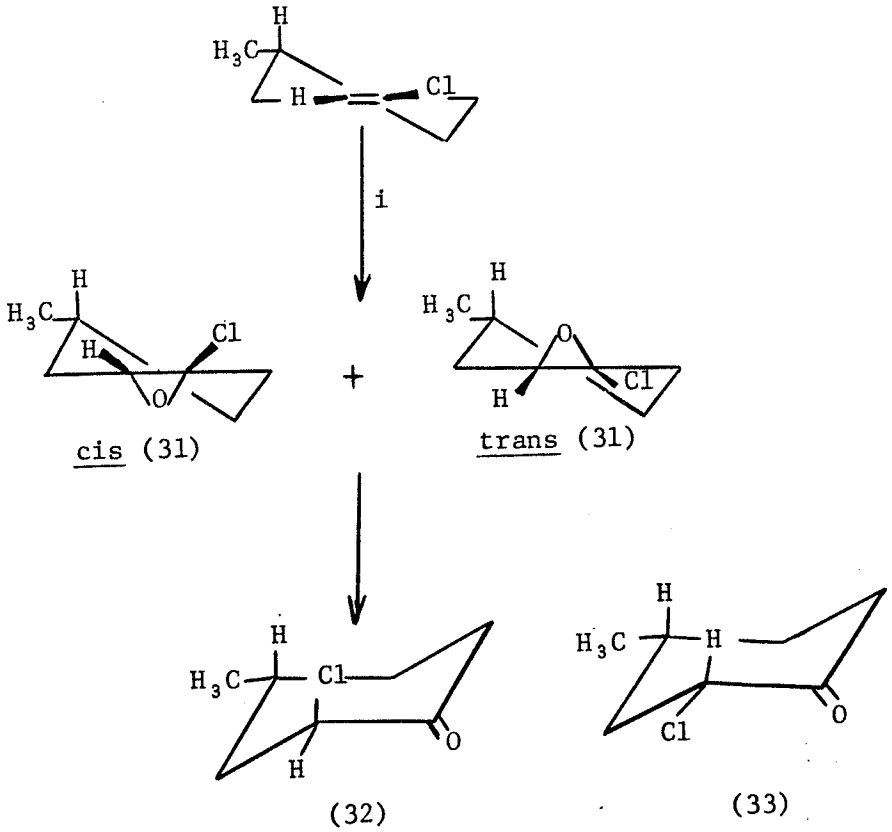


SCHEME 8

McDonald and Tabor[26,27] selected 1-chloro-4-methylcyclohexene oxide (31) to study the stereochemistry of the rearrangement product. Epoxidation of 1-chloro-4-methylcyclohexene, using m-chloroperbenzoic acid, produced a

mixture of 1-chloro-cis- and trans-4-methyl cyclohexene oxide (cis, trans - 31) (Scheme 9).

Neat thermal rearrangement of the mixture (cis, trans-31) at 80°C produced only trans-2-chloro-4-methylcyclohexanone (32). In their research chlorine was established as the migrating species; also the reaction was found to proceed stereospecifically to yield trans-2-chloro-4-methylcyclohexanone (32) from both isomers. After 35% of the rearrangement have taken place, trace amounts of cis-2-chloro-4-methylcyclohexanone (33), the more stable isomer, begin to appear. The α-chloroketone (33) is thought to be the result of acid-catalyzed isomerization of 32 from the hydrogen chloride produced during the reaction. Treatment of the mixture of cis (31) and trans (31) with zinc chloride gave a mixture of 32 and 33.

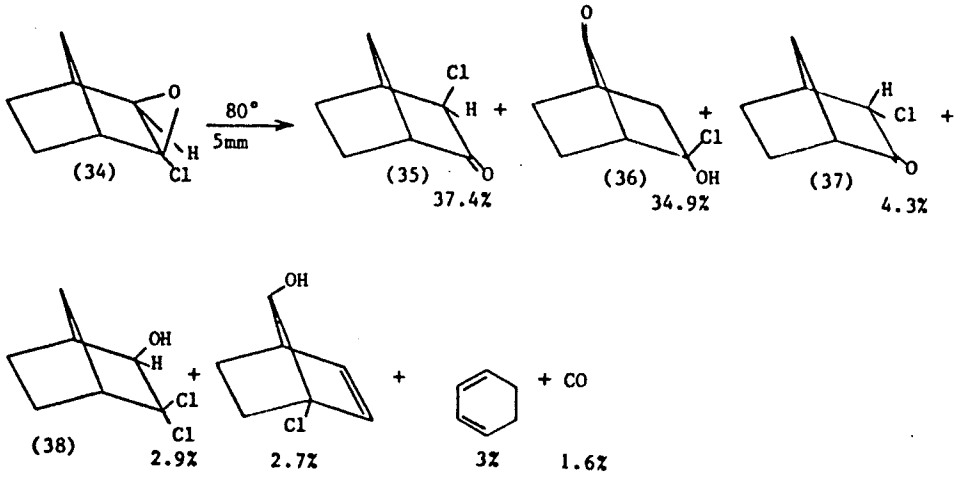


SCHEME 9

i. $ClC_6H_4CO_3H$

2-Chlorobicyclo[2.2.1]heptene exo-oxide (34) has been prepared by peracid oxidation of the corresponding vinyl chloride to study the mechanism of its rearrangement to the corresponding α-chloroketone[28].

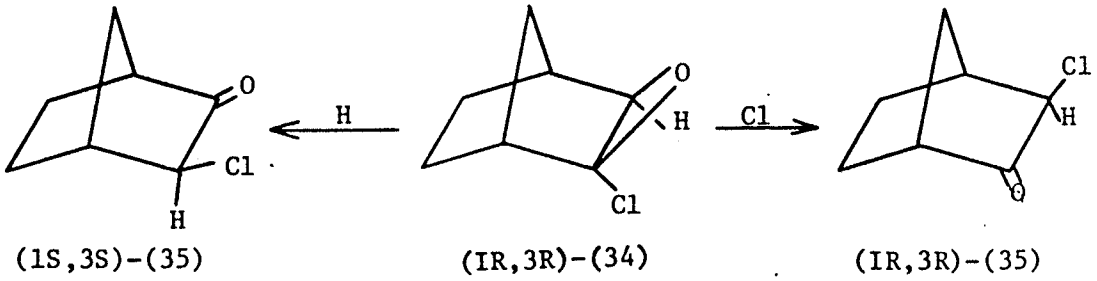
Pyrolysis of the exo-oxide (34) gave the products shown in Scheme 10.



SCHEME 10

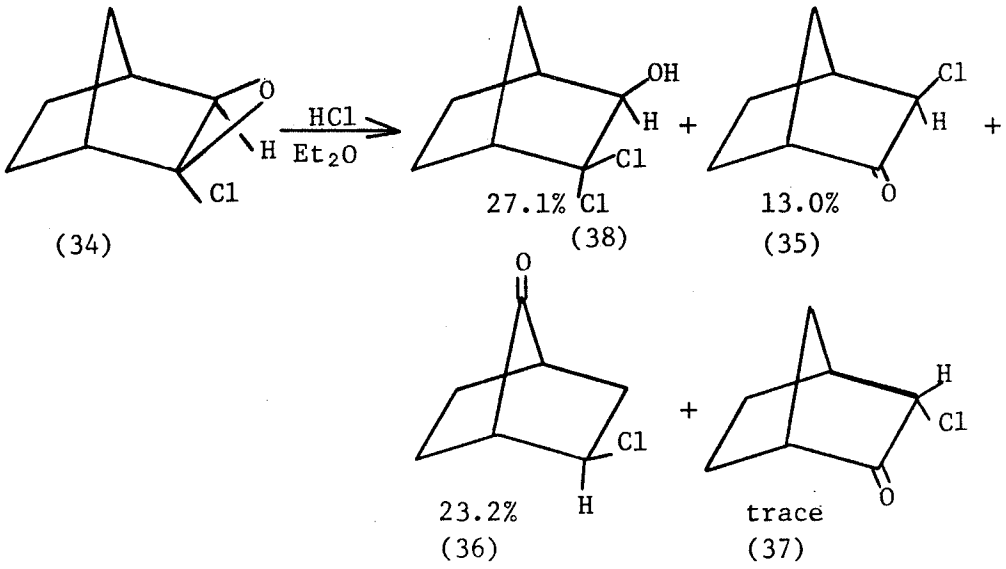
Products 35-38 (Scheme 10) were stable to the rearrangement conditions in the absence, or presence, of hydrogen chloride[1].

The formation of the major products (35,36) can be explained by chlorine or hydrogen migration[29,30], to differentiate between the two possible mechanisms. McDonald and Steppel[31,32] started with optically active 34. Compound 34-(+) - (1R,3R) has been synthesized and rearranged, and from three separate rearrangements the extent of chlorine migration were shown to be $\geq$ 90%.



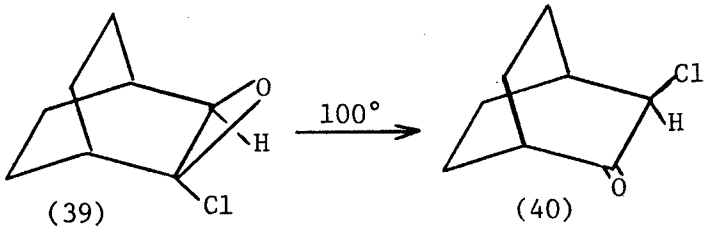
SCHEME 11

Hydrogen chloride catalysis rearrangement of 34 gave dichloroalcohol (38) as the major product[28] (Scheme 12).



SCHEME 12

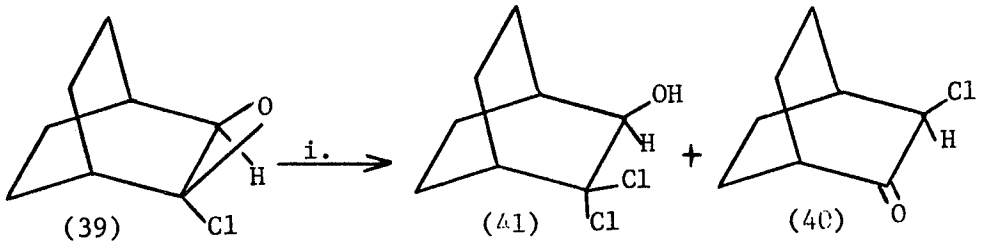
Neat, thermal rearrangement of 2-chlorobicyclo[2.2.2]octene oxide (39) gave 3-chlorobicyclo [2.2.2] octan-2-one (40) in 90% yield[33] (Scheme 13).



SCHEME 13

Hydrogen chloride catalysis of 39 produced 2:1 mixture of 3,3 -dichlorobicyclo[2.2.2]octan-2-ol (41) and 3-chlorobicyclo[2.2.2]octan-2-one (40) (Scheme 14). It was thought that the amount of 40 produced resulted from hydrogen chloride elimination from 3,3 -dichlorobicyclo[2.2.2]octan-2-ol (41) by ketonization [33].

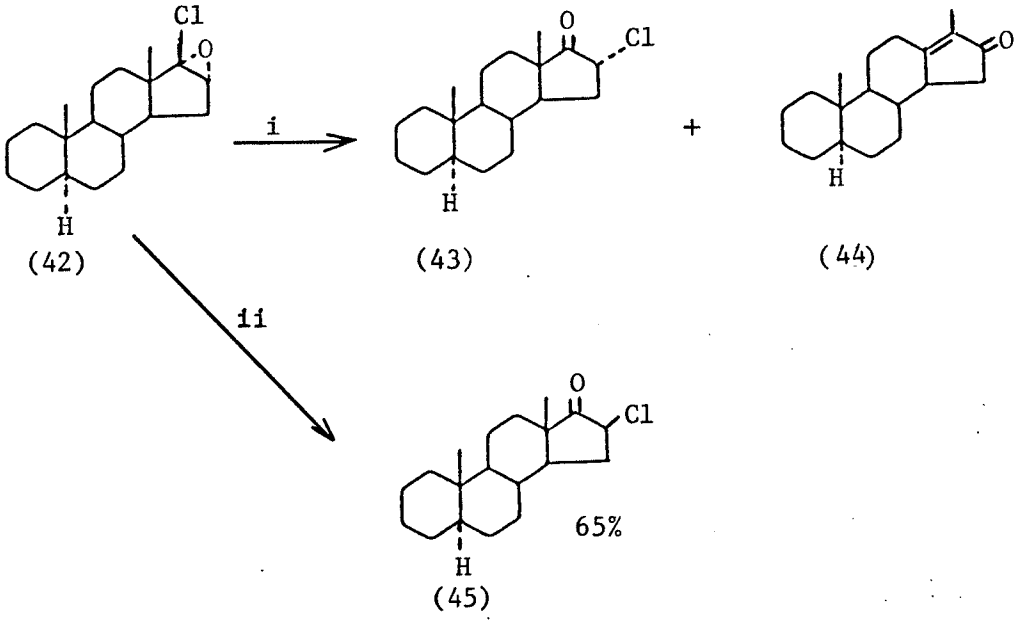
This rearrangement has been applied to the steroid skeleton in the rearrangement of 17β -chloro-16α,17α -epoxy-5α -androstane (42), which was prepared by perbenzoic acid oxidation of the corresponding vinyl chloride[34]. Pyrolysis of the chloroepoxide (42) gave a chloroketone (43) and a conjugated ketone (44) (Sch-



SCHEME 14

i. HCl,Et_2O

eme 15). 17β-Chloro -5α-androstan-16-one, has properties similar to those of the 16α-chloro-5α-androstan-17-one (43)[35], but the 16α-chloro-17-ketone is mechanistically more likely[36] because it is the product of chlorine migration. Hydrogen chloride catalysis rearrangement of the chloroepoxide (42) gave the 16 β-chloro-17-ketone (45) [36], in both rearrangements (in the pyrolysis and the acid catalysis rearrangements), chlorine was the migrating species.



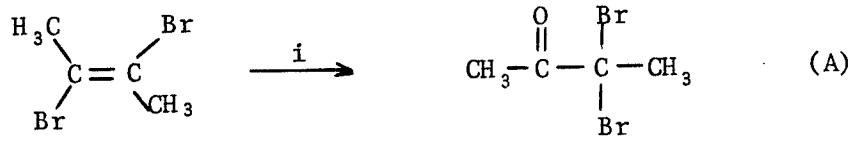
SCHEME 15

i. Δ
ii. HCl, Dioxane

B. α-Bromoepoxides

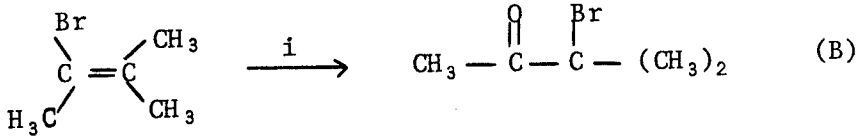
Only a few reports have been published concerning α-bromoepoxide rearrangement. Heating 17β-bromo-16α,17α-epoxysteroids gave 16α-bromo-17-keto steroids [37].

Oxidation of 2,3-dibromo-2-butene using trifluoroperacetic acid-boron trifluoride gave 3,3-dibromo-2-butanone (46)[4] (Scheme 16A). Similar oxidation of 2-bromo-3-methyl-2-butene gave 3-bromo-3-methyl-2-butanone (47)[4] (Scheme 16B).



(A)

(46)

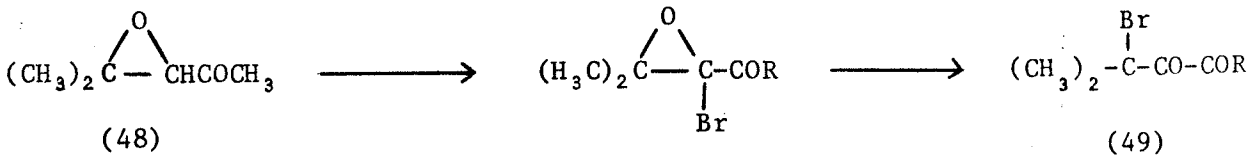


(B)

(47)

SCHEME 16 (A,B)
i. CF_3CO_3H,BF_3

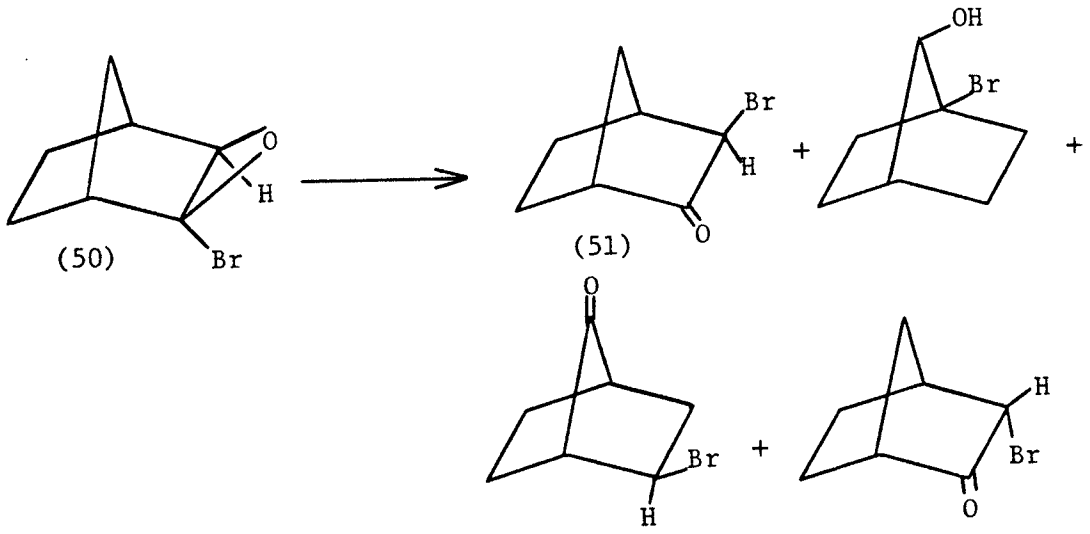
The previous three reactions are expected to occur through bromine migration. On bromination of 4-methyl-3,4-epoxypentan-2-one (48) the product of bromine migration (49) was formed[5].



(48) (49)

SCHEME 17

Attempts to study the synthesis and rearrangement of 2-bromonorbornene exo-oxide (50) have shown that this compound is unstable and the reaction leads occasionally to an explosion. The major component analysed from the explosion was found to be the exo-3-bromonorcamphor (51) accompanied by three other minor products (Scheme 18)[1].

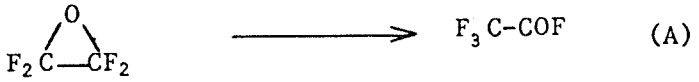


SCHEME 18

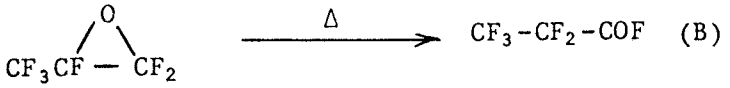
C- -Fluoroepoxides

A series of research papers have been reported on the chemistry of tetrafluoroethylene oxide (52)[6-10] and hexafluoropropylene oxide (54)[10-14].

Tetrafluoroethylene oxide was found to rearrange to trifluoroacetyl fluoride (53) below room temperature[6] (Scheme 19A). Heating hexafluoropropylene oxide (54) at high temperature produced the rearranged product 2,2-difluoro-3,3,3-trifluo-



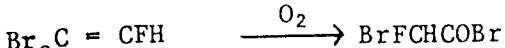
(52) (53) (A)



(54) (55) (B)

SCHEME 19 (A,B)

ropropionyl fluoride (55)[14] (Scheme 19B). Oxidation of 1,1-dibromo-2-fluoroethylene (56) is reported to give a 49% yield of bromofluoroacetyl bromide (57)[38] (Scheme 20).



(56) (57)

SCHEME 20

1-chloro-1-fluoro-2,2-difluoroethylene oxide (58) was found to rearrange to 1-chloro-1,1-difluoroacetyl fluoride (59) at 10° over a 3-day period[39] (Scheme 21).

(58) (59)

SCHEME 21

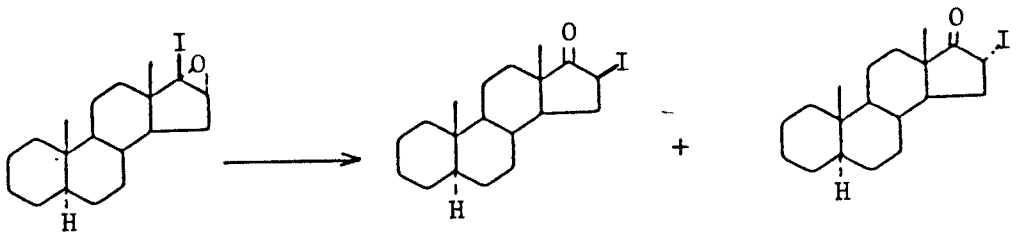
1,1-dichloro-2,2-difluoroethylene oxide (60) was found to rearrange to 2,2-dichloro-2-fluoroacetyl fluoride (61) when allowed to stand at 10° for 3 days [39] (Scheme 22).

(60) (61)

SCHEME 22

D. α-Iodoepoxides

Only one study has been reported on the rearrangement of α-iodoepoxides[35]. When a solution of iodoepoxide (62) in benzene was passed through aluminum oxide a mixture of 16β-iodo and 16α-iodoketones (63,64) was observed (Scheme 23).

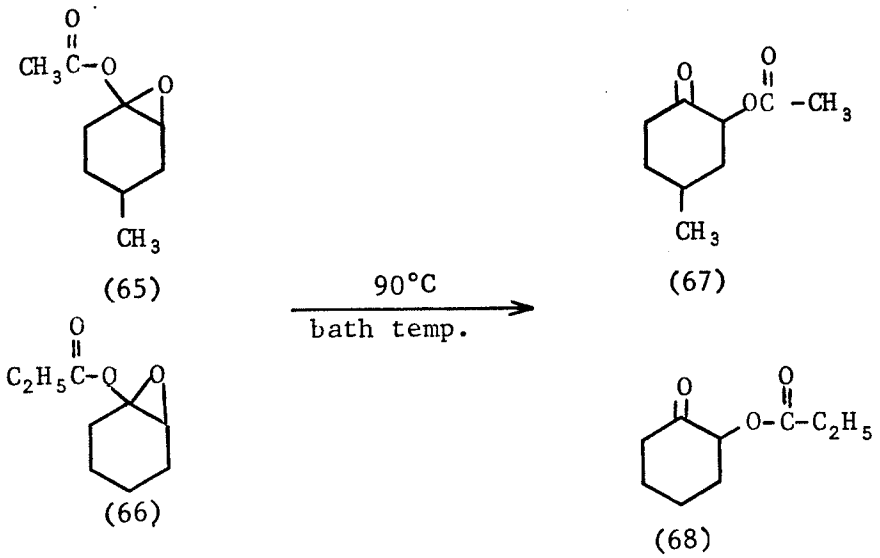


(62) (63) (64)

SCHEME 23

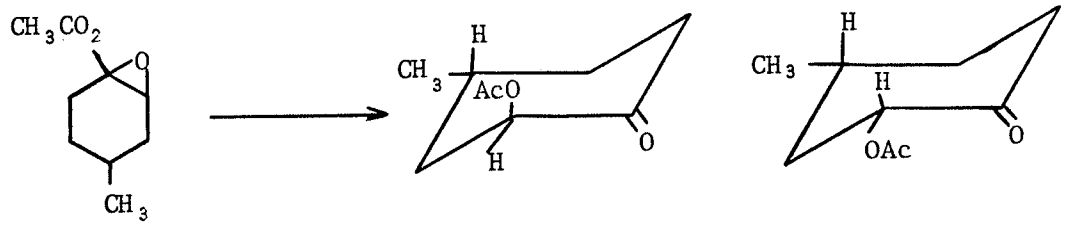
E. α-Acetoxyepoxides

Shine et al.[40] reported a study of considerable importance when they pyrolysed a mixture of 1-acetoxy-4-methylcyclohexene oxide (65) and 1-propionoxycyclohexene oxide (66), and no crossed products were detected. (i.e. neither 1-propionoxy-4-methylcyclohexanone nor 1-acetoxycyclohexanone were detected Scheme 24). This establishes the rearrangement as an intramolecular 1,2-migration of the acyloxy group.



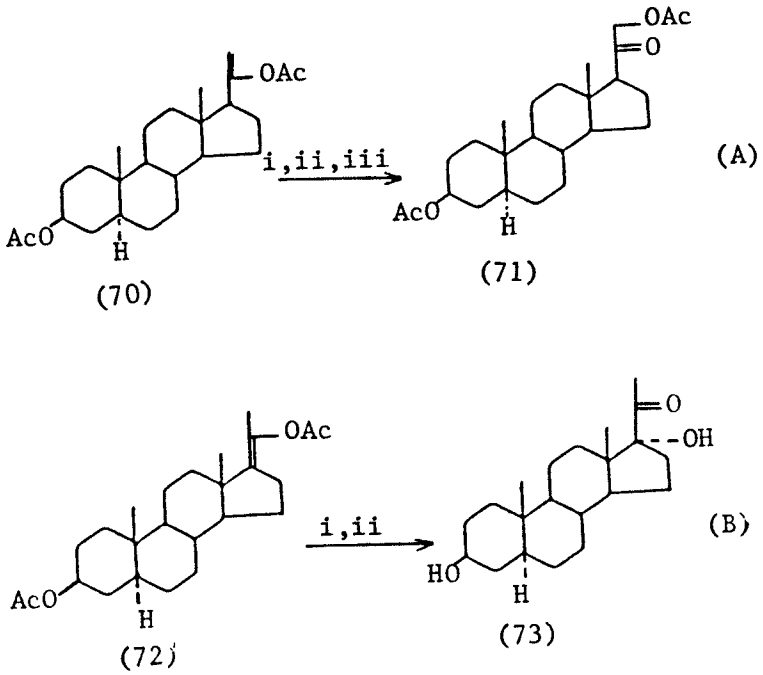
SCHEME 24

Thermal rearrangement of the acetoepoxide (65) gave predominantly trans-2-acetoxy-4-methyl-cyclohexanone (67)[26] (Scheme 25).



SCHEME 25

Gallagher et al.[41] have applied this rearrangement to the steroid molecule. 3 β,20-Diacetoxy-5 α-pregn-20-ene (70) was found to rearrange to 3β,21-diacetoxy-5α -pregnan-20-one (71) (Scheme 26A), while 3 β,20-diacetoxy-5 α-pregn-17(20)-ene(72) rearranged to 3β,17α-dihydroxypregnan-20-one (73)[42] (Scheme 26B).

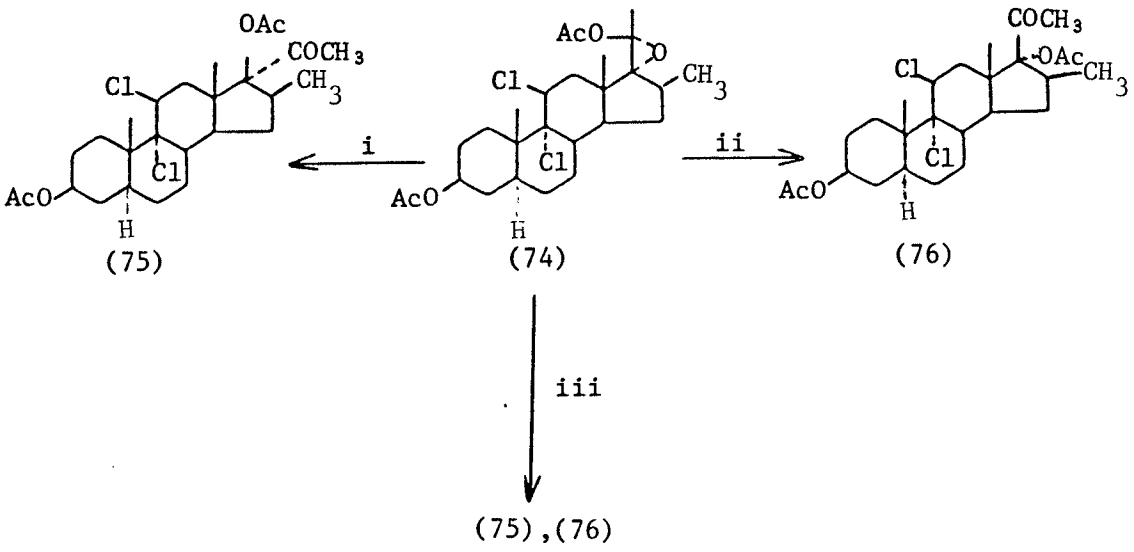


SCHEME 26 (A,B)

i. $C_6H_5CO_3H$
ii. -OH
iii. Ac_2O

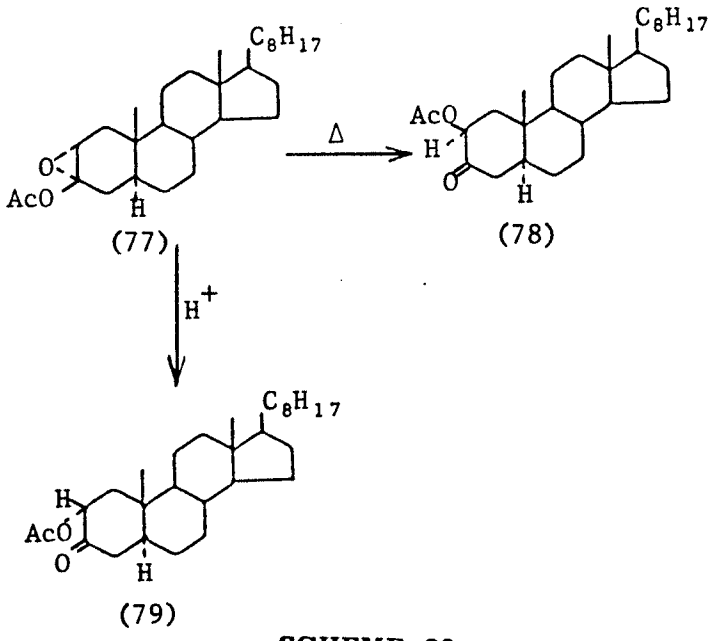
Neat thermal rearrangement of 3 β,20-diacetoxy-9 α,11 β -dichloro-16β -methyl-17(20)-epoxypregnane (74) gives the ketoacetate (75) as the rearranged product [43]. However, treatment of 74 with acetic acid and a small amount of aqueous sulfuric acid gave the other isomer (76) as the product. In the mixed solvent methanol-dichloromethane containing aqueous sulfuric acid both products were observed (75,76) (Scheme 27).

This rearrangement has been also applied to the steroid ring-A. Thermal rearrangment of 2α,3α-epoxy-3 β-acetoxycholestane (77) was found to produce 2 β-acetoxycholestan-3-one (78). Acid-catalyzed rearrangement of 77 produced 2 α-acetoxycholestan-3-one (79); it was established that this reaction involved intramolecular acetate migration and that 79 was not formed via acid catalysis of 78 [45].



SCHEME 27

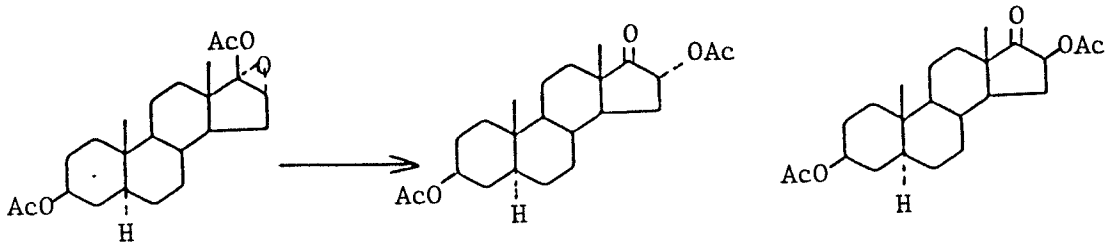
i. Δ
ii. HOAc, H_2SO_4
iii. Methanol–CH_2Cl_2, H_2SO_4



SCHEME 28

Gallagher et al.[46] reported that when 16α-17α-epoxyandrostane-3β, 17β-diol diacetate (80) is either chromatographed on silica gel, heated above its melting point, or subjected to acid hydrolysis and followed by acetylation, 5α-androstane-3β, 16α-diol-17-one diacetate (81) is formed (Scheme 29).

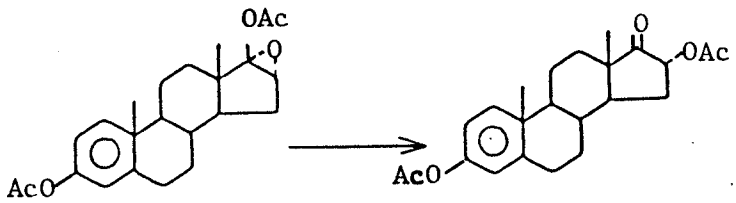
Johnson et al.[47] demonstrated that under the previous set of conditions androstane-3β,16β-diol-17-one diacetate (82) cannot be inverted to 81; also these authors have repeated the effect of silica gel chromatography on 80 and obtained a mixture of both isomers 81 and 82. From these results the authors concluded that the mechanism involves acetoxy migration to 81 without isomerization of 82 to 81.



(80) (81) (82)

SCHEME 29

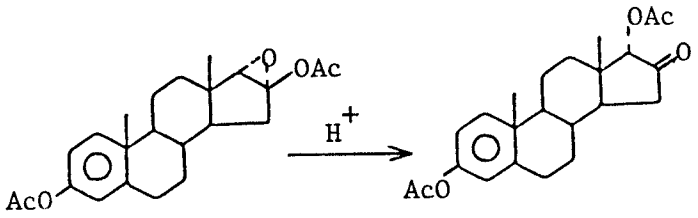
Treatment of 16α,17α-epoxyestra-1,3,5(10)-triene-3,17β-diol diacetate (83) with perchloric acid in acetic acid or passing it over silica gel was reported to give estra-1,3,5(10)-triene-3,16α-diol-17-one diacetate (84)[46] (Scheme 30).



(83) (84)

SCHEME 30

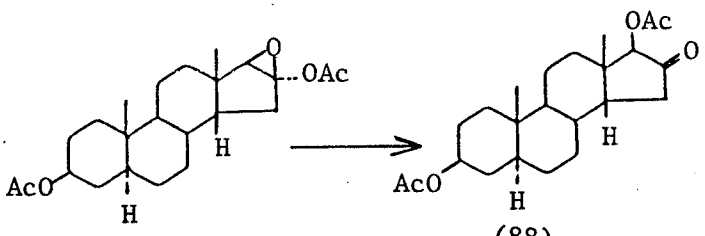
Also treatment of 16α,17α-epoxyestra-1,3,5(10)-triene-3,16β-diol diacetate (85) with perchloric acid-acetic acid yielded quantitatively estra-1,3,5(10)-triene-3,17α-diol-16one diacetate (86)[48] (Scheme 31).



(85) (86)

SCHEME 31

This rearrangement was applied to the 14β-series when 16β,17β-epoxy-5α,14β-androstane-3β,16α-diol diacetate (87) was treated with dilute sulfuric acid, the rearrangement product was found to be 5α,14β-androstane-3β,17β-diol-16-one diacetate (88)[49] (Scheme 32).

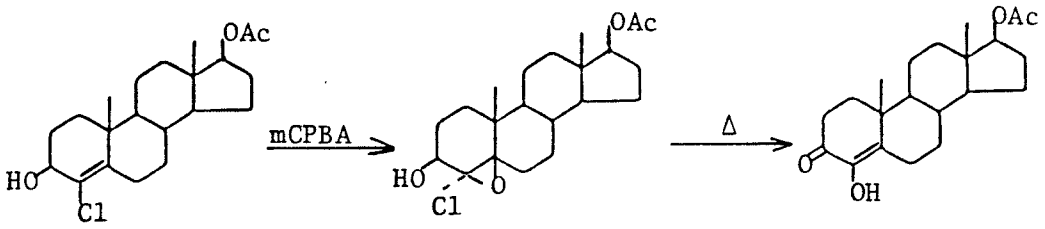


(87) (88)

SCHEME 32

F. α-Haloepoxides with a Functional Group Adjacent to the Halogen Atom

Recently Zeglam[50] has studied the thermal rearrangement of steroid chloroepoxides with a hydroxyl and acetoxyl function adjacent to the chloride atom. 4α-Chloro-4,5-epoxy-5β-androstane-3β,17β-diol 17-acetate (90) was prepared by the epoxidation of 4-chloroandrost-4-ene-3β,17β-diol 17-acetate (89). Neat thermal rearrangement of the α-chloroepoxide (90) at 200°C for 10 minutes gave the androst-4-ene-4,17β-diol-3-one 17 acetate (91) (Scheme 33).

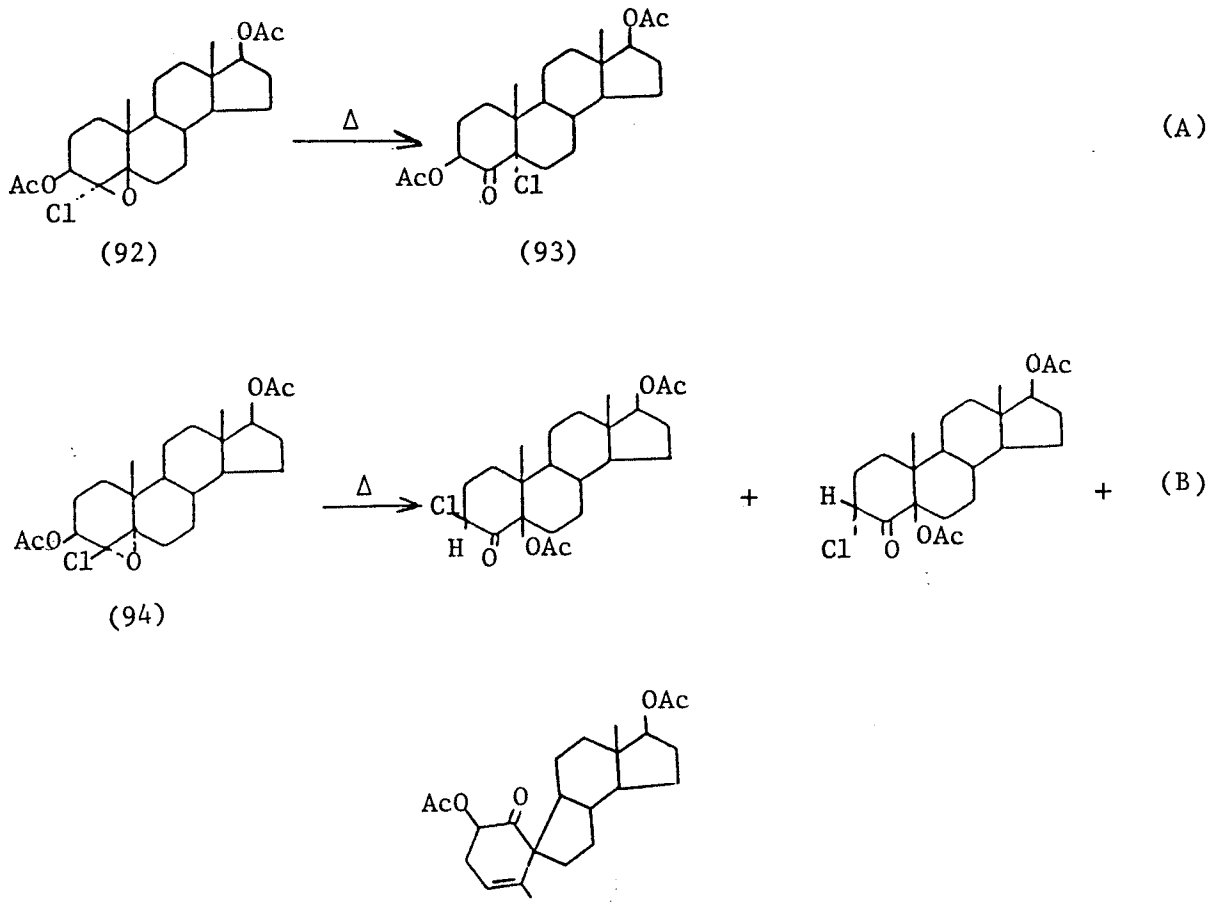


(89) (90) (91)

SCHEME 33

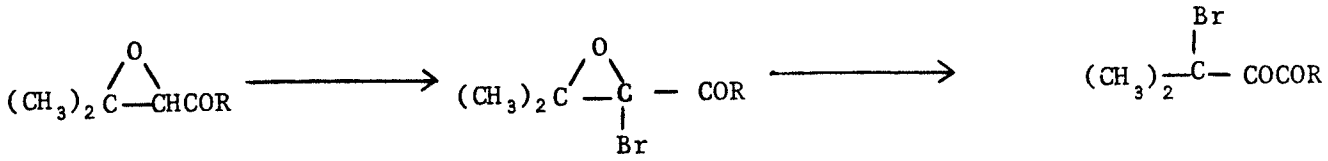
Acetylation of the α-chloroepoxide (90) produced 4α-chloro-4,5-epoxy-5β-androstane-3β,17β-diol diacetate (92) which on pyrolysis gave 5-chloro-5α-androstan-3β,17β-diol-4-one diacetate (93) with chlorine as the migrating species (Scheme 34A). Pyrolysis of 4β-chloro-4,5-epoxy-5α-androstane-3β,17β-diol diacetate (94) was also investigated.

4β-Chloro-4,5-epoxy-5α-androstane-3β,17β-diol diacetate (94) was prepared by treatment of 4-chloroandrost-4-ene-3β, 17β-diol diacetate with m-chloroperbenzoic acid. The product (94) was heated at 200°C for 10 minutes. While pyrolysis of the 5β-epoxide (92) led to the expected product with the chlorine as the migrating species, pyrolysis of the 5α-epoxide (94) gave three major products (Scheme 34B).



SCHEME 34 (A,B)

Only one study has been reported concerning a compound with a keto group adjacent to the α-bromoepoxide[51]. Bromination of 4-methyl-3,4-epoxypentan-2-one (95) led to the product of rearrangement with bromine migration from the intermediate α-bromoepoxide. Bromination of 3-methyl-2,3-epoxybutyrophenone (96) also led to the product of the rearrangement with the bromine as the migrating species. The intermediacy of 2-bromo-3-methyl-2,3-epoxybutyrophenone (98) was shown by spectral data.



[95 : R = CH_3]
[96 : R = C_6H_5]

97 : R = CH_3
98 : R = C_6H_5

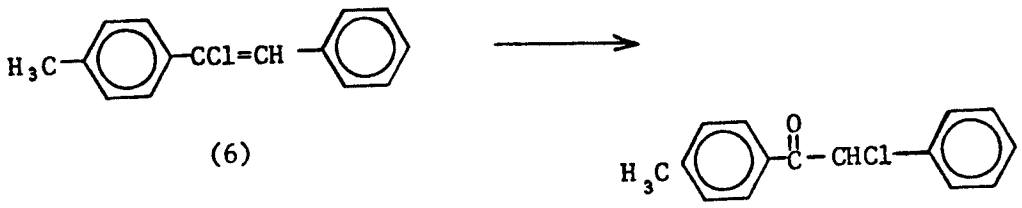
SCHEME 35

Mechanisms of α-Substituted Epoxides Rearrangements

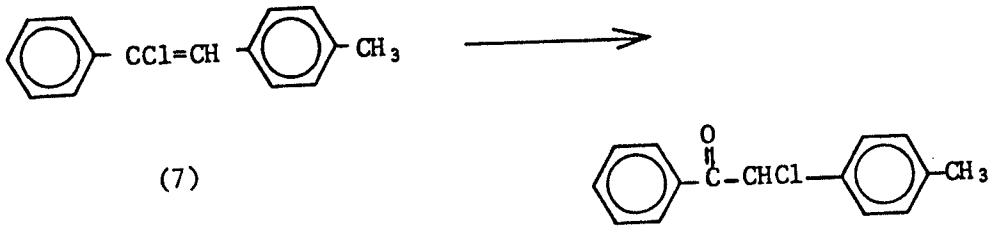
Shine et al.[40,52] have studied the thermal rearrangement of α-acetoxyepoxides. In their studies they established that these reactions undergoes intramolecular, 1,2-migration of the acyloxy group to give the α-acetoxy ketone stereospecifically[53]. Also in their studies on α-chloroepoxide rearrangement McDonald and Schwab[19] did not observe any benzoin acetate as a product from the reaction of α-chlorostilbene with peracetic acid in acetic acid-dichloromethane solution containing added sodium acetate. A high yield of α-chloroketone was observed instead.

R.N. McDonald et al.[19] have also established that the chlorine is the migrating species in most α-chloroepoxides when they chose to study the peracid oxidation of trans-1-chloro-1-(p-tolyl)-2-phenylethylene (6) and trans - 1-phenyl-2-(p-tolyl) ethylene (7). In both cases the only product isolated was that of chlorine migration (Scheme 36).

Although previous results on related molecular rearrangements[54] showed hydrogen to be the migrating atom, the migration of the acetoxy group in the Shine et al.[52] study together with the migration of chlorine in the McDonald et al. [12] study supports the idea that halogens and pseudohalogens are the migrating



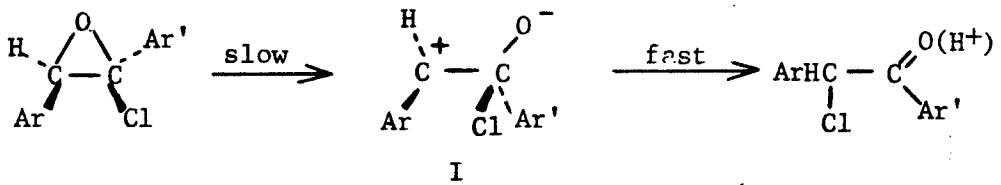
(6)



(7)

SCHEME 36

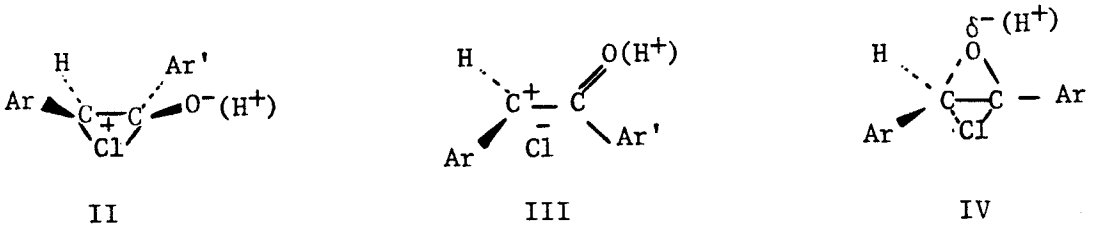
species in the epoxide-carbonyl rearrangements. Three mechanisms were proposed to account for the results obtained from different epoxide carbonyl rearrangements 12. The first mechanism proposed was the opening of the epoxide ring to give a carbonium ion followed by a fast chlorine migration to yield the observed α-chloroketone. Because the chlorine migration was shown to be intramolecular, chlorine migration might be through a chloronium ion (II) followed by a rotation about the central C-C bond, or an intimate ion pair, (III), followed by bond formation leading to the product (Scheme 37,38).



I

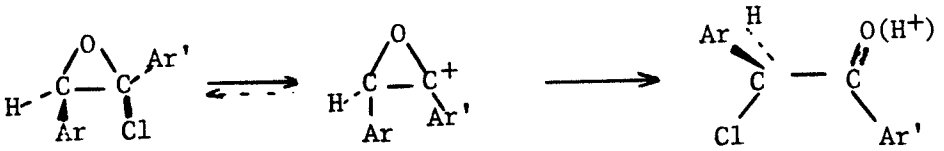
SCHEME 37

The second mechanism was through a concerted process, however, this mechanism was discarded because it involves considerably more C-O bond breaking then C-Cl bond making in the transition state (IV) which needs high energy strain that prevents the rearrangement from proceeding. Also in the concerted mechanism there is a rotation of 76° about the C-C single bond of the epoxide to bring the migrating group into a transoid position to the breaking C-O bond; to allow this rotation to happen an epoxide ring rupture must occur, which makes the concerted mechanism the same as the first mechanism proposed. The third proposed mechanism involves an oxiranylcation intermediate (V). In this mechanism there is no strain problem as there is in the one involving the concerted mechanism (Scheme 38,39).



II III IV

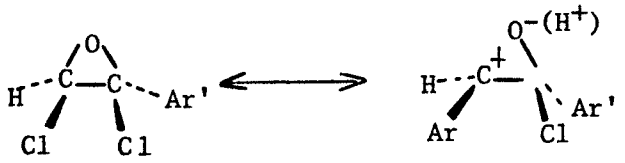
SCHEME 38



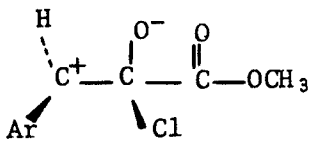
V

SCHEME 39

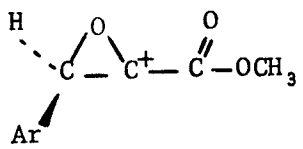
The breaking of the C_β-O bond in the previous mechanism, rather than the C_α-O bond (VI) is attributed to the higher stability of the (VI) isomer, due to the destabilization of that carbonium ion by the attached chlorine. In a later work McDonald et al.[56] preferred the α-ketocarbonium ion-chloride ion pair mechanism because they used a carbomethoxy group as a substituent on the α-carbon. In this compound α-ketocarbonium ion-chloride ion pair (VII) is better stabilized than the oxiranyl cation (VIII) (Scheme 40).



VI



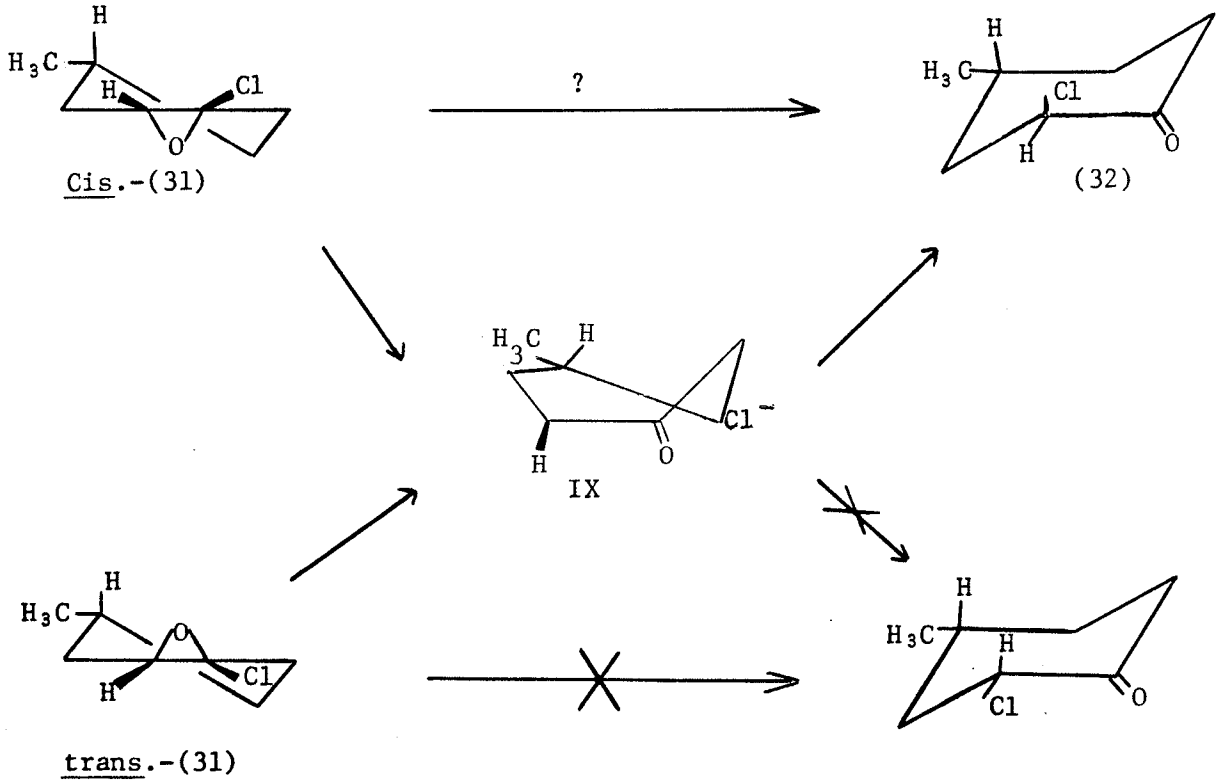
VII



VIII

SCHEME 40

In 1967 McDonald et al.[27] reported one of the most important studies in this area when he pyrolysed a mixture of 1-chloro-cis-(cis 31) and -trans-4-methyl-cyclohexene oxide (trans 31). The product isolated was trans-2-chloro-4-methyl-cyclohexanone (32) from both isomers. From these results which indicate the stereospecificity of the rearrangement, the authors concluded that the α-ketocarbonium ion-chloride ion pair (IX) is the intermediate compound (Scheme 41).



Cis.-(31)

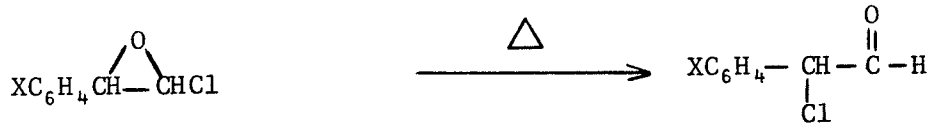
(32)

IX

trans.-(31)

SCHEME 41

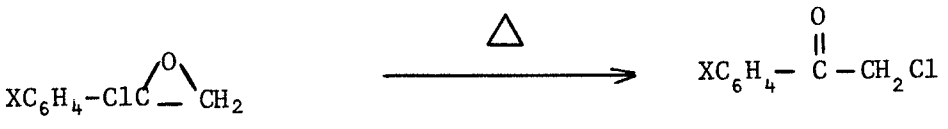
The authors excluded the oxiranyl cation as an intermediate because in that case one would expect two different products from the two isomers. Recently McDonald et al.[57] have studied the kinetic of rearrangement of the substituted trans-β-and -α-chlorostyrene oxides (99,100) (Scheme 42,43). From their kinetic data they concluded that the rate limiting step in the rearrangements of these α-chloroepoxides involves the formation of ionic or ion-pair intermediates with cleavage of the C_β-O bond of the α-chloroepoxide, and based on these results they concluded that the formation of the oxiranyl cation-chloride ion pair was not involved.



(99)

[X=p-CH_3H, p-Br, m-Cl, p-NO_2]

SCHEME 42



(100)

X=p-CH_3, H, p-NO_2

SCHEME 43

More recently, Zeglam[50] has studied the thermal rearrangement of the 4α-chloro-4,5-epoxy-5β-androstane-3β,17β-diol diacetate (92) and the 4α-chloro-4,5-epoxy-5α-androstane-3β,17β-diol diacetate (94). In this study different epimeric α-chloroketones were observed from each compound (92,94) (Scheme 34).

From these results, it was concluded that a common reactive intermediate from both the α- and β-epoxide cannot be involved and that these reaction products are better rationalized when considering the oxiranyl cation as an intermediate. In this case the chloride ion can be added stereospecifically to give the

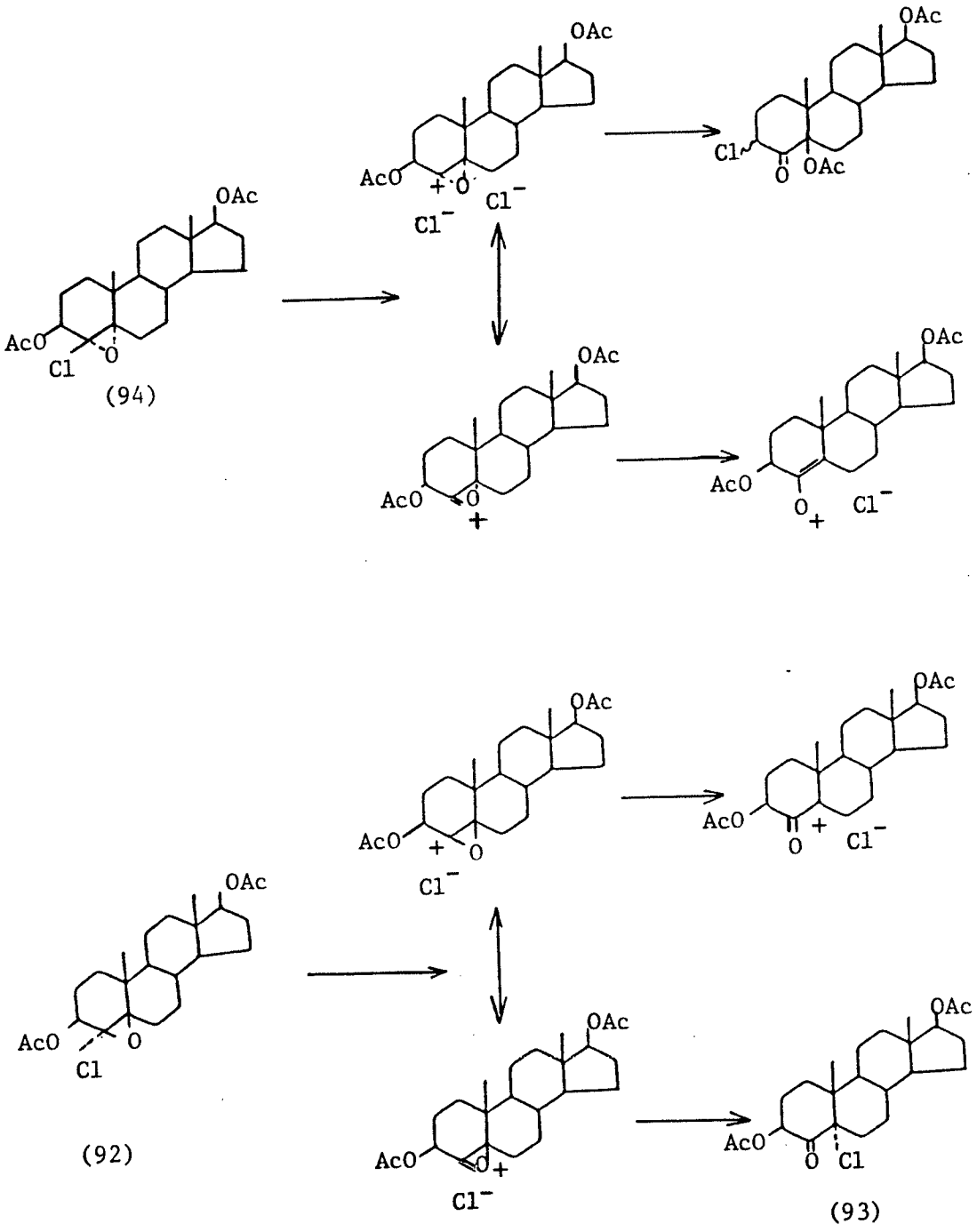
observed major product. Although McDonald and Cousins[57] have provided evidence that the rate limiting step in the rearrangements of the α-chloroepoxides studied does not involve the formation of an oxiranyl cation-chloride ion pair which does not prove that an oxiranyl cation-chloride ion pair cannot be an intermediate.

The idea of an oxiranyl cation-chloride ion pair as an intermediate in these epoxysteroid studies is supported by the fact that the β-epoxide (92) rearranges quantitatively while the α-epoxide (94) rearranges with the formation of several products. The 5β-epoxide (92) has an A,B-cis ring junction; the approach of the chloride ion from the α-position yields the more favourable trans ring junction, while approach of the chloride ion from the β-position in the 5α-epoxide (94) encounters more steric hindrance from the 19-methyl group and yields the less favourable cis ring junction. The energetically less favoured addition of chloride to the β-face, therefore, allows competing reactions to occur (Scheme 44).

Although the rearrangements of α-chloroepoxides have been extensively studied, there are only few investigations carried out on α-chloroepoxide with a functional group adjacent to the chloride atom.

The general objective of this thesis was the chemical synthesis of compounds capable of acting as inhibitors of the biosynthesis of specific steroid hormone enzymes. The particular aim of this research was to study the product and mechanism of rearrangements of steroid C-3 substituted 4-chloro-4,5-epoxides with an oxo group adjacent to the chloride atom which was a continuation of the research started by Zeglam[50] on the thermal rearrangement of chloroexpoxides with a hydroxyl-acetoxyl function adjacent to the chloride atom.

From these thermal rearrangements we were able to develop different routes for the preparation of 4-hydroxytestosterone in a high yield. Previous synthesis of this compound appeared to be complicated and to give low yield[59,70,71].

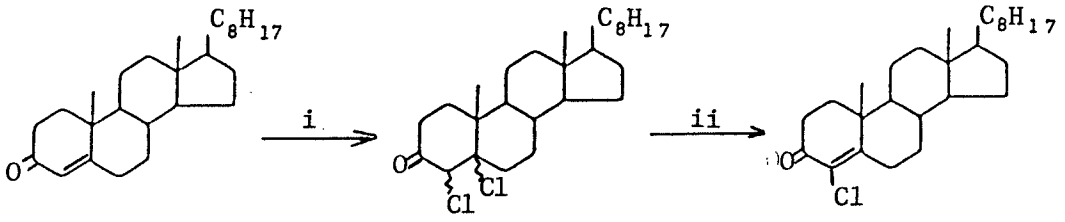


SCHEME 44

The enzyme aromatase catalyses the final stage of estrogen biosynthesis[81]. Estrogen is required for the growth of breast cancer, consequently if one could block the aromatization of androgens to estrogens, one could effectively prevent biologically active estrogens from reaching the tumor. It has been shown[82,83] that the 17-keto derivative of 4-hydroxytestosterone acetate, i.e. 4-hydroxy-androst-4-ene-3,17-dione, is a highly effective inhibitor of the peripheral aromatization of androgens and could reduce the levels of circulating estrogens below a critical point needed for certain biological activities. Since estrogens produced by peripheral aromatization in adipose tissue, muscle[84] and some breast tumors themselves may contribute to the growth of hormone-dependent tumors, 4-hydroxyandrost-4-ene-3,17-dione might be a useful therapeutic agent for the treatment of those breast cancers identified as estrogen dependent. In fact, both 4-hydroxy and 4-acetoxyandrost-4-ene-3,17-dione were found to be highly effective in causing regression of 7,12-dimethylbenz [α] anthracene-induced mammary tumors of the rat[89,90]. This compound has been found also to have a high anabolic activity and a low androgenic effect[59] .

RESULTS

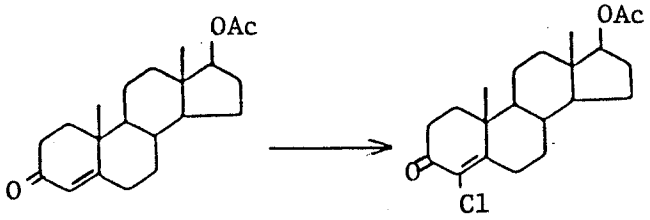
4-Chloro-4-en-3-one-steroids were synthesized by Kirk et al.[58], in 1956. Kirk has shown that treatment of cholest-4-en-3-one (101) (Scheme 45) with chlorine in the presence of propionic acid led to the 4ξ,5ξ-dichloro-3-one derivative (102) which on dehydrochlorination with pyridine gave 4-chlorocholest-4-en-3-one (103).



(101) (102) (103)

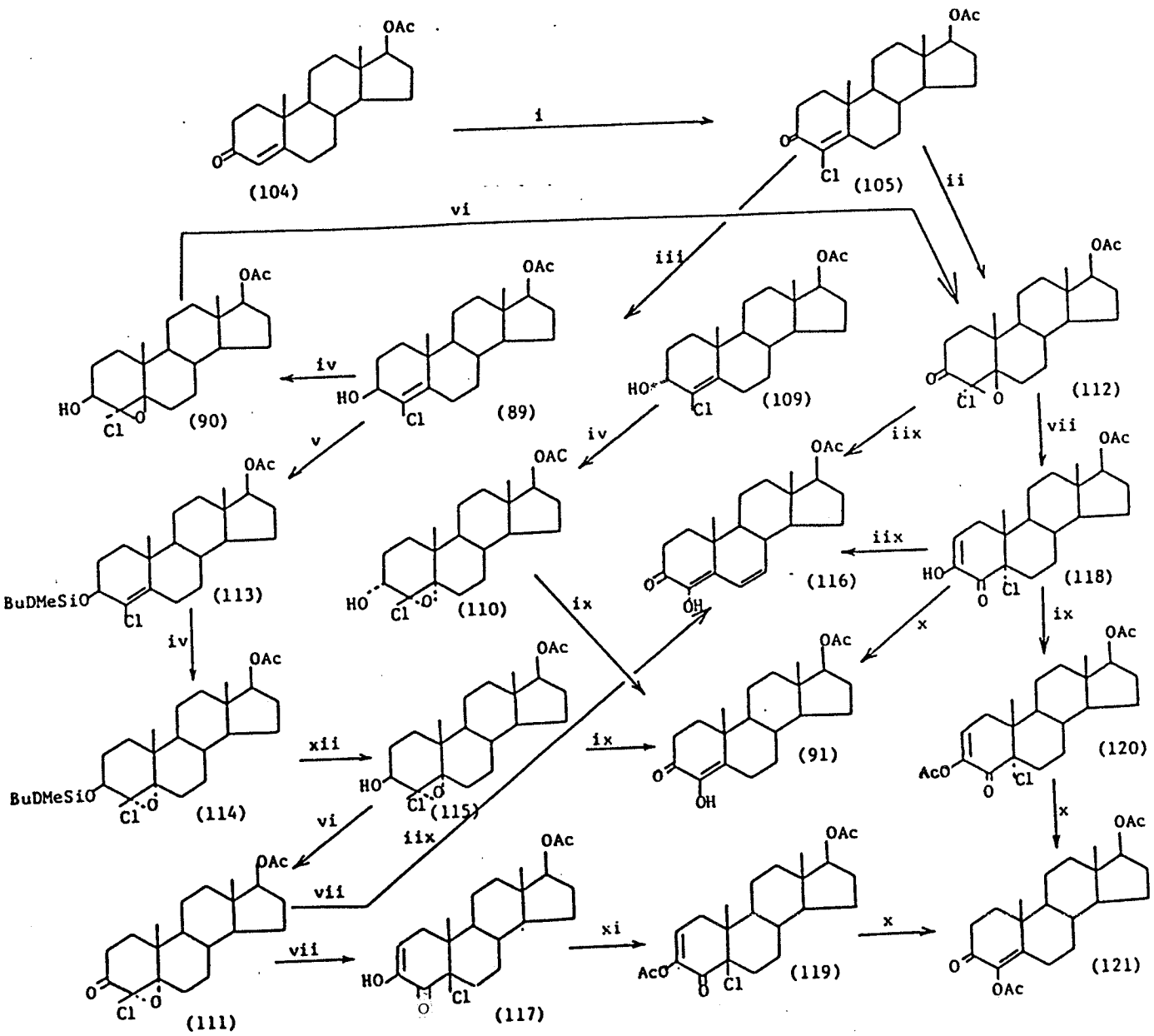
SCHEME 45
I. Cl_2, CH_3CH_2COOH
ii. C_5H_5N

This procedure gives a low yield of the product. A better result was obtained by Mori[59] when he treated testosterone acetate (104) (Scheme 46) with sulfuryl chloride instead of chlorine[58]. This reagent in the presence of pyridine converted testosterone acetate directly (104) into the 4-chloro-4-en-3-one steroid (105).



(104) (105)

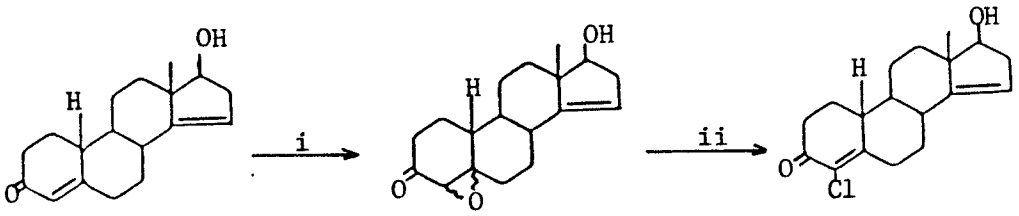
SCHEME 46



SCHEME 48

i. SO_2Cl_2; ii. H_2O_2,NaOH; iii. LTBA; iv. mCPBA; v. BuDMeSiCl; vi. Jones; vii. pyridine, reflux; viii. Δ,240°C; ix. Δ,200°C; x. Zn/Cu; xi. $(AcO)_2$ O, pyridine; xii. F^-.

A third method of synthesising the 4-chloro-4-en-3-one-steroids has been published in 1956[60,61]. The product was obtained by epoxidation of the testosterone derivative followed by acid opening of the epoxide produced, in 1984 Schubert [62] converted the nortestosterone derivative (106) to the epoxyketone (107) with hydrogen peroxide under alkaline conditions[63] (Scheme 47). Ring opening of the product (107) with hydrogen chloride in acetone[64,65,66,67] gave the 4-chloro derivative (108) in 75% yield.



(106) (107) (108)

SCHEME 47
i. H_2O_2, NaOH
ii. HCl

The method of Mori[61] was chosen for the preparation of 4-chlorotestosterone acetate (105) (Scheme 48) and the product showed a melting point consistent with that reported earlier[61]. Examination of the ^1H NMR spectrum showed the chemical shift of the C-13 methyl and the C-10 methyl groups to be in agreement with the expected values. There was no evidence for a C-4 vinylic proton consistent with the presence of the C-4 chlorine atom. Reduction with lithium tri-t-butoxyaluminumhydride gave a product with two components on TLC corresponding to the 4-chloroandrost-4-ene-3-α and 3β,17β-diol 17-acetate (109,89) (Scheme 48). The major product was the 3β-alcohol (89) and the ratio of 3β-to 3α-alcohol was 9.3:0.7 (by HPLC). Column chromatography over silica gel gave the 3β-alcohol (89) which showed a molecular ion cluster at m/z 366,368 in its mass spectrum. Chlorine and hydrogen chloride were lost from the molecular ion giving rise to fragment ions at m/z 331 and 330. The ^1H NMR shows the chemical shift of the C-3 proton downfield from the methylene envelope as an

unresolved multiplet. The stereochemistry of the C-3 β alcohol was assigned the equatorial configuration based on the coupling of the C-3 proton ($w_{\frac{1}{2}}$ = 16Hz) which is in agreement with the value published for the analogous C-3 allylic alcohol[68]. Reduction of the unsubstituted α,β-unsaturated ketone with lithium tri-t-butoxyaluminum hydride is known to give the 3β-alcohol as the major product[69]. The 3α-alcohol (109) was isolated as the minor product and the stereochemistry of this alcohol was assigned the axial configuration, based on the pseudoequatorial C-3 proton coupling ($w_{\frac{1}{2}}$ = 8Hz). Epoxidation of the 3β-alcohol (89) with m-chloroperbenzoic acid has been shown to give the 3β-epoxide (90)[50].

Epoxidation of the 3α-alcohol (109) with m-chloroperbenzoic acid gave mainly 4β-chloro-4,5-epoxy-5α-androstane-3α,17β-diol 17-acetate (110) as expected from the stereoselective effect of alcohols on epoxidation observed in the epoxidation of the non-chlorinated analog [72]. ^{1}H NMR showed a chemical shift of the C-3 proton at 4.30 ppm (j=5.5Hz) as a doublet; the C-13 methyl and C-10 methyl groups were at 0.81 and 1.08 ppm respectively.

Epoxidation of 4-chlorotestosterone acetate (105) with hydrogen peroxide under basic conditions gave a product with two components on TLC identified as the 5α-and 5β-epoxyketone (111,112); (5α :5β 2:3 by HPLC). Recrystallization gave 17β-acetoxy-4α-chloro-4,5-epoxy-5β-androstan-3-one (112) which showed a molecular ion cluster at m/z 380,382 in its mass spectrum, hydrogen chloride was lost from the molecular ion giving rise to a fragment at m/z 344. The stereochemistry of the epoxyketone was assigned the β-configuration based on comparison of the ^{1}H NMR spectrum of this ketoepoxide and that obtained from the oxidation of the 5β-epoxyalcohol (90) using Jones reagent. Examination of the ^{1}H NMR spectrum showed the chemical shifts of the C-13CH_3, C-10CH_3 and 17β-OAc proton peaks to be consistent for both products; the melting point of both reaction products were identical. Treatment of the 3β-alcohol (89) with

t-butyldimethylsilyl chloride (BDMSiCl) yielded the silylated derivative 4-chloroandrost-4-ene-3β,17β-diol 3-t-butyldimethylsiloxane 17-acetate (113). The ^1H NMR spectrum shows the chemical shift of the C-3 dimethyl and the C-3 butyl group at 0.11, 0.14 and 0.92 ppm respectively.

Epoxidation of the silylated derivative (113) with m-chloroperbenzoic acid gave mainly 4β-chloro-4,5-epoxy-5α-androstane-3β,17β-diol 3-t-butyldimethylsiloxane 17-acetate (114) which showed a chemical shift of the C-3 proton at 3.99 ppm (J=8.2 Hz) as a triplet. The stereochemistry of the C-3-t-butyldimethylsiloxane group was assigned by the coupling constant of this downfield proton which corresponds to an axial proton undergoing axial-axial coupling, J = 8.2 Hz.

Treatment of the 5α-silylepoxide (114) with fluoride ion gave 4β-chloro-4,5-epoxy-5α-androstane-3β,17β-diol 17-acetate (115). ^1H NMR showed the 3αH as a triplet at 4.05 ppm, J = 8Hz. The mass spectrum showed a weak molecular ion at m/z 382 from which hydrogen chloride was lost giving rise to a fragment ion at m/z 346. Oxidation of the 5α-epoxyalcohol (115) with Jones reagent gave 17β-acetoxy-4β-chloro-4,5-epoxy-5α-androstan-3-one (111). The ^1H NMR spectrum of the 5α-epoxyketone (111) showed the chemical shift of the C-13 methyl and the C-10 methyl groups to be in agreement with that of the 5α-epoxyketone obtained by HPLC from the epoxidation reaction of 4-chlorotestosterone acetate (105) (Scheme 48), there was no evidence for a C-3 proton downfield from the methylene envelope consistent with the oxidation of the C-3 hydroxy group to the C-3 keto group. The mass spectrum showed a molecular ion cluster at m/z 380; 382 and a signal at m/z 344; corresponding to the loss of hydrogen chloride from the molecular ion.

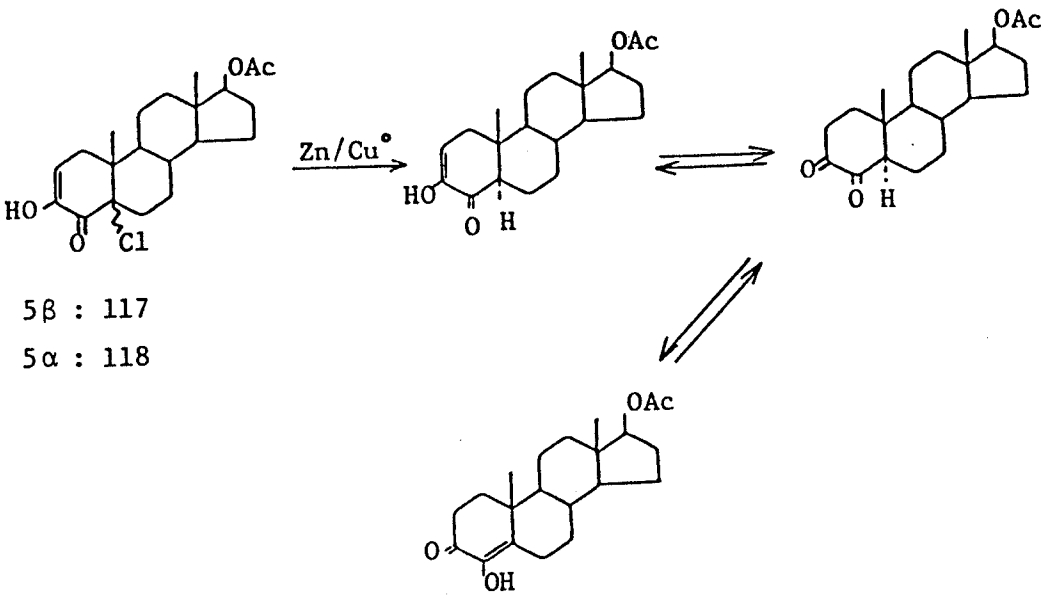
Pyrolysis of the two epoxyalcohols (110,115) at 200°C for 10 minutes gave an identical product which showed a positive ferric chloride test[59] and was identified as the diosphenol (91). The ^1H NMR spectrum showed the chemical

shift of the C-13 methyl and the C-10 methyl at 0.83 and 1.18 ppm respectively, the enolic hydrogen of the 4-hydroxy group showed a chemical shift at 6.06 ppm. The ^1H NMR results together with the m.p. were in agreement with previously published data[70,71]. Examination of the mass spectrum showed a molecular ion at m/z 346& a signal at m/z 331 assigned to the loss of a methyl radical. The mass spectrum pattern showed no evidence of the presence of chlorine.

Pyrolysis of the 5α- and 5β-epoxyketone (111,112) at 240°C for five minutes gave androst-4,6-dien-3-one-4,17β-diol 17-acetate (116) as the major product; this product gave a positive ferric chloride test. The ^1H NMR showed two downfield doublets of doublets at 6.01,6.66 ppm corresponding to the C-6 and C 7 vinylic protons, and a singlet at 6.2 ppm corresponding to the enolic proton of the C-4 hydroxy group. The mass spectrum showed a molecular ion at m/z 344, loss of ketene gave rise to a signal at m/z 302, and the pattern of the mass spectrum showed no evidence of chloride.

The 5α- and 5β-epoxyketone (111,112) on refluxing with pyridine underwent stereospecific rearrangement to give 5β- and 5α-chloroandrost-2-ene-3,17β-diol-4-one 17-acetate (117,118) respectively. The mechanism of the rearrangement is discussed below (see page43).

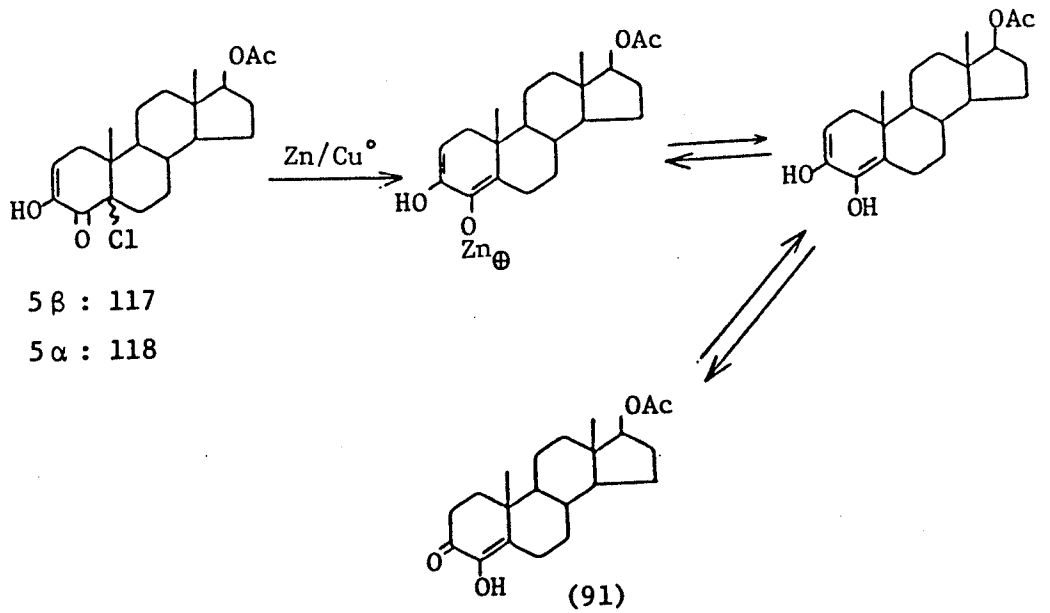
Examination of the ^1H NMR of the 5β-chloroketone (117) showed a chemical shift of the C-10 methyl group at 1.23 ppm which is greater (+ 0.13 ppm) than the chemical shift of the C-10 methyl in the 5α-chloroketone (118) the formation of a different product is indicative of the stereospecificity of the rearrangement. The ^1H NMR of both products (117,118) showed a downfield doublet of doublets at 5.93 and 5.94 ppm respectively, corresponding to the C-2 vinylic proton in agreement with the proposed structures. The mass spectrum of the 5β- and 5α-chloroketone (117,118) showed a molecular ion cluster at m/z 380,382; a signal at m/z 344 was consistent with a species arising by loss of hydrogen chloride from the parent compound.



5β : 117

5α : 118

(91)



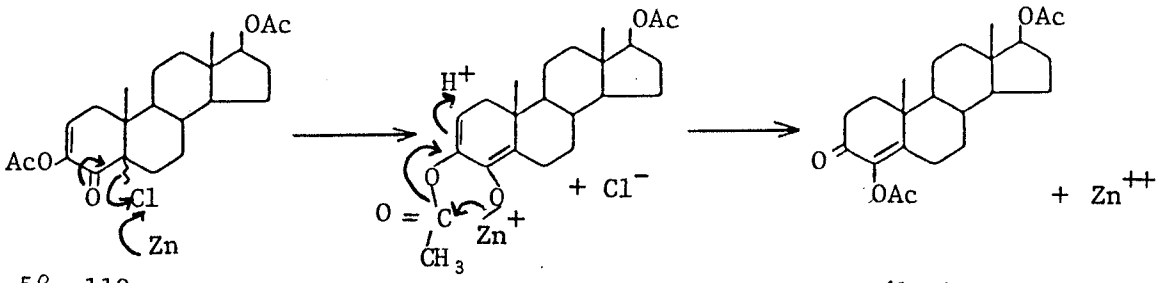
5β : 117

5α : 118

(91)

SCHEME 49

Treatment of 5β-and 5α-chloro-androst-2-en-4-one-3,17β-diol 17-acetate (117,118) with acetic anhydride in pyridine gave the corresponding acetates. Examination of the ^{1}H NMR spectrum of the products (119,120) showed the chemical shift of the C-3 acetate protons at 2.24 ppm downfield compared to the C-17 acetate protons peak at 2.04 and 2.01 ppm, respectively, and consistent with an enolic acetate. Treatment of the 5β- and 5α-chloroandrost-2-en-3,17β-diol-4-one 17-acetate (117,118) with zinc-copper couple gave the same dechlorinated product androst-4-en-4,17β-diol-3-one 17-acetate (91). A mechanism for its formation is shown in Scheme 49. This compound was characterized by comparison with published data [m.p., ^{1}H NMR][70,71] and the previously prepared samples. Treatment of either 5β- or 5α-chloroandrost-2-ene-3,17β-diol-4 one diacetate (119,120) with zinc-copper couple gave androst-4-ene-4,17β-diol-4-one diacetate (121) as the major product. A mechanism for this reaction is proposed in Scheme 50.



5β: 119

5α: 120

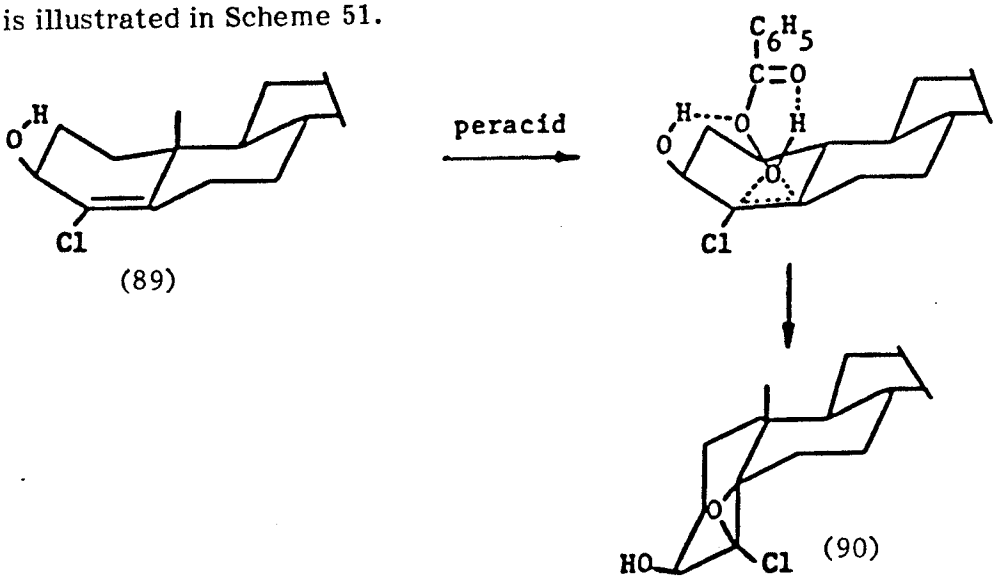
(121)

SCHEME 50

The ^{1}H NMR of the diosphenol diacetate (121) showed a downfield C-4 acetate protons at 2.23 ppm and the C-17 acetate protons at 2.04 ppm which together with the m.p. is in agreement with previously obtained data[70,71]. The absence of a vinylic proton rules out alternative enolic derivatives.

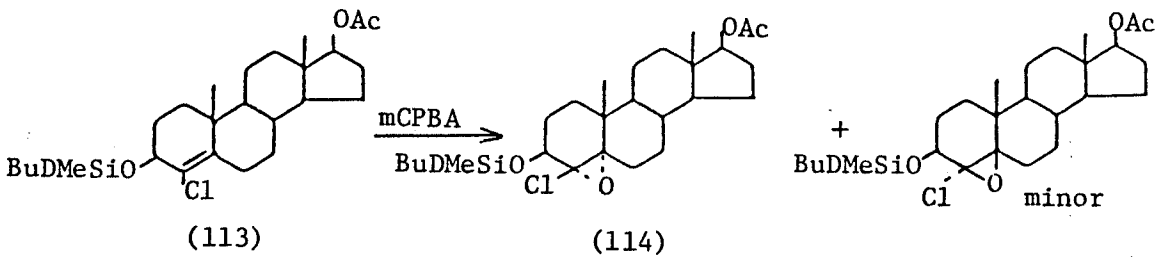
DISCUSSION

Epoxidation of the 3β-alcohol (89) with m-chloroperbenzoic acid gives the 5β-epoxyalcohol (90) [see p 22][50] as the major product (5α:5β;1:4 by HPLC). This product is obtained because of the directive effect of the C-3 hydroxyl group which has been suggested to arise from the hydrogen bonding between the hydroxyl group and the attacking peracid[72,73]. The optimum geometry for this epoxidation state is illustrated in Scheme 51.



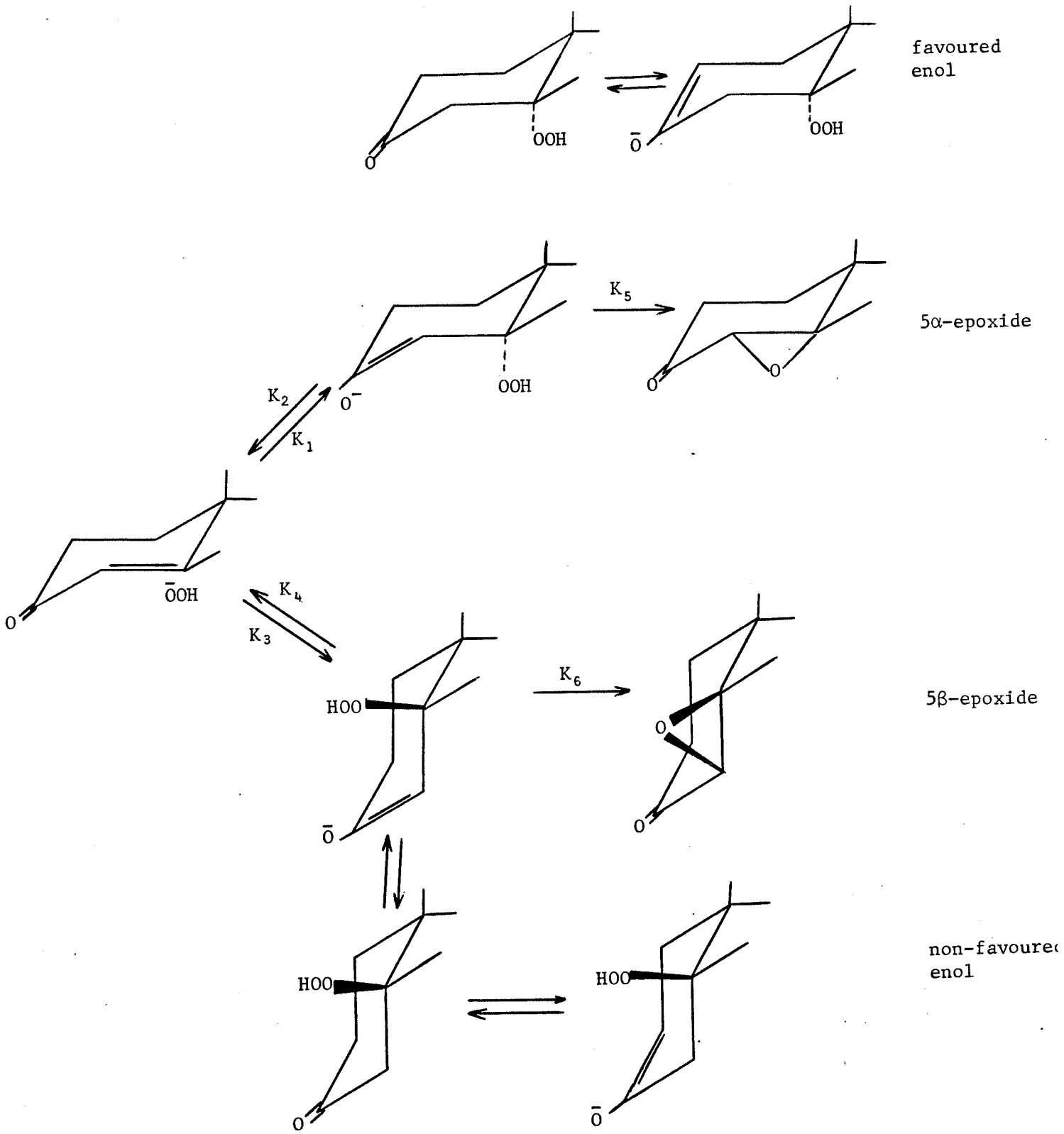
SCHEME 51

To obtain the 5α-epoxyalcohol (115), the 3β-alcohol (89) was silylated to prevent the hydrogen bonding between the hydroxyl group and the attacking peracid. This observation was supported by the fact that when epoxidation of the silylated product (113) (Scheme 52) was carried out it gave the 5α-epoxide (114) as the major product.



SCHEME 52

The preponderance (α:β;30:70) of 5β-epoxide over 5α-epoxide in the C-10 CH_3 congugated ketosteroids on epoxidation with a peroxide has been rationalized by Henbest et al. in the following way:



SCHEME 53

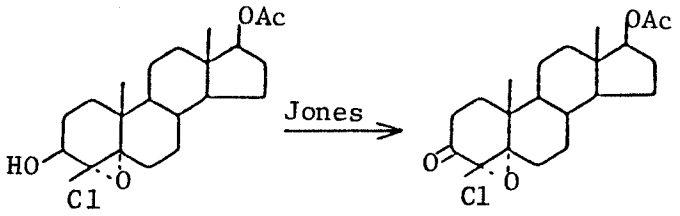
Although α-face (axial) attack of the hydroperoxide ion at C-5 would be favoured over attack from the β-face for electronic as well as steric (C-10 CH_3 hinderance), i.e. $K_1 > K_3$, formation of the 5α-epoxide is slower than formation of the 5β-epoxide, i.e. $K_6 > K_5$, thereby giving the 5β-epoxide as the major product.

A further reason for the preponderance of 5β-over 5α-epoxide may result from the relative instability of the C-3 enol in the 5α-series[78] versus the C-3 enol in the 5β-series. The C-3 enol in the 5α-series would therefore preferably exist in the ketone form (and possibly as the C-2 enol) whereas the C-3 enol would be favoured in the 5β-series, and therefore be present to form the 5β-epoxide.

The even greater proportion (α:β;10:90) of 5β-epoxide in the 19-norsteroids can be rationalized by the relatively greater rate of formation of the 5β-hydroperoxide (C-10 CH_3 steric hindrance having been removed) over the 5α-hydroperoxide. The preference for the C-2 over the C-3 enol is much less marked in the 19-nor series[79].

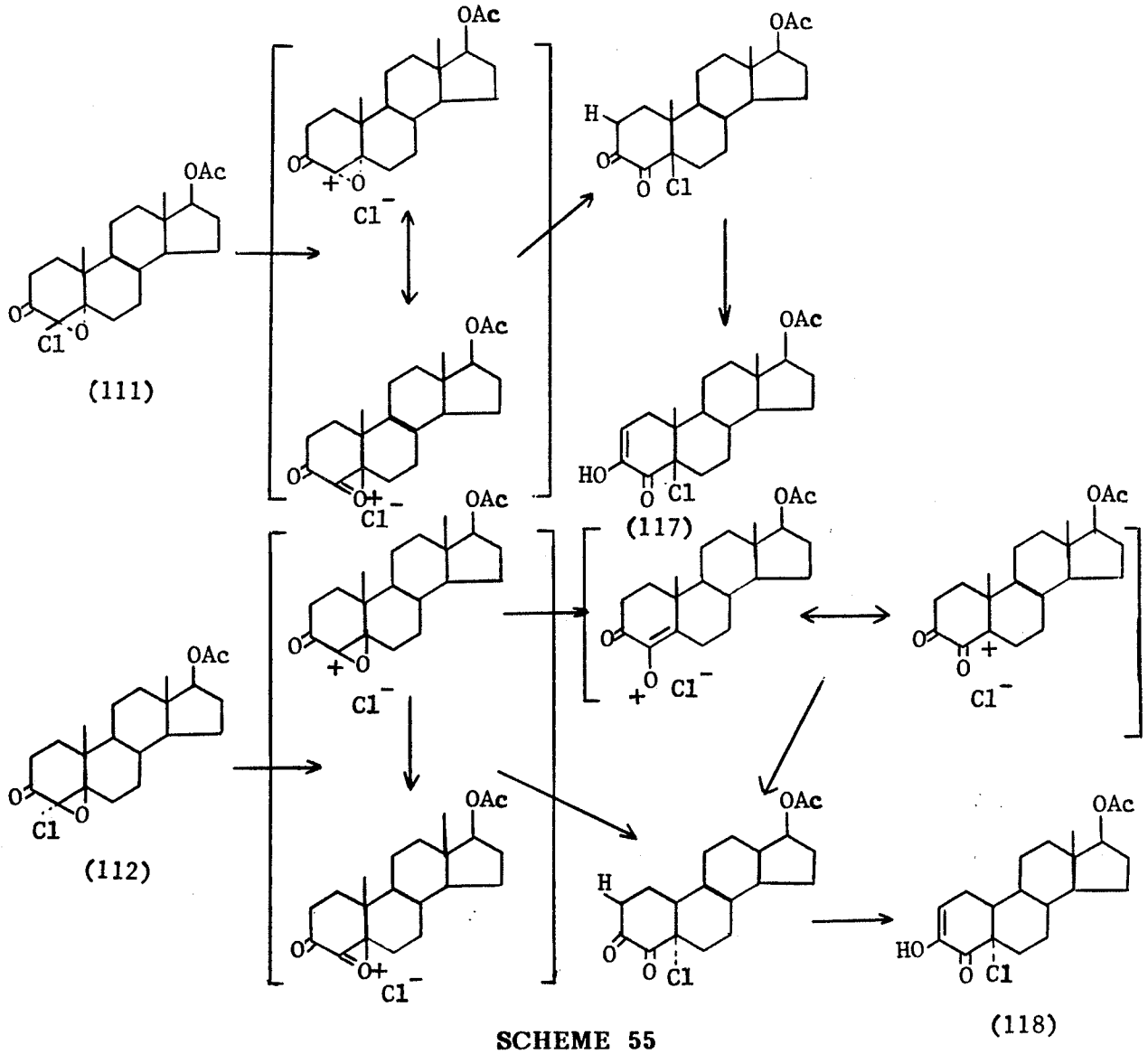
Chlorine substitution at C-4 in the C-10 CH_3 series still gives a preponderance of the 5β-epoxide (α:β;40:60) although the ratio is decreased. This can occur either by decreasing the relative rate of attack at C-5 by the hydroperoxide ion, i.e. K_1 is closer to K_3 or K_2 to K_4 or by altering the relative rates of K_5 and K_6, i.e. K_5 is a little greater or K_6 is a little slower relative to the non-chlorinated compound. The stereoelectronic reason for this change in the ratio of 5α- to 5β-epoxide is not clear. Relief of steric strain between the C-4 chlorine and one of the C-6 hydrogen (probably the 6αH) may be a factor

The 5β-epoxyketone (112) was the major product in the epoxidation of the 4-chlorotestosterone acetate (105). Thus in order to obtain the 5α-epoxyketone (111) in high yield the 5α-epoxyalcohol (115) was oxidised using Jones reagent (Scheme 54).



SCHEME 54

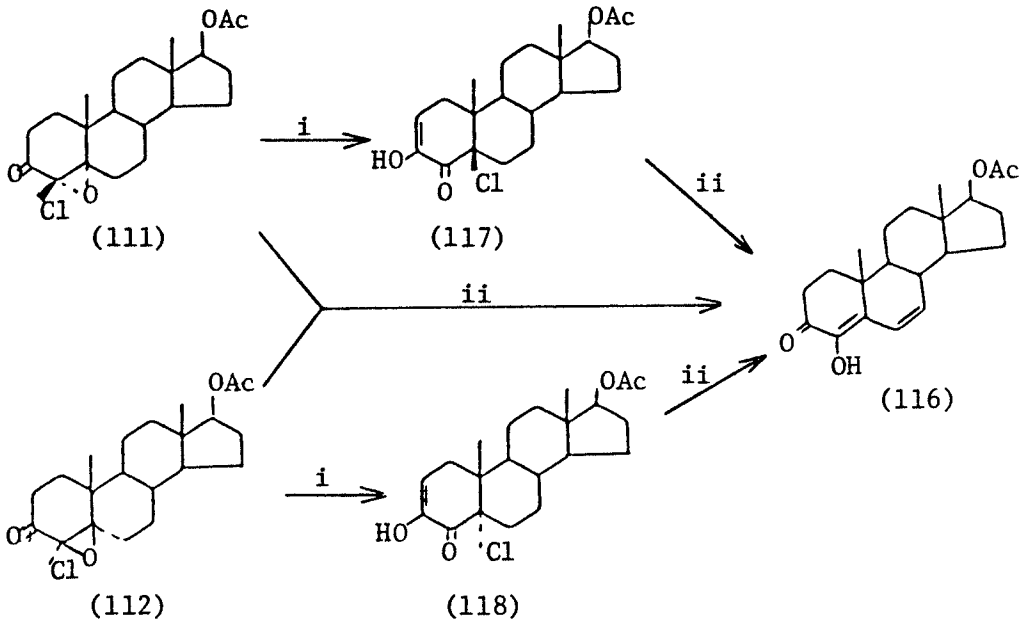
Refluxing the α-epoxyketone (111) and β-epoxyketone (112) in pyridine (Scheme 55) gave different epimeric α-chloroketones from each, therefore, a common reactive intermediate from both the α- and β-epoxyketone (111,112) cannot be involved and the rearrangement, in this case, requires an intermediate which retains stereochemical preference.



SCHEME 55

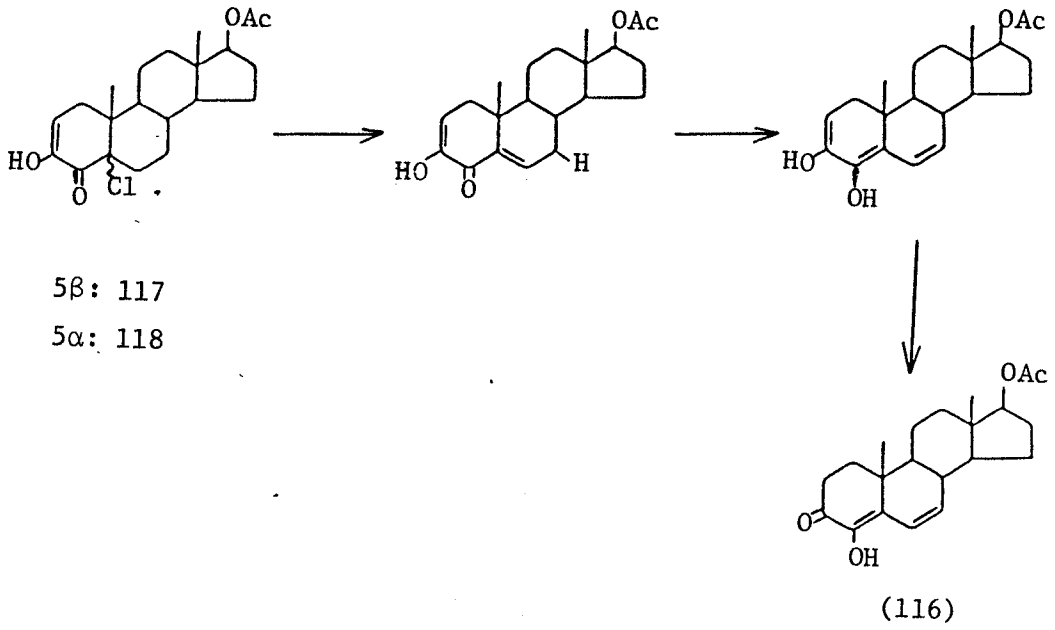
These results are in agreement with that of Zeglam[50] [p. 28] who preferred the oxiranyl cation intermediate to account for the different epimers obtained from the α- and β-acetoepoxides (92,94). The oxiranyl cation intermediate can also account for the epimeric α-chloroketones (117,118) obtained from the α- and β-epoxyketones (111,112), respectively. A stereospecific intermediate is consistent with the observation that the β-epoxyketone (112) rearranges quantitatively to give the 5α-chloroandrost-2-en-3,17β-diol-4-one 17-acetate (118) whereas the α-epoxyketone (111) rearranges at a lower yield to give the 5β-chloroandrost-2-en-3,17 β-diol-4-one 17-acetate (117). Examination of the stereochemistry of the 5β-epoxyketone (112) shows that approach of chloride ion to C-5 leads to epoxide ring opening and a trans ring junction.

1,3-Diaxial hydrogen interactions are encountered on the approach of chloride ion to C-5 to give the axial chloride product. Alternatively, in the 5α-epoxyketone (111), the approach of chloride ion to C-5 encounters a 1,3-diaxial hydrogen and one, more severe, 1,3-diaxial methyl interaction, which leads to the more strained cis ring junction with an axial chloride. The energetically less favoured addition of chloride to the β-face, therefore, allows competing reactions to occur. This difference in reactivity between the steroid 5α- and 5β-epoxyketones (111,112) would not be predicted if a common intermediate were involved. Thermolysis of the 5α- and 5β-epoxyketones (111,112) at a higher temperature (240°C) produced the diosphenol diene (116) as the major product. Thermolysis of the α-chloroketone epimers (117,118) at the same temperature produced the same product (116) which leads to the conclusion that the α-chloroketone epimers are intermediate in the formation of the diosphenol (116). At higher temperature the α-chloroketone epimers lose hydrogen chloride and enolize to yield the diosphenol (116) (Scheme 56).



SCHEME 56
i. pyridine, reflux
ii. Δ 240°

Whereas different epimeric α-chloroketones were produced from the pyrolysis of the α- and β-epoxyketones (111,112), in contrast, pyrolysis of the three epoxyalcohols (90,110,115) produced the same diosphenol (91) (Scheme 58). The novel thermal rearrangement which occurs with the epoxyalcohols (90,110,115) leads quantitatively to the diosphenol (91) (Scheme 58). This rearrangement apparently proceeds through initial formation of the oxiranyl cation intermediate (or in this case possibly the α-ketocarbenium ion) which undergoes proton loss at the 3-alcohol position and a 1,3-hydride shift of the C-3H to the C-5 position. The resulting 3,4-diketone then enolizes to the unsaturated ketone

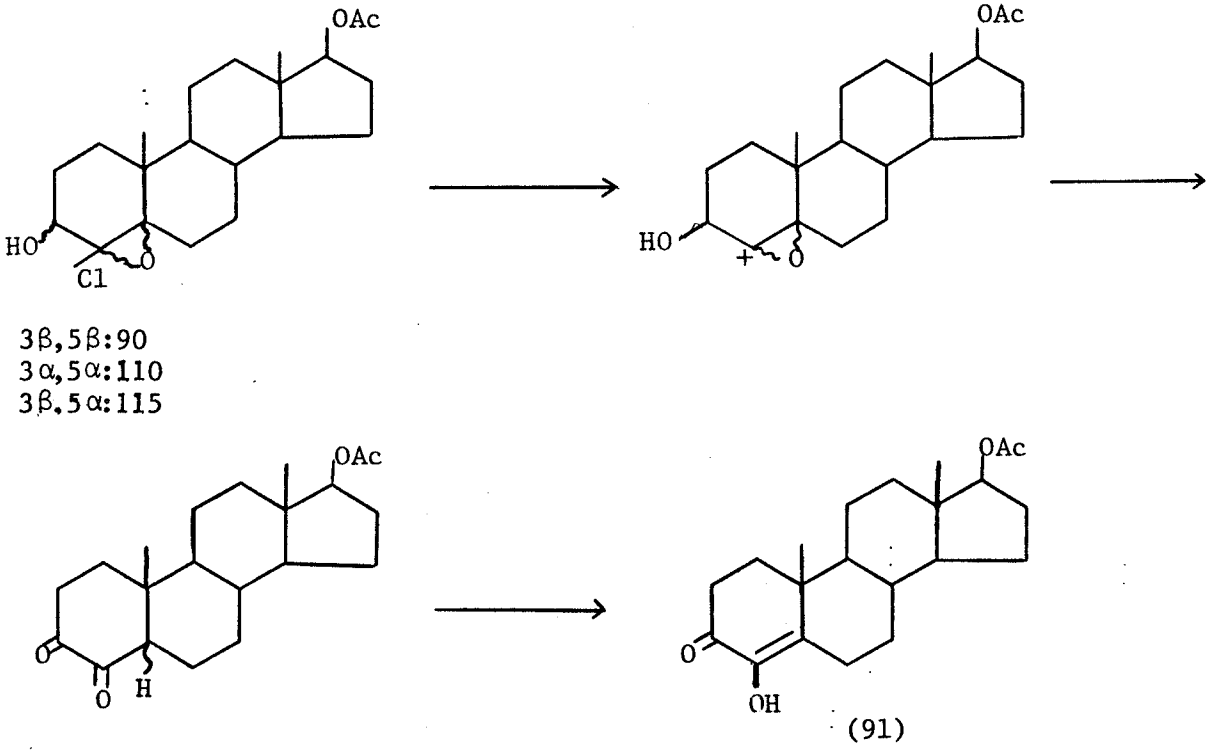


5β: 117

5α: 118

(116)

SCHEME 57



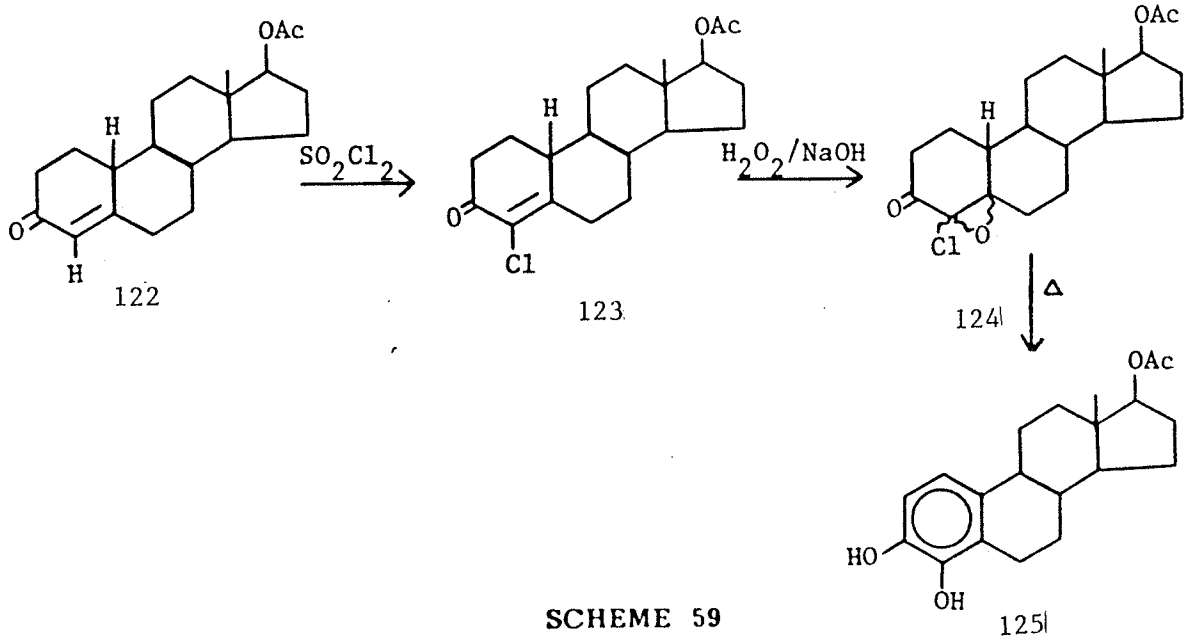
3β,5β:90
3α,5α:110
3β,5α:115

(91)

SCHEME 58

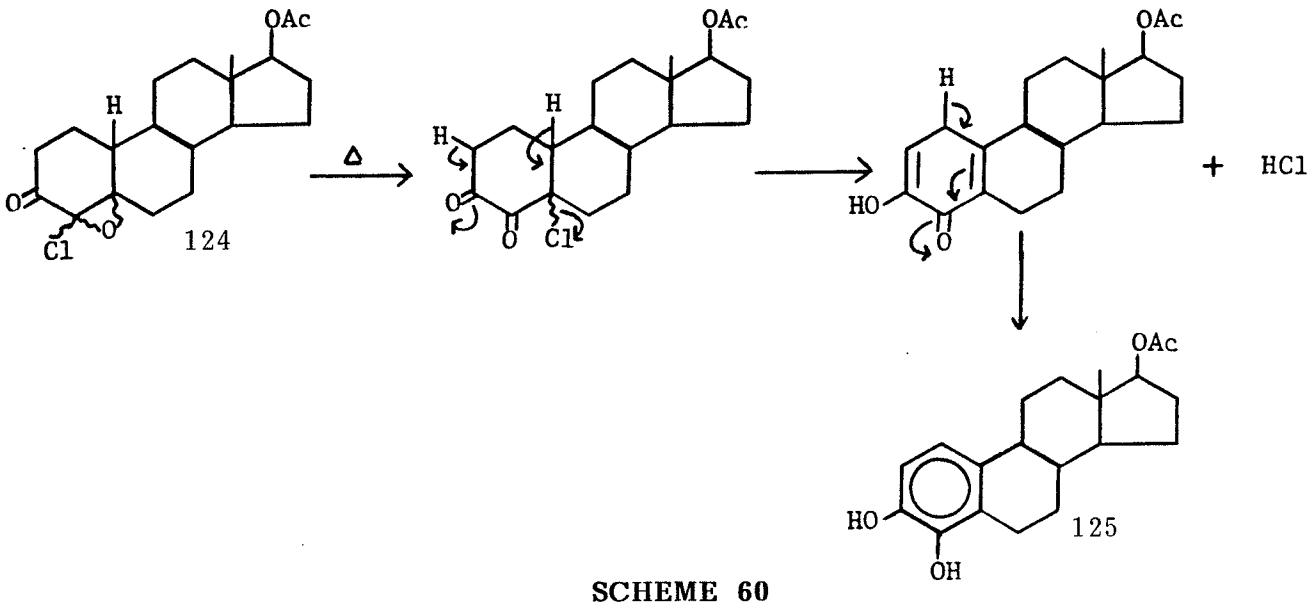
The catecholestrogens are a major metabolic product of the female sex hormone estradiol [93]. The first metabolic step of estradiol is the oxidation to estrone [94] followed by hydroxylation in the 16 -[95], 2-[96] or 4-[97] positions. Although the exact mechanism of action of the catecholestrogen is not clearly understood [98] their peripheral estrogenic activity, as well as their activity in the central estrogen target tissues in the regulation of pituitary hormone release[99], has been demonstrated. It has also been established that the catecholestrogens have a competitive interaction with the catecholamines of the catechol O-methyltransferase system [100,101] which suggests that the catecholestrogens [102] might be involved in the regulation of gonotrophin release. It has also been shown that catecholestrogens behave as an antiestrogen in suppressing the tumor cell proliferation in human breast cancer cell culture [98].

As an application of the thermal rearrangement of α-chloroepoxide the synthesis of the catecholestrogen 4-hydroxyestradiol was attempted as outlined in Scheme 59. The mechanism proposed for the thermal rearrangement is shown in Scheme 60.



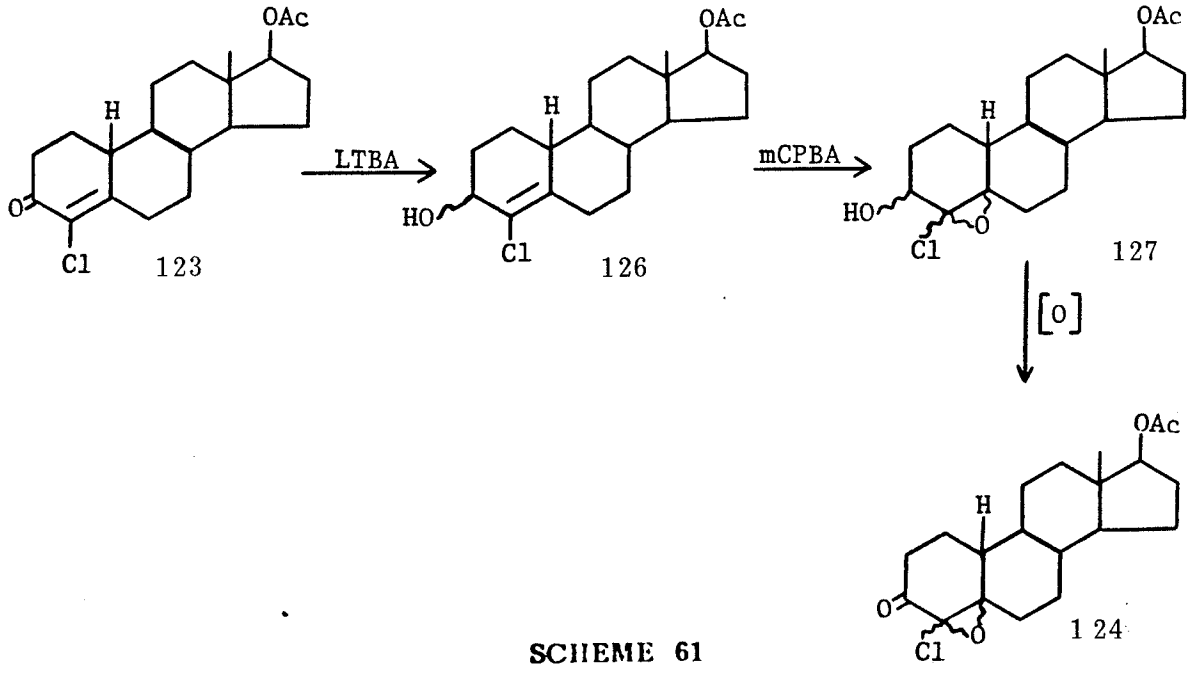
122 123 124 125

SCHEME 59



SCHEME 60

Synthesis of 4-hydroxyestradiol was also attempted, as shown in Scheme 61, however, attempts to make the chloroepoxyketone was unsuccessful and a mixture of products, one of which was an unidentified acidic substance,was obtained in both cases.



SCHEME 61

From the previous results we concluded that the 19-norchloroepoxyketone is sensitive to any basic or acidic conditions, and the synthesis of this compound might be possible using neutral reagents. Further research on this synthesis may lead to a successful result.

CONCLUSIONS

This thesis describes the thermal rearrangement of C-3 oxo-4-chloro-4,5-epoxysteroids and related C-3 hydroxy-4-chloro-4,5-epoxysteroids. These novel rearrangements lead new synthesis of C-3, 4-diosphenol derivatives. A mechanism for these rearrangements has been presented. Application of this reaction to the estrane series in an attempted synthesis of 3,4-catecholestrogens is described.

EXPERIMENTAL

Instruments

Melting points (mp) were determined with a Kofler hot plate and are uncorrected. Infrared (IR) spectra were recorded with a Perkin-Elmer Model 237 Infrared spectrophotometer either as a KBr disc or in CCl_4 solution as indicated below. Proton magnetic resonance (^1H NMR) spectra were recorded using deuteriochloroform ($CDCl_3$) as the solvent and tetramethysilane (TMS) as the internal standard using the Bruker AM (300 MHz) instrument recorded at the Department of Chemistry, University of Manitoba, Winnipeg, Manitoba. The following designations are used in characterizing ^1H NMR signals: singlet (s), doublet (d), triplet (t), doublet of doublet (dd), multiplet (m) and width at half height ($W\frac{1}{2}$). Mass spectra (MS) were recorded on a Finnigan Quadrupole Model 1015 mass spectrophotometer at 70 eV using the direct probe method at the Department of Chemistry, University of Manitoba. Elemental analyses were performed by Mr. W. Baldeo at the Microanalytical Laboratory, School of Pharmacy, University of London, England or Guelph Chemical Laboratories Limited, Guelph, Ontario. High pressure liquid chromatography (HPLC) was carried out on a Waters Scientific Limited M45G solvent delivery system with U6K Universal liquid chromatogram injector using RCM-100 radial Compresison Separation System (RCSS), and with μ-Porasil column (10μ) (7.8 mm x 30 cm) and RCSS silica guard pak. The detector used was R 401 refractive index detector-differential refractometer. The sample solution injected has a concentration of about 50μg/μL in 10% v/v ethyl acetate/hexane for 4-chloro-4-androstene-3β, 17β-diol 17-acetate and 4-chloro-4-androstene-3α, 17β-diol 17-acetate and 10μg/μL in 1% ethanol/dichloromethane for 17β-acetoxy-4α-chloro-4,5-epoxy-5β-androstan-3-one and 17β-acetoxy 4β-chloro-4,5-epoxy-5α-androstan-3-one (filtered and degassed) and the flow rate was 1.5 mL/min. unless stated otherwise. The standards and

their retention times (RT) were as follows: 4-chloro-4-androstene-3β, 17β-diol 17-acetate (10 min), 4-chloro-4-androstene-3α, 17β-diol 17-acetate (11.4 min), 17 β-acetoxy-4 β-chloro-4,5-epoxy-5 α-androstan-3-one (21 min), 17 β-acetoxy-4α -chloro-4,5-epoxy-5β-androstane-3-one (28 min).

Materials:

Thin-layer chromatography (TLC) was carried out on Analtech 25 precoated silica gel GHLF plates 0.25 mm thickness using one of the following liquid phases: a) 10% ethyl acetate/petroleum ether; b) 25% ethyl acetate/petroleum ether 60° to 90°C; and c) 2% acetone/dichloromethane. The TLC plates were viewed under an ultraviolet (UV) source and/or spraying with a 4% v/v solution of concentrated sulfuric acid in 95% ethanol followed by heating at approximately 100°C in an oven for 5 to 10 minutes to produce a color (R_f data are given in Table 5). Column chromatography was carried out with the following: alumina (Brockmann activity II aluminum oxide for chromatographic adsorption analysis, BDH Chemicals Limited), neutral alumina was prepared by immersing the BDH alumina in ethyl acetate, letting the mixture stand for at least 2 days with occassional shaking, filtering and drying at 80°C, or silica gel (Merck Silica Gel 60H for TLC).

4-Chlorotestosterone Acetate (105)

4-Chlorotestosterone acetate (105) m.p. 228-231°C (lit.,[59] m.p. 228-230°C) was prepared from testosterone acetate (104) by the method of Mori[61] IR_{max} (KBr): 1730(17β-OAc), 1685(C-3 C=0), 1588(C-4 C=C-Cl) cm^{-1}; ^1H NMR δ: 0.80(C-13CH_3) , 1.00(C-10CH_3), 2.00(17β-OAc), 4.61(17α-H) ppm.

4-Chloroandrost-4-ene-3α-(109) and 3β(89), 17β-diol 17-acetate

4-Chlorotestosterone acetate (105) (2g) (5.5 mmole), and 85% lithium tri-t-butoxyaluminum hydride (3.4g) (11.2 mmole) were dissolved in freshly distilled

tetrahydrofuran (100 mL) in an ice-bath under argon, and stirred for 3 hours, at which time no starting material remained by TLC (2% v/v acetone/dichloromethane). The reaction mixture was poured into 10% hydrochloric acid (100 mL) and extracted with dichloromethane. The organic layer was washed with saturated sodium hydrogen carbonate, water, dried over anhydrous sodium sulfate and evaporated to give a crystalline residue, which showed one major and one minor component on TLC (2% acetone/dichloromethane) (3α:3β; 0.7: 9.3 by HPLC). Column chromatography over silica gel in 10% dichloromethane/cyclohexane gave on elution with 15% dichloromethane/hexane increased by 5% increments to dichloromethane the 3 β-alcohol (89) (1.34g) m.p. 172°-4°C from dichloromethane/ethyl acetate. IR(CCl_4)ν_{max}: 3600(OH str.), 1737 (17 β-OAc) cm^{-1}; ^1H NMR δ: 0.81(C-13 CH_3), 1.10(C-10 CH_3), 2.03(17 β-OAc), 4.14, m, $w_{\frac{1}{2}}$ = 16 Hz(3α-H), 4.58, dd, J = 7.5, 9 Hz(17 α-H) ppm; m.s./m/z: 368, 366(M^+), 330(M^+-HCl). Found: C, 68.50; H, 8.68; Cl, 9.73, C_{21} H_{31} O_3 Cl requires C, 68.74; H, 8.52; Cl, 9.66%. Elution with 2-3% acetone/dichloromethane gave fractions (0.102g) which on three crystallizations gave the 3 α-alcohol (109) (50 mg) m.p. 177-179°C (from dichloromethane/ethyl acetate); ^1H NMR δ:0.81(C-13CH_3), 1.04(C-10CH_3), 2.04(17 β-OAc), 2.94, octet, J = 2.7, 4.1, 14.3 Hz(2H), 4.14, $w_{\frac{1}{2}}$ = 8 Hz(3 β-H), 4.58, dd, J = 7.7 and9.1 Hz(17α-H) ppm; (Found: C, 68.60; H, 8.62; Cl, 9.46C_{21} H_{31} O_3 Cl requires C, 68.74; H, 8.52; Cl, 9.66%).

4β-Chloro-4,5-epoxy-5α-androstane-3α, 17β-diol 17-acetate (110)

The 3α-alcohol (109) (254mg) in dichloromethane (2 mL) was cooled in an ice bath and 85% m-chloroperbenzoic acid (447 mg) was added. After 24 hours the reaction was not complete by TLC and a second portion of m-CPBA (152 mg) was added and the reaction time continued for a further 24 hours at which time the reaction was worked up as for the 5α-epoxyalcoholsiloxane (114) to give a

product which on recrystallization gave the 5α-epoxyalcohol (110) (mg) m.p. 134-6°C (from dichloromethane/methanol); ^1H NMR δ: 0.81(C-13CH_3), 1.08(C-10CH_3), 2.04(17β-OAc), 4.30, d, J = 5.5 Hz(3β-H), 4.61, dd, J = 7.7 & 9.1 Hz(17α-H) ppm; (Found: C, 65.94; H, 8.50; Cl,9.29. C_{21} H_{31} O_4 Cl requires C, 65.87; H, 8.16; Cl, 9.26%).

4α-Chloro-4,5-epoxy-5β-androstane-3β,17β-diol 17-acetate (90)

To 4-chloro-4-androstene-3β,17β-diol 17-acetate (89) (500mg) in dichloromethane (100ml) was added 85% w/w m-chloroperbenzoic acid (550mg) and the solution was allowed to stand at room temperature until no starting material was observed by TLC (18 hrs.) The organic layer was washed thoroughly with saturated aqueous 10% w/v sodium sulfite, excess 5% w/v aqueous sodium carbonate, water, dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure at room temperature to give a crystalline residue on addition of ether. Recrystallization from dichloromethane/ethyl acetate gave the 5β-epoxyalcohol (90) (356mg) m.p. 128-131°C; ^1H NMR δ: 0.81 (C-13 CH_3), 1.04(C-10 CH_3), 2.05(17β -OAc), 4.30, dd, J = 3.1, 1.5 Hz(3αH), 4.60, dd, J = 7.9 Hz(17α-H) ppm.

Androst-4-ene-4,17β-diol-3-one17-acetate (91) from (110) and (115)

i) A flask containing 4β-chloro-4,5-epoxy-5α-androstane-3β, 17β-diol 17-acetate (115) (100 mg) attached to a water pump was immersed in an oil bath preheated to 200°C and the temperature maintained at 190-200°C for 10 minutes. The residue which showed one major component on TLC was recystallized from dichloromethane/methanol to give (91) (55mg) m.p. 184-186°C (lit.[59] m.p. 194-196°C ^1H NMR δ:0.83 (C-13 CH_3), 1.18(C-10 CH_3), 2.04(17β-OAc), 4.60, dd, J = 7.3 and 8.9 Hz(17α-H) ppm; ms/m/z: 3.46 (M^+).

ii) When the 3α-hydroxy-4β-chloroepoxide (110) (22 mg) was treated as above

the diosphenol (91) (14 mg) m.p. 190-2°C was obtained identical ^{1}H NMR spectra was observed.

Androst-4-ene-4,17β-diol-3-one 17-acetate (91) from (117) and (118)

i) To 5α-chloroandrost-2-ene-4,17β-diol-4-one 17-acetate (118) (100mg) in 100% ethanol (5mL)was added 2% Zn/Cu couple (13 g)and heated to reflux for 30 minutes to give the diosphenol (91) (40mg) m.p. 188-193°C.

ii) Treatment of 5β-chloroandrost-2-ene-4,17β-diol-4-one 17-acetate (117) (70mg) with 2% Zn/Cu couple (900mg) in 100% ethanol (3 mL) gave the diosphenol (91) (30mg) m.p. 189-192°C. ^{1}H NMR spectra were identical with those of (91) obtained earlier.

17β-Acetoxy-4β-chloro-4,5-oxido-5α-androstan-3-one (111)

4β-Chloro-4,5-oxido-5α-androstane-3β,17β-diol 17-acetate (115) (300mg) in acetone was treated with excess Jones reagent for 5 minutes. The reaction was diluted with ice-water, ether extracted, washed with water and dried over anhydrous sodium sulfate to give the 3-oxo-4 β-chloro-4,5 α-epoxide (111) (225mg) m.p. 161-163°C, ^{1}H NMR δ: 0.83 (C-13 CH_3), 1.11 (C-10 CH_3), 2.04 (17β-OAc), 2.56, octet, J = 2.2, 6.2, 19.5 Hz(6 -H), 4.63, dd, J = 7.9 and 8.9 (17α-H) ppm; (Found: C, 66.22; H,7.64; Cl,9.44, $C_{21}H_{29}O_3Cl$ requires C,66.22; H, 7.67, Cl, 9.31%)

4-Chloroandrost-4-ene-3β,17β-diol 3-t-butyldimethysiloxane 17-acetate (113)

To a stirred solution of the 3β-alcohol (89) (6.7g) (18.3 mmole) in dry dimethylformamide (13.4 mL) was added t-BDMSiCl (3.3g) (21.9 m.mole) and imidazole (3.1g) (45.5 m.mole) as described by Corey [91]. After 20 minutes at room temperature the reaction was diluted with sodium hydrogen carbonate solution and extracted with ether to give a product which on recrystallization from acetone gave the t-BDMSi derivative (113) (6.4g) m.p. 146-149°C; ^{1}H NMR δ: 0.11, 0.15, 0.92(t-BDMSiO), 0.80(C-13 CH_3), 1.09(C-10 CH_3), 2.04(17β-OAc), 2.98, ddd, J=2.8, 4.0, 14.2, Hz(6 -H), 4.15, septet, J=1.7, 6.8, 6.8 Hz(3α-H), 4.58, dd, J=7.7, 9.1 Hz(17α -H) ppm; (Found: C, 67.48; H, 9.37; Cl 7.18, C_{27} $H_{45}O_3ClSi$ requires C, 67.39; H, 9.43; Cl; 7.37%).

4β-Chloro-4,5-epoxy-5α-androstane-3β,17β-diol 3-t-butyldimethylsiloxane 17-acetate (114)

To a solution of siloxane (113) (6g) (12.5 m.mole) in dichloromethane (100mL) was added 85% m-chloroperbenzoic acid (5.1g) (25 mmole) and the solution allowed to stand at room temperature until no starting material remained by TLC (18 hours). The organic layer was washed thoroughly with 10% aqueous sodium sulfite, 5% aqueous sodium carbonate, dried over sodium sulfate and evaporated at reduced pressure at room temperature to give a product which on recrystallization from acetone gave the epoxide derivative (114) (2.9g) m.p. 170-173°C; ^{1}H NMR δ: 0.11, 0.15, 0.92(t-BDMSi0), 0.81(C-13 CH_3), 1.12(C-10 CH_3) 2.03(17β-OAc), 3.99, t, J=8.2 Hz(3α-H), 4.60, dd, J=7.8, 9.1 Hz(17α-H) ppm. (Found: C, 65.22; H, 9.02; Cl 7.01, $C_{27}H_{45}O_3ClSi$; requires C, 65.23; H, 9.12; Cl, 7.13%).

4β-Chloro-4,5-epoxy-5α-androstane-3β,17β-diol 17-acetate (115)

To a solution of the epoxysiloxane (114) (2g) (4 mmole) in dry

tetrahydrofuran (21.2mL) was added tetra-n-butylammonium fluoride (9.3 ml, 2.3 equiv.), as described by Corey [91]. After 30 minutes the reaction mixture was diluted with water and extracted with ether to give the 5α-epoxyalcohol (115) (1.5g) which was recrystallized from methanol to give 300mg, m.p. 120-124°C; ^{1}H NMR δ:0.8, (C-13 CH_3), 1.13 (C-10 CH_3), 2.04(17β-OAc), 4.05, t, J=8 Hz(3α-H), 4.60, dd, J=7.7 & 9.1 Hz(17α-H) ppm; (Found: C, 66.01; H, 8.29; Cl, 9.15, $C_{21}H_{31}O_4Cl$ requires C, 65.94; H, 8.20; Cl, 9.29%).

17β-Acetoxy-5β-chloroandrost-2-ene-3,17β-diol-4-one (117)

17β-Acetoxy-4β-chloro-4,5-epoxy-5α-androstan-3-one (111) (200mg) was heated to reflux in pyridine for 45 minutes at which time no starting material remained by TLC. The solution was poured into ice-water, extracted with ether, washed with water, dried over anhydrous sodium sulfate and evaporated to give a crystalline residue which showed one component major on TLC; recrystallization from cyclohexane gave 117 (120mg) m.p. 162-166°C, ^{1}H NMR δ: 0.77(C-13 CH_3), 1.23, (C-10 CH_3) 2.02 (17β-OAc), 4.53, dd, J=7.8 and 9.1 Hz(17α-H), 5.93, dd, J=2.9 and 7.1 Hz(2-H) ppm; (Found: C,66.50;H,7.62;Cl,9.08, $C_{21}H_{39}O_4Cl$, requires C, 66.22; H, 7.67; Cl, 9.31%).

Androsta-4,6-dien-4,17β-diol-3-one 17-acetate (116) from (111), (112), (117) and (118).

i) A flask containing 17β-acetoxy-4β-chloro-4,5-epoxy-5α-androstan-3-one (111) (600mg) attached to a water pump was immersed in an oil bath preheated to 240°C for 5 minutes. The residue, which showed one major component

on TLC, was recrystallized from dichloromethane/acetone to give the dienol (116) (150mg) m.p. 197-198°C; ^{1}H NMR δ: 0.88 (C-13 CH_3), 1.10(C-10 CH_3), 2.05(17β-0Ac), 4.64, dd, J=7.2 and 8.9 Hz(17α-H), 601, dd, J=2.1, 9.9 Hz(6-H), 6.66, dd, J=2.8, 9.9 Hz(7-H) ppm; (Found: C, 73.10; H, 8.42, $C_{21}H_{28}O_4$ requires C, 73.23; H, 8.19%).

ii) When the β-epoxyketone (112) (200mg) was treated as above the dienol (116) (105mg) m.p. 188-194°C was obtained.

iii) When the diosphenol (118) (240mg) was treated as above the dienol (116) (123mg) m.p. 189-193°C was isolated.

iv) When the diosphenol (117) (350mg) was treated as above the dienol (116) (220mg) m.p. 186-190°C was isolated. All products (116) gave identical ^{1}H NMR spectra.

5β-Chloro-androst-2-ene-3,17β-diol-4-one-diacetate (119)

5 β -Chloro-2-androstene-3,17 β -diol-4-one 17-acetate (117) (100mg) was dissolved in dry pyridine (1 mL) and acetic anhydride (0.5 mL) was added. After standing at room temperature overnight the reaction mixture was poured into ice-water, acidified, extracted with ether; the organic layer was washed with water, dried over sodium sulfate and evaporated at reduced pressure to give the diacetate (119) which on recrystallization from dichloromethane/acetone gave (70mg) m.p. 198-201°C, ^{1}H NMR δ: 0.77 (C-13 CH_3), 1.25(C-10 CH_3), 2.02(17β -0Ac), 2.24(3-0Ac), 4.57, dd, J=7.7,9.1 Hz(17α-H), 6.40, dd, J=2.4, 7Hz(2-H) ppm. (Found: C,65.55;H,7.36;Cl,8.10; $C_{23}H_{31}O_5Cl$ requires C, 65.25; H, 7.38 ; Cl, 8.48%).

Androst-4-ene-4,17β-diol-3-one diacetate (121) from (119) and (120)

To the 5β-chlorodiacetate (119) (100mg), in 100% ethanol (5mL) was added freshly prepared 2% Zn/Cu couple (1.3g) and the mixture heated to reflux for 30 minutes, filtered and evaporated at reduced pressure to give a product which was passed over neutral alumina in dichloromethane/hexane to give the diosphenol diacetate (121) (54mg) m.p. 168-171°C, (lit.[70] m.p. 170-172°C); ^{1}H NMR δ: 0.84 (C-13 CH_3), 1.25(C-10 CH_3), 2.04(17β-OAc), 2.23(4-OAc), 4.6, dd, J=7.8, 9.1 Hz(17α-H) ppm. The diosphenol (91) (22mg) m.p. 189-192°C (lit.[59], m.p. 194-196°C) was also obtained. Similar treatment of the 5α-chlorodiosphenol (120) (100mg) gave the diosphenol diacetate (121) (53mg) m.p. 168-171°C and the diosphenol (91) (20mg) m.p. 186-190°C.

17β-Acetoxy-4α-chloro-4,5-epoxy-5β-androstan-3-one (112) from (105)

To 4-chlorotestosterone acetate (105) (1.1g) in methanol (105mL) cooled to 5°C was added 4 M NaOH (4.5mL) and 10% H_2O_2(4.5mL) and cooling maintained for 18 hours. The mixture was acidified with glacial acetic acid (about 1mL), diluted with water, ether extracted, washed with water, dried over sodium sulfate and evaporated at reduced pressure to give a crystalline product which was dissolved in dry pyridine (10mL) and acetic anlydride (5mL) was added. After standing overnight at 20°C the reaction mixture was poured into ice-water, acidified and ether extracted to give (1.0g) consisting of two components on TLC (5α:5β-epoxides; 2:3 by HPLC). Recrystallization from dichloromethane/acetone gave the 5β-epoxide (112) 230mg m.p. 153-162°C. Several recrystallization gave a sample m.p. 162-166°C, ^{1}H NMR δ: 0.82(C-13 CH_3), 1.17(C-10 CH_3), 2.04(17β-OAc), 4.60 dd, J = 7.7, 9.1 Hz(17α-H) ppm; m.s. m/z: 380, 382(M^+), 345(M^+-Cl); (Found: C, 66.37; H,7.72; Cl, 9.42, $C_{21}H_{29}O_3Cl$ requires (C, 66.22; 7.67, Cl, 9.31%).

17β-Acetoxy-4α-chloro-4,5-epoxy-5β-androstane-3-one (112) from (90)

4α-Chloro-4,5-epoxy-5 β-androstane-3 β,17 β-diol 17-acetate (90) (100mg) in acetone was treated with excess Jones reagent for 5 minutes. The reaction was diluted with ice-water, ether extracted, washed with water and dried over anhydrous sodium sulfate to give the 3-oxo-4 α-chloro-4,5 β-epoxide (112) (70mg) after recrystallization from acetone m.p. 160-165°C, ^{1}H NMR spectra was identical with those of 112 obtained earlier.

17β-Acetoxy-5α-chloroandrost-2-ene-3, 17β-diol-4-one (118)

17β-Acetoxy-4α-chloro-4,5-epoxy-5β-androstan-3-one (112) (60mg) was heated to reflux in pyridine for 45 minutes at which time no starting material remained on TLC and a more polar component had formed. The solution was diluted with ice-water and extracted with ether to give a crystalline residue which gave the diosphenol (118) recrystallized from acetone (45mg) m.p. 178-184°C; ^{1}H NMR δ: 0.80(C-13 CH_3), 1.07(C-10 CH_3), 2.04(17β-OAc), 4.64, dd, J=7.7, 9.1(17α-H), 5.94, dd, J=2.8 & 6.7 Hz(2H)ppm; m.s. m/z: 380, 382(M^+), 344(M^+-HCl); (Found: C, 65.98; H, 7.64; Cl, 9.41. $C_{21}H_{39}O_4Cl$ requires C, 66.22; H, 7.67; Cl, 9.31%).

5α-Chlorandrost-2-ene-3,17 β-diol-4-one diacetate (120)

The 5 α-chlorodiosphenol (118) (200mg) was treated with acetic anhydride: pyridine (1:2) (3mL). After standing at room temperature overnight the reaction mixture was poured into ice-water, acidified with hydrogen chloride, ether extracted, washed with water and dried over sodium sulfate to give the diacetate (120), recrystallization from dichloromethane/acetone gave (150mg) m.p. 207-210°C, ^{1}H NMR δ: 0.80(C-13 CH_3), 1.14(C-10 CH_3), 2.04(17β-OAc), 2.24(3-OAc), 4.64, dd, J=7.8 Hz(17α-H), 6.4, dd, J=2.4, 6.5 Hz(2 -H) ppm. (Found: C, 64.98; H, 7.45; Cl, 8.49, $C_{23}H_{31}O_5Cl$ requires C, 65.25; H, 7.38; Cl, 8.48%).

17β-Acetoxy-4-chloroestr-4-en-3-one (123)

To a solution of 17β-acetoxy-4-chlorestr-4-en-3-one (2g) in dry pyridine (20 mL), sulfuryl chloride (10.4 mL) was added dropwise at 15°C over a period of 5 minutes, stirring was continued for an additional 5 minutes. The reaction was then poured into excess 3% hydrochloric acid (50 mL) and ether extracted. The organic layer was washed thoroughly with 10% hydrochloric acid, 5% sodium carbonate, water, dried over sodium sulfate and evaporated at reduced pressure to give a product which on several recrystallization from dichloromethane/methanol gave the chloro derivative 123 (1.04g) m.p. 174-180°C; ^{1}H NMR δ: 0.85 (C-13 CH_3), 1.25 (C-10 CH_3), 2.04 (17β-OAc), 4.62, dd, J=7.9, 9 Hz(17α-H) ppm.

Transformations of 17β-acetoxy-4-chlorestr-4-en-3-one (123)

i) **LTBA Reduction of 123**

17β-Acetoxy-4-chloroestr-4-en-3-one (123) (2g) and 85% lithium tri-t-butoxyaluminum hydride (3.6g) were dissolved in freshly distilled tetrahydrofuran (100 mL) in an ice bath under argon and stirred for 3 hours, at which time no starting material remained by TLC. The reaction was worked up as for the testosterone derivative (89,109) to give one major and one minor product on TLC (127) (1.95g).

ii) **Epoxidation of 126**

To a solution of 126 (1.95g) in dichloromethane (35 mL) was added 85% m-chloroperbenzoic acid (1.8g) and the solution was allowed to stand at room temperature for 18 hours. The reaction was worked up as for the testosterone derivative (114) to give four products consistent with 127.

iii) **Oxidation of 127**

The crude product from the above reaction (127) (100mg) in acetone was treated with excess Jones reagent for 5 minutes. The reaction was diluted with ice-water, ether extracted and the organic layer washed with water and dried over anhydrous sodium sulfate to give acidic material which was not further characterized.

iv) **Attempted epoxidation of 17β-acetoxy-4-chloroestr-4-en-3-one (123)**

To 17β-acetoxy-4-chlorestr-4-en-3-one (150mg) (123) in methanol (15 mL) cooled to 5°C was added 4M sodium hydroxide (0.7 ml) and 10% hydrogen peroxide (0.7 mL) and cooling maintained for 3 hours. The mixture was acidified with glacial acetic acid and worked up as for the testosterone derivative (112) to give an acidic product which was not further characterized.

REFERENCES

1. McDonald, R., in "Mechanisms of molecular migration". Vol. 3, B.S. Thygarajan, Ed., Wiley, New York, (1971), p. 67.

2. Smith, J., Synthetics, 8, 629, (1984).

3. Hassner, A. and Catsoulacos, P.J., Org. Chem., 31, 3149, (1966).

4. Hart, H. and Lerner, L.R., J. Org. Chem., 32, 2669 (1967).

5. Cantacuzene, J. and Ricard, D., Bull. Soc. Chim. France, 3555 (1967).

6. Caglioti, V., Delle Site, A., Lenzi, M. and Mele, A., J. Chem. Soc., 5430 (1964).

7. Caglioti, V., Lenzi, M. and Mele, A., Nature, 201, 610 (1964).

8. du Pont de Nemours, E.I. and Co., French Pat., 322, 597 (1963).

9. du Pont de Nemours, E.I. and Co., British Pat., 931, 587 (1963).

10. Belen 'Ku', G.G., German, L.S. and Knunyants, I.L., Bull. Acad. Sci., USSR, Div. Chem. Sci., (English Transl.), 538 (1968).

11. Sianesi, D., Pasetti, A. and Tarli, F., J. Org. Chem., 31, 2312 (1966).

12. Pasetti, A. and Sianesi, D., Gazz. Chim. Ital., 98, 265 (1968).

13. Belen 'Ku', G.G., German, L.S. and Knunyants, I.L., Izv. Akad. Nauk USSR, Ser. Khim., 2780 (1967).

14. du Pont de Nemours, E.I. and Co., British Pat., 904, 877 (1960).

15. Denny, W.A., Kumar, V., Meakins, G.D., Pragnell, J. and Wicha, J., J.C.S. Perkin Trans. I, 486 (1972).

16. Zief, M. and Schramm, C.H., Chem. Ind. (London), 660 (1964).

17. Walling, C. and Fredericks, P.S., J. Am. Chem. Soc., 84, 3326 (1962).

18. Razuvaev, G.A. Etlis, V.S. and Trofimov, N.N., Zh. Organ. Khim., 1, 2128 (1965).

19. McDonald, R.N. and Schwab, P.A., J. Am. Chem. Soc., 85, 4004 (1963).

20. Kirrmann, A. and Nouri-Bimorghi, R., Bull. Soc. Chim., (France), 3213 (1968).

21. Nouri-Bimorghi, R., Compt. Rend., Ser. C., 262, 759 (1966).

22. Mousseron, M., Winternitz, F. and Jacquier, R., Compt. Rend., 223, 1014 (1946).

23. Mousseron, M., Winternitz, F. and Jacquier, R., Bull. Soc., Chim., (France), 260 (1948).

24. Mousseron, M. and Jacquier, R., Bull. Soc. Chim., (France), 698 (1950).

25. Mousseron, M., Winternitz, F. and Jacquier, R., Bull. Soc. Chim. (France), 83 (1947).

26. McDonald, R.N. and Tabor, T.E., Chem. Commun., 655 (1966).

27. McDonald, R.N. and Tabor, T.E., J. Am. Chem. Soc., 89, 6573 (1967).

28. McDonald, R.N. and Tabor, T.E., J. Org. Chem., 33, 2934, (1968).

29. Beckman, S. and Eder, G., Chem. Ber. 1, 91, 2878 (1958).

30. Berson, J.A., Hammons, J.H., McRowe, A.W., Bergman, R.G., Remanick, A. and Houston, D., J. Am. Chem. Soc., 89, 2590 (1967).

31. McDonald, R.N. and Steppel, R.N., J. Am. Chem. Soc., 91, 782 (1969).

32. McDonald, R.N. and Steppel, R.N., J. Am. Chem. Soc., 92, 5664 (1970).

33. McDonald, R.N. and Steppel, R.N., J. Org. Chem., 35, 1250 (1970).

34. Mamlock, L. and Jacques, J., Bull. Soc. Chim., France, 484 (1960).

35. Brutcher, F.V. and Bauer, W., J. Am. Chem. Soc., 84, 2236 (1962).

36. Denny, W.A., Kumar, V., Meakins, G.D., Pragnell, J. and Wicha, J., J. Chem. Soc., Perkin Trans. I, 486 (1972).

37. Hassner, A. and Catsoulacos, P., J. Org. Chem., 31, 3149 (1966).

38. McBee, E.T., Pierce, O.R. and Christman, D.L., J. Am. Chem. Soc., 77, 1581 (1955).

39. Chow, D., Jones, M.H., Thorner, M.P. and Wong, E.C., Can. J. Chem., 47, 2491 (1969).

40. Shine, H.J. and Hunt, G.E., J. Am. Chem. Soc., 80, 2434 (1958).

41. Vanderhaeghe, H., Katzenellenbogen, E.R., Dobriner, K. and Gallagher, T.F., J. Am. Chem. Soc., 74, 2810 (1952).

42. Kritchevsky, T.H. and Gallagher, T.F., J. Biol. Chem., 179, 507 (1949).

43. Attenburrow, J., Connett, J.E., Graham, W., Oughton, J.F., Ritchie, A.C. and Wilinson, P.A., J. Chem. Soc., 4547, (1961).

44. Williamson, K.L. and Johnson, W.S., J. Org. Chem., 26, 4563 (1961).

45. Williamson, K.L., Coburn, J.I. and Herr, M.F., J. Org. Chem., 32, 3934 (1967).

46. Leeds, N.S., Fukushima, D.K. and Gallagher, T.F., J. Am. Chem. Soc., 76, 2943 (1954).

47. Johnson, W.S., Gartambide, B. and R. Pappo., J. Am. Chem. Soc., 79, 1991 (1957).

48. Rhone, J.R. and Huffman, M.N., Tetrahedron Letters, 1395 (1965).

49. Nambara, T. and Fishman, J., J. Org. Chem., 27, 2131 (1962).

50. Zeglam, T.H., M.Sc. Thesis, University of Manitoba, (1984).

51. Camtacuzene, J. and Ricard, D., Bull. Soc. Chem., (France), 3555 (1967).

52. Draper, A.L., Heilman, W.J., Schaefer, W.E., Shine, H.J. and Shoolery, J.N., J. Org. Chem., 27, 2727 (1962).

53. Williamson, K.L. and Johnson, W.S., J. Org. Chem., 26, 4563 (1961).

54. Collins, C.J., Quart. Rev. (London), 14, 357 (1960).

55. Parker, R.E. and Isaacs, N.S., Chem. Rev., 59, 737 (1959).

56. McDonald, R.N. and Schwab, P.A., J. Org. Chem., 29, 2459 (1964).

57. McDonald, R.N. and Cousins, R.C., J. Org. Chem., 45, 2976 (1980).

58. Kirk, D.M., Pateland, D.K. and Petrow, C., J. Chem. Soc., 1184 (1956).

59. Mori, H., Chem. Pharm. Bull., 10, 429 (1962).

60. Ringold, H.J., Batres, E., Mancera, O. and Rosenkranz, G., J. Org. Chem., 21, 1432 (1956).

61. Camerino, B., Patelli, B. and Vercellone, A., J. Am. Chem. Soc., 78, 3540 (1956).

62. Schubert, G., Ponsold, K. and Eibisch, U., Pharmazie, 39, 92 (1984).

63. Mathews, G.H. and Hassner, A. in: J. Fried and J.A. Edwards (Eds). Organic reactions in steroid chemistry, Vol. 2, Chapter 2, Van-Nostrand-Reinhold, New York (1972).

64. Huttenrauch, R. and Schubert, A., Arch. Pharmaz., 299, 1011 (1966).

65. Neeman, M. and O'Grodnick, J.S., Tetrahedron Letters [London], 783 (1972).

66. Shaw, J.I. and Stevenson, R., J. Chem. Soc., 3549 (1955).

67. Vida, J.A., Androgens and anabolic steroids, p. 265, Academic Press, New York, London (1969).

68. Ohloff, G., Maurer, B., Winter, B. and Giersch, W., Helv. Chim. Acta, 66, 192 (1983).

69. Ward, M.G., Orr, J.C. and Engel, L.L., J. Org. Chem., 30, 1421 (1965).

70. Kaufmann, S., J. Org. Chem., 29, 1348 (1964).

71. Jennings, B.H. and Bengtson, J.M., Steroids, 31, 49 (1978).

72. Chamberlain, P., Roberts, M.L. and Whitham, G.H., J. Chem. Soc., B, 1374 (1970).

73. Keller, P., Eggart, Frl., Whrli, H., Schaffner, K. and Jeger, O., Helv. Chim. Acta, 50, 2259 (1976).

74. Plattner, P.A., Heusser, H. and Kulkarim, A.B., Helv. Chim. Acta, 31, 1822 (1948).

75. Henbest, H.B. and Jackson, W.R., J. Chem. Soc., (C), 2460 (1967).

76. House, H.O. and Ro, R.S., J. Am. Chem. Soc., 80, 2428 (1958).

77. Wasserman, H.H. and Aubrey, N.E., J. Am. Chem. Soc., 77, 590 (1955).

78. Dauben, W.G., Michelli, R.A. and Eastham, J.F., J. Am. Chem. Soc., 74, 3852 (1952).

79. Hertshorn, M.P. and Wallis, A.F.A., J. Chem. Soc., 3839 (1962).

80. Mihailovic, M.J., Forsek, J. and Lorenc, L.J., Tetrahedron, 33, 235 (1977).

81. Siiteri, P.K., Cancer Res., 42, 3269 (1982).

82. Schwarzel, W.C., Kruggel, W. and Brodie, H.J., Endocrinology, 92, 866 (1973).

83. Brodie, M.H. and Longcope, C., Endocrinology, 106 (1980).

84. Longcope, C., Pratt, J.H., Schneider, S.H. and Fineberg, S.E., J. Clin. Endocrinol Metab., 46, 146 (1978).

85. Miller, W.R. and Forrest, A.P.M., Lancet, 2, 866 (1974).

86. Thibault de Boesinghe, L.de., Lacroise, E., Eechant, W. and Lansen, I., Lancet, 2, 1268 (1974).

87. Li, K., Chandra, D.P., Foo, T., Adams, G.B. and McDonald, D., Steroids. 28, 561 (1976).

88. Varela, R.M. and Dao, T.L., Cancer Res., 38, 2429 (1978).

89. Brodie, A.M.H., Schwarzel, W.C., Shaikh, A.A. and Brodie, H.J., Endocrinology, 100, 1684 (1977).

90. Brodie, A.M.H., Marsh, D. and Brodie, H.J., J. Steroid Biochem., 10, 423 (1979).

91. Corey, E.J. and Venkateswarbu, A., J. Am. Chem. Soc., 94, 6190 (1970).

92. Kaufmann, S., J. Org. Chem., 29, 1348 (1964).

93. Fishman, J., Neuroendocrinology, 22, 363 (1977).

94. Fishman, J., Bradlow, H.L. and Gallagher, T.F., J. Biol. Chem., 235, 3104 (1960).

95. Marrian, G.F., Loke, K.H., Watson, E.J.D. and Panattoni, M., Biochem. Journal, 66, 60 (1957).

96. Fishman, J., Cox, R.I. and Gallagher, T.F., Archiv. of Biochem. and Biophy., 90, 318 (1960).

97. Ball, P. and Knuppen, R., J. Clin. Endocr., 47, 732 (1978).

98. Schneider, J., Huh, M.M., Bradlow, H.L. and Fishman, J., J. Biol. Chem., 259, 4840 (1984).

99. Fishman, J., J. Endocr., 89, 59 p, (1981).

100. Kamberi, I.A., In: Raspe G., Ed. Advances of the Biosciences, 15, 249 (1974).

101. Ball, P., Knuppen, R., Haupt, M. and Breuer, H., J. Clin. Endocr., 34, 736 (1972).

102. Gelbke, H.P., Ball, P. and Knuppen, R., In: Briggs, M.H. and Christie, G.A., Eds. Advances in sterioid biochemistry and pharmecology. Academic Press, New York, 6, 81 (1977).