ASPECTS OF PHOTOCHEMICAL AND ACID CATALYSED STEROIDAL REARRANGEMENTS

by

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TO MY PARENTS

ACKNOWLEDGEMENTS

DECLARATION

I hereby declare that the following thesis is of my own composition;
that it is a record of the results of experiments performed by myself
and that it has not been submitted in any previous application for a
Higher Degree.

CONTENTS

PART ONE.   Photolysis of β,γ-epoxy-ketones.

INTRODUCTION

In contrast to the well documented reports on the photolysis of α,β-epoxy ketones[1] few reports have appeared in the literature in connection with the photolysis of β,γ-epoxy ketones[2-6].

The earliest reported example[2] of β,γ-epoxy ketone photochemistry was the investigation into the photolysis of (1) by Starr and Eastman in 1966. No well defined products were isolated in either cyclohexane or methanol. Shortly afterwards Padwa and co-workers[3] in 1967 gave an account of the photochemical behaviour of trans-1,4-diphenyl-3,4-epoxybutan-1-one (2). Four products, which were formed via a Norrish type II bond cleavage, were identified as acetophenone, phenylacetic acid, dibenzoylethane and cis-1,2-diphenyl-2,3-epoxy-1-cyclobutanol. In 1977 Coxon and Hii[4] investigated similar cyclobutanol formation from the photolysis in benzene of 3,4-epoxy-1-phenylbutan-1-one (3A) and its 2,2-dimethyl derivative (3B).

(1)   (2)   (3)   A R=H
                                                       B R=Me
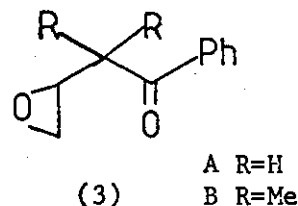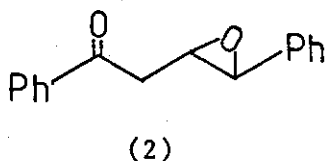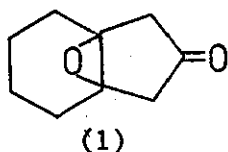
Chambers and Marples[5], in 1972, published the first constructive report on the photochemistry of cyclic β,γ-epoxy ketones, namely the epimeric 9ξ,10ξ-epoxy-3β-methoxy-5-methyl-5β-cholestan-6-ones (4).

                        A 9α,10α
                (4)   B 9β,10β
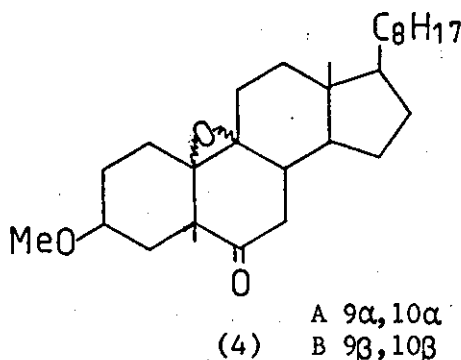
With no readily accessible γ-proton to aid Norrish type II bond cleavage, Norrish type I cleavage, that is α-cleavage, predominates. Irradiation of an ethereal solution of (4A) resulted in rapid decarbonylation and the formation of an unsaturated epoxide (5), plus several minor products one of which was identified as (6).

(5)   (6)
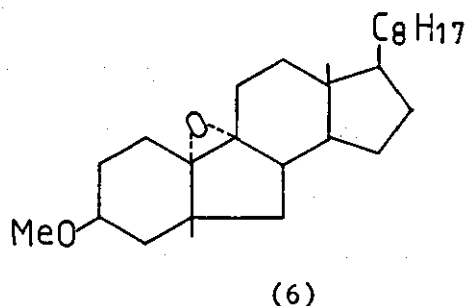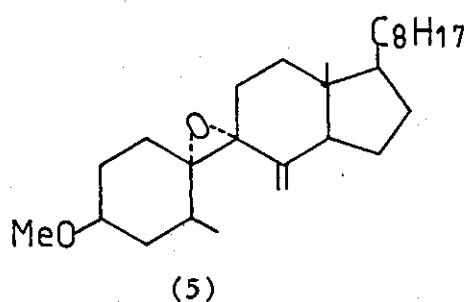
Similar irradiation in methanol gave the methyl ester (7).

(7)
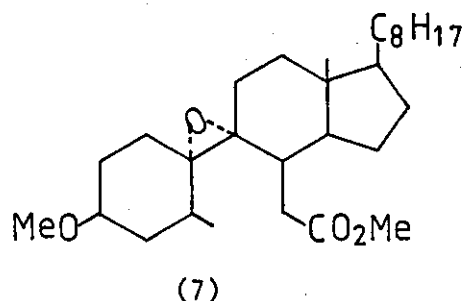
The 9β,10β-epoxy ketone (4B), however, remained unchanged in ether and no well defined products were obtained in methanol. No explanation was put forward to explain this anomaly. The mechanism for the photochemical transformation is given below (Scheme I) and was supported by deuterium labelling. When the photolysis was carried out in methanol the ketene, which can be formed from the first formed diradical intermediate, was trapped as the methyl ester thus driving the reaction in this direction.
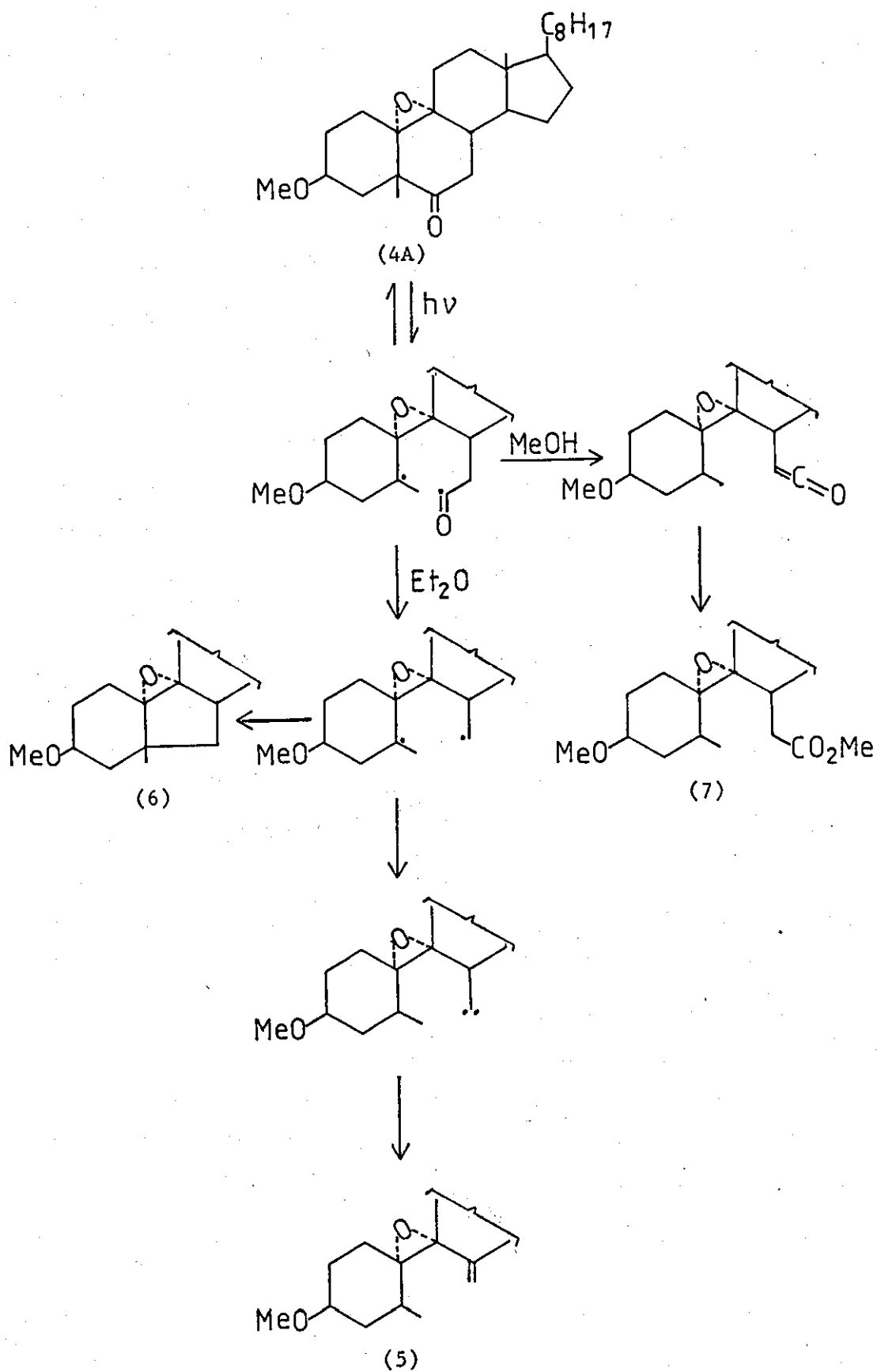
Scheme I

In 1975 Murray and co-workers proposed a general scheme illustrating the photochemistry of cyclic β,γ-epoxy ketones[6]. They propose an initial Norrish type I bond cleavage giving a diradical species (8) which ring-opens to an acylalkoxy diradical species (9). Provided the process is not hindered sterically this diradical species can ring-close to lactone (10). Similarly if the ring is unsubstituted at the γ- position then intramolecular hydrogen transfer is possible giving an unsaturated aldehyde (11).
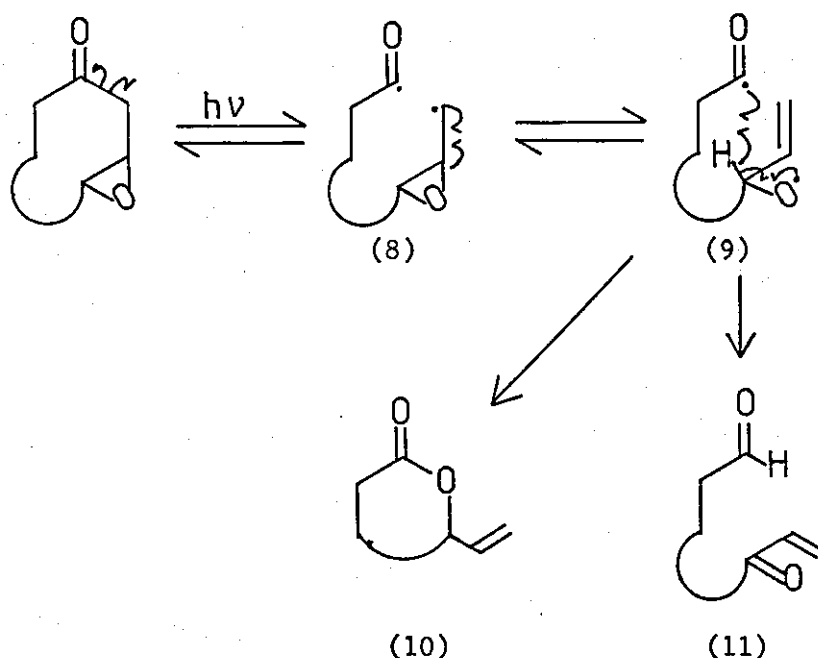
If the formation of (10) is prevented, that of (11) predominates and vice versa. However, if the formation of both of these products is prevented (8) decarbonylates to give diradical (12) which can either ring-close to (13) or undergo intramolecular hydrogen transfer to (14).
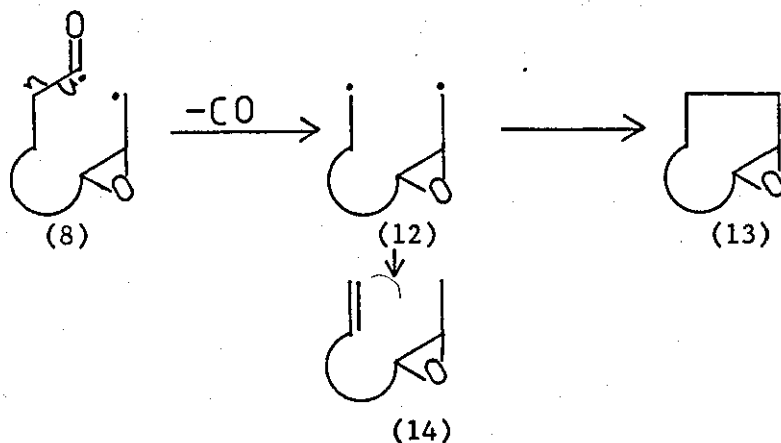
The work was originally confined to mono and bicyclic systems such as (15) to (19).

(15)   (16)   (17)

(18)   (19)
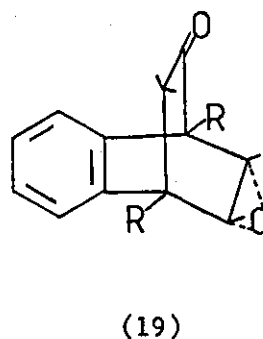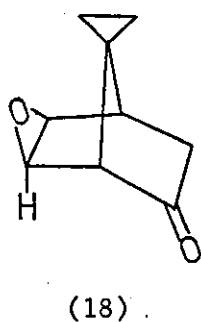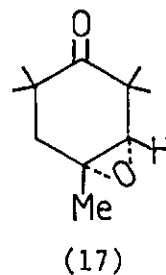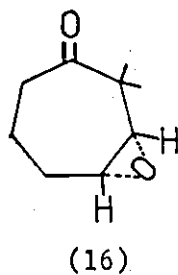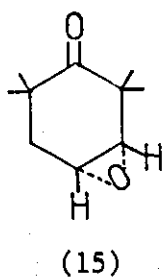
The scheme was also supported by Carlson et al [7a] who photolysed compound (20) and isolated products of general structure (10) and (11).

(20)
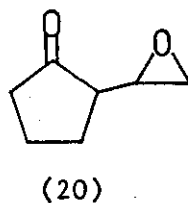
A similar scheme has recently been presented, by Murray, explaining the general photochemistry of exocyclic epoxy ketones[7b].

Imam and Marples[8] studied the photolyses in ether and methanol of the epimeric 4,4-dimethyl-5ξ,6ξ-epoxy-cholestan-3-ones (21).

(21)   A 5α,6α
              B 5β,6β
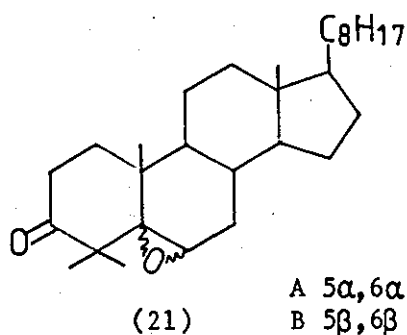
The mechanism of the observed rearrangement is well understood. Initial excitation led to Norrish type I bond cleavage giving a diradical species (22).
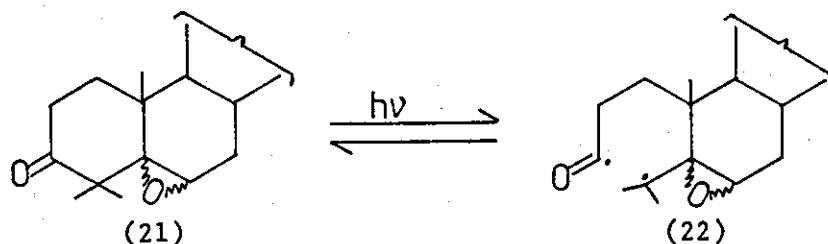
In methanol (22) underwent a 1,5-hydrogen transfer giving a ketene intermediate (23) from which the methyl ester (24) was derived via attack by methanol.
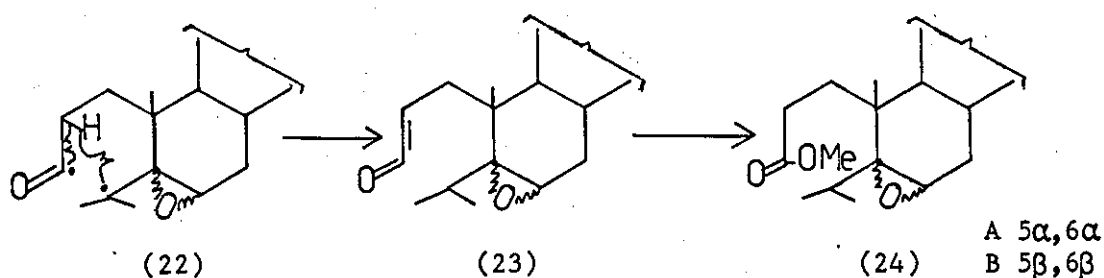
An unsaturated aldehyde (25) was obtained as a minor product, presumably via a 1,7-hydrogen shift.
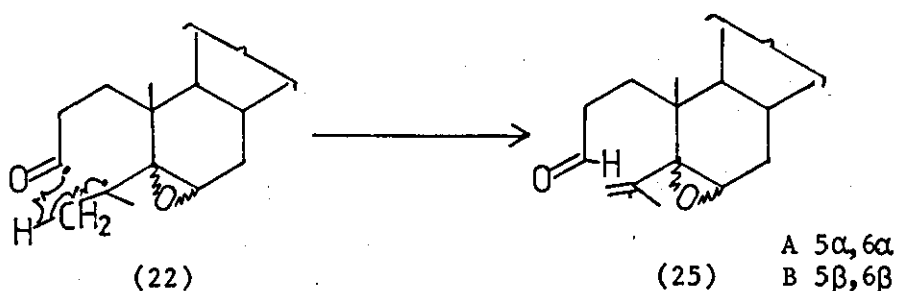
In ether the α-epoxide gave no well defined products. On the other hand the β-epoxide rapidly decarbonylated to the olefin (26) and the A-nor epoxide (27).

(26)   +   (27)
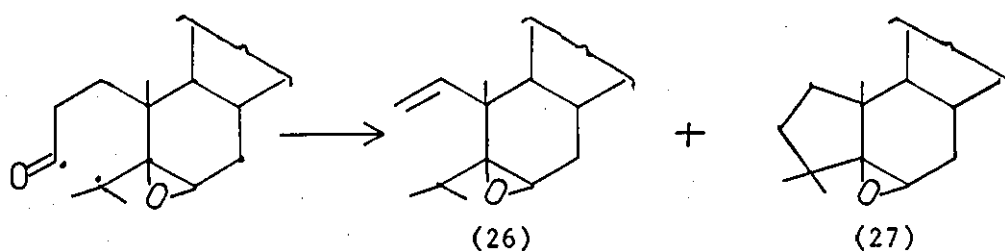
It is evident from the results of Imam and Marples, and Chambers and Marples that the epoxide ring does not necessarily play such an important role in secondary photochemical reactions as suggested by Murray's general scheme.

Although (4) cannot form an unsaturated aldehydo-ketone an inspection of molecular models suggests that, in principle, it should be capable of ring-closing to lactone (28). Indeed, the non-reactivity of the $9\beta,10\beta$-epoxide is surprising since it should most readily be capable of forming the lactone (28B).

Similarly, (21A) should easily form a lactone (29) as well as an unsaturated aldehydo-ketone (30), and although (21B) would be incapable of ring-closure to a lactone owing to excessive ring strain, it should be capable of undergoing intramolecular hydrogen transfer to an unsaturated aldehydo-ketone (30).

(28A)

(28B)

(29)

(30)
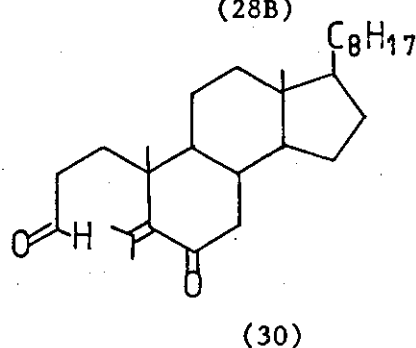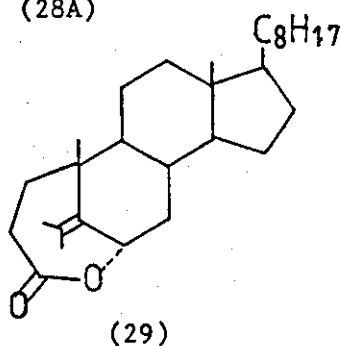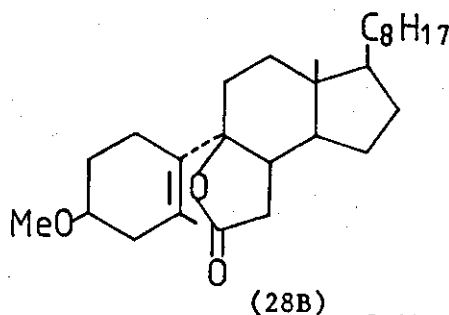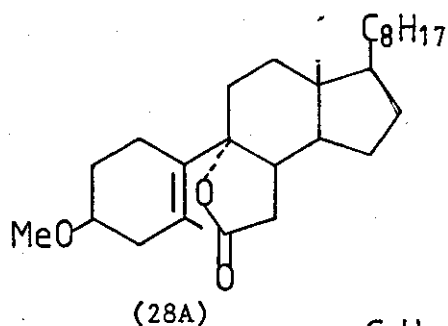
We decided to investigate the photolyses of 5ξ,10ξ-epoxy-oestran-17β-ol-3-one (31), and 4,4-dimethyl-5ξ,6ξ-epoxy-oestran-17β-ol-3-one (32).

(31)   A 5α,10α
       B 5β,10β

(32)   A 5α,6α
       B 5β,6β
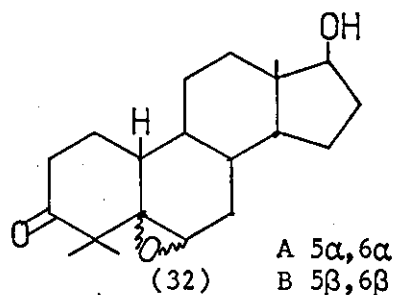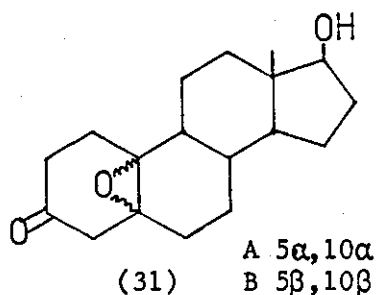
The endocyclic nature of the epoxide ring in (31) in relation to the carbonyl group would provide an example which could be compared with Chambers and Marples example of β,γ-epoxy ketone photochemistry and give further information about the general behaviour of β,γ-epoxy ketones. There could be little dispute that in terms of Murray's general scheme in this case lactone formation is not precluded although clearly aldehydo-ketone formation is.

In relation to X-ray work on 4,4-dimethyl steroids Whalley[9] has established that Δ^5-4,4-dimethyl compounds carrying a C-10 methyl have a skew-boat A-ring with C-3 and C-10 above the C-1, C-2, C-4, C-5 plane. The B-ring adopts a half-chair conformation with C-8 above and C-9 below the C-5, C-6, C-7, C-10 plane, and the C-ring adopts a normal chair conformation with slight flattening at the B-junction.
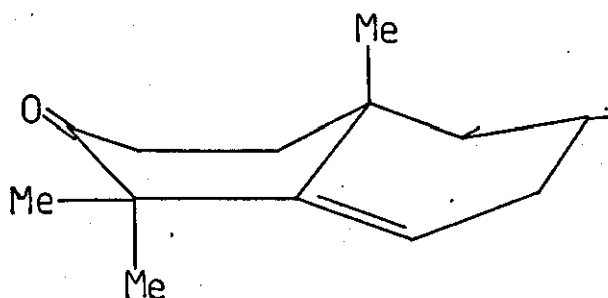
The move away from the normal chair conformation in the A-ring is due largely to the C-10, C-4β-methyl steric repulsion which severely distorts the ring.

It seems reasonable to assume that in steroids of this type in which the Δ^5-unsaturation has been replaced by an epoxide ring, whether α-orβ-, similar conformations for the A-ring, and B and C, would exist. The X-ray structures of 19-nor-4,4-dimethyl-Δ^5-compounds have not been reported. However, the C-10, C-4 -methyl interactions are now absent and hence a more normal chair/skew-chair/chair conformation in these, and the 5,6-epoxides, would be expected. A comparison[10] of 19-nor steroids with those having a 10β-methyl in saturated (5α) steroids shows that the former are not distorted whilst the latter are.

When photolysed the ground state conformations may be expected to be maintained in the transition state and hence any difference in reactivity between compounds (21) and (32) may reflect a dependence on ground state conformations.

It was of interest therefore, to compare the photolyses of (21) and (32) and further to compare their photolytic behaviour with that reported (principally by Murray[6,7b]) for less conformationally rigid molecules.

RESULTS AND DISCUSSION

Attempted preparation of 5,10-epoxy-oestran-17β-ol-3-ones (31A) and (31B)

Treatment of 17β-hydroxyoestr-5(10)-en-3-one (33) with monoperphthalic acid was reported[11] by Ruelas et al to give a pure epoxide (31B) which was assigned the 5β,10β-stereochemistry. The corresponding α-epoxide (31A) has never been reported except when the carbonyl group is protected, for example by ethanediol[12]. We wished to prepare epimers (31A) and (31B) as part of our investigation into the photochemistry of β,γ-epoxy ketones.

Reaction of oestradiol (34) with an ethereal solution of diazomethane afforded the 3-methyl ether (35)[13]. Reduction of (35) by the method of Birch[14] with sodium in liquid ammonia gave 1,4-dihydrooestradiol-3-methyl ether (36)[13], which on treatment with an aqueous methanolic solution of oxalic acid yielded the $\Delta^{5,10}$-ene-3-one (33)[13](Scheme II).
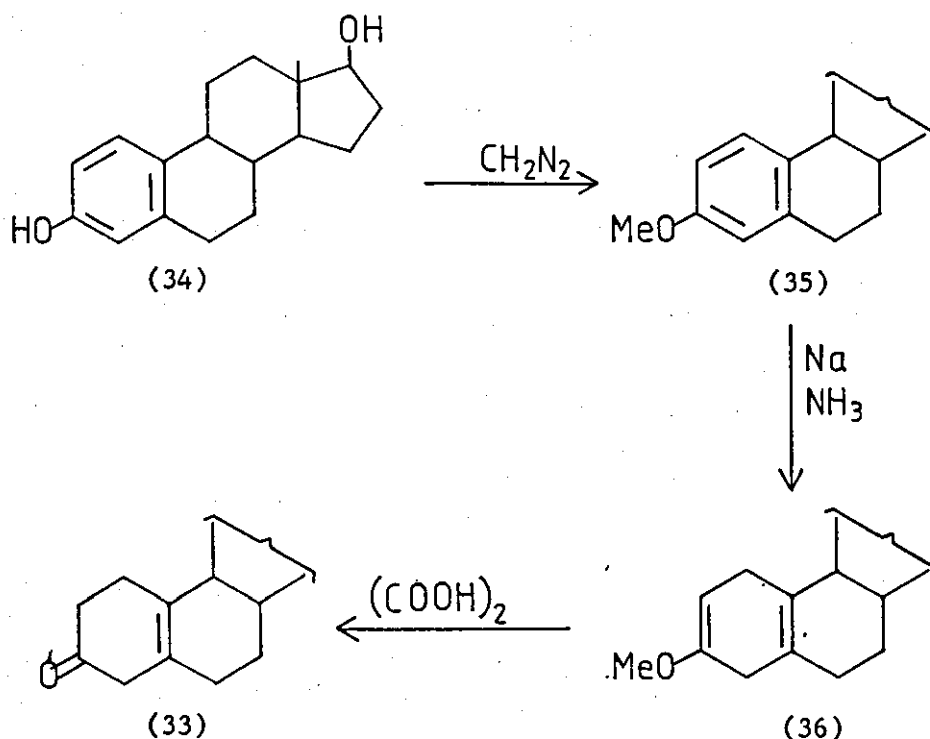
Scheme II

Oxidation of (33) with monoperphthalic acid gave a white crystalline solid. Although the product was recrystallised several times a sharp

melting point comparable to that in the literature[11] of 208-10°C could

not be obtained. Rather, the solid gradually melted in the range 175-200°C,

resolidified, and finally melted again in the range 216-22°C. No

indication of its purity could be obtained from t.l.c. Several attempts

to partially purify the crude product showed that it rearranged easily

on t.l.c. to a compound which fluoresced on activated silica gel (Merck

PF 254). It is suggested that the major product of the rearrangement on

silica gel was probably the γ-hydroxy-α,β-unsaturated ketone (37)[11],

having $\nu_{max.}$ 1660cm^{-1} (C=O) and 3350cm^{-1} (O-H). Weight was added to this

argument when the preparation of the α-epoxide was attempted. Treatment

of (33) with N-bromosuccinimide and perchloric acid afforded the

bromohydrin (38)[12]. Attempted ring-closure with ethanolic potassium

acetate solution however, again gave a compound which fluoresced on

activated silica gel. The infrared spectrum was similar to that of (37).

The product was thought to be the γ-hydroxy-α,β-unsaturated-ene-one (39)[12]

(Scheme III).
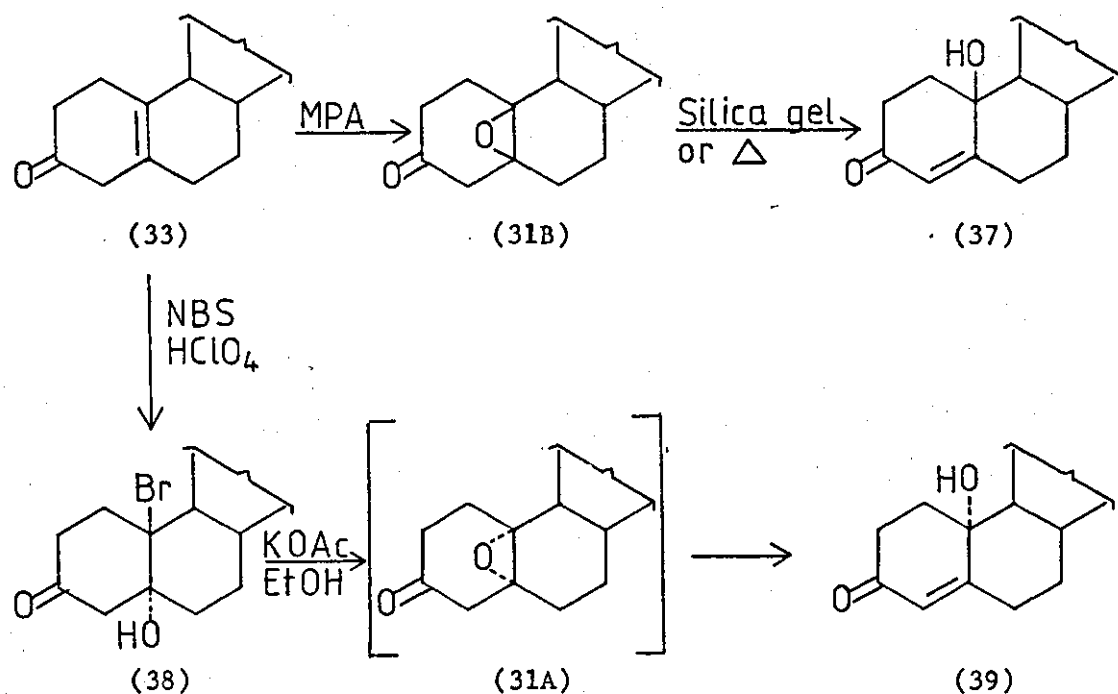
Scheme III

Our assumption was supported by the observation[15] that compounds (40) and (41) were found to rearrange readily on silica gel or in ethanolic triethylamine to the γ-hydroxy-ene-ones (42) and (43) (Scheme IV).
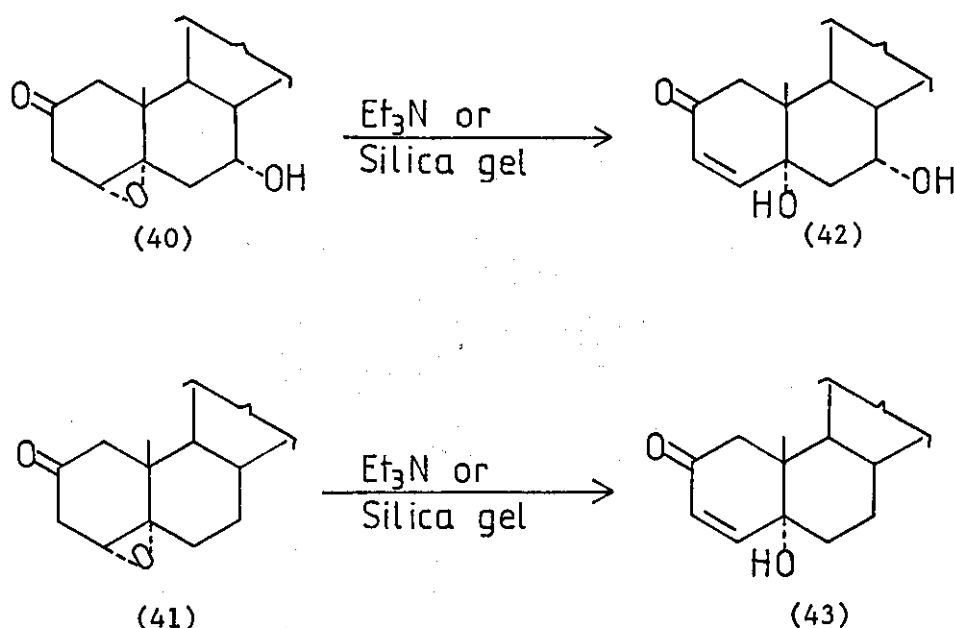
Scheme IV

In fact Ruelas has shown that the 5β,10β-epoxide (31B) rapidly isomerises in methanolic potassium hydroxide solution to the γ-hydroxy-ene-one (37)[11]. Barton suggests a simple mechanism for the isomerisation of (40) proceeding via the anionic intermediate (44).
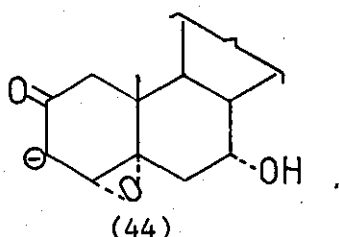
The intermediate will not deuteriate because, as Barton suggests, the rate of collapse to the γ-hydroxy-α,β-unsaturated ketone is faster than the rate of deuteriation. He also compared the rate of isomerisation of (40) with its α,α'-dideuteride and established that a large kinetic isotope effect was in operation. Hence the anion (44) probably does not exist as a discrete entity and the isomerisation may be concerted. It is the authors view that since the isomerisation not only occurs in

triethylamine but also on the relatively acidic medium of silica gel the enol form may exist as a discrete intermediate. However, rather than equilibrating with ketone (40), the enol, once formed, rearranges immediately to the γ-hydroxy-ene-one (42) (Scheme V).

(40)   (42)
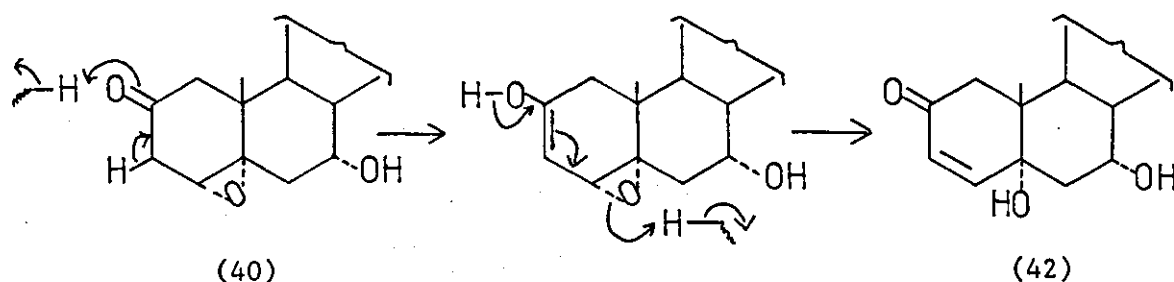
Scheme V

As previously mentioned the 5β,10β-epoxide (31B) has been reported by Ruelas et al[11], and Cross prepared the 5β,10β-epoxide of oestr-5(10)-ene-3,17-dione[16]. However, an earlier attempt by Colton at this peracid oxidation gave only a mixture of 10α- and 10β-hydroxy-oestr-4-ene-3,17-diones[17]. Although no firm evidence exists for the formation of the 10α-hydroxy compound, the formation of the 10β-hydroxy compound is interesting since it compares with our own observations. The α-epoxide (31A),on the other hand, is not known. Cross successfully ring-closed the bromohydrin (45)[16].

(45)   (46)
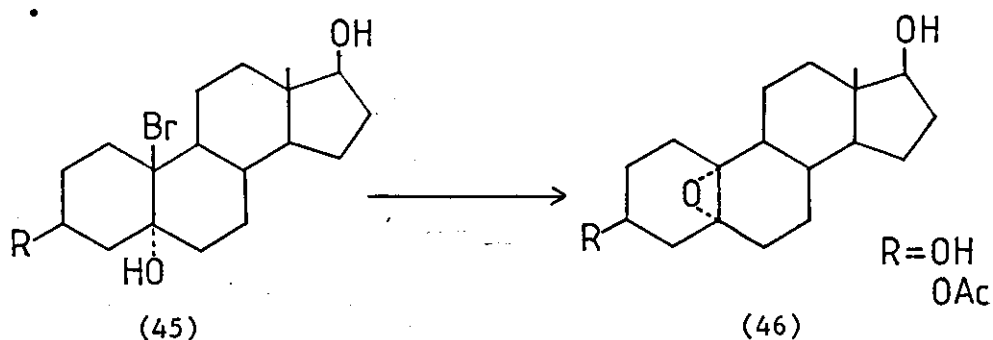
Ponsold[12] prepared similar compounds where R=OH
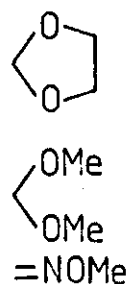
However, treatment of bromohydrin (38) with triethylamine gave only the

γ-hydroxy-4-ene-3-one (39). Likewise, Gardi et al prepared 5β,10β-epoxy-

oestran-3,17-dione-bis(ethylene ketal)[18]. Acid hydrolysis however, gave

only 5,10β-dihydroxy-5α-oestran-3,17-dione. The ready ring-opening of

the epoxide moiety under such mild conditions and the ease with which it

hydrolyses when carbonyl protecting groups are removed caused us

eventually to abandon our proposed photochemical study of this series of

compounds. With no means of determining the purity we could never be sure

whether the photo products were those from the original 5,10-epoxide or

from a rearranged form of the 5,10-epoxide. However, our interest also

lay with a pair of epimeric 4,4-dimethyl-5,6-epoxides which, by their

very nature of having both α-protons substituted cannot undergo similar

rearrangements. The preparation and photolysis of these are described

below.

Preparation of 4,4-dimethyl-5ξ,6ξ-epoxy-oestran-17β-ol-3-ones(32A) and (32B)

The epoxy ketones (32A) and (32B) were prepared from oestradiol-3-methyl
ether (35)[13] according to scheme VI. Hydrolysis of 1,4-dihydrooestradiol-
3-methyl ether (36)[13](p.10) with dilute hydrochloric acid in methanol
gave the α,β-unsaturated ketone (47)[13]. Methylation of (47) with a mixture
of potassium t.-butoxide and methyl iodide in t.-butyl alcohol afforded
the 4,4-dimethyl-Δ^5-en-3-one (48)[19]. Treatment of (48) with an ethereal
solution of monoperphthalic acid gave a mixture containing both 5α,6α-
and 5β,6β-epoxides (32A) and (32B). The α-epoxide was isolated in 75%
yield by fractional crystallisation. Similarly, treatment of (48) with
N-bromosuccinimide and perchloric acid gave mainly bromohydrin (49A).
Ring-closure was achieved with hot ethanolic potassium acetate solution
and gave a mixture again containing both α- and β-epoxides. The β-epoxide
was obtained in 44% yield again by fractional crystallisation. Although
fractional crystallisation of a mixture of the α- and β-epoxides gave a
pure form of the epoxide in significant excess, an approximately equimolar
mixture was difficult to separate by crystallisation, nor could a
satisfactory chromatographic method be found. Table I gives spectroscopic
data for epimers (32A) and (32B).

(35)　　　　　　　　(36)　　　　　　　　(47)

(32) A 5α,6α　　　　(49) A X=Br, Y=OH　　　(48)
     B 5β,6β　　　　　　 B X=OH, Y=Br

Scheme VI
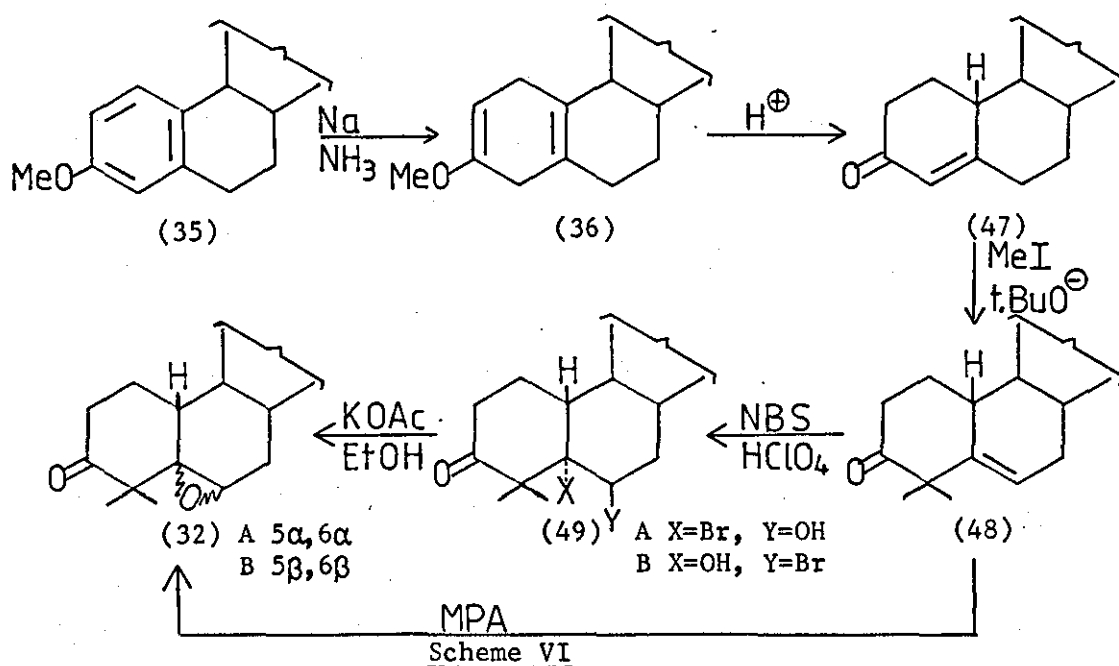
TABLE I

INFRARED SPECTRA

COMPOUND	$\nu(cm^{-1})$	ASSIGNMENT
32A	3510	-O-H
	1719	C=O
32B	3500	-O-H
	1700	C=O

PROTON NUCLEAR MAGNETIC RESONANCE SPECTRA

COMPOUND	δ	J(Hz)	No. of PROTONS	MULTIPLICITY	ASSIGNMENT
32A	3.14	5	1	Doublet	6β-methine
	0.88	-	3	Singlet	4α-methyl
	1.28	-	3	Singlet	4β-methyl
32B	3.18	3	1	Doublet	6α-methine
	1.02	-	3	Singlet	4β-methyl
	1.10	-	3	Singlet	4α-methyl

Photolysis of 4,4-dimethyl-5α,6α-epoxy-oestran-17β-ol-3-one(32A) in methanol

Photolysis of a methanolic solution of 5α,6α-epoxy ketone (32A) gave a
mixture from which the major product, the methyl ester (50A) was separated
by preparative t.l.c. in 56% yield. The remaining fractions were either
starting material (32A), or unidentified minor components.

Compound (50A) was an oil. Its infrared spectrum had characteristic ester
carbonyl ($1740cm^{-1}$) and hydroxyl (br. $3450cm^{-1}$) bands. The 90MHz ^{1}H n.m.r.
spectrum had important peaks at δ3.67 (3H, s, CO_2Me), δ0.71 and δ0.98
(6H, 2xd, J 7Hz, CH(Me)$_2$) and δ2.93 (1H, d, J 6Hz, 6β-H) indicating that
the epoxide ring was intact and had not isomerised. The mass spectrum had
a molecular ion peak at m/e 350 which fragmented by loss of 43$[(Me)_2CH-]$
to the base peak at m/e 307 which further fragmented by loss of 18(H_2O)
to m/e 289. Alternatively, the molecular ion could lose 18 to m/e 332
which then lost 43 to m/e 289. The molecular ion could also lose 31(MeO-)
or 32(MeOH) giving peaks at m/e 319 and 318 respectively.
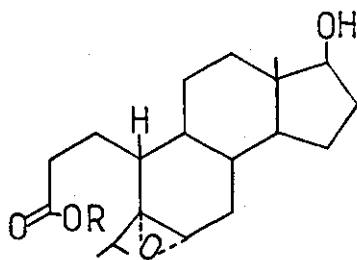
(50A) R=Me
(51A) R=H

Compound (50A) was hydrolysed in 10% methanolic potassium hydroxide
solution to its corresponding acid (51A), a white crystalline solid.
Elemental analysis confirmed the molecular formula and spectroscopic
analysis confirmed the structural assignments. When treated with
diazomethane the methyl ester (50A) was recovered in high yield.

These photolyses were repeated several times with reproducible results.
However, in one photolysis, which we have never been able to repeat, the
aldehyde (52A) and the allyl alcohol (53) were isolated in yields of 11%

and 13% respectively from (32A).

(52A) (53)
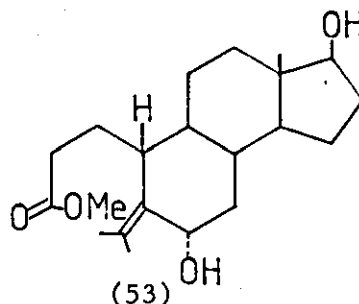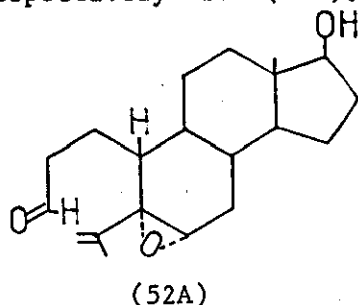
The infrared spectrum of compound (52A) had characteristic carbonyl

($1725cm^{-1}$), hydroxyl (br. $3460cm^{-1}$), aldehydic C-H ($2720cm^{-1}$) and olefinic

($1640cm^{-1}$) bands. The 90MHz ^{1}H n.m.r. spectrum confirmed the presence of

an aldehyde by a characteristic one proton multiplet ($W\frac{1}{2}$ 3Hz) at δ9.72.

Other important peaks were evident at δ4.86 and δ5.05 (2H, 2xm, $W\frac{1}{2}$ 5Hz,

C=CH$_2$), δ1.8 (3H, s, H$_2$C=C<u>Me</u>), and δ2.76 (1H, d, J 6Hz, 6β-H) indicating

that the epoxide ring was intact and had α-stereochemistry.

The molecular ion at m/e 318 in the mass spectrum readily fragmented by

loss of 28(CO) to m/e 290 which further fragmented by loss of 43(C$_3$H$_7$)

to m/e 247. Alternatively, the molecular ion could lose 43 to m/e 275

which further fragmented by loss of 28 to m/e 247. Unfortunately, although

preparation of the semicarbazone was attempted, no derivative is available

for compound (52A) owing to extensive aerial oxidation and decomposition

which aldehydes of this type seem to readily undergo.

The allyl alcohol (53) had characteristic ester carbonyl ($1725cm^{-1}$) and

hydroxyl (br. $3430cm^{-1}$) bands. In the 90MHz ^{1}H n.m.r. spectrum the 6β-

methine doublet (J 9Hz) occurred at δ4.86 having shifted downfield slightly

owing to the deshielding effect of the double bond of the isopropylidene

group.

Other important peaks occurred at δ3.65 (3H, s, CO$_2$Me) and at δ1.75 and

δ1.7 (6H, 2xs, C=C(Me)$_2$). Confirmation of the molecular weight was gained

from the mass spectrum which had a molecular ion peak at m/e 350.

Compound (53) was acetylated in pyridine and acetic anhydride giving the

diacetate (54).
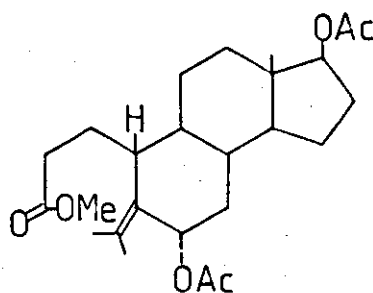
(54)

The 90MHz ^{1}H n.m.r. spectrum of (54) had peaks at $\delta 1.69$ and $\delta 1.82$ (6H, 2xs, C=C(Me)$_2$), $\delta 2.02$ and $\delta 2.05$ (6H, 2xs, 2xOAc), $\delta 3.66$ (3H, s, CO$_2$Me) and $\delta 5.93$ (1H, d, J 8Hz, 6β-H). A noteable downfield shift of one of the isopropylidene methyl resonances and the 6β-methine resonance occurred owing to the acetylation of the 6α-hydroxy group. Accurate mass measurements could not detect a molecular ion at m/e 434. However, a peak at m/e 374.2457 was observed and corresponded to the loss of CH$_3$COOH from the molecular ion which is not an uncommon fragmentation for allylic acetates.

Photolysis of 4,4-dimethyl-5β,6β-epoxy-oestran-17β-ol-3-one(32B) in methanol

The photolysis of the β-epoxide (32B) in methanol behaved essentially the same as that of the α-epoxide, the only difference being the photolysis time necessary for maximum reaction (see however p.21). The major product isolated by preparative t.l.c. was the methyl ester (50B) in 48% yield as an oil, having ν_{max} 1740cm^{-1} (C=O) and 3460cm^{-1} (br. O-H). The 60MHz ^{1}H n.m.r. spectrum had important peaks at δ0.71 and δ0.98 (6H, 2xd, J 7Hz, CH($\underline{Me}$)$_2$), δ3.17 (1H, d, J 3Hz, 6α-H) and δ3.66 (3H, s, CO$_2$Me). In the mass spectrum the molecular ion was evident at m/e 350 which fragmented by loss of 43 $\left[(Me)_2CH\right]$ to the base peak at m/e 307, and other fragment-ations are shown in the scheme below.

$$M^+ \; m/e \; 350 \xrightarrow[-43]{-(Me)_2CH} m/e \; 307 \xrightarrow[-32]{-MeOH} m/e \; 275$$

$$m/e \; 350 \xrightarrow[\quad]{-32 \quad -MeOH} m/e \; 318 \xrightarrow[-43]{-(Me)_2CH} m/e \; 275$$

$$M^+ \; m/e \; 350 \xrightarrow[-C_3H_6]{-42} m/e \; 308 \xrightarrow[-15]{-Me} m/e \; 293$$
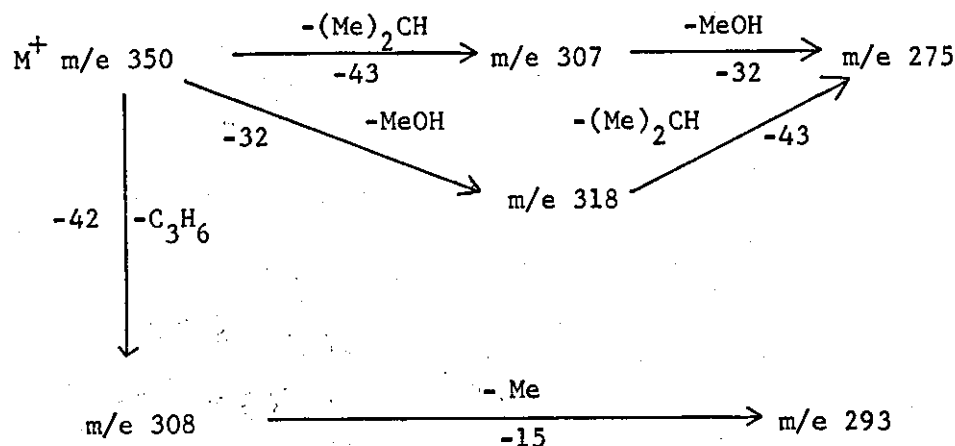
A peak at m/e 293 can be explained by the consecutive loss of 42(C_3H_6) and 15(Me) from the molecular ion, although a significant peak at m/e 308 was not observed.

Hydrolysis of the ester in methanolic potassium hydroxide solution gave the corresponding acid (51B).

A second fraction was mainly unreacted starting material (32B) which contained a small amount of the aldehyde (52B), detected in the ^{1}H n.m.r. spectrum by a low field multiplet (W½ 3Hz) at δ9.65. Extensive chromatography, however, failed to isolate the aldehyde and it eventually

decomposed, presumably owing to aerial oxidation.
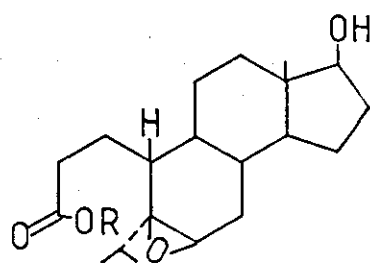
(50B) R=Me
(51B) R=H
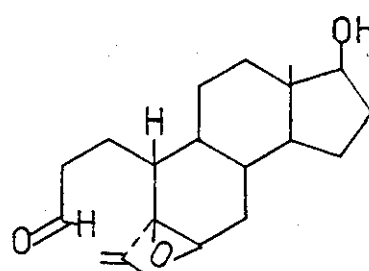
(52B)

Initial experiments on the photolysis of the β-epoxide (32B) in methanol did not give the methyl ester (50B). The major product was in fact the lactone (55A) in 38% yield, having carbonyl ($1715 cm^{-1}$) and hydroxyl (br. $3480 cm^{-1}$) bands in the infrared spectrum. The 90MHz ^1H n.m.r. spectrum had peaks at δ1.08 and δ1.16 (6H, 2xs in $CDCl_3$, 2xd in $DMSOd_6$, J 7Hz, CH($\underline{Me}$)$_2$), δ2.49 (1H, t, J 8Hz, C-2axial H) and δ4.06 (1H, m, W½ 7Hz, 6α-H). The high resolution accurate mass spectrum indicated a molecular ion at m/e 336.2304.

Other measured peaks are given in table II below.

Table II

m/e	molecular formula
336.2304	$C_{20}H_{32}O_4$
318.2198	$C_{20}H_{30}O_3$
293.1756	$C_{17}H_{25}O_4$
275.1648	$C_{17}H_{23}O_3$
257.1543	$C_{17}H_{21}O_2$
247.1700	$C_{16}H_{23}O_2$
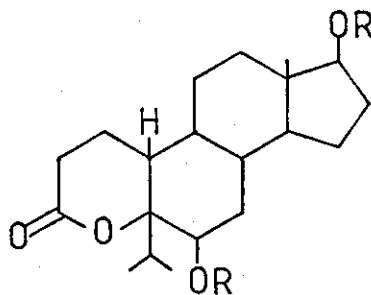
(55A)   R=H
(55B)   R=Ac

Peaks at m/e 239 and m/e 229, although not measured, could arise from the loss of $18(H_2O)$ from m/e 257 and m/e 247 respectively. Metastable peaks at m/e 258.1, m/e 240.2, and m/e 222.3 confirm the following fragmentations

$$293 \longrightarrow 275 \ (-H_2O)$$

$$275 \longrightarrow 257 \ (-H_2O)$$

$$257 \longrightarrow 239 \ (-H_2O)$$
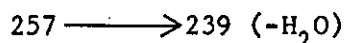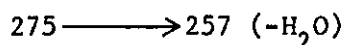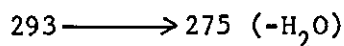
The lactone (55A) could not be reduced with sodium borohydride. Lithium aluminium hydride, however, reduced it to a very polar material (56), which, when acetylated, gave a triacetate (57). Compound (57) still contained an alcohol function (v_{max} br. $3540cm^{-1}$) together with carbonyl (v_{max} $1740cm^{-1}$) and C-O (v_{max} $1250cm^{-1}$) groups. The ^1H n.m.r. spectrum showed important peaks at $\delta 0.91$ and $\delta 0.94$ (6H, 2xd, J 7Hz, CH(<u>Me</u>)$_2$), $\delta 2.02$ (9H, 3xs, 3xOAc), $\delta 3.98$ (2H, t, J 6Hz, C<u>H</u>$_2$OAc), and $\delta 4.85$ (1H, m, W½ 4Hz, 6α-H). The mass spectrum had a molecular ion at m/e 466, in accordance with the molecular formula, which fragmented by loss of 43 $\left[(Me)_2CH \right]$ to m/e 423. This further fragmented by three consecutive losses of 60(MeCOOH) to m/e 363, m/e 303 and m/e 243, with metastable peaks respectively at m/e 311.5, m/e 252.9 and m/e 194.9 confirming these fragmentations.

Photolysis of 4,4-dimethyl-5ξ,6ξ-epoxy-oestran-17β-ol-3-ones(32) in ether

The photolysis of the α-epoxide in ether required several hours for

complete reaction of starting material and gave a complex mixture from

which no one product could be isolated and identified. The spectra of the

crude product gave little indication as to possible structural assignments

although a faint carbonyl peak in the infrared spectrum was observed.

On the other hand, the β-epoxide under the same conditions of photolysis

gave mostly unreacted starting material after preparative t.l.c., plus

a second fraction which turned out to be a complex mixture. When

photolysed for a comparatively long period in an attempt to remove all the

starting material only a very complex mixture was obtained from which

again no one product could be isolated and identified. The relatively long

photolysis time required for complete reaction of the β-epoxide is

interesting, especially since the photolysis in methanol also required a

relatively long period of photolysis compared to that of the α-epoxide.

Photolysis of 4,4-dimethyl-5α,6α-epoxy-oestran-17β-ol-3-one(32A) in benzene

The photolysis of the α-epoxide in benzene over seven hours gave a mixture, which, when chromatographed on silica gel, gave several fractions, all mixtures, only one of which could be identified by its [1]H n.m.r. spectrum as a mixture of the starting material (32A) and the aldehyde (52A), previously observed in the methanol photolysis of (32A). Chromatography failed to separate the two compounds. The mixture was treated with 2,4-dinitrophenylhydrazine and conc. hydrochloric acid in ethanol in an attempt to obtain a mixture of 2,4-dinitrophenylhydrazones which would be stable and separable by t.l.c. When chromatographed on silica gel a compound having an isopropylidene group (by [1]H n.m.r.) was obtained. The epoxide ring had opened as indicated by the absence of the 6β-methine doublet, and the absence of signals owing to the terminal olefinic protons was also noted. A broad singlet at $\delta 4.15$ appeared. The compound was not further investigated.

The photolysis was repeated for ten hours, the crude mixture chromatographed and the fraction containing aldehyde treated with sodium borohydride giving a mixture which was chromatographed on silica gel eluting with chloroform. However, no one fraction was obtained in sufficient quantity for a true identification. The epoxide ring, however, appeared again to have opened up. It was not further investigated.

Photolysis of 4,4-dimethyl-5β,6β-epoxy-oestran-17β-ol-3-one(32B) in benzene

The photolysis of the β-epoxide in benzene gave a highly complex mixture

from which the keto-aldehyde (58) was isolated by preparative t.l.c. in

8% yield.

(58)
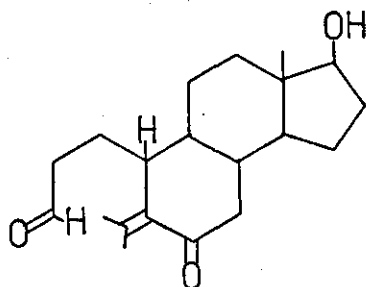
Compound (58) had ν_{max} 1608cm^{-1} (C=C), 1678cm^{-1} (α,β-unsaturated C=O),

1725cm^{-1} (C=O) and 3440cm^{-1} (O-H). The 60MHz ^{1}H n.m.r. spectrum had important

peaks at δ1.75 and δ1.86 (6H, 2xs, C=C(Me)$_2$) and δ9.62 (1H, m, W½ 3Hz,

CHO). The high resolution accurate mass spectrum had a molecular ion peak

at m/e 318.2215 ($C_{20}H_{30}O_3$) for which fragmentations are shown below:

$$M^+ \; m/e \; 318 \xrightarrow[-15]{-Me} m/e \; 303 \xrightarrow[-18]{-H_2O} m/e \; 285$$

-18(H₂O)   -15(Me)

m/e 300

-28(CO)

m/e 290

-30(CH₂O)

m/e 288

-43(CH₂CHO)

m/e 275

-44(MeCHO)

m/e 274

-57((CH₂)₂CHO)

m/e 261
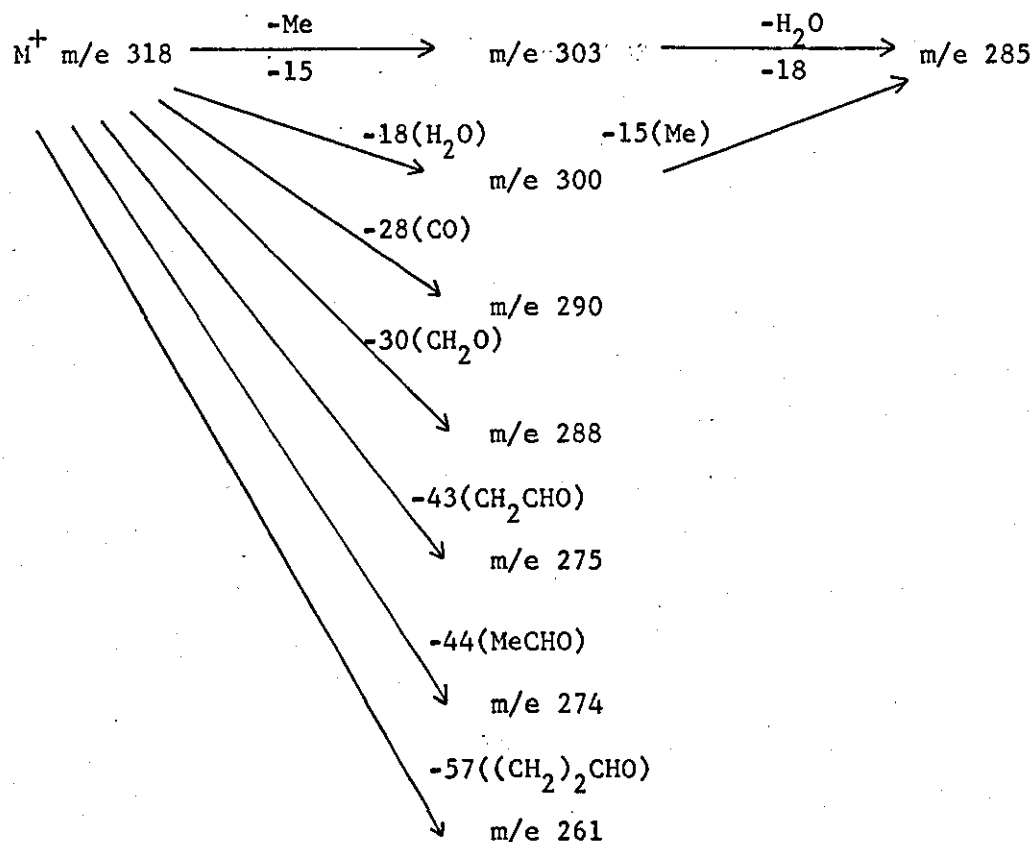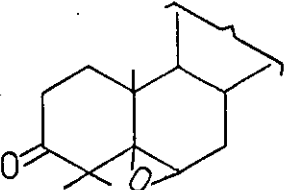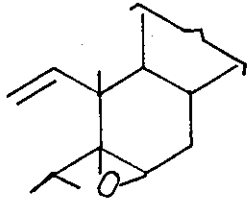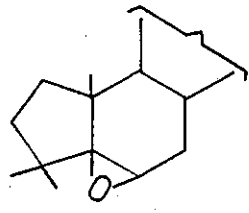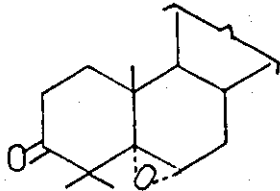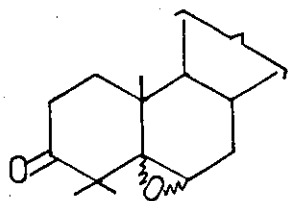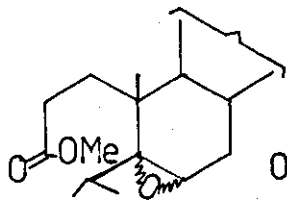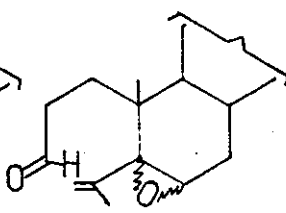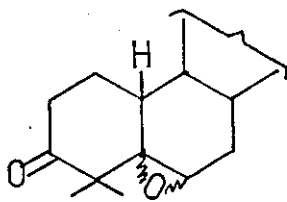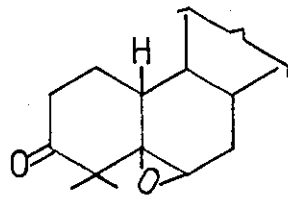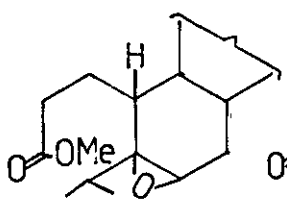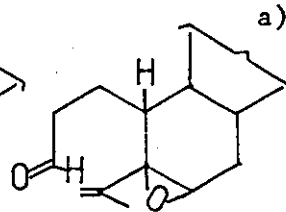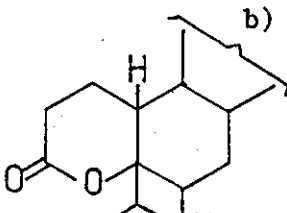
Table III summarises the results of photolysis so far:

Table III

REACTANT	SOLVENT	PRODUCTS

(21B) ether (26) (27)

(21A) ether no well defined products

(21) methanol (24) (25)

(32) ether no well defined products

(32B) methanol (50B) a) (52B) b) (55A)

Table III (cont.)

(32A)   methanol   (50A)

c)   c)

(52A)   (53)

a)

(32A)   benzene   (52A)

(32B)   benzene   (58)

KEY:

a)   detected only by ^{1}H n.m.r.

b)   detected only in contaminated methanol

c)   detected only in one photolysis

The oestranes (32A) and (32B) behave similarly to their cholestane
counterparts (see Introduction) when photolysed in methanol. Irradiation
in ether of either of the epimeric epoxides, however, gave such a complex
mixture that no one product could be isolated and identified. It may
be pointed out that t.l.c. indicated that the products were in general
more polar than the starting material and a large percentage of material
remained on the base line. If decarbonylation had occurred giving the
olefin (59) or the A-nor-epoxide (60) these compounds would be expected
to be significantly less polar than the starting material. No such
fraction was observed in any significant amount.

(59)   (60)
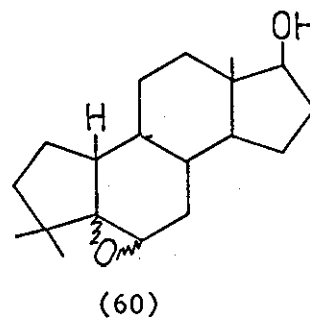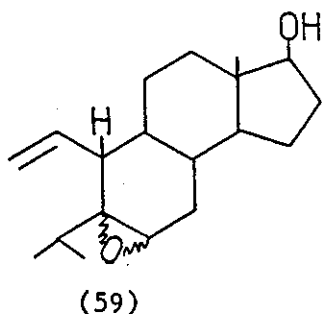
No evidence of epoxide involvement in the photochemical reaction was
observed. According to Murray's scheme the lactone (61) or the unsaturated
keto-aldehyde (58) may have been expected but neither of these compounds
was isolated.

(61)   (58)
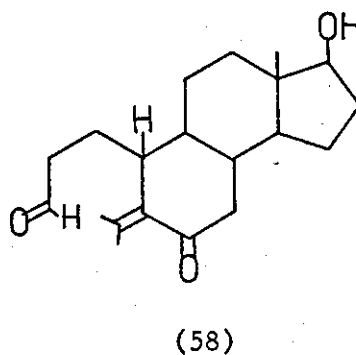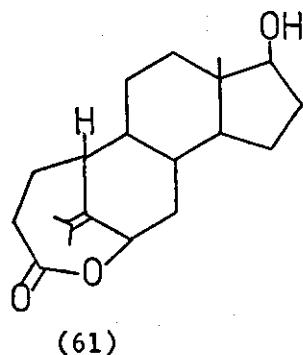
The mechanism of the rearrangement in methanol is probably identical to
that described by Imam and Marples for the cholestane series.
Initial irradiation causes a $n \rightarrow \pi^*$ transition of the n electrons of the
carbonyl group, resulting in a weakening of the C—C=O bond which cleaves

to give the most highly substituted, and hence the most stable, diradical intermediate. In fact Murray comments on the necessity for α-substitution during carbonyl photolysis to give a "rewarding" reaction.

(32)   (62)
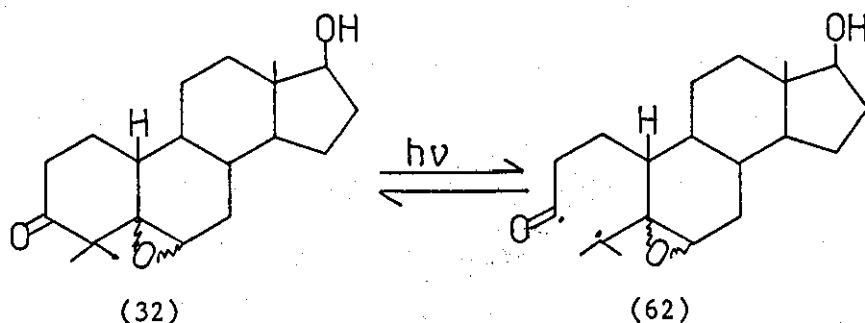
Diradical (62) then undergoes a 1,5-hydrogen transfer giving a ketene intermediate (63) from which the methyl ester (50) is derived via attack by methanol.

(62)   (63)   (50)
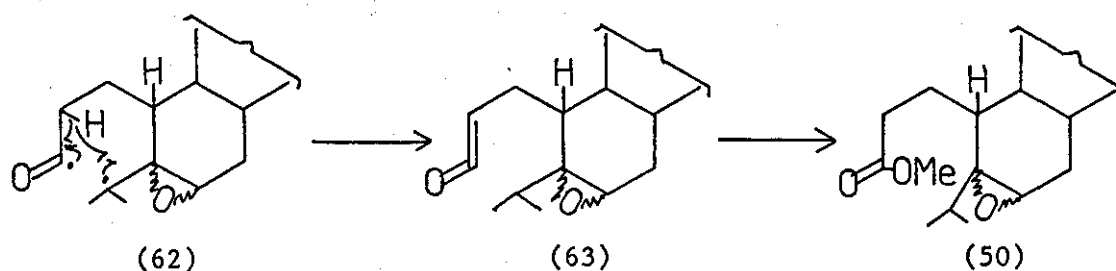
The unsaturated aldehyde (52) is obtained, presumably, via a 1,7-hydrogen shift.

(62)   (52)
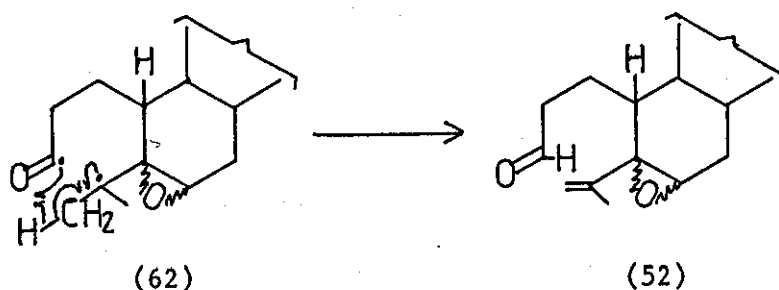
The unfortunate instability of the aldehydes precludes their ready characterisation. The isolation of the more stable allyl alcohol (53), however, was rather surprising, especially since the reaction could not be repeated and also since it was the only occasion when the aldehyde (52A) was isolated from methanol. A photochemical mechanism to account

for the allyl alcohol is not difficult to envisage.

If it is assumed that the methyl ester group, as normal, was formed via a ketene, then the hydrogen migration from the carbonyl radical probably did not proceed directly to the isopropyl radical as in (62) to (63). Rather an initial involvement of the epoxide moiety occurred giving an isopropylidene group and an alkoxy radical which then abstracted a hydrogen from the carbonyl radical (see below).

(62)

(53)
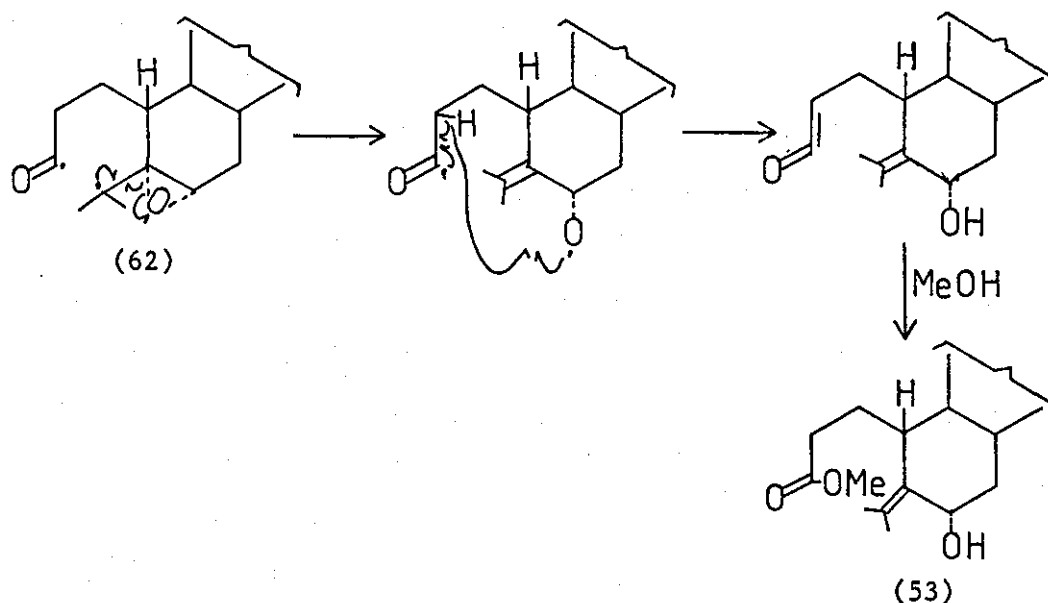
Such 1,6-hydrogen transfers are uncommon and if the alkoxy radical was involved it is intriguing to ask why it preferred this particular pathway to that described in Murray's scheme which would simply involve either ring-closure or a similar 1,6-hydrogen shift from C-6 to C-3.
Since the experiment could not be repeated the possibility of a non-photochemical pathway cannot be ruled out. For example, traces of acid (or base) could give rise to (53) either during the photolysis or on work-up.

(50A)   (53)
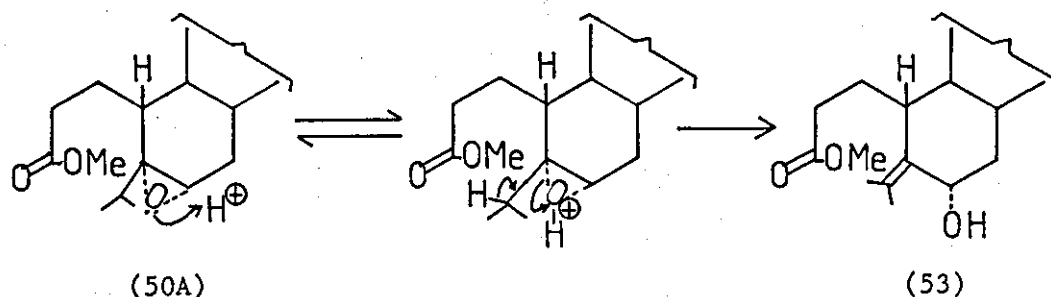
The importance of acid catalysis in some of these reactions was demonstrated by the isolation of the lactone (55A) from the β-epoxide (50B) (see page 21). It was established that treatment of the methyl ester (50B) with an anhydrous solution of hydrochloric acid in methanol gave the lactone (55A) as the major product. A mechanism for the formation of (55A) is shown in scheme VII.
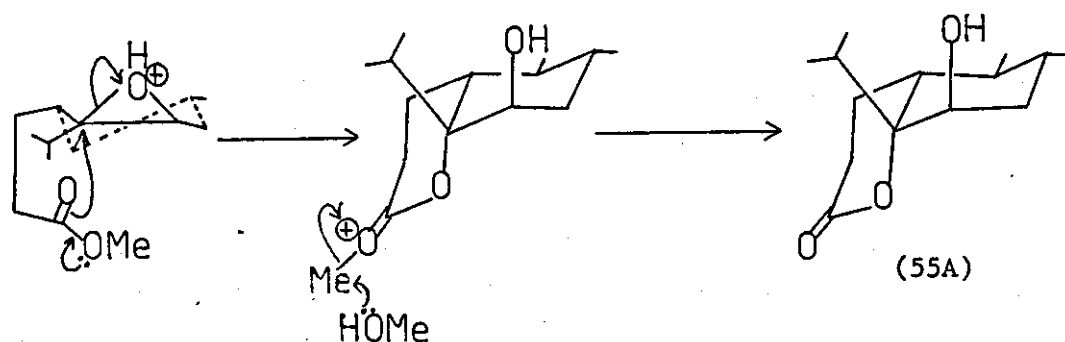
Scheme VII

The 5-isopropyl group is thought to have β-stereochemistry. The ester group would be expected to attack as shown giving diaxial opening of the epoxide.

A second compound, tentatively assigned the structure (64), was also isolated.

(64)
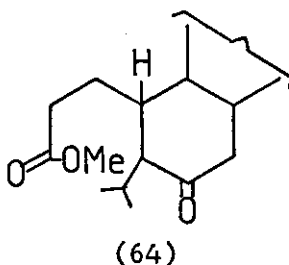
The most interesting photolysis, however, was that of the β-epoxide (32B) in benzene. A low yield (8%) of the unsaturated aldehydo-ketone (58) was obtained, whereas in contrast, the α-epoxide (32A) in benzene gave the aldehyde (52A) similar to that described in Imam's scheme. The results suggest that the configuration of the β-epoxide,compared to that of the α-epoxide, has a considerable influence over the photochemical pathway

which may be related to the ground state energy of the molecule. Further-
more the solvent also seems to play an important role in these
photolyses.

Inspection of models suggests that for both α- and β-epoxides, when the
initial C_{α}-C=O cleavage has occurred, a very simple conformational
rearrangement of the resultant isopropyl radical by twisting about the
C(4)-C(5) bond will bring the protons of the methyl groups within close
proximity of the carbonyl radical thus allowing hydrogen transfer. The
isolation of the aldehyde (52A) suggests that this does in fact occur.
An inspection of models also suggests that, in the case of the β-epoxide,
there is a competing photochemical process in which the epoxy-isopropyl
radical rearranges to an alkoxy- isopropylidene radical from which the
carbonyl radical can abstract the 6α-proton (see below).

(62B)   (58)
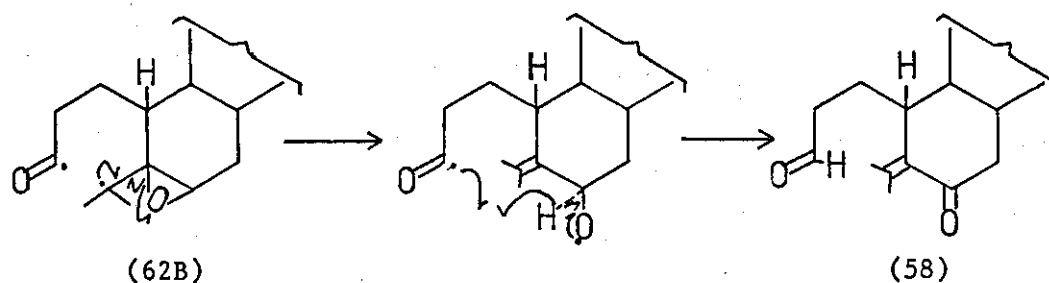
Cyclisation to a lactone is precluded owing to the trans-configuration
of the 10-substituent and the 6β-oxygen. Similar considerations indicate
that in the case of the α-epoxide a great deal of strain would ensue for
the carbonyl radical to conformationally rearrange into such a position
that abstraction of the 6β-proton was easy. Hence, in this case the
formation of the aldehyde (52A) is preferred, although the lactone (61)
is also a possible product.

Decarbonylation, on the other hand, which was observed in the β-epoxide
in the cholestane series, does not require conformational rearrangement
to bring the carbonyl radical within close proximity of any proton. For

this reason it would appear to be the favoured process except where very ready rearrangement can occur. Since there are no obvious differences in the configurations of the α- and β-epoxide no explanation can be forwarded to account for the differences in reactivity.

Formation of the ketene (giving methyl ester) also requires the abstraction of a proton from C-2 by the isopropyl radical. Other competing photochemical processes are probably involved and hence the initial proximity of the C-2 proton and the isopropyl radical, and the time taken for the conformational rearrangement to bring these close to each other are probably important factors, although the presence of methanol, driving the rearrangement process in the direction of the ketene, must also be considered.

Benzene is known to interact with carbonyl groups and it may be that stabilisation of the carbonyl in benzene occurs allowing it to arrange itself into its most favourable position for abstraction of the C-6α proton. As indicated, this of course cannot happen with the α-epoxide owing to the ring strain involved. It soon became apparent that an investigation of the photolyses in benzene of the 4,4-dimethyl-5,6-epoxy-cholestan-3-ones was necessary to determine whether or not benzene caused any difference. To recap, Imam observed that both epoxides in methanol gave mainly the methyl ester plus the aldehyde. In ether, the α-epoxide gave no well defined products, whereas the β-epoxide readily decarbonyl-ated giving an olefin and an A-nor epoxide. No involvement of the epoxide moiety in secondary photochemical reactions was observed.

Photolysis of 4,4-dimethyl-5,6α-epoxy-5α-cholestan-3-one (21A) in benzene

The epoxy-ketone was photolysed in benzene. The reaction was monitored by t.l.c. until all the starting material was removed. The photolysis gave a complex mixture of products. Separation by preparative t.l.c. was attempted but each fraction which was obtained from the t.l.c. plate was still a complex mixture. No one product could easily be isolated. However, the 60MHz ^{1}H n.m.r. spectra of the various impure fractions indicated that they did not appear to contain any of the following which may have been expected by analogy with the photolysis of the 19-nor-compounds.

(25A)   (30)

(65)   (66)   (29)
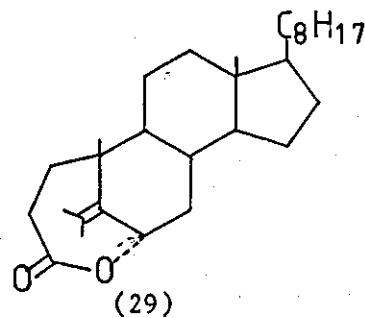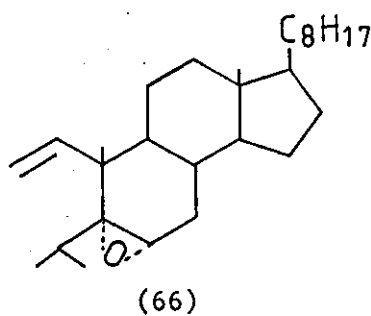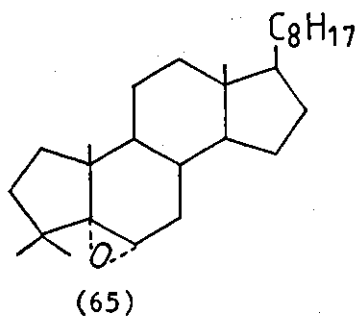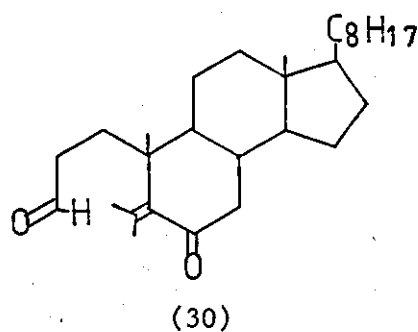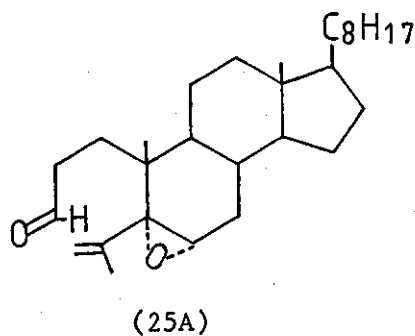
The aldehydes (25A) and (30) would be easily distinguished by their aldehydic protons at low field. In fact no aldehydic protons were detected. No 6β-methine doublets were observed which rules out compounds (65) and (66), and compound (66) would also have been easily distinguished by the ABX pattern of the olefinic protons. Compound (29) was also not present as inferred by the lack of signals at δ1.8 owing to the isopropylidene methyls.

The complexity of the fractions precluded any further identification. It would appear that in this case benzene does not have a particularly

significant effect over ether where a similarly complex result was
observed.

Photolysis of 4,4-dimethyl-5,6β-epoxy-5β-cholestan-3-one (21B) in benzene

The epoxy-ketone was photolysed in benzene and the reaction was monitored by t.l.c. until all the starting material was removed. As in the photolysis of the α-epoxide that of the β-epoxide gave a complex mixture of products. In this case the formation of a lactone is precluded owing to ring strain but the products of decarbonylation (26) and (27) and the aldehydes (25B) and (30) may still be expected.

(26)   (27)

(25B)   (30)
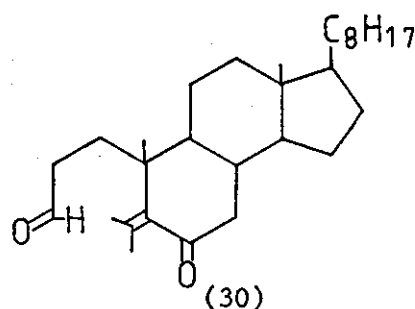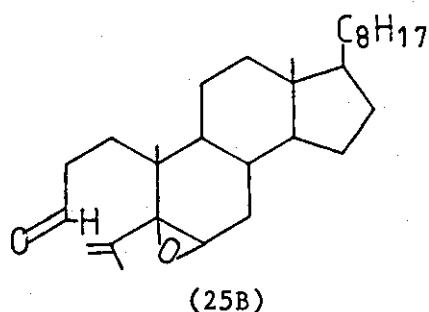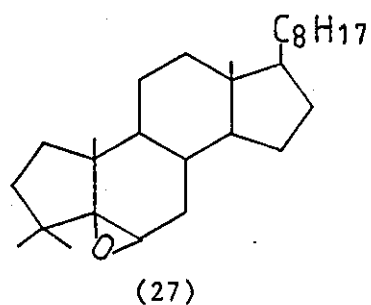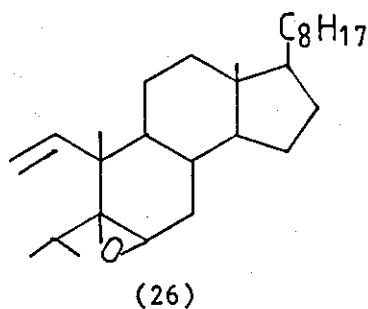
In fact the only product isolated in 8% yield was the aldehyde (25B)[8]. The 60MHz ^{1}H n.m.r. spectrum had important peaks at δ9.57 (1H, m, $W_{\frac{1}{2}}$ 5Hz, CHO), δ4.86 and δ4.80 (2H, 2xm, $W_{\frac{1}{2}}$ 4Hz, C=CH$_2$), δ3.18 (1H, m, $W_{\frac{1}{2}}$ 4Hz, 6α-H) and δ1.94 (3H, s, C=CMe). The 60MHz ^{1}H n.m.r. spectrum of the 2,4-dinitrophenylhydrazone of (25B) had δ3.2 (1H, m, $W_{\frac{1}{2}}$ 4Hz, 6α-H), δ4.86 (2H, d, Jgem 4Hz, C=CH$_2$) and δ7.85 and δ8.99 (aromatic protons). Although weak, a molecular ion peak at m/e 608 in the mass spectrum, in accordance with the molecular weight of the 2,4-dinitrophenylhydrazone, was observed. Fragmentation to m/e 425 occurred, probably owing to loss of $C_6H_5N_3O_4$, and a peak at m/e 410 occurred probably owing to loss of $C_6H_6N_4O_4$. Loss of H_2O from m/e 410 gave m/e 392 whereas loss of CO gave m/e 382.

The remaining t.l.c. fractions of the photolysis mixture were still complex mixtures. However, it may be pointed out that the three other possibilities envisaged were not present. Compounds (26) and (27), known from previous photolyses in ether, were not present, nor was any aldehyde other than (25B).

It appears that the photolyses are markedly dependant on a) solvent

b) epoxide configuration c) the presence of the 10-Me group.

a) With regard to the photolyses of the epoxy cholestanes (21A) and (21B), and the epoxy oestranes (32A) and (32B) in ether and benzene, it seems evident that a solvent effect is in operation. In both ether and benzene (21A) gave a highly complex mixture from which no one photoproduct could be identified. On the other hand, (21B) in ether gave products of photodecarbonylation (26) and (27), whereas in benzene the aldehyde (25B) was obtained as a result of a 1,7-hydrogen migration.

Similarly, the compounds (32A) and (32B) in ether gave complex mixtures, whereas in benzene, (32A) gave aldehyde (52A) as a result of a 1,7-hydrogen migration, and (32B) gave aldehyde (58) as a result of a 1,6-hydrogen migration accompanied by ring-opening of the epoxide moiety. Benzene is known to interact with carbonyl groups in solution[20] and it may be that some stability is conferred on the acyl radical by a similar interaction preventing decarbonylation in preference to hydrogen migrations. This, however, is speculative and requires further investigation.

b) There appear to be differing reactivities depending on the configuration of the epoxide moiety.

In ether (21A) gave a complex mixture whereas (21B) gave products of photodecarbonylation (26) and (27). In benzene (21A) again gave a complex mixture whereas (21B) gave aldehyde (25B).

Similarly, although in ether both (32A) and (32B) gave complex mixtures, in benzene (32A) gave aldehyde (52A) and (32B) gave aldehyde (58).

In the case of (32A) and (32B) a similar photoreactivity was observed in ether since both isomers gave complex mixtures, and in the case of the benzene photolysis, the aldehyde (58) which was produced from (32B) can, in fact, not be formed from (32A) since the acyl radical cannot position itself for ready abstraction of the 6β-hydrogen. In methanol the

reactivities are similar for compounds (32) as well as (21). However, the
differences in reactivity between (21A) and (21B) in ether and benzene
are not so easy to explain.

c) Differences in reactivity are also apparent when the α- or β-isomers
of the 10-Me and 19-nor compounds are compared in the same solvents.
Although reactivities are similar in methanol and both (21A) and (32A)
in ether behave similarly, (21B) in ether gave products of photodecarbonyl-
ation (26) and (27) whereas, in contrast, (32B) gave a complex mixture.
Similarly, in benzene (21A) gave a complex mixture, whereas (32A) gave
aldehyde (52A), and (21B) gave aldehyde (25B), whereas (32B) gave aldehyde
(58).

The differences in reactivity between similar isomers of the 10-Me and
19-nor compounds may arise as a result of the aforementioned differences
in the configuration of the A and B rings. However, since there are also
differences in reactivity between each particular isomer in each series
(19-nor or cholestane) this is obviously not the only factor involved.
No clear pattern emerges at this stage and it is apparent that additional
factors to those already discussed are involved. Murray's scheme appears
therefore to apply only for relatively simple molecules where
conformational mobility is reasonably high. The importance of conformation-
al mobility is implied in some of Murray's work. An inspection of models
suggests that contrary to Murray's opinion (19) is capable through
conformational rearrangement of the diradical species (19A) of forming
a lactone (19B).
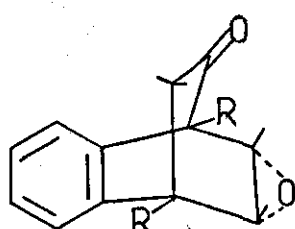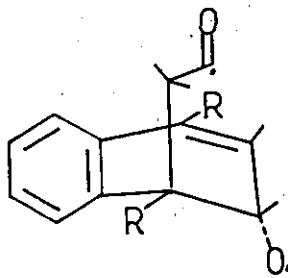
(19)   (19A)
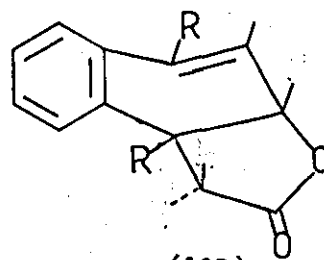
(19B)

EXPERIMENTAL

Solutions were dried over anhydrous magnesium sulphate and solvents were removed in vacuo on a rotary evaporator. Plates (0.75mm. thick) of Kieselgel PF 254 (Merck) or Camag alumina were used for preparative t.l.c. Infrared spectra were determined with a Perkin-Elmer 177 spectrophotometer. Proton nuclear magnetic resonance spectra were determined for solutions in deuteriochloroform at 60MHz with a Varian EM 360A, or at 90MHz with a Perkin-Elmer R32 spectrometer. Carbon-13 nuclear magnetic resonance spectra were determined on both Bruker WP80 and Jeol FX90Q spectrometers. Low resolution mass spectra were recorded with an A.E.I. MS12 spectrometer. Rotations were measured for solutions in chloroform with a Bendix polarimeter 143C. Accurate mass measurements were determined at the Physico-Chemical Measurements Unit on a Kratos AEI MS 50 spectrometer and elemental analyses at the University of Manchester. Photolyses were carried out using a Hanovia medium pressure mercury vapour lamp. Solutions were degassed by bubbling nitrogen through for half an hour and the system purged with nitrogen for half an hour before photolyses were begun.

Oestradiol-3-methyl ether (35)

Oestradiol (5g) was dissolved in methanol (400cm^3), cooled to 0°C and an ethereal solution of diazomethane (10 mole excess) added. The yellow solution was allowed to stand at room temperature overnight, then the solvent removed in vacuo yielding a white crystalline solid which was chromatographed on grade 3 alumina (300g). Elution with benzene gave oestradiol-3-methyl ether (4.75g), (90%). m.p. 118-21°C (lit.[13]m.p.120.5 -121.5^{o}C).

1,4-Dihydrooestradiol-3-methyl ether (36)

Ammonia (82cm^3) was condensed in a 250cm^3 round bottomed flask surrounded by a cardice-acetone bath and fitted with a mechanical stirrer, gas inlet tube, dropping funnel and cardice-acetone condenser. Isopropyl alcohol (28cm^3) was added followed by a solution of oestradiol-3-methyl ether (5g, 0.017 moles) in dry tetrahydrofuran (32cm^3). Sodium (4.56g, 0.19 moles) was added in portions to the well stirred mixture, then the cardice-acetone bath removed and stirring continued for a further 1.5 hours. Methanol (23cm^3) was added and the ammonia allowed to bubble off. The apparatus was flushed with nitrogen, and water (132cm^3) added slowly. A white precipitate was extracted into chloroform, the organic layer dried and evaporated in vacuo giving a white crystalline solid. Recrystallisation from ethanol, 60:80 pet.-ether gave 1,4-dihydrooestra-diol-3-methyl ether (4.1g) (82%). m.p. 112-18°C (lit.[13]m.p. 118-119.5^{o}C).

17β-Hydroxyoestr-4-en-3-one (47)

1,4-Dihydrooestradiol-3-methyl ether (3.5g) was dissolved in methanol (190cm^3) and warmed to 60-70°C. Dilute hydrochloric acid (150cm^3) was added over five minutes. The temperature of 60-70°C was maintained for a further twenty minutes, then the mixture allowed to stand at room temperature overnight. The excess methanol was removed in vacuo, the

residue taken up in chloroform, washed with saturated sodium bicarbonate solution and brine, the organic layer dried and evaporated in vacuo yielding an oil. Recrystallisation from ether gave 17β-hydroxyoestr-4-en-3-one (2.25g) (68%). m.p. 122-8°C (lit.[13] m.p. 123.8-124.6°C).

4,4-Dimethyl-17β-hydroxyoestr-5-en-3-one (48)

Potassium (3.16g, 0.081 moles) was dissolved in dry t.-butyl alcohol (150cm^3) under nitrogen. A solution of 17β-hydroxyoestr-4-en-3-one (7.27g, 0.026 moles) in dry t.-butyl alcohol (50cm^3) was added. The resultant orange solution was stirred for ten minutes, then methyl iodide (10cm^3, 0.16 moles) was added and the mixture stirred at room temperature for a further four hours, during which time a white precipitate was deposited. Water was added. The excess t.-butyl alcohol was removed in vacuo and the residue extracted with ether. The combined ether extracts were washed with water, dried and evaporated in vacuo to a white crystalline solid. Purification by preparative t.l.c. on silica gel, eluting five times with 50% ether, 50% 40:60 pet.-ether followed by recrystallisation from ether, 40:60 pet.-ether gave 4,4-dimethyl-17β-hydroxyoestr-5-en-3-one (5.09g) (63%) m.p. 151-3°C (lit.[19] m.p. 149.5-150°C.).

4,4-Dimethyl-5α,6α-epoxy-oestran-17β-ol-3-one (32A)

4,4-Dimethyl-17β-hydroxyoestr-5-en-3-one (0.4g, 1.32 mmoles) was dissolved in chloroform (3cm^3) and ether (10cm^3) and cooled to 0°C. Ethereal monoperphthalic acid solution (6.6 mmoles) was added and the solution was allowed to stand in the refrigerator overnight. It was washed successively with water, saturated sodium bicarbonate solution and water, then the organic phase dried and evaporated in vacuo to a white crystalline solid. Recrystallisation from ether, 40:60 pet.-ether gave 4,4-dimethyl-5α,6α-epoxy-oestran-17β-ol-3-one (318mg) (75%) m.p. 183-8°C. Two further recrystallisations from acetone/cyclohexane raised the melting

point to 187-8°C. $[\alpha]_D$ -14.7°(c 4.0) ν_{max} 1719cm^{-1} (C=0), 3510cm^{-1} (O-H), δ0.75 (s, 13β-Me), δ0.88 (s, 4α-Me), δ1.28 (s, 4β-Me), δ3.14 (d, J 5Hz, 6β-H), δ3.65 (t, J 8Hz, 17α-H). M$^+$ 318. Base peak m/e 123. (Found C, 75.5; H, 9.8 $C_{20}H_{30}O_3$ requires C, 75.43; H, 9.49%).

4,4-Dimethyl-5β,6β-epoxy-oestran-17β-ol-3-one (32B)

4,4-Dimethyl-17β-hydroxyoestr-5-en-3-one (0.5g, 1.82 mmoles) was dissolved in dichloromethane (2cm^3), t.-butyl alcohol (14cm^3) and water (2cm^3) and the stirred mixture cooled to 0°C. Perchloric acid (2cm^3 from 0.43cm^3 60% perchloric acid in 40cm^3 water) was added followed by N-bromo-succinimide (0.59g, 3.65 mmoles) and the mixture stirred for fifteen minutes at 0°C. An aqueous solution of sodium sulphate containing sodium metabisulphite was added, the mixture extracted with dichloromethane, the organic layer washed with water, dried and evaporated in vacuo to a pale yellow oil. The yellow oil was dissolved in absolute ethanol (350cm^3) containing potassium acetate (8g) and the solution heated under reflux for two and a half hours. It was allowed to cool, the excess ethanol removed in vacuo, water added to the residue and extracted with chloroform. The chloroform layer was dried and evaporated in vacuo giving a yellow oil.

The oil was purified by preparative t.l.c. eluting in 15% 40:60 pet.-ether, 85% ether. Recrystallisation from acetone/cyclohexane gave 4,4-dimethyl-5β,6β-epoxy-oestran-17β-ol-3-one (230mg) (44%) m.p. 186-8°C $[\alpha]_D$ +19.6°(c 2.68) ν_{max} 1700cm^{-1} (C=0), 3500cm^{-1} (O-H), δ0.75 (s, 13β-Me), δ1.02 (s,4β-Me), δ1.1 (s, 4α-Me), δ3.18 (d, J 3Hz, 6α-H), δ3.65 (t, J 8Hz, 17α-H). M$^+$ 318. Base peak m/e 123. (Found C, 75.3; H, 9.8 $C_{20}H_{30}O_3$ requires C, 75.43; H, 9.49%).

Photolysis of 4,4-dimethyl-5α,6α-epoxy-oestran-17β-ol-3-one(32A)in methanol

4,4-Dimethyl-5α,6α-epoxy-oestran-17β-ol-3-one (270mg) was photolysed in

dry methanol (600cm^3) for seven and a half hours. The methanol was removed in vacuo and the residual mixture separated by preparative t.l.c. eluting three times in 30% 40:60 pet.-ether, 70% ether. The major band (166mg) (56%) was the methyl ester methyl 5α,6α-epoxy-5β-isopropyl-A-nor-3,5-seco-oestran-17β-ol-3-oate, (50A), an oil, having $\left[\alpha\right]_D$ +2.4° (c 1.02), v_{max} 1740cm^{-1} (ester C=O), 3450cm^{-1} (O-H), δ0.72 (s, 13β-Me), δ0.71 (d, J 7Hz, isopropyl Me), δ0.98 (d, J 7Hz, isopropyl Me), δ2.93 (d, J 6Hz, 6β-H), δ3.63 (t, J 8Hz, 17α-H), δ3.67 (s, CO$_2$Me). M$^+$ 350. Base peak m/e 307.

Hydrolysis in 10% methanolic potassium hydroxide solution gave the corresponding acid m.p. 177-80°C. (ethyl acetate). δ0.66 (s, 13β-Me), δ0.69 (d, J 7Hz, isopropyl Me), δ0.97 (d, J 7Hz, isopropyl Me), δ2.89 (d, J 5Hz, 6β-H), δ3.51 (t, J 8Hz, 17α-H). (Found C, 71.7; H, 10.1 $C_{20}H_{32}O_4$ requires C, 71.4; H, 9.6%).

In one experiment the aldehyde 5α,6α-epoxy-17β-hydroxy-5β-isopropenyl-A-nor-3,5-seco-oestran-3-al (52A), was isolated (30mg) (11%) having v_{max} (KBr) 1640cm^{-1} (C=C), 1725cm^{-1} (C=O), 3460cm^{-1} (br. O-H), δ0.73 (s, 13β-Me), δ1.8 (s, Me-C=C), δ2.76 (d, J 6Hz, 6β-H), δ3.64 (t, J 8Hz, 17α-H), δ4.86 and δ5.05 (2xm, W½ 5Hz, H$_2$C=C), δ9.72 (m, W½ 3Hz, CHO). M$^+$ 318. Base peak m/e 83.

In the same experiment the allyl alcohol methyl 6α-hydroxy-5-isopropyl-idene-A-nor-3,5-seco-oestran-17β-ol-3-oate (53), was also isolated (40mg) (13%) having v_{max} 1725cm^{-1} (ester C=O), 3430cm^{-1} (br. O-H), δ0.71 (s, 13β-Me), δ1.7 and δ1.75 (2xs, (Me)$_2$C=C), δ3.64 (t, J 8Hz, 17α-H), δ3.65 (s, CO$_2$Me), δ4.86 (d, J 9Hz, 6β-H). M$^+$ 350. Base peak m/e 83.

Acetylation in the normal manner gave the corresponding diacetate (54) having δ0.78 (s, 13β-Me), δ1.69 and δ1.82 (2xs, (Me)$_2$C=C), δ2.02 and δ2.05 (2xs, acetate Me's), δ3.66 (s, CO$_2$Me), δ4.6 (t, J 7Hz, 17α-H), δ5.93 (d, J 4Hz, 6β-H). (Found 374.2452 $C_{23}H_{34}O_4$ (M$^+$-MeCO$_2$H) requires

374.2457 and 404.2568 $C_{24}H_{36}O_5$ (M^+-HCHO) requires 404.2563).

Photolysis of 4,4-dimethyl-5β,6β-epoxy-oestran-17β-ol-3-one (32B) in methanol

4,4-Dimethyl-5β,6β-epoxy-oestran-17β-ol-3-one (400mg) was photolysed in dry methanol (700cm³) for thirteen hours. The methanol was removed in vacuo and the residual mixture separated by preparative t.l.c. eluting in 95% ether, 5% chloroform. The main fraction (210mg) (48%) was the methyl ester methyl 5β,6β-epoxy-5α-isopropyl-A-nor-3,5-seco-oestran-17β-ol-3-oate (50B), an oil, $[\alpha]_D$ +21.4° (c 6), ν_{max} 1740cm⁻¹ (ester C=O), 3460cm⁻¹ (br. O-H), δ0.71 (d, J 7Hz, isopropyl Me), δ0.98 (d, J 7Hz, isopropyl Me), δ0.74 (s, 13β-Me), δ3.17 (d, J 3Hz, 6α-H), δ3.56 (t, J 8Hz, 17α-H), δ3.66 (s, CO_2Me). M^+ 350. Base peak m/e 307.

Hydrolysis in 10% methanolic potassium hydroxide solution gave the corresponding acid (51B) m.p. 253-4°C. (ethyl acetate) M^+ 336. Base peak m/e 293. (Found 293.1746 $C_{17}H_{25}O_4$ (M^+-C_3H_7) requires 293.1746).

A second fraction (173mg) (43%) was mainly unphotolysed starting material containing a small amount of the aldehyde 5β,6β-epoxy-17β-hydroxy-5α-isopropenyl-A-nor-3,5-seco-oestran-3-al (52B). However, extensive chromatography failed to separate the pure aldehyde.

Photolysis of 4,4-dimethyl-5β,6β-epoxy-oestran-17β-ol-3-one (32B) in contaminated methanol

4,4-Dimethyl-5β,6β-epoxy-oestran-17β-ol-3-one (420mg) was photolysed in dry methanol (1dm³) for seven and a half hours. The methanol was removed in vacuo and the residual mixture separated by preparative t.l.c. eluting in 30% 40:60 pet.-ether, 70% ether three times. The major band (170mg) (38%) was the A-ring lactone 6β,17β-dihydroxy-5-isopropyl-5β-4-oxaoestran-3-one (55A) m.p. 255-7°C. (acetone/cyclohexane), ν_{max} (CHCl₃) 1715cm⁻¹ (C=O), 3480cm⁻¹ (br. O-H), δ0.77 (s, 13β-Me), δ1.08 and δ1.16 (2xs,

isopropyl Me's), δ2.49 (t, J 8Hz, 2-H), δ3.67 (t, J 8Hz, 17α-H), δ4.06 (m, W½ 7Hz, 6α-H). M$^+$ 336. Base peak m/e 293. M* 240.2 (275-257), 258.1 (293-275), 222.3 (257-239). (Found 336.2304 $C_{20}H_{32}O_4$ requires 336.2300 (Found C, 71.8; H, 9.9 $C_{20}H_{32}O_4$ requires C, 71.39; H, 9.58%).

Acetylation of 6β,17β-dihydroxy-5-isopropyl-5β-4-oxaoestran-3-one (55A)

The lactone (40mg) was dissolved in a mixture of acetic anhydride (1cm^3) and benzene (1cm^3) and 60% perchloric acid (1 drop) added. It was allowed to stand at room temperature for forty eight hours, then diluted with ether, washed successively with saturated sodium bicarbonate solution and water, dried and evaporated in vacuo to a brown oil (19mg) (38%) ν_{max} 1740cm^{-1} (C=O), δ0.83 (s, 13β-Me), δ1.01 (d, J 7Hz, isopropyl Me), δ1.04 (d, J 7Hz, isopropyl Me), δ2.03 and δ2.08 (2xs, acetate Me's), δ4.61 (t, J 8Hz, 17α-H), δ5.1 (m, W½ 6Hz, 6α-H). M$^+$ 420. Base peak m/e 275.

Reduction of 6β,17β-dihydroxy-5-isopropyl-5β-4-oxaoestran-3-one (55A)

A. With sodium borohydride.

The lactone (5mg) in absolute ethanol (0.5cm^3) was treated with an excess of sodium borohydride and allowed to stand at room temperature for four hours. Acetic acid (1 drop) was added, followed by water and extraction with ether. The ether extract was dried and evaporated in vacuo giving white crystals of Rf value and infrared spectrum identical to the original starting material.

B. With lithium aluminium hydride.

The lactone (30mg) was dissolved in freshly dried tetrahydrofuran (3cm^3) and excess lithium aluminium hydride added under nitrogen. The mixture was heated under reflux for four hours, acetic acid added, followed by water and extraction with ether. The ether extract was dried and evaporated in vacuo to an oil which was acetylated in the usual way,

giving the tri-acetate (57), having v_{max} 1740cm^{-1} (C=O), 3540cm^{-1} (O-H),

δ0.82 (s, 13β-Me), δ0.91 and δ0.94 (2xd, J 7Hz, isopropyl Me's), δ2.02

(3xs, acetate Me's), δ3.98 (t, J 6Hz, C$\underline{H}_2$OCOMe), δ4.55 (t, J 7Hz, 17α-H),

δ4.85 (m, W$\frac{1}{2}$ 4Hz, 6α-H). M$^{\dot+}$ 466. Base peak m/e 303.

466-423 (43) (Me)$_2$CH   243-225 (18) H$_2$O

M* 311.5 (423-363 MeCOOH)   M* 252.9 (363-303 MeCOOH)

M* 194.9 (303-243 MeCOOH)

6β,17β-Dihydroxy-5-isopropyl-5β-4-oxaoestran-3-one (55A)

A solution of acetyl chloride (2 drops) in dry methanol (2cm^3) was

prepared. This solution (2 drops) was added to a solution of methyl 5β,

6β-epoxy-5α-isopropyl-A-nor-3,5-seco-oestran-17β-ol-3-oate (50B) (40mg)in

dry methanol (1cm^3) and allowed to stand in a stoppered vessel in a

dessicator for three days. It was diluted with ether, washed with water,

the ether layer dried and evaporated in vacuo to a colourless oil (35mg).

Preparative t.l.c. eluting in ether gave 6β,17β-dihydroxy-5-isopropyl-

5β-4-oxaoestran-3-one (7mg) (18%) having infrared, proton nuclear

magnetic resonance and mass spectra identical to the sample obtained by

photolysis. The Rf value of 0.15 was also identical.

A second product having Rf 0.32 was also isolated, and was thought to be

methyl 5β-isopropyl-6-oxo-A-nor-3,5-seco-oestran-17β-ol-3-oate (64)

(14mg) (35%) having v_{max} 1710cm^{-1} (C=O), 1740cm^{-1} (C=O), 3450cm^{-1} (br.

O-H), δ0.79 (s, 13β-Me), δ0.95 and δ1.05 (2xd, J 6Hz, isopropyl Me's),

δ3.66 (s, ester Me). M$^{\dot+}$ 350. Base peak m/e 263. M* 197.6 (350-263)

(MeCO$_2$(CH$_2$)$_2$).

Photolysis of 4,4-dimethyl-5β,6β-epoxy-oestran-17β-ol-3-one(32B)in benzene

4,4-Dimethyl-5β,6β-epoxy-oestran-17β-ol-3-one (100mg) was photolysed

in dry benzene (130cm^3) for six and a half hours. The benzene was

removed in vacuo and the residue purified by preparative t.l.c eluting

in 75% ether, 25% 40:60 pet.-ether. Chromatography of the major band on alumina eluting in chloroform gave 17β-hydroxy-5-isopropylidene-6-oxo-A-nor-3,5-seco-oestran-3-al (58) (8mg) (8%) having ν_{max} 1608cm^{-1} (C=C), 1678cm^{-1} (α,β-unsaturated C=O), 1725cm^{-1} (aldehydic C=O), 2733cm^{-1} (aldehydic C-H), 3440cm^{-1} (O-H), λ_{max} 252nm. (ε 3867), δ0.79 (s, 13β-Me), δ1.75 and δ1.86 (2xs, C=C(Me)$_2$), δ3.65 (t, J 8Hz, 17β-H), δ9.62 (m, W½ 3Hz, CHO). (Found 318.2215 $C_{20}H_{30}O_3$ requires 318.2187).

Photolysis of 4,4-dimethyl-5β,6β-epoxy-cholestan-3-one (21B) in benzene

4,4-Dimethyl-5β,6β-epoxy-cholestan-3-one (150mg) was photolysed in dry benzene (130cm^3) for two and a half hours. The benzene was removed in vacuo. Extensive chromatography of the residue eluting in 20% ether, 80% 60:80 pet.-ether gave 5β,6β-epoxy-5α-isopropenyl-A-nor-3,5-seco-cholestan-3-al[8] (25B) (12mg) (8%), δ0.64 (s, 13β-Me), δ1.11 (s, 10β-Me), δ0.81 and δ0.90 (side chain methyls), δ1.94 (s, C=CMe), δ3.18 (m, W½ 4Hz, 6α-H), δ4.8 and δ4.86 (2xm, W½ 4Hz, C=CH$_2$), δ9.57 (m, W½ 5Hz, CHO). The 2,4-dinitrophenyl-hydrazone had m.p. 210-14°C. (CHCl$_3$/EtOH). M$^+$ 608. Fragmentations 608-425 ($C_6H_3(NO_2)_2NH_2$), 608-410 ($C_6H_3(NO_2)_2NHNH_2$), 410-392 (H_2O), 410-382 (CO) were observed.

PART TWO. Rearrangement of 3,5-epoxy steroids.

INTRODUCTION

The boron trifluoride catalysed rearrangement of 5,6-epoxides containing electron withdrawing substituents at C-3 has been well studied[21-27]. As early as 1957, Henbest and Wrigley[21] studied the effects of boron trifluoride etherate on 3β-acetoxy-5,6α-epoxy-5α-cholestane (67), and reported the isolation of a fluorohydrin (68A) as major product (60-75%) together with starting material and a polar fraction which was not further examined.

(67)   (68A)
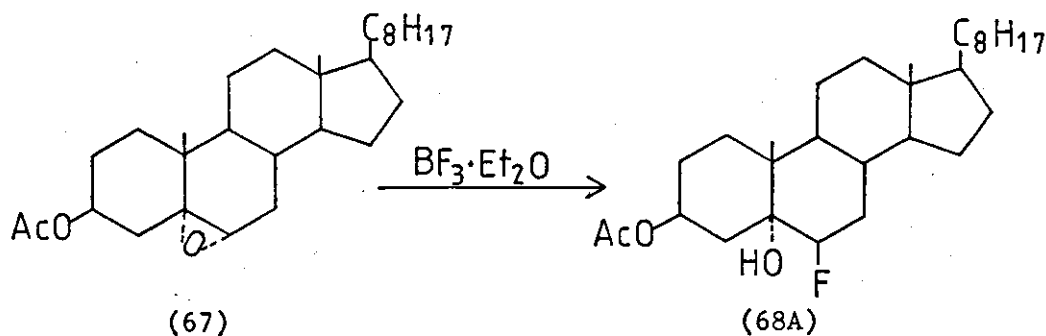
In 1966 Blunt, Hartshorn and Kirk[22] re-examined this reaction in an attempt to identify the unknown polar fraction. Not only did they identify the polar fraction as the rearranged dimer (69) in 10% yield, but they also found that the use of purified boron trifluoride etherate considerably reduced the yield of fluorohydrin (68A) and increased the yield of dimer (69) to 32%.

(69)
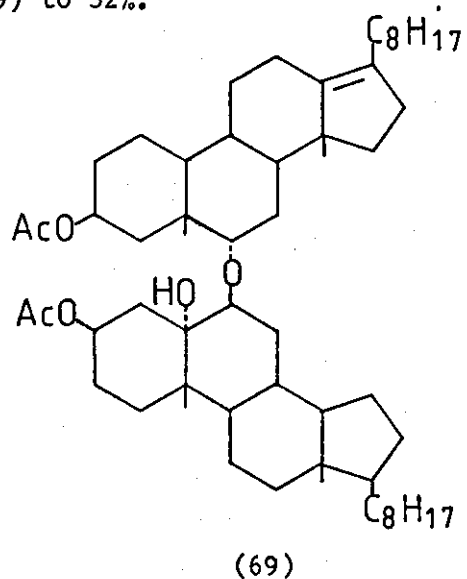
They conclude that in order for boron trifluoride etherate to exert its full Lewis acid potential it must be distilled free of fluoroboric acid prior to use. The fluorohydrin therefore, is not strictly the product of a Lewis acid rearrangement in so far as residual fluoride ions trap the first formed carbonium ion giving a stable product which will not easily rearrange further under the conditions of the reaction. In 1958, Bowers and Ringold[23] examined the effect of boron trifluoride etherate on an ether-benzene solution of cholesterol α-epoxide (70) and again isolated a fluorohydrin (68B) in high yield (65%) presumably owing to the use of boron trifluoride etherate containing fluoroboric acid.

(70)   (68B)
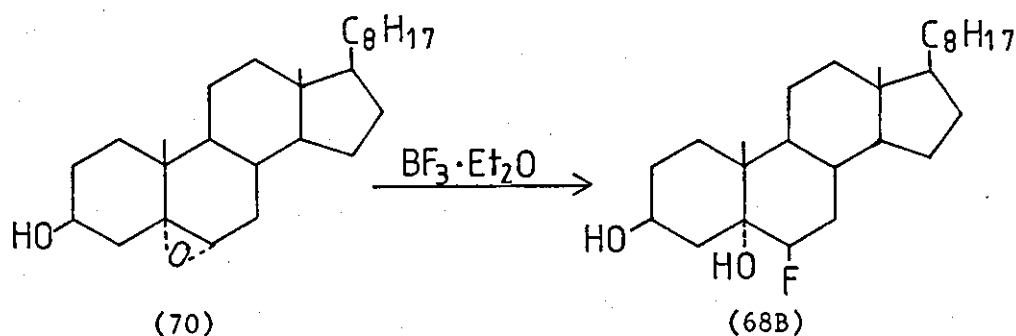
In fact, they later determined that an increase in fluoroboric acid concentration (as added HF) caused an enhancement in the yield of the fluorohydrin[24].

In 1969 Coxon, Hartshorn and Muir[25] studied the effect, in benzene, of boron trifluoride etherate on the 5,6-epoxides of epicholesterol (71A and 71B) and epicholesteryl acetate (71C).

(71)   A R=H,   5β,6β
               B R=H,   5α,6α
               C R=Ac, 5β,6β
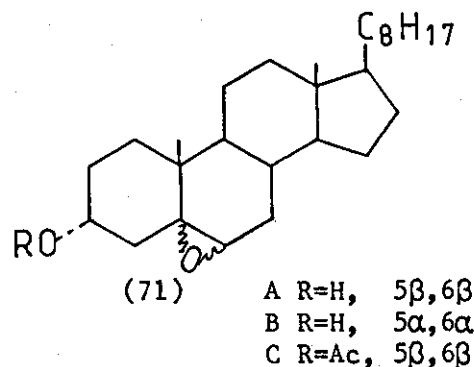
Compound (71A) on treatment with boron trifluoride etherate gave a

$3\alpha,10\alpha$-epoxide (72A) (28%), together with starting material (71A) (7%), a 6-ketone (73A) (19%) and a backbone rearranged product (74A) (36%). Prolonged treatment gave the backbone rearranged product (74A) (41%) and a Δ^9-olefin (75A) (22%) presumably by further rearrangement of the 3,10-epoxide (72A).

Compound (71B) on treatment with boron trifluoride etherate in benzene also gave a $3\alpha,10\alpha$-epoxide (72B) (13%) together with a fluorohydrin (76) (47%), a 6-ketone (73B) (14%) and a backbone rearranged product (74B) (10%). Again, treatment of the $3\alpha,10\alpha$-epoxide (72B) gave the backbone rearranged product (74B).

Compound (71C) with boron trifluoride etherate in methylene chloride gave a 5α-acetate (77) as sole product resulting from hydrolysis of a $3\alpha,5\alpha$-acetoxonium ion intermediate (78).

(72)   A 6βOH
        B 6αOH

(73)   A 5αH, 3αOH
        B 5βH, 3αOH
        C 5αH, 3βOH
        D 5βH, 3βOH

(74)   A 3αOH, 6βOH
        B 3αOH, 6αOH
        C 3βOH, 6αOH
        D 3βOH, 6βOH

(75)   A 3αOH, 6βOH
        B 3βOH, 6αOH

(76)

$$71C \longrightarrow (78) \longrightarrow (77)$$
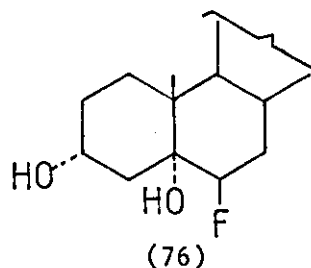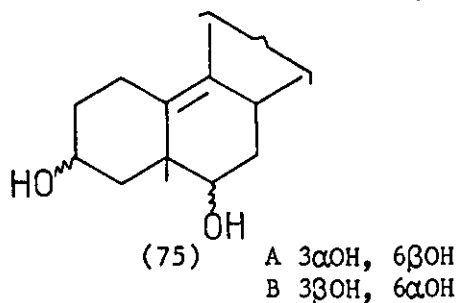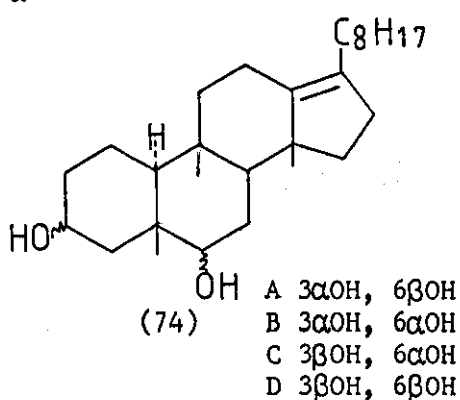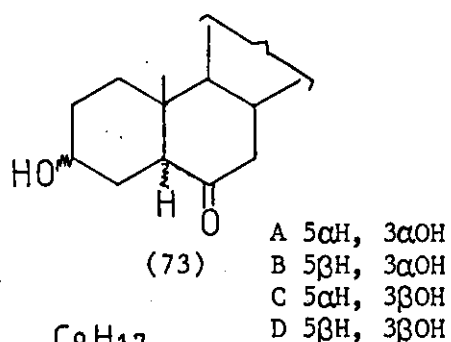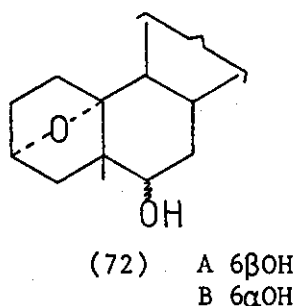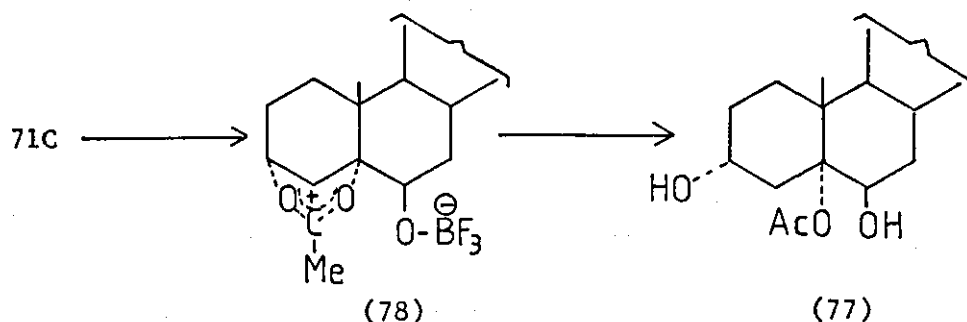
"An increase in the electronegativety of the substituent at C-3 suppresses the C-5 carbonium ion character resulting in preferential C(6)-O bond cleavage." This statement is generally accepted and appears to be correct except where specific stabilisation of a C-5 carbonium ion can occur, for example, via an acetoxonium ion intermediate. Guest and Marples[26] re-examined the action of boron trifluoride etherate on cholesterol-α-epoxide. Their results differed markedly from those of Bowers and Ringold in that they only isolated a 2% yield of the fluoro-hydrin (68B). Several other products were isolated from the reaction mixture and were identified as 3β-hydroxy-5α-cholestan-6-one (73C) (4.5%), 3β-hydroxy-5β-cholestan-6-one (73D) (11%), a backbone rearranged product (74C) (10%), a Δ^9-olefin (75B) (7%) and a second backbone rearranged product (74D) (17%).

Whereas Bowers and Ringold carried out their reaction in mixtures of ether and benzene, Guest and Marples used boron trifluoride etherate solely in benzene. This considerably increases the Lewis acid nature of the boron trifluoride by effectively releasing it from the bound ether ligand. Guest and Marples[26,27] compared the action of boron trifluoride etherate in a series of 5,6-epoxides containing different electron withdrawing substituents (OAc, OH, OMe) at the 3β-position. The results showed that a change from -OMe to -OH to -OAc progressively suppressed BF$_3$-catalysed C(5)-O cleavage. A comparison[27] was drawn between 3β-substituted 5,6-epoxides of pregnane and/or androstane with cholestane and it was suggested

that the electronegativety not only of the C-3 substituent but also of
the C-17 substituent has a considerable effect on the epoxide cleavage.
An increase in the electronegativety of the C-17 substituent destabilises
the build up of positive charge at C-5 which is involved in the C(5)-0
cleavage. Although there has been extensive work on 5,6-epoxides, and
this is briefly reviewed above, there have been few similar studies of
the rearrangements of steroidal 3,5- or 5,7-epoxides, which should be
similarly susceptible to Lewis acid catalysed cleavage and rearrangement.
The action of boron trifluoride etherate on 3α,5-epoxy-5α-cholestane (79)
was reported by Clayton, Henbest and Smith[28] in 1957 to give epicholesterol
(80) presumably via a C-5 carbonium ion and loss of a proton from C-6.
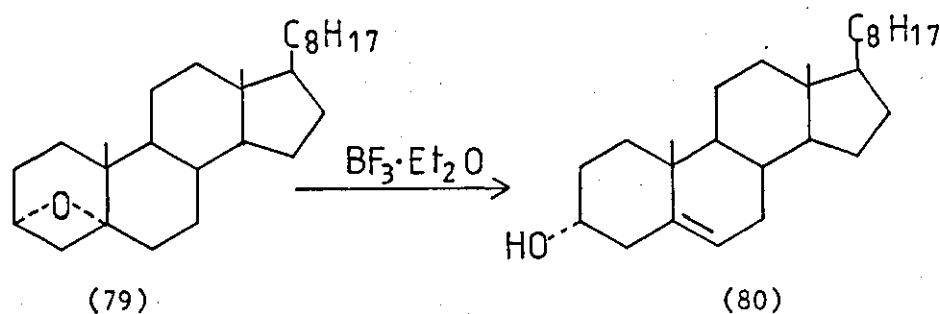
However, the 3β,5-epoxy-5β-cholestan-6-one (81B) was found by Rowland[29]
to be unreactive towards boron trifluoride etherate and the 6α-acetate
(82A) and its trifluoroacetoxy analogue (82B) were reported to be un-
reactive towards a number of acidic reagents.
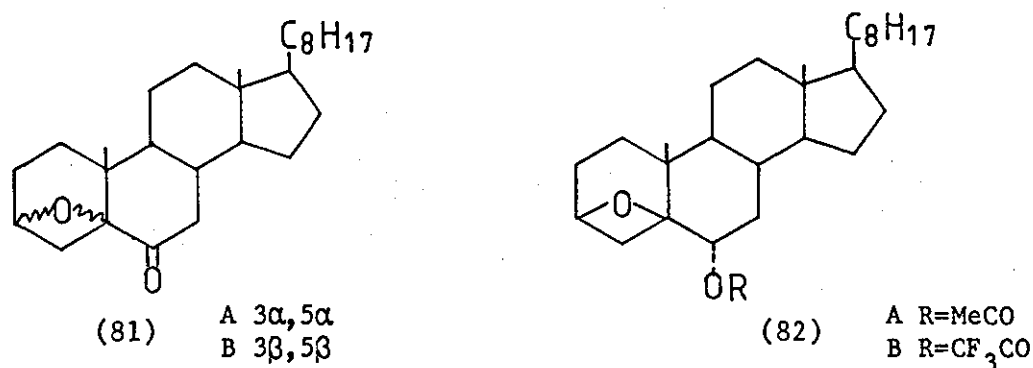
This lack of reactivity was ascribed by Rowland to the configuration of
the 3β,5β-epoxide bridge. Since it has already been shown that destabil-
isation of a carbonium ion can result from electronegative substituents,

we decided to investigate this further. Accordingly, we have investigated

the boron trifluoride etherate catalysed rearrangement of the 6β-acetoxy-

3α,5-epoxide (83A) and its 3β,5β-epimer (83B).

(83)   A 3α,5α
       B 3β,5β
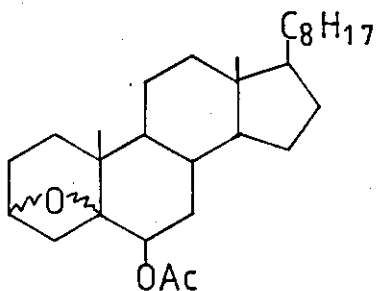
Also following our interest in epoxy-ketones it was intended to examine

the photolysis of epoxy-ketones (81) (see Part III).

RESULTS AND DISCUSSION

Preparation of 6β-acetoxy-3α,5-epoxy-5α-cholestane (83A)

6β-Acetoxy-3α,5-epoxy-5α-cholestane (83A) was prepared from cholesterol according to scheme VIII.

Tosylation of cholesterol with p-toluenesulphonyl chloride in pyridine gave cholesteryl tosylate (84)[30]. Treatment of (84) with ethereal mono-perphthalic acid gave the isomeric 5,6-epoxides (85)[31], which, when treated with 60% perchloric acid in methyl ethyl ketone gave 5,6β-dihydroxy-5α-cholesteryl tosylate (86)[32]. Compound (86) underwent ring-closure to the 3α,5α-epoxide (87A)[33] when treated with two equivalents of potassium t.-butoxide, and acetylation of (87A) with acetic anhydride in pyridine gave (83A)[33] in 77% yield after one recrystallisation from methanol.
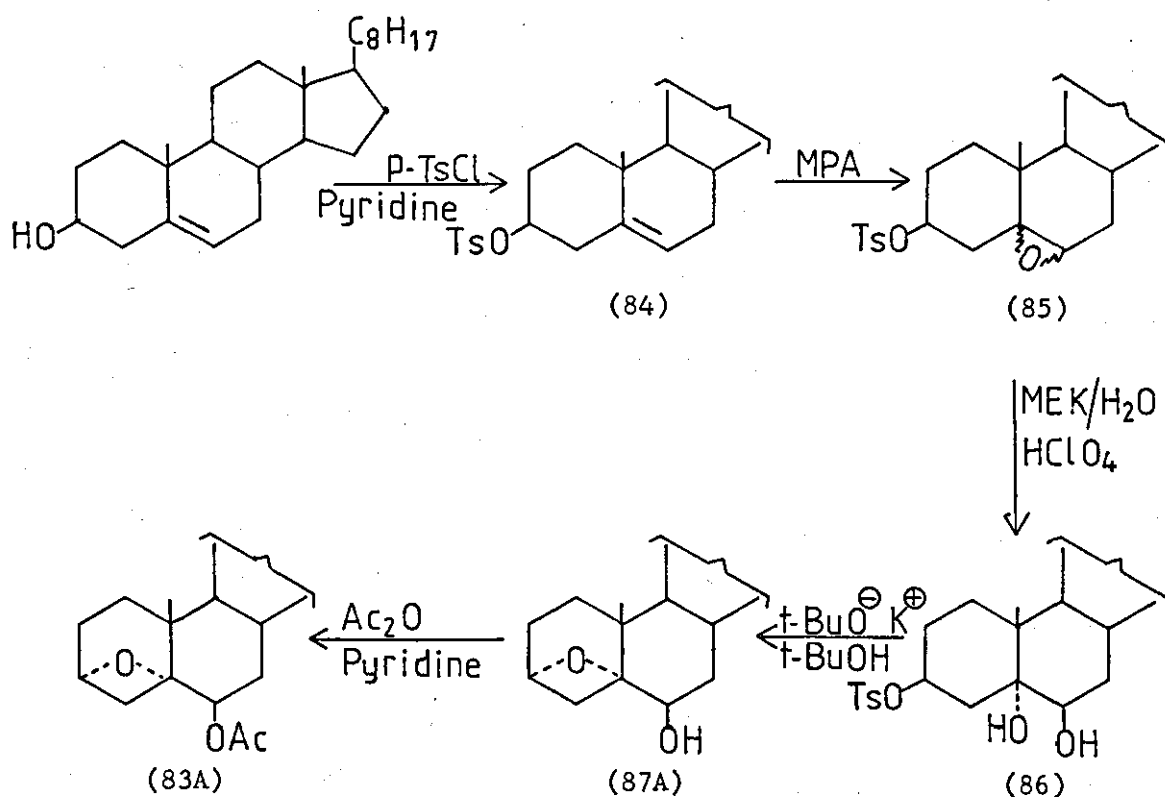
Scheme VIII

The structure of a by-product from the ring-closure of (86) will be discussed in Part IV.

Compound (83A) had v_{max} 1750cm^{-1} (ester C=O) and 1250cm^{-1} (C-O). The 60MHz ^{1}H n.m.r. spectrum had important peaks at δ5.0 (1H, m, W½ 4Hz, 6α-H),

$\delta 4.47$ (1H, d, J 7Hz, 3β-H), $\delta 2.58$ (1H, q, J_{vic}(3β) 7Hz, J_{gem}(4β) 9Hz, 4α-H) and $\delta 1.74$ (1H, d, J_{gem}(4α) 9Hz, 4β-H).

Fragmentations of the molecular ion at m/e 444 in the mass spectrum are given below:
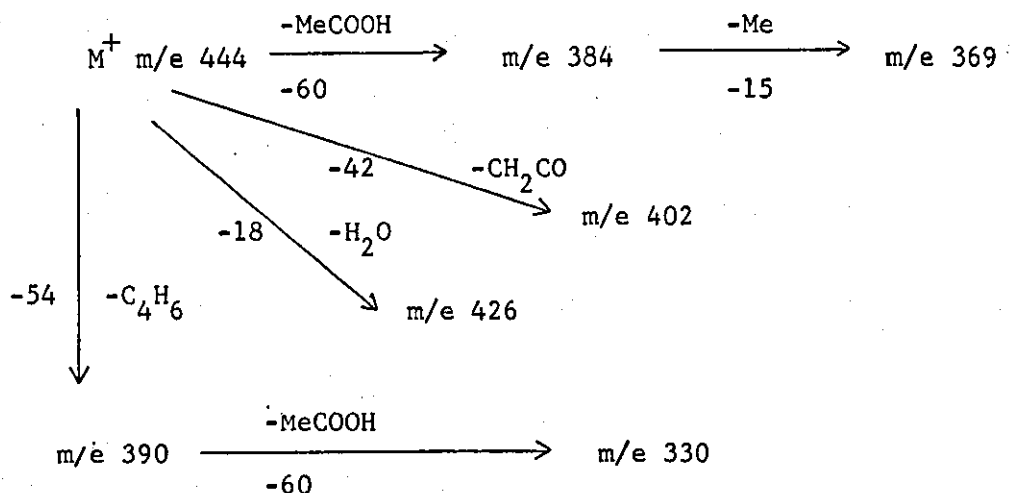
The loss of 54 (C_4H_6) from the molecular ion can be explained as indicated below. It is suggested that the C(3)-O bond cleaves initially and is followed by the migration of a hydrogen to the oxygen radical. The final loss of C_4H_6 by cleavage of the C(1)-C(10) and C(4)-C(5) bonds is a retro Diels-Alder reaction.
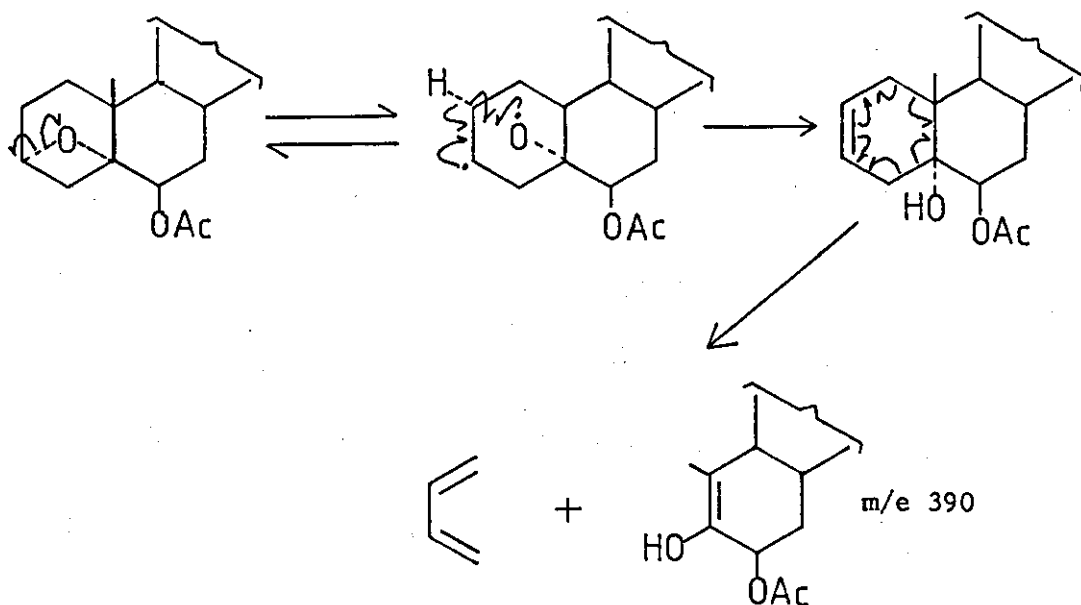
Reaction of 6β-acetoxy-3α,5-epoxy-5α-cholestane (83A) with boron trifluoride diethyl etherate

We have investigated the boron trifluoride-catalysed rearrangement of 6β-acetoxy-3α,5-epoxy-5α-cholestane (83A). Treatment of a benzene solution of (83A) with boron trifluoride etherate at room temperature for fifteen minutes revealed a variety of products of which several have been isolated and identified. The pure products were isolated by preparative t.l.c. on silica gel and identified by spectroscopic analysis together with, in some cases, their unambiguous synthesis.

The major and most polar product (88) was isolated in 26% yield. Its infrared spectrum had characteristic ester carbonyl (1740cm^{-1}) and hydroxyl (br. 3400cm^{-1}) bands. The 60MHz ^{1}H n.m.r. spectrum had important peaks at δ2.08 (3H, s, MeCO$_2$), δ4.69 (1H, m, W½ 5Hz, 6α-H) and δ3.95 (1H, m, W½ 20Hz, 3β-H). The mass spectrum confirmed a molecular weight of 462 and on this basis the structure (88) was tentatively assigned.

(88)
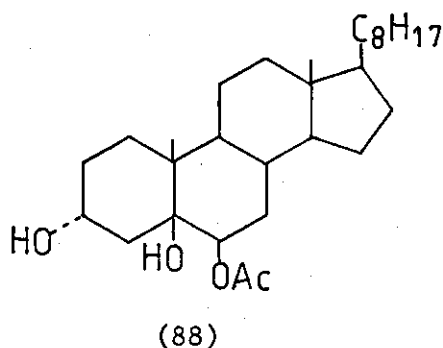
The mass spectral fragmentations were in agreement with this assignment and were as follows, although the molecular ion was barely discernable.
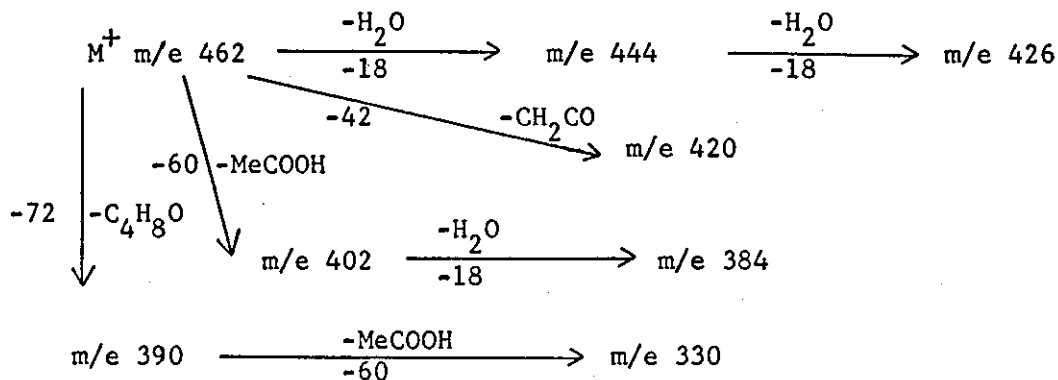
A metastable peak at m/e 279.2 confirmed the loss of CH_3COOH from m/e 290 and a metastable peak at m/e 349.8 confirmed the loss of CH_3COOH from m/e 462.

Acetylation of (88) gave a diacetate (89). The 60MHz ^1H n.m.r. spectrum of (89) was similar to that of (88) and differed only in the extra peak at $\delta 1.98$ owing to the additional acetate function, together with a shift in the broad 3β-methine multiplet at $\delta 3.95$ by 1.02p.p.m. downfield. The infrared spectrum continued to show a hydroxyl absorption ($3480cm^{-1}$) and the ester carbonyl stretching frequencies were readily apparent at $1735cm^{-1}$. The molecular weight was confirmed by the mass spectrum which showed a molecular ion at m/e 504. The diacetate (89) was an oil and could not be readily crystallised. The 3,5-dinitrobenzoate of (88) however, was a solid m.p. 156-8°C. Its ^1H n.m.r. and infrared spectra were in accordance with the expected structure and confirmation of the molecular formula was gained from elemental analysis.

Successive oxidation and dehydration of the acetoxy-diol (88) gave an α,β-unsaturated ketone (90)[34] (Scheme IX) and the unambiguous synthesis of (90) gave final confirmation of the structure (88). Oxidation of compound (88) in acetone with Jones reagent gave (91) having v_{max} $1710cm^{-1}$ (ketone C=O), $1750cm^{-1}$ (ester C=O) and $3450cm^{-1}$ (O-H). The 60MHz ^1H n.m.r. spectrum had important peaks at $\delta 4.65$ (1H, m, W$\frac{1}{2}$ 5Hz, 6α-H) and $\delta 2.79$ (1H, d, J_{gem}(4β) 15Hz, 4α-H). The mass spectrum confirmed a molecular weight of 460 and loss of CH_3COOH from the molecular ion gave the base peak at m/e 400. Finally, dehydration of (91) in pyridine and thionyl chloride gave (90). The infrared spectrum had characteristic ester carbonyl ($1740cm^{-1}$) and α,β-unsaturated carbonyl ($1683cm^{-1}$) bands, and showed no O-H absorption. The 60MHz ^1H n.m.r. spectrum had important peaks at $\delta 5.38$ (1H, m, W$\frac{1}{2}$ 5Hz, 6α-H), $\delta 5.9$ (1H, s, 4-H) and $\delta 1.29$ (3H, s, 10β-Me). Again, the mass spectrum confirmed the molecular weight. A molecular ion peak at m/e 442 fragmented to the base peak at m/e 400 by loss of CH_2CO and a metastable

peak at m/e 361.99 confirmed this fragmentation.
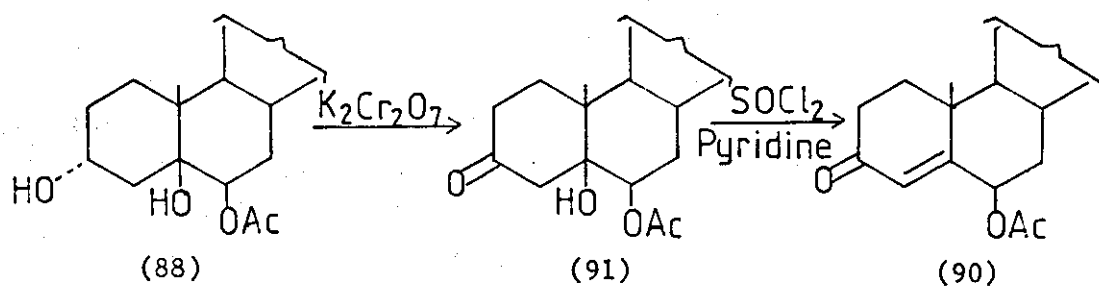
Scheme IX

Compound (90) was prepared unambiguously by the following route (Scheme X)
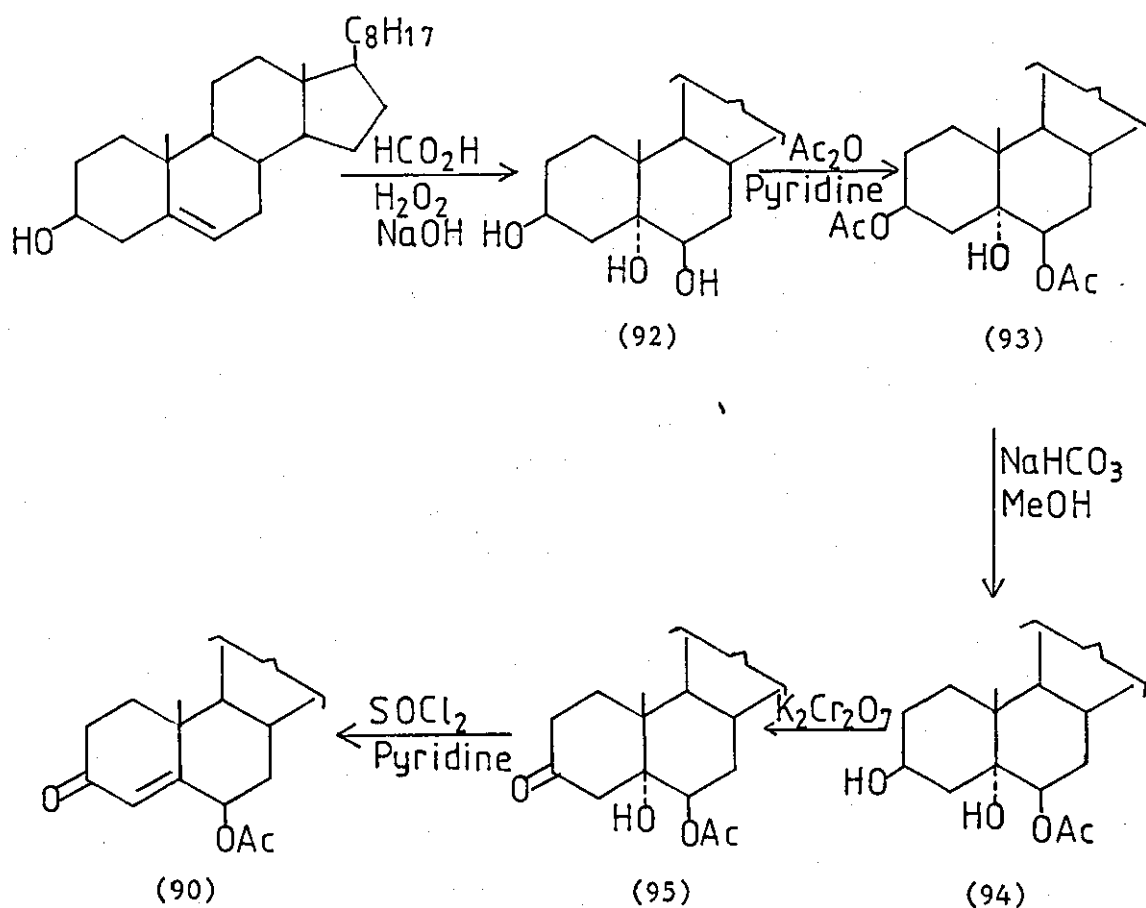
Scheme X

Epoxidation and concurrent hydrolysis of cholesterol gave the 3β,5α,6β-triol (92)[35] which was acetylated in the normal manner to give the diacetate (93)[36]. Partial hydrolysis of (93) was accomplished by treatment

with methanolic sodium bicarbonate solution giving the acetoxy-diol (94)[37] which was oxidised and dehydrated giving compound (90).

The spectra of compound (90) prepared by this route were identical to those of compound (90) derived by oxidation and dehydration of (88) and a mixed melting point gave no depression. It was also interesting to note that the ^{1}H n.m.r. spectra of compounds (88) and (94) were sufficiently dissimilar, as were those of (91) and (95)[38], thus proving the absolute configuration of (88). (Table IV).

The 60MHz ^{1}H n.m.r. spectrum of (91) was similar to that of (95) in most respects, the main difference being the chemical shift of the 10β-methyl, δ1.08 in (91) and δ1.3 in (95), the 5β-OH having a shielding effect on this methyl in compound (91). The 60MHz ^{1}H n.m.r. spectra of (88) and (94) were also very similar except that the chemical shift of the 10β-methyl again differed, δ0.98 in (88) and δ1.13 in (94), the 5β-OH again causing a shielding effect for this methyl. Allowing for slight differences in peak height the mass spectral fragmentation patterns of (88) and (94) were identical as were those of (91) and (95).

TABLE IV

COMPOUND NO.	CHEMICAL SHIFT				
	10β-Me	13β-Me	OAc	6α-H	3-H
91	1.08	0.7	2.04	4.65(W½ 5Hz)	————
95	1.3	0.7	2.05	4.64(W½ 4Hz)	————
88	0.98	0.67	2.08	4.69(W½ 5Hz)	3.95(W½ 20Hz)
94	1.13	0.67	2.05	4.68(W½ 4Hz)	4.02(W½ 20Hz)

The second product (16%) was (96), a white crystalline solid having a melting point of 118-20°C. The mass spectrum had a molecular ion peak at m/e 444 corresponding to $C_{29}H_{48}O_3$ and indicating that (96) was isomeric with the starting material. The infrared spectrum had ν_{max} 1745cm^{-1} (ester C=O) and showed no O-H absorption. The 60MHz ^{1}H n.m.r. spectrum had peaks at δ4.84 (1H, t, W½ 20Hz, 6α-H) and δ4.29 (1H, t, W½ 12Hz, 3β-H). The acetate methyl characteristically appeared at δ2.02. ^{13}C N.m.r. data for compound (96) can be found in table VII. Hydrolysis of (96) in methanolic potassium hydroxide solution gave an alcohol (97) having ν_{max} 3480cm^{-1} (O-H) in the infrared spectrum. In the ^{1}H n.m.r. spectrum the signal for the C-19 angular methyl shifted from δ1.15 in compound (96) to δ1.07 in compound (97) and the 6α-methine signal shifted similarly from δ4.84 to δ3.74.

Oxidation of (97) gave (98), a ketone, having ν_{max} 1718cm^{-1} (C=O) and no O-H absorption in the infrared spectrum. In the ^{1}H n.m.r. spectrum of (98) the C-18 methyl signal had shifted slightly to δ0.72. The C-19 methyl however, was deshielded by 0.23p.p.m. and gave a singlet at δ1. 3, a shift not characteristic of a 10β-methyl when a 6β-hydroxyl is oxidised. However, it is characteristic of a 5β-methyl. The 6α-methine had disappeared and the remaining methine appeared as a triplet (W½ 10Hz) centred at δ4.27. The mass spectrum of (98) indicated a molecular ion at m/e 400, which fragmented by loss of 15(Me) to m/e 385, 18(H_2O) to m/e 382 and 28(CO) to m/e 372. Further fragmentation of 18(H_2O) from m/e 385 to m/e 367 also occurred. Two peaks of equal intensity at m/e 247 and m/e 248 arose owing to fragmentations of the side chain from the molecular ion.

The product (96) was an ether, inferred by the lack of hydroxyl or keto absorptions in the infrared spectrum with presumably, one linkage at saturated carbon since only one methine in the ^{1}H n.m.r. spectrum could be assigned to an ether linkage. The B-ring was 6-membered as judged by

the stretching frequency of the C-6 carbonyl in (98). Furthermore, the

shift of the C-19 methyl after hydrolysis and oxidation suggested that it

was, in fact, a 5β-methyl. It therefore seemed reasonable to assume that

the product was the 3α,10α-epoxide (96), the result of a C-10 to C-5

methyl transfer.
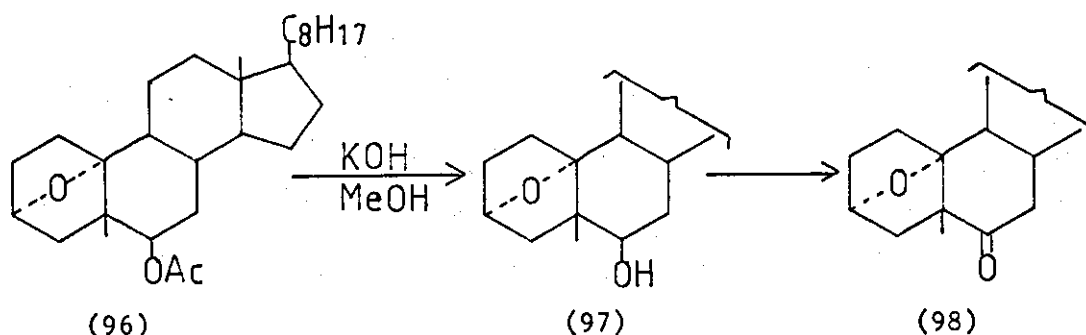
An inspection of the literature revealed that (97) had been isolated by

Coxon[25] when he investigated the boron trifluoride-catalysed rearrange-

ment of epicholesterol 5β,6β-epoxide. Oxidation of his product also gave

compound (98), all physical data being identical. Further investigation

of the literature revealed that (96) was also known. Glotter[39] isolated

it as the major product in the thallium triacetate acetylation of epi-

cholesterol. We are indebted to Professor Glotter for supplying us with

an authentic sample of his 3α,10α-epoxide which had an undepressed

mixed melting point with (96).

The third product, isolated in 10% yield, had structure (99). It too, was an acetoxy-ether, isomeric with the starting material, having one end of the ether linkage attached to a secondary carbon atom and the other end attached to a tertiary carbon atom. This was deduced from the spectroscopic data. The infrared spectrum had v_{max} 1750cm^{-1} (ester C=O) and no hydroxyl or other carbonyl absorptions. The 60MHz ^{1}H n.m.r. spectrum had peaks at δ5.2 (1H, m, W½ 5Hz, 6α-H) and δ4.4 (1H, t, J 5Hz, 2β-H). The acetate methyl signal appeared characteristically at δ2.03. The high resolution accurate mass spectrum had a molecular ion peak at m/e 444.3610 ($C_{29}H_{48}O_3$) which fragmented by loss of 60 (MeCOOH) to m/e 384.3394 ($C_{27}H_{44}O$). Other fragmentations included loss of 42 (CH_2CO) from the molecular ion, loss of 15 (Me) from m/e 384 and loss of 18 (H_2O) from m/e 369. The ^{13}C n.m.r. data are given in table VII.

(99)
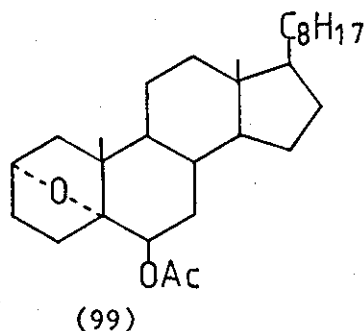
Hydrolysis of (99) with methanolic potassium hydroxide solution gave (100) having v_{max} 3460cm^{-1} (O-H) in the infrared spectrum. The 60MHz ^{1}H n.m.r. spectrum was largely unchanged, except for a shift of the 6α-methine and the absence of the acetate peak.

Oxidation of (100) with Jones reagent gave the epoxy-ketone (101) having v_{max} 1717cm^{-1} (ketone C=O) in the infrared spectrum and no O-H absorption. In the 60MHz ^{1}H n.m.r. spectrum a slight upfield shift (compared with (99)) of 0.12p.p.m. was observed for the 10β-methyl signal, the remaining methyl resonances were largely unchanged. A triplet centred at δ4.59 (J 5Hz) was assigned to the 2β-methine proton. The mass spectrum showed a molecular ion peak at m/e 400 which was also the base peak. Other

fragmentations are shown below:

$$M^+ \; m/e \; 400 \xrightarrow[-18]{-H_2O} m/e \; 382 \xrightarrow[-15]{-Me} m/e \; 367$$

$$-28 \Big| -CO \qquad\qquad \xrightarrow{-15 \quad -Me} m/e \; 385 \qquad \xrightarrow[-28]{-18 \quad -H_2O \quad -CO} m/e \; 357$$

$$m/e \; 372$$

(99)   (100)   (101)
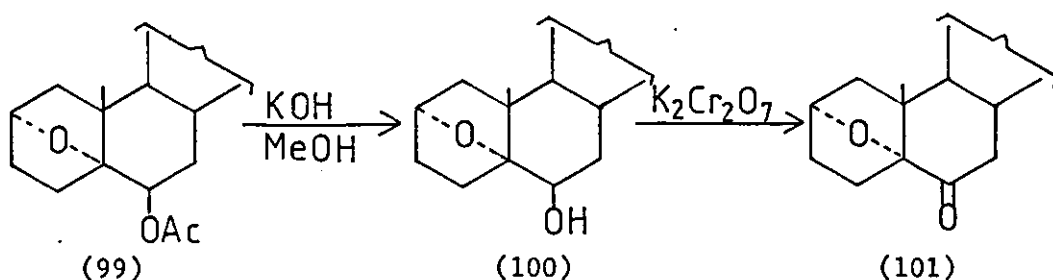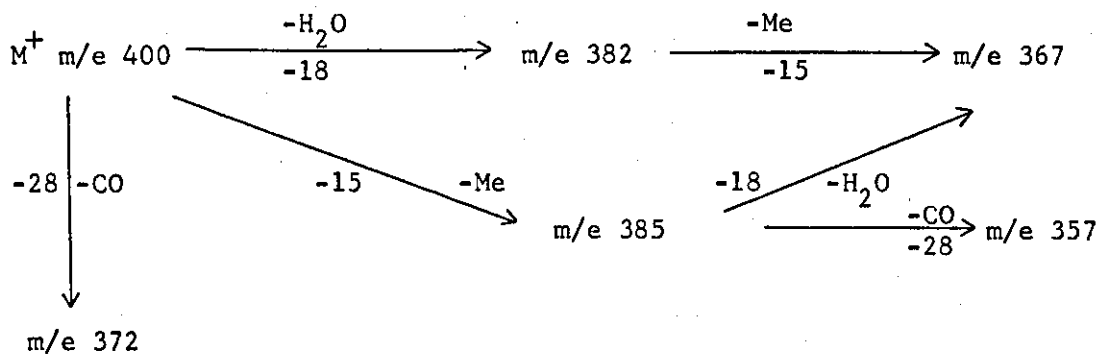
The product (99) when treated with boron trifluoride in acetic acid and

acetic anhydride underwent a backbone rearrangement giving (102),

inferred from the 90MHz [1]H n.m.r. spectrum. A double resonance exper-

iment irradiating 134Hz downfield of the C-21 methyl doublet caused it

to collapse to a singlet. This is typical of backbone-rearranged

cholestanes. The C-20 methine occurs at low field, typically $\delta 2.4$, owing

to its proximity to the $\Delta^{13,17}$ double bond and can be decoupled from the

C-21 methyl. This backbone-rearranged product did not match any of the

normal backbone rearranged products[25,40] with acetates epimeric at C-3

and C-6. Epimerisation about C-3 or C-6 could have occurred by the

following mechanisms (Schemes XI and XII).
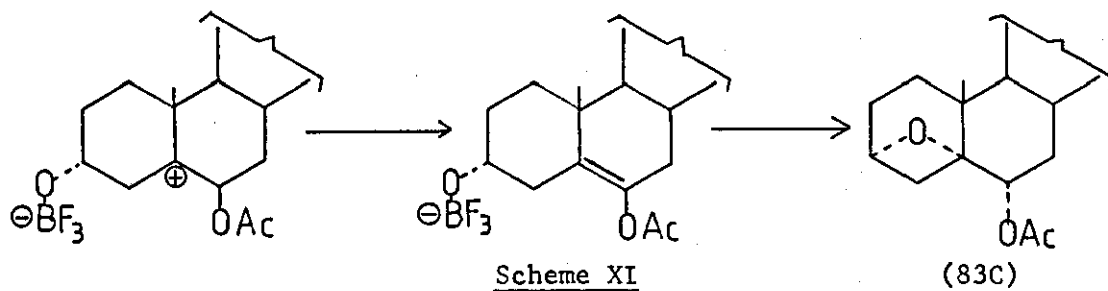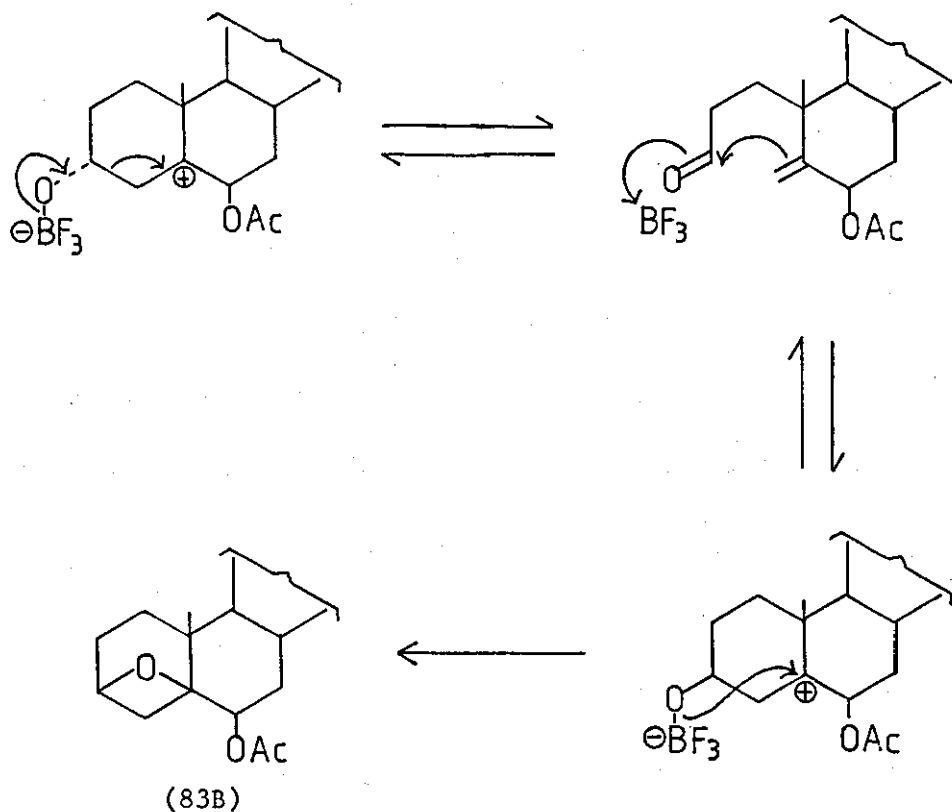
Scheme XI   (83C)

Scheme XII

A similar mechanism was invoked by Guest and Marples[26] to explain the isolation of a 6β-alcohol (74D) from a backbone rearranged 5,6α-epoxy-3β-hydroxy-5α-cholestane (70) during boron trifluoride-etherate-catalysed rearrangement, although they could not determine if it proceeded initially via a C-10 or a C-8 carbonium ion (Scheme XIII).

(70)

O-BF₃

O-BF₃

BF₃

BF₃

C₈H₁₇

(74D)
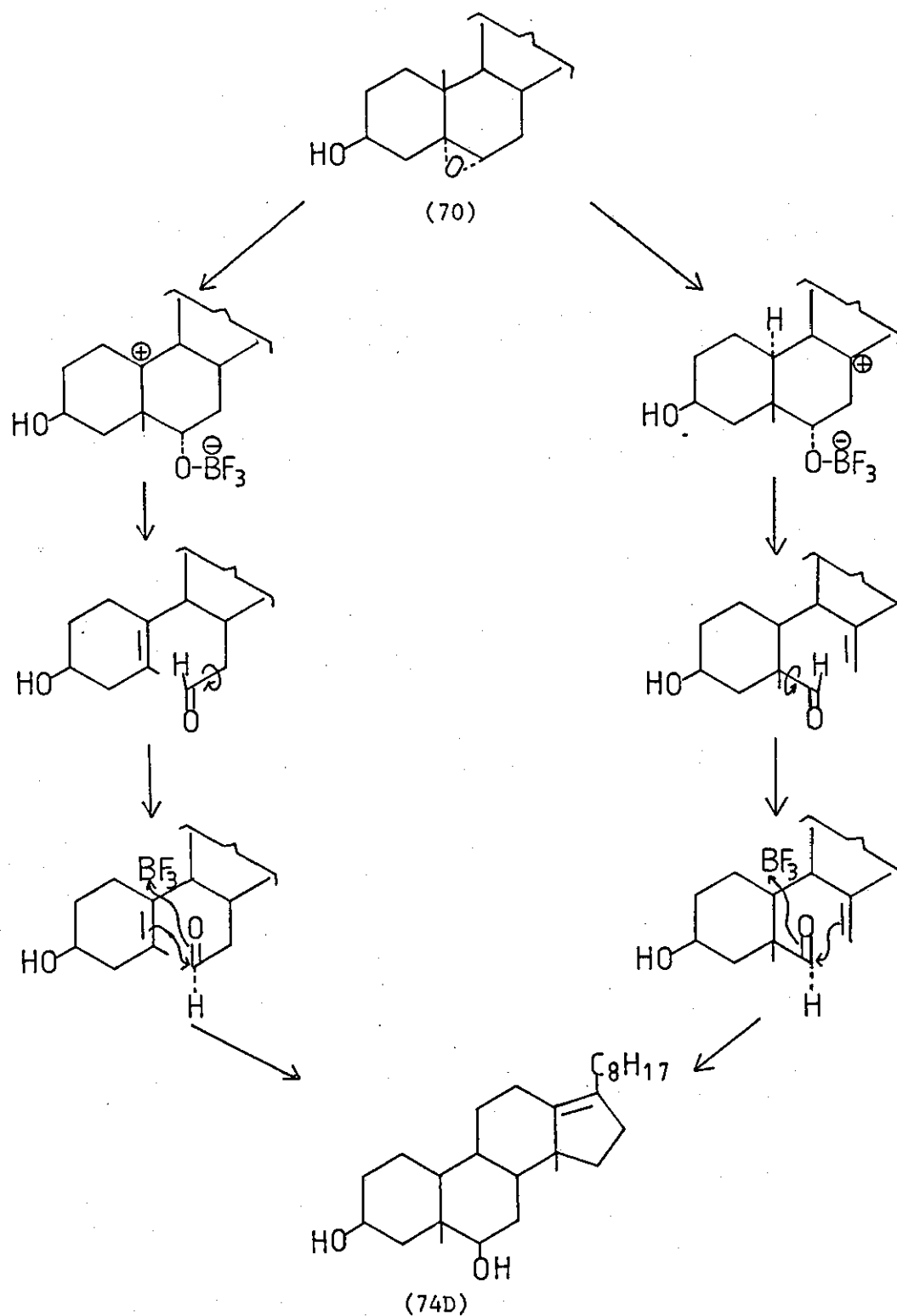
Scheme XIII

The rearranged compound (102) had ν_{max} 1738cm^{-1} (ester C=O). The 90MHz ^{1}H n.m.r. spectrum had peaks at δ0.81 (14β-Me), δ0.87 (5β-Me), δ0.91 and δ0.92 (25-Me's) and δ0.99 (left hand branch of the 20-Me doublet).

The acetate methyls appeared characteristically at $\delta 2.03$ and $\delta 2.06$ having methines, not necessarily respectively, at $\delta 5.08$ (m, W½ 8Hz) and $\delta 4.66$ (q, J_{outer} 7Hz, J_{inner} 4Hz). The mass spectrum confirmed the backbone rearrangement, having a molecular ion peak at m/e 486 $(C_{31}H_{50}O_4)$, which fragmented by loss of 113 $(C_8H_{17}$ side chain) to the base peak at m/e 373. This important loss of the side chain is typical of backbone-rearranged compounds[41]. Fragmentation of part of the side chain was indicated by a peak at m/e 401 owing to the loss of 85 (C_6H_{13}) from the molecular ion. Other fragmentations are shown below:

$$M^+ \; m/e \; 486 \xrightarrow[-113]{-C_8H_{17}} m/e \; 373$$

with additional pathways:

- $-85(C_6H_{13}) \rightarrow m/e\;401 \xrightarrow{-28(C_2H_4)} m/e\;373$
- $-15(Me) \rightarrow m/e\;471 \xrightarrow[-60]{-MeCOOH} m/e\;411$
- $-MeCOOH \; (-60) \rightarrow m/e\;426 \xrightarrow[-15]{-Me} m/e\;411$
- $m/e\;426 \xrightarrow[-60]{-MeCOOH} m/e\;366 \xrightarrow[-15]{-Me} m/e\;351$
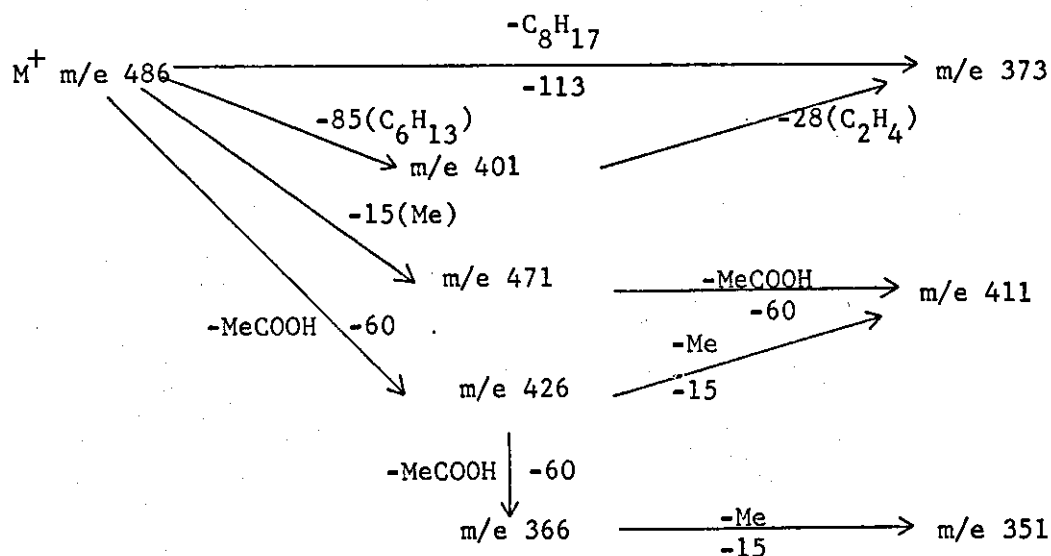
Hydrolysis of the rearranged compound (102) to (103) followed by oxidation to (104) showed no cyclopentanone in the infrared spectrum since the carbonyl stretching frequency occurred at 1710cm^{-1}, and hence the A-ring was assumed to be six-membered, giving further evidence for the structure (99).

102	R=β-OAc,H R'=α-OAc,H
103	R=β-OH,H R'=α-OH,H
104	R=R'=O

69
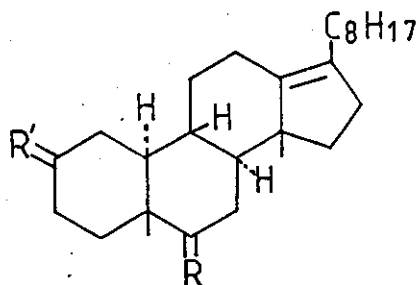
Final proof for the structure (99) was obtained by its unambiguous synthesis and our 5,6β-dihydroxy-5α-cholesteryl tosylate (86) gave us the ready starting material. (Scheme XIV).
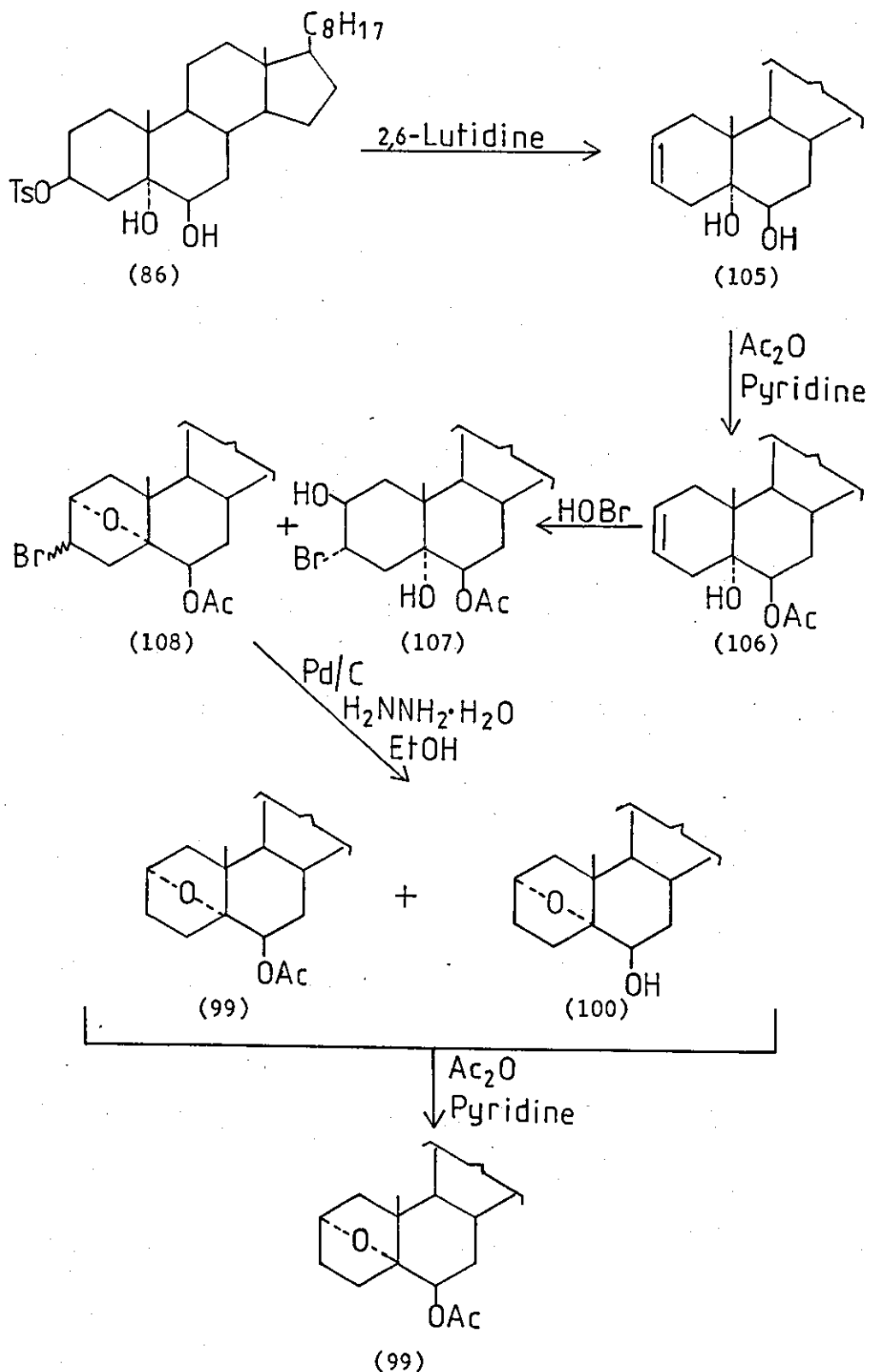
Scheme XIV

Treatment of (86) with 2,6-lutidine gave a virtually quantitative yield

of 5,6β-dihydroxy-5α-cholest-2-ene (105) which was acetylated to give

the 6-acetate (106). Treatment of (106) with hypobromous acid gave a

mixture of two compounds, the bromohydrin (107) and the epoxy-bromide

(108) which were separated by preparative t.l.c. Debromination of (108)

was achieved by treatment with hydrazine hydrate in ethanol and 5%

palladium on charcoal. The crude isolated product contained some

hydrolysed material (100) and was therefore acetylated giving (99), which

had all spectroscopic data identical to the product obtained from the

boron trifluoride etherate rearrangement of (83A). The melting point was

also identical and a mixed melting point was not depressed.

An initial speculation however, was that all the products of the boron

trifluoride etherate catalysed rearrangement of (83A) were derived from

C(5)-O bond cleavage. This assumption was drawn from the knowledge that

the previous products (88) and (96) were derived via this type of cleavage.

It therefore followed that unless epimerisation at C-3 had occurred

(see page 66) then C-9 must be the point of attachment for the ether link-

age since positions 5 and 10 could be ruled out on the grounds of the

hydrolysis and oxidation results. An inspection of the models suggested

that a 5β,10β-cis ring junction was necessary for a 3α,9α-ether. Structure

(109), rather than (99), was initially proposed for our third rearrange-

ment product and indeed, the 10β-methine would account for an abnormal

backbone product.

(109)
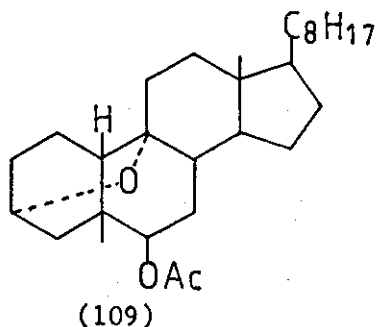
For such a compound to be produced, a deprotonation-protonation mechanism proceeding via a Δ^9-intermediate (110A) would have to be invoked (Scheme XV).
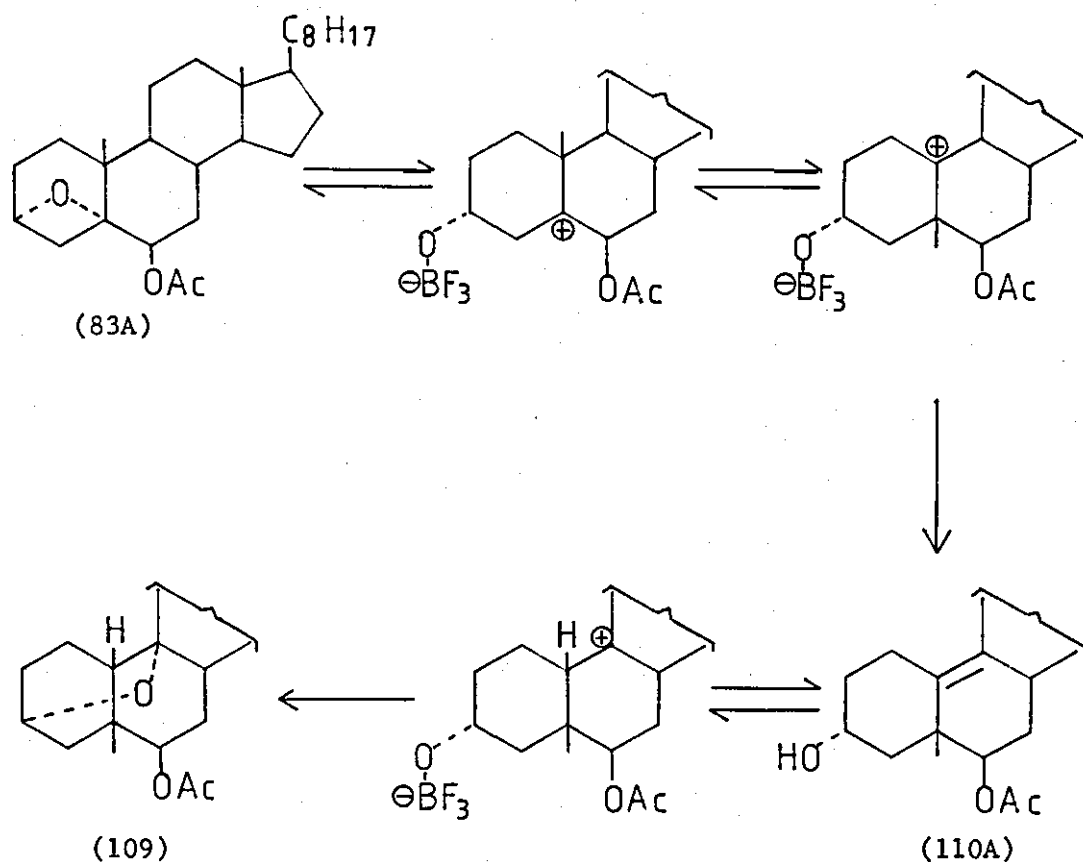
Scheme XV

The Δ^9-intermediate (110A) was prepared from (110B) by successive oxidation [to (111)] sodium borohydride reduction and preparative t.l.c. of the resultant mixture of (110A) and (110B). However, when (110A) was subjected to the reaction conditions of rearrangement ($BF_3.Et_2O-C_6H_6$) no reaction occurred.

A 3α-OH
B 3β-OH
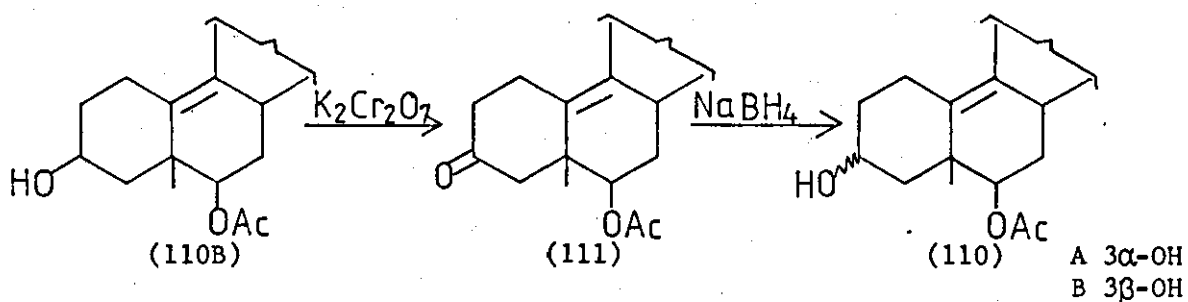
Furthermore, when both (110A) and (110B) were treated with boron tri-fluoride etherate in acetic acid and acetic anhydride only acetylation of the hydroxyl functions occurred. None of our supposed 3,9-ether was detected and this began to throw considerable doubt on our initial assignment of the structure (109). We began to suspect that perhaps owing to the electron withdrawing effect of the 6-acetate some C(3)-O bond cleavage was occuring albeit to a small extent. An inspection of models showed that 6β-acetoxy-2α,5-epoxy-5α-cholestane (99) would fit the spectroscopic data and also all the derivatives investigated would be in agreement.

To explain the isolation of compounds (88), (96) and (99) two possible mechanisms are involved proceeding via a) C(5)-O bond cleavage (Scheme XVI) and b) C(3)-O bond cleavage (Scheme XVII).
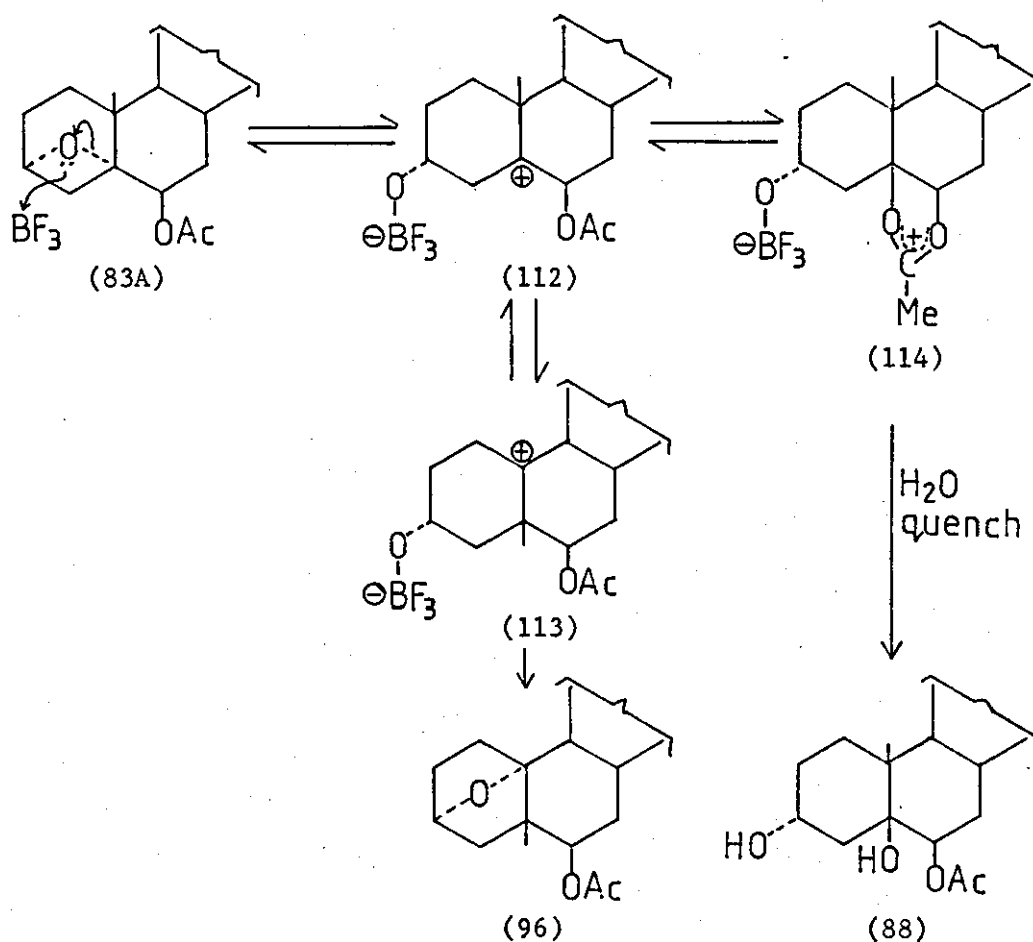
Scheme XVI
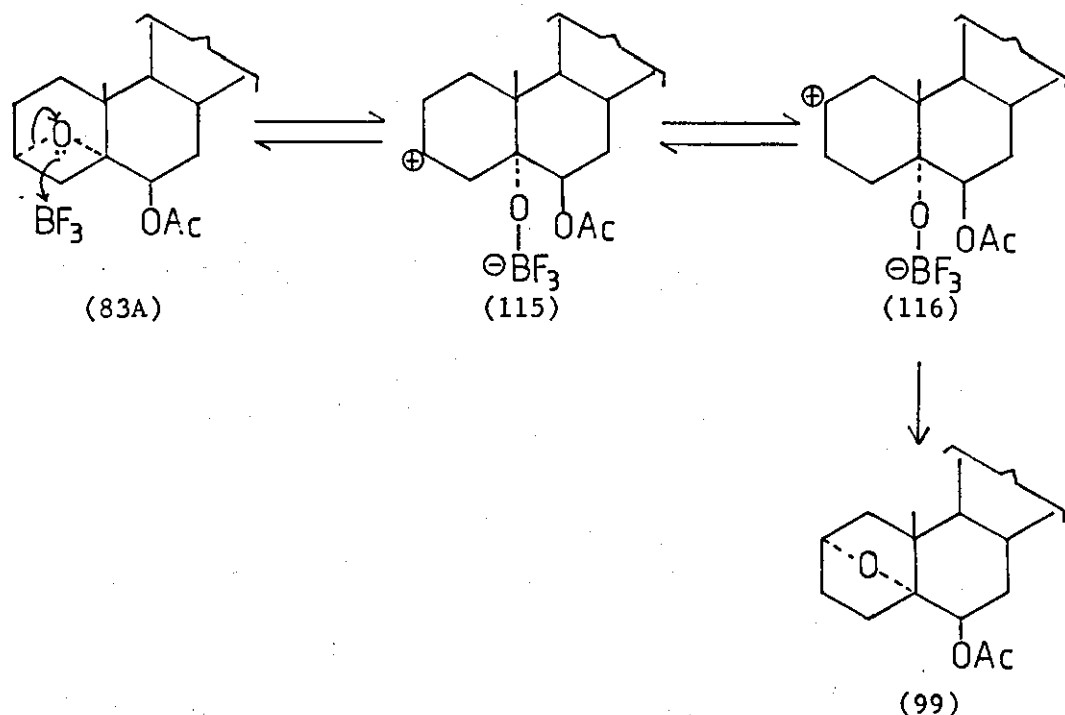
Scheme XVII

In mechanism a) cleavage of the C(5)-O bond occurs initially producing a carbonium ion at C-5, and an oxygen anion which is stabilised by the boron trifluoride. This species (112) can rearrange by a C-10 to C-5 methyl transfer giving (113) followed by ring-closure to (96). Alternatively, the C-5 carbonium ion can be stabilised by the 6-acetate via an acetoxonium ion intermediate (114). Hydrolysis on work up allows the isolation of the acetoxy-diol (88).

Mechanism b) involves initial C(3)-O bond cleavage giving species (115) with a carbonium ion centred at C-3. Hydride transfer from C-2 to C-3 occurs, giving species (116) which undergoes ring-closure to (99).

Since (88) is the major product it would appear that the mechanism via the acetoxonium ion intermediate is the preferred pathway. That this does indeed occur was illustrated when the rearrangement of (83A) was carried out in ether in the presence of sodium borohydride. Isolation of the acetal (117), that is, the reduction product of the acetoxonium ion, confirmed the

presence of this intermediate.

1)NaBH₄ → 2)H₂O

(114)   (117)
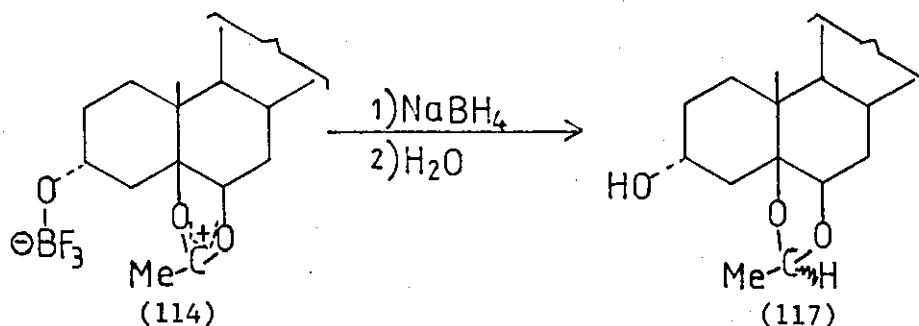
The infrared spectrum of (117) showed a broad O-H absorption (3440cm⁻¹).

The mass spectrum had a molecular ion at m/e 446 in agreement with the

expected molecular formula and fragmented by initial loss of 44 (MeCHO)

to m/e 402 followed by loss of 18 (H₂O) to m/e 384. A possible

fragmentation mechanism is as follows:
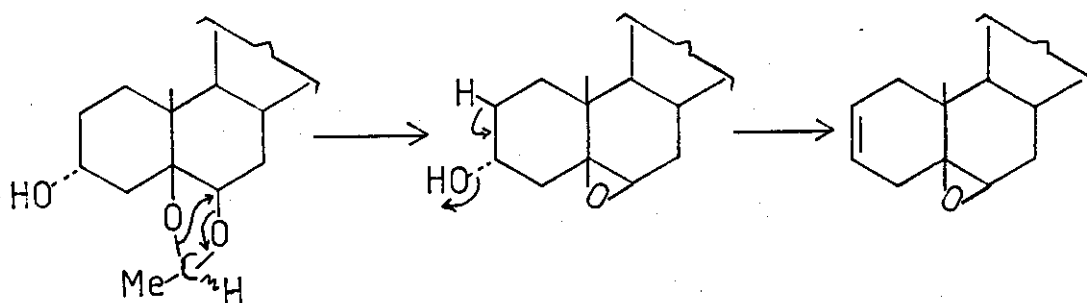
Confirmation of the structure of (117) was gained from its ¹H n.m.r.

spectrum in conjunction with spin decoupling experiments.

The 90MHz ¹H n.m.r. spectrum of (117) had important peaks at δ0.65 (3H,

s, 13β-Me), δ0.97 (3H, s, 10β-Me), δ0.87 (6H, d, 25-Me's) and δ0.92 (3H,

d, 20-Me). A three-proton doublet (J 5Hz) centred at δ1.43 was assigned

to the methyl of the acetal coupled to the acetal methine, which gave a

quartet (J 5Hz) centred at δ5.12. A broad doublet (J 5Hz) at δ3.58 was

assigned to the 3β-methine. A double irradiation experiment irradiating

the acetal methine at δ5.12 caused the methyl doublet at δ1.43 to collapse

to a singlet.

Morrison[42] used similar techniques to prove the intermediacy of an

acetoxonium ion in the boron trifluoride etherate catalysed rearrangement

of 5,6α-epoxy-3β-methoxy-5α-cholestan-4β-yl acetate (118). The

rearrangement involves neighbouring group participation of the 4β-acetoxy

group.By carrying out the rearrangement in the presence of sodium boro-

hydride the intermediate 4β,5β-acetoxonium ion was reduced to the acetal

(119) which was isolated. (Scheme XVIII)

(118)

(119)   (120)
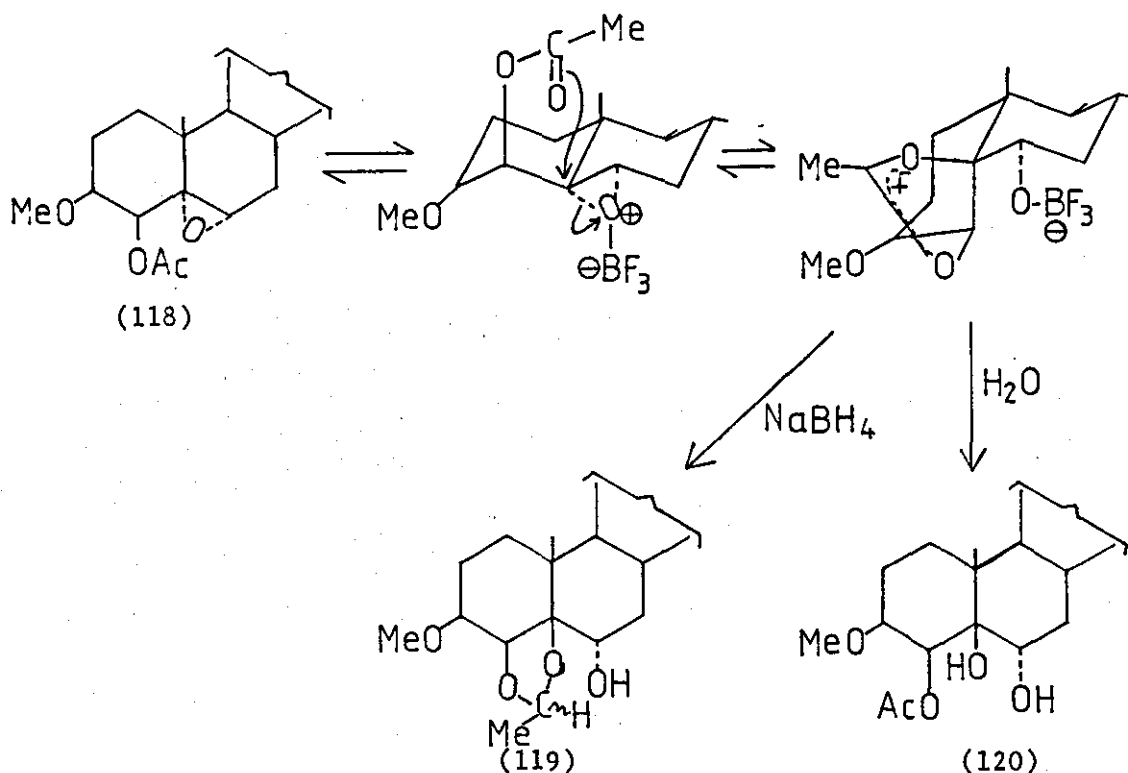
Scheme XVIII

The acid-catalysed rearrangement of 3α,5-epoxy-6β-hydroxy-5α-cholestane

(87A) has also been studied. The hydroxy 3α,5α-epoxide (87A) was dissolved

in deuteriochloroform and the rearrangement followed by observing the

^{1}H n.m.r. spectrum. After standing overnight at room temperature little

or no change had occurred. However, at a constant 35°C. the rate of

rearrangement was greatly enhanced. The disappearance of the 6α-methine

multiplet at δ3.87 and the broad doublet at δ4.5 was coupled with the

appearance of a doublet at δ2.98 (J 2Hz) and a broad multiplet at δ4.08

(W½ 8Hz). The 10β-methyl became slightly more shielded and its signal

moved upfield by 0.13p.p.m. to δ0.99. The final product was in fact,

epicholesterol β-epoxide (71A) and its [1]H n.m.r. spectrum was identical

with that of a previously prepared sample.

(87A)

(71A)

. . . .
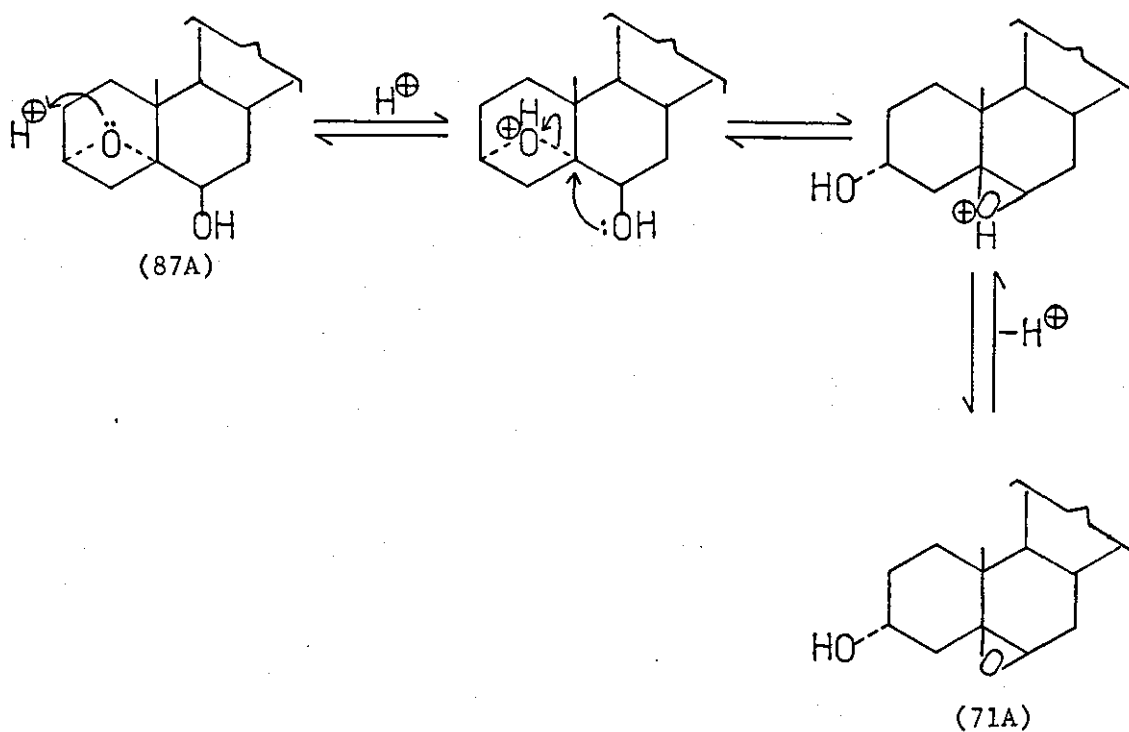
In view of the reactivity of the 3α,5α-epoxy-6β-acetoxy compound (83A) with boron trifluoride etherate, doubt was thrown on the structural assignment of a ketone isolated by Rowland[29] during the solvolysis of 3β-tosyloxy-5-hydroxy-5β-cholestan-6-one (121). Structure (81B) was originally assigned by Rowland to this compound and we are indebted to Professor Rowland for supplying us with a generous sample of his product for comparison purposes.

(121)   (81B)
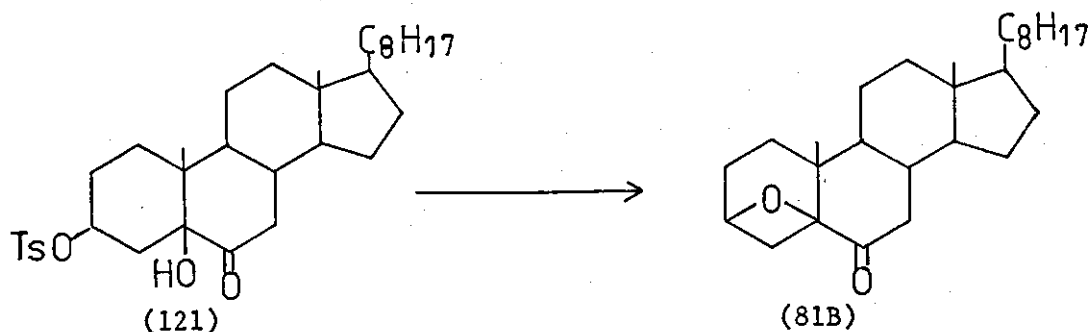
A reassessment of the spectral data of Rowland's compound caused us to suspect the assigned structure. Comparison of this with the spectral data of 3α,5α-epoxy-6-ketone (81A) and certain of the reactions of the solvolysis product led to the conclusion that it could be formulated as the A-homo-B-nor-3α,5α-epoxide (122) formed by participation of the 6-carbonyl oxygen. The advantage of this mechanism over that of Rowland's is that the oxygen anion may displace the tosyloxy group in a concerted (S_N2) fashion.

(121)   (122)
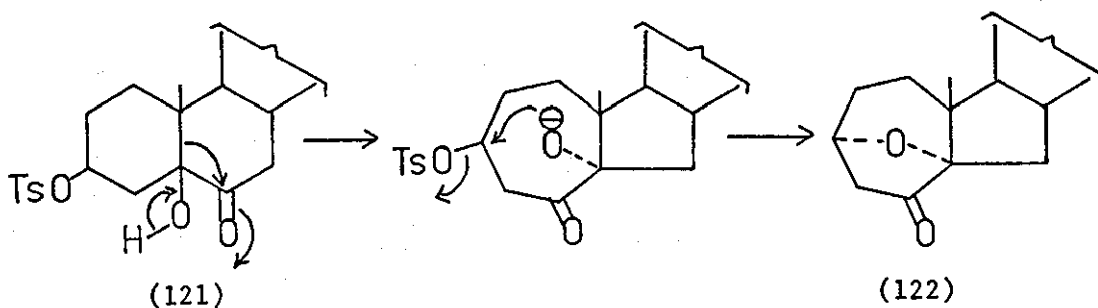
Rowland's ketone had ν_{max} 1750cm^{-1}. The 90MHz [1]H n.m.r. spectrum had peaks at δ0.66 (3H, s, 13β-Me), δ0.75 (3H, s, 10β-Me), δ0.84 and δ0.92 (25-Me's),

δ0.96 (left hand branch of the 20-Me doublet) and δ4.67 (1H, br. d, J 7Hz, 3β-H). The mass spectrum had a molecular ion peak at m/e 400. A possible fragmentation pattern to the base peak at m/e 318 is shown below:
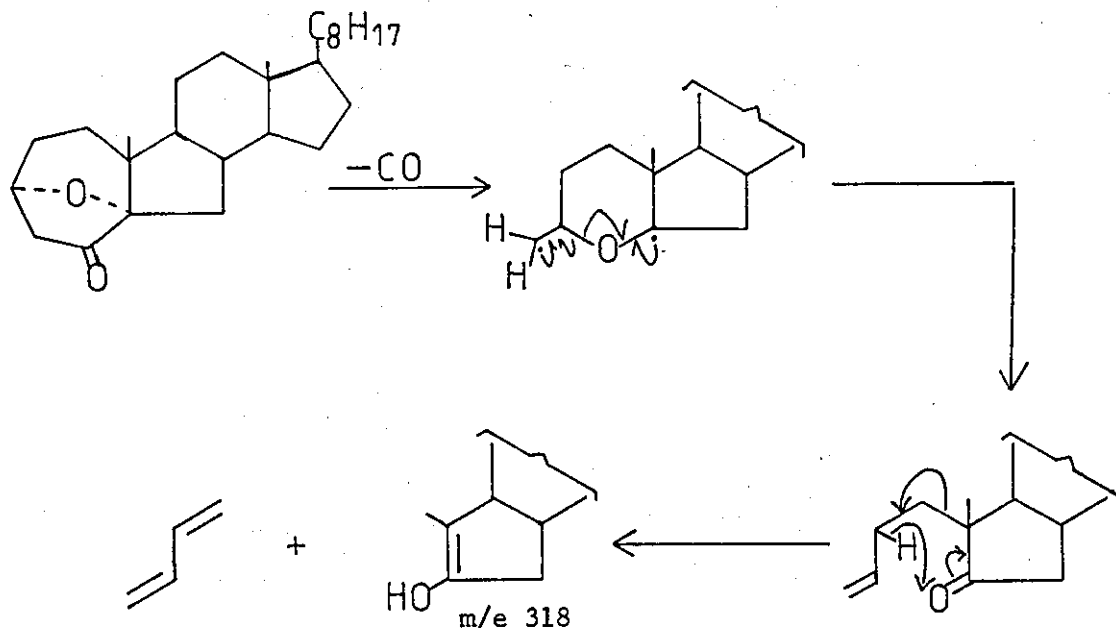
Rowland's epoxy-ketone (122) was found to be quite unreactive towards photolysis* and on enol acetylation a mixture was obtained consisting largely of unreacted (122).

When reduced with sodium borohydride in ethanol a single alcohol (123) was obtained having 4aβ-stereochemistry.

(123)
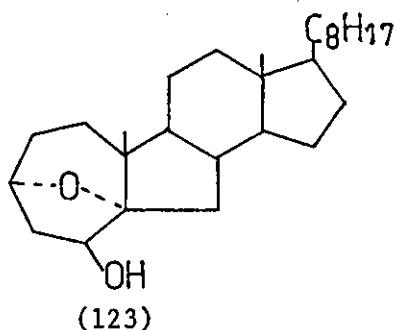
The infrared spectrum of alcohol (123) had v_{max} 3470cm^{-1} (O-H). The 60MHz ^{1}H n.m.r. spectrum had peaks at δ0.66 (3H, s, 13β-Me), δ1.04 (3H, s, 10β-Me),

* (The photolytic stability is compared with epoxy-ketones in Part III).

$\delta 0.81$ and $\delta 0.9$ (side chain methyls) and $\delta 4.06-4.34$, a multiplet owing

to the 3β- and $4a\alpha$- methines superimposed on each other. The mass spectrum

had a molecular ion peak at m/e 402 which fragmented by loss of 84

(C_5H_8O), to the base peak at m/e 318. A metastable peak at m/e 251.5

confirmed this fragmentation. A possible mechanism to account for this

fragmentation is shown below:

(123)
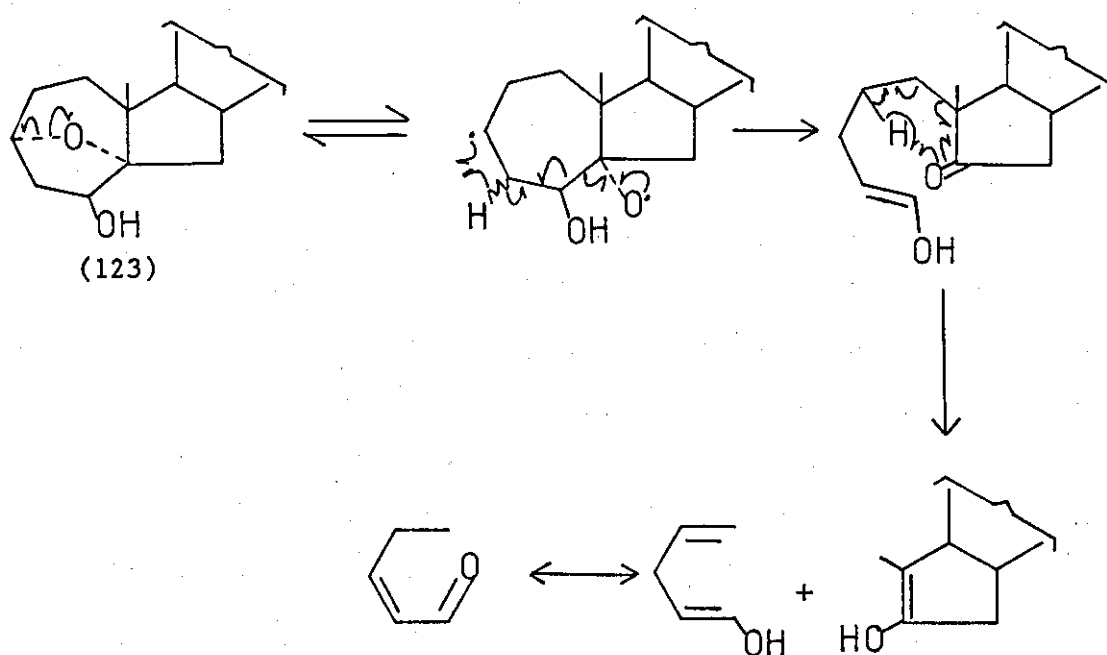
Oxidation with Jones reagent of (123) gave back the original ketone.

Rowland's epoxy-ketone (122) was treated with D_2O in dioxane containing

triethylamine. Only one proton was exchanged even after prolonged

treatment giving (124). When treated with NaOD in dioxane both protons

adjacent to the carbonyl were exchanged giving (125). In the [1]H n.m.r.

spectrum of the undeuteriated epoxy-ketone a broad triplet (J 7Hz) at

$\delta 4.67$ was assigned to the 3β-proton, whereas the 3β-H signal in the

$3\alpha,5\alpha$-epoxy-6-ketone (81A) appeared as a broadened doublet (J 7Hz) at

$\delta 4.45$. A perturbed quartet (J 7Hz and 18Hz) at $\delta 2.62$ was assigned to the

4α-proton which was vicinally spin-spin coupled (J 7Hz) to the 3β-proton

and geminally spin-spin coupled (J 18Hz) to the 4β-proton. The 4α-H in

(81A) was a quartet at δ3.0 (J 7Hz and 10Hz) whilst a doublet at δ1.86

(J 10Hz) was assigned to the 4β-H. The 4β-proton in (122) was a doublet

centred at δ2.08 (J 18Hz), not easily discernable except by double

irradiation experiments, coupled geminally to the 4α-proton but not to

the 3β-proton.

In the monodeuteriated epoxy-ketone (124) the 3β-proton collapsed to a

broad doublet (J 7Hz) and the 4β-proton to a singlet. Double irradiation,

irradiating at δ4.67 did not have any effect on the 4β-proton thus proving

that it was not coupled to the 3β-proton. The 4α-proton quartet had, of

course, disappeared altogether since it had been deuteriated.

The spectrum of the dideuteriated epoxy-ketone (125) was similar to that

of the monodeuteriated compound except that the 4β-singlet had also

disappeared. The 3β-proton remained as a broad doublet (J 7Hz).

(124)   (125)
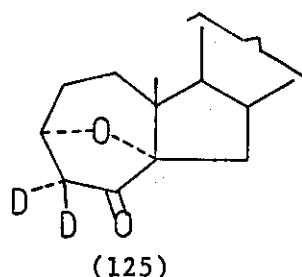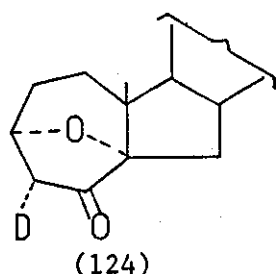
The reluctance of the 4β-proton to exchange significantly in triethylamine

presumably relates to the hindered nature of the base and of the β-face

of the 4,4a-enolate. This is confirmed by the reduction of the ketone

(122) to the alcohol (123). The loss of CO and C_4H_5D in the mass spectrum

of (124) gives the base peak at m/e 318 and further supports the structural

assignment.

Subsequent to our correction[43A] of the structure of Rowland's epoxy-ketone

(122)[29] an independent corroboration was reported by Dave and Warnhoff[43B].

Having shown that Rowland's compound did not have structure (81B) it became necessary to prepare an authentic sample of this epoxy-ketone for a photochemical study (described in part III) together with its 6-acetoxy analogue to investigate its reactivity towards boron trifluoride etherate. Compound (88), obtained from the rearrangement of (83A), was a suitable starting material (Scheme XIX).
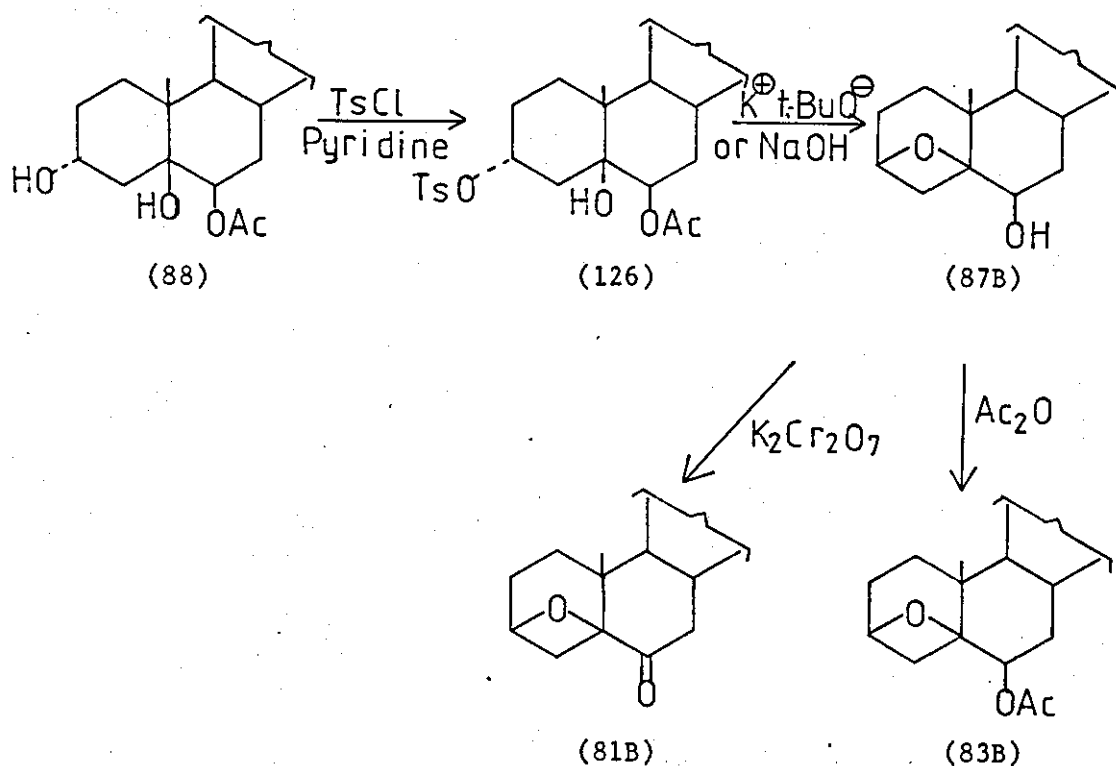
Scheme XIX

Treatment of (88) with p-toluenesulphonyl chloride in pyridine gave (126) which underwent ring-closure and concurrent hydrolysis when treated with either potassium t.-butoxide or sodium hydride giving (87B).

Alternatively, (87B) could be prepared via Rowland's compound. Treatment of cholesterol with performic acid followed by hydrolysis gave the triol (92) which could be selectively oxidised to the dihydroxy-ketone (127C) with N-bromosuccinimide. Isomerisation at C-5 to the 5β-hydroxyl compound (127B) was achieved via the A-homo-B-nor dihydroxy-ketone (128) by treating (127C) with methanolic potassium hydroxide solution. Rowland's compound

(122) could then be obtained via tosylation of (127B) to (129) followed by ring-closure with concurrent rearrangement. Treatment of (122) with perchloric acid gave the dihydroxy-ketone (127A) which could be tosylated and reduced to the diol-tosylate (131). Ring-closure was afforded by treatment with sodium hydride giving the epoxide (87B). (Scheme XX).
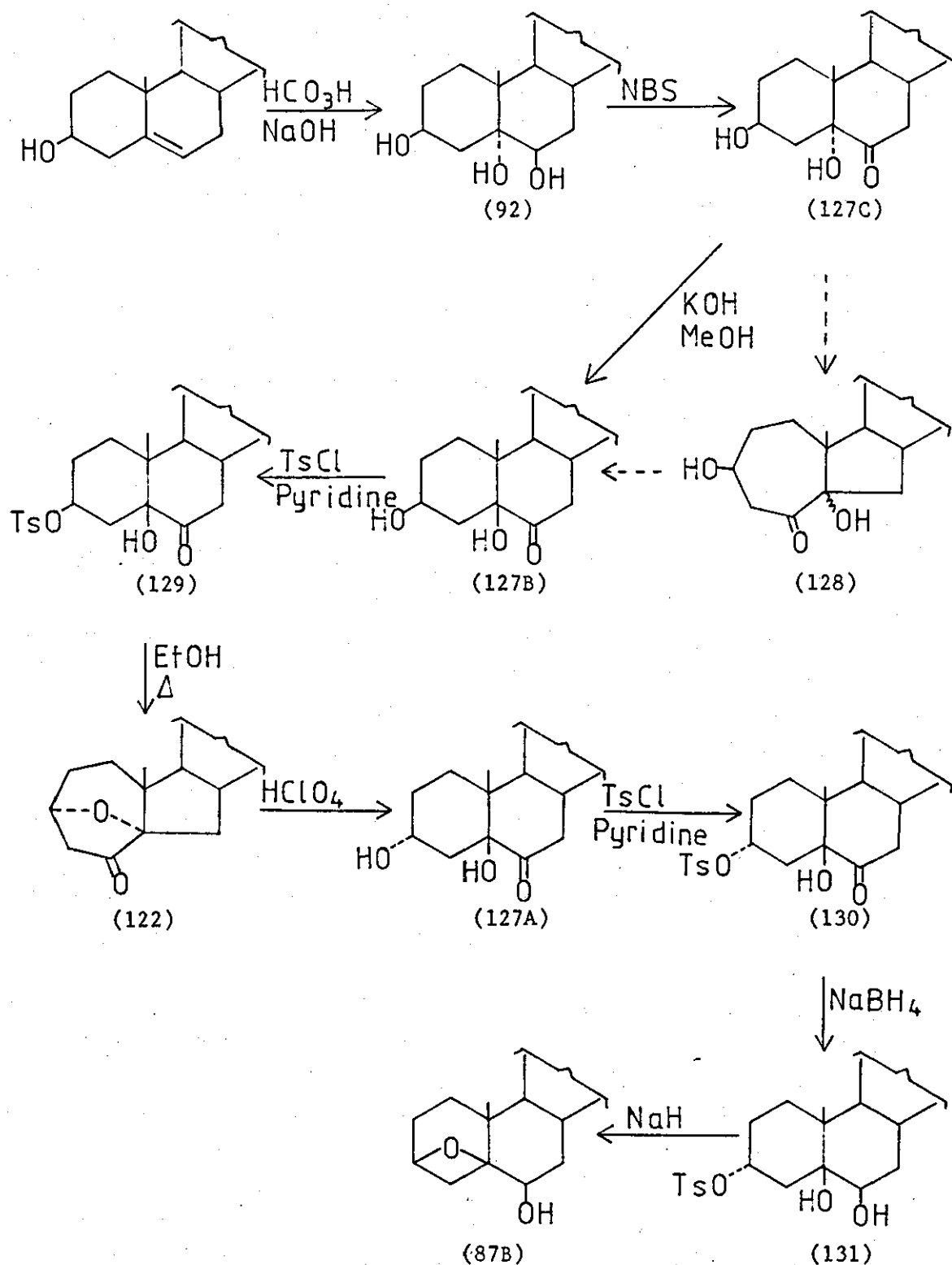
Scheme XX

Compound (87B) had V_{max} 3440cm^{-1} (O-H). The 60MHz ^{1}H n.m.r. spectrum had

peaks at δ0.68 (3H, s, 13β-Me), δ1.24 (3H, s, 10β-Me) and at δ0.81 and

δ0.9 (side chain methyls). A multiplet (W½ 4Hz) at δ3.85 was assigned to

the 6α-methine and a broad doublet (J 6Hz) at δ4.45 was assigned to the

3α-methine. In contrast, the 3β-methine in the α-epoxide (87A) was a

multiplet (W½ 13Hz) at δ4.52. In the mass spectrum of (87B) a molecular

ion peak at m/e 402, in agreement with the expected molecular formula,

fragmented by loss of 54 (C_4H_6) to the base peak at m/e 348. Other

fragmentations included the loss of 18 (H_2O) from the molecular ion to

m/e 384, and the loss of 15 (Me) from m/e 384 to m/e 369. These fragment-

ations were confirmed by accurate mass measurements for peaks at m/e

402.3504, m/e 384.3384, m/e 369.3167 and m/e 348.3039. Also in the mass

spectrum a peak at m/e 345.3157 could arise only by loss of C_3H_5O from

the molecular ion and was of equal intensity to that at m/e 384.3384.

Hence, two fragmentations of equal ease could occur from the molecular

ion as shown below:
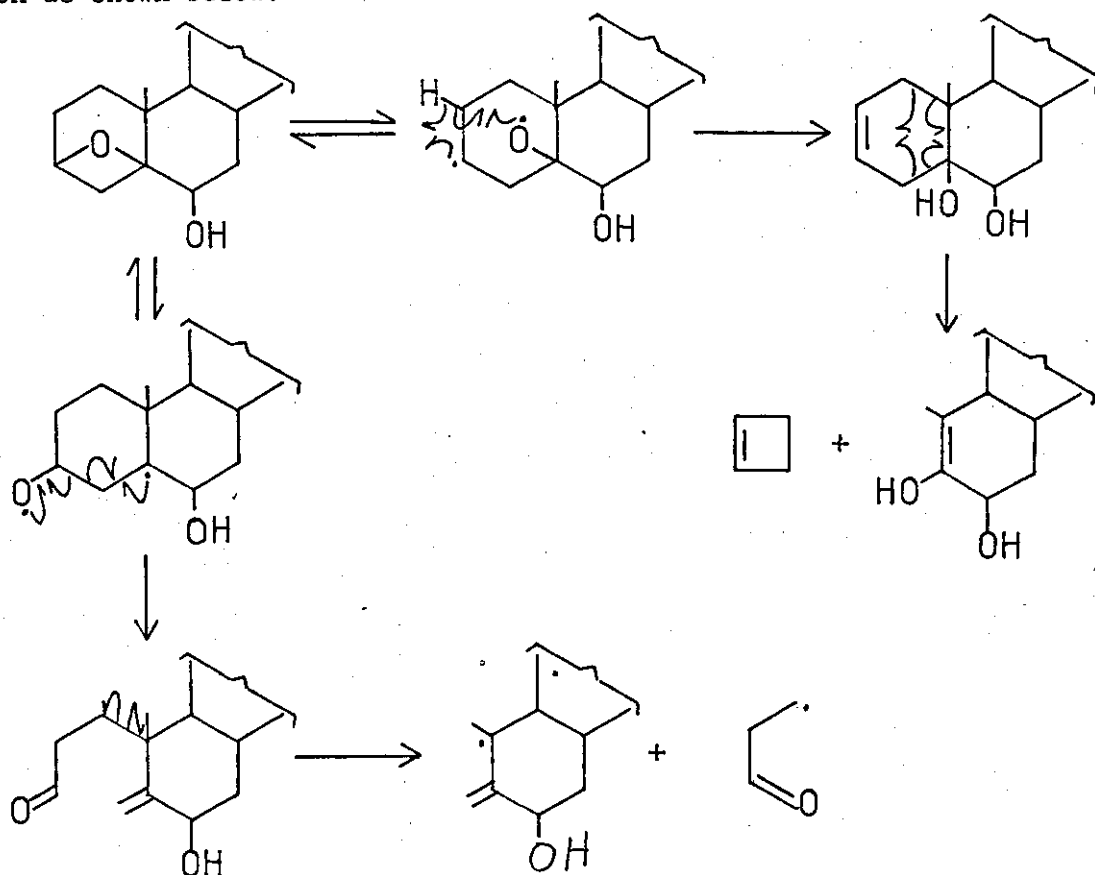
Acetylation of (87B) with acetic anhydride in pyridine heated under reflux gave the acetoxy-epoxide (83B) having v_{max} 1745cm^{-1} (ester C=O). The 60MHz ^{1}H n.m.r. spectrum had peaks at δ4.42 (1H, d, J 6Hz, 3α-H) and δ5.0 (1H, m, W$\frac{1}{2}$ 5Hz, 6α-H). The mass spectrum showed no molecular ion at m/e 444, the highest measurable mass occurred at m/e 402.3500 ($C_{27}H_{46}O_2$) which fragmented to the base peak at m/e 330.2921 by loss of 72 (C_4H_8O). A peak at m/e 390.3132 ($C_{25}H_{42}O_3$) could only arise by the loss of 54 (C_4H_6) from a molecular ion at m/e 444. Other significant peaks occurred at m/e 387.3270 ($C_{26}H_{43}O_2$) and m/e 384.3396 ($C_{27}H_{44}O$) owing to losses of 15 (Me) and 18 (H_2O) from m/e 402.

m/e 402

m/e 330   m/e 402

m/e 390
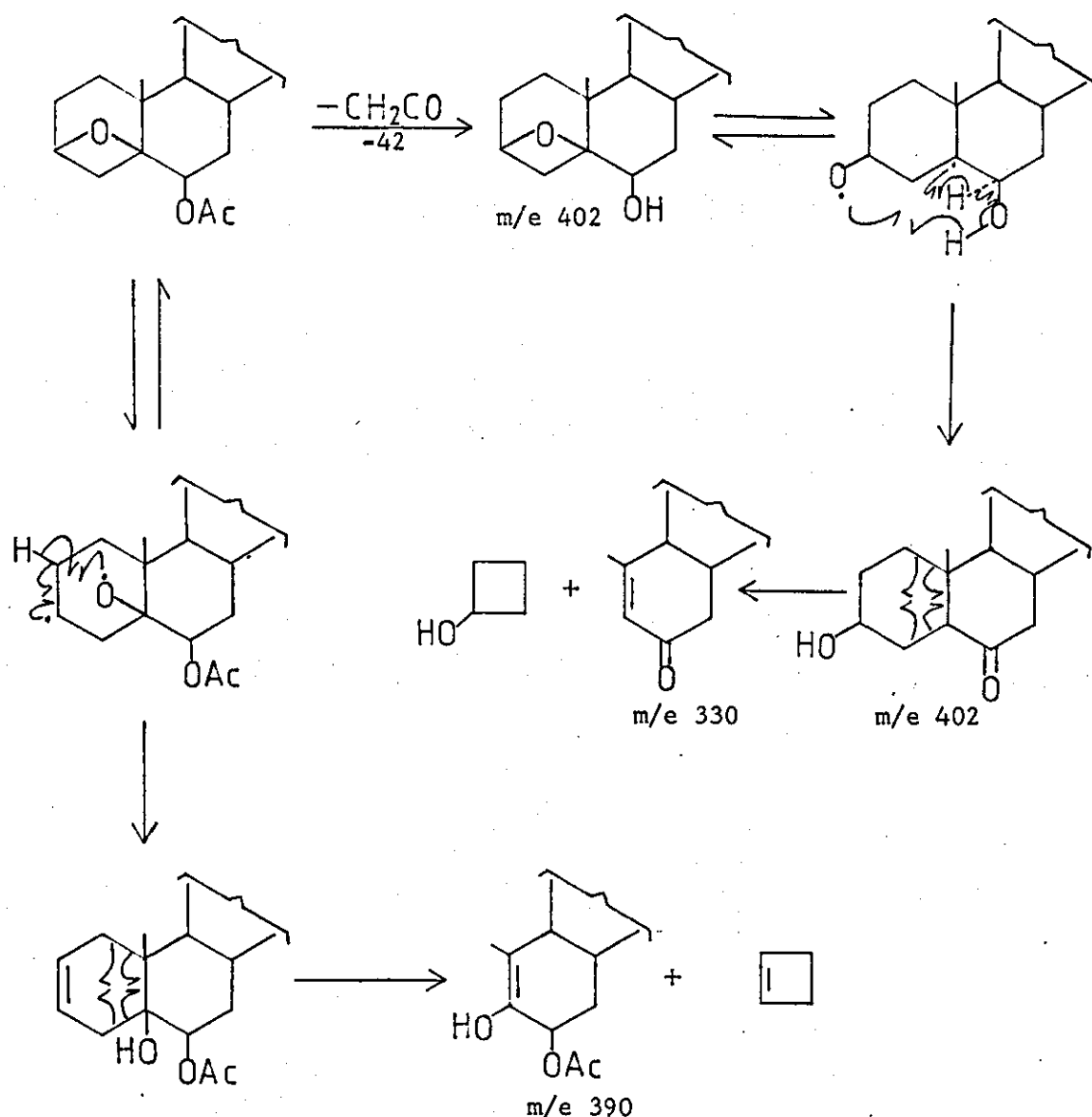
Reaction of 6β-acetoxy-3β,5-epoxy-5β-cholestane (83B) with boron trifluoride diethyl etherate.

Treatment of a benzene solution of (83B) with boron trifluoride etherate for ten minutes at room temperature gave a mixture of products consisting largely of one compound, namely 6β-acetoxy-3β,5-dihydroxy-5β-cholestane (132) (60%). The acetoxy-diol (132) had ν_{max} 3430cm^{-1} (O-H) and 1740cm^{-1} (ester C=O). The 60MHz ^{1}H n.m.r. spectrum had important peaks at δ2.06 (3H, s, MeCO$_2$), δ4.69 (1H, m, W½ 6Hz, 6α-H) and δ3.92 (1H, m, W½ 5Hz, 3α-H). Two other singlets at δ3.83 and δ3.35 were assigned to the protons of the hydroxyl functions since they could easily be exchanged with D$_2$O. Oxidation with Jones reagent gave the known 6β-acetoxy-5-hydroxy-5β-cholestan-3-one (91) previously obtained from the oxidation of the acetoxy-diol (88), a rearrangement product of the 3α,5α-epoxide in boron trifluoride etherate (Scheme XXI).
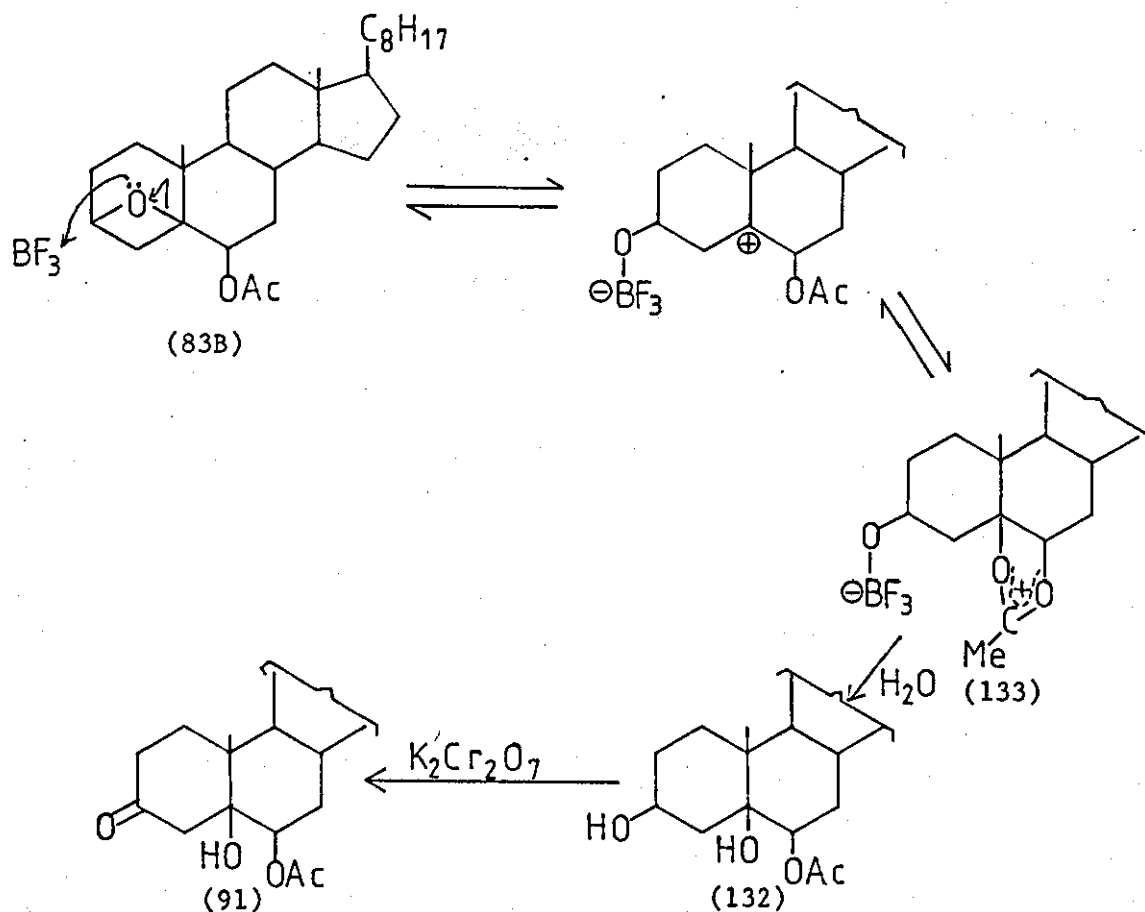
Scheme XXI

Although unproven, it seems reasonable to assume that a stable acetoxonium ion intermediate (133) was involved from which the product (132) was derived via hydrolysis under work up conditions.

EXPERIMENTAL

Cholesteryl tosylate (84)

Cholesterol (10g, 0.026 moles) was dissolved in pyridine (100cm^3) and p-toluenesulphonyl chloride (20g, 0.105 moles) added. The solution was allowed to stand at room temperature overnight, then poured onto ice and extracted with ether. The combined ether extracts were washed with water, dried and evaporated in vacuo to an off-white solid. Residual pyridine was removed by azeotroping with benzene. Recrystallisation from acetone gave pure cholesteryl tosylate (13g) (93%) m.p. 138-40°C. (lit.[30] 131.5-132.5°C.).

5ξ,6ξ-Epoxy-cholesteryl tosylate (85)

Cholesteryl tosylate (12g) was dissolved in dry ether (200cm^3) and dry chloroform (20cm^3). The solution was cooled to 0°C. and ethereal mono-perphthalic acid solution (10 molar equiv.) added. It was allowed to stand in the refrigerator overnight, then washed with water, 4% w/v sodium bicarbonate solution, water, dried and evaporated in vacuo to an oily, white solid. Recrystallisation from 40:60 pet.-ether gave pure 5ξ,6ξ-epoxy-cholesteryl tosylate (10.2g) (83%) m.p. 126-9°C. (lit.[31] m.p. for pure α-epoxide 124°C., for pure β-epoxide 110°C.).

5,6β-Dihydroxy-5α-cholesteryl tosylate (86)

5ξ,6ξ-Epoxy-cholesteryl tosylate (4g) was dissolved in ethyl methyl ketone (150cm^3) and to this well stirred solution was added 60% perchloric acid (0.5cm^3) dropwise. The solution was stirred at room temperature for fifteen minutes, diluted with ether, washed with saturated sodium bicarbonate solution and water, the ether phase dried and evaporated in vacuo to an off-white, crystalline solid. Recrystallisation from acetone, 40:60 pet.-ether gave 5,6β-dihydroxy-5α-cholesteryl tosylate (3.5g) (85%) m.p. 145-8°C. (dec.) (lit.[32] m.p. 148-50°C.).

6β-Hydroxy-3α,5-epoxy-5α-cholestane (87A)

5,6β-Dihydroxy-5α-cholesteryl tosylate (12.3g, 0.021 moles) was dissolved in dry t.-butyl alcohol ($1dm^3$), the solution placed in a steam bath at 50°C. and, under nitrogen, a solution of potassium t.-butoxide (4.65g, 0.042 moles) in t.-butyl alcohol ($40cm^3$) added. The solution was kept at 50°C. for two hours, then poured onto ice, acidified with dilute hydrochloric acid and extracted with ether. The combined ether extracts were washed with saturated sodium bicarbonate solution, dried and evaporated in vacuo to a colourless oil. The oil was passed down a column of grade 3 alumina (450g) and eluted with benzene.

The first major fraction was a compound found to be 5-hydroxy-3β-methyl-A-nor-5β-cholestan-6-one described in part IV.

The second major fraction was the epoxide, 6β-hydroxy-3α,5-epoxy-5α-cholestane (4.3g) (50%). Recrystallisation from methanol gave (87A) m.p. 123-132°C. (2.4g) and second crop m.p. 125-33°C. (1.38g) (lit.[33] m.p. 121-22°C.).

6β-Acetoxy-3α,5-epoxy-5α-cholestane (83A)

6β-Hydroxy-3α,5-epoxy-5α-cholestane (87A) (0.5g) was dissolved in pyridine ($50cm^3$) and acetic anhydride (200mg) added. The solution was allowed to stand overnight, then poured onto water and extracted with ether. The ether extract was dried and evaporated in vacuo to a colourless oil. Excess pyridine was removed as an azeotrope in benzene, and recrystallisation from methanol gave (83A) (426mg) m.p. 82-4°C. (lit.[33] not crystalline). A second crop (30mg) had m.p. 77-8°C. ν_{max} $1750cm^{-1}$ (ester C=O) and $1250cm^{-1}$ (C-O), δ5.0 (1H, m, W½ 4Hz, 6α-H), δ4.47 (1H, d, J 7Hz, 3β-H), δ2.58 (1H, q, J_{vic}(3β) 7Hz, J_{gem}(4β) 9Hz, 4α-H), δ2.02 (3H, s, $MeCO_2$), δ1.74 (1H, d, J_{gem}(4α) 9Hz, 4β-H), δ0.9 and δ0.8 (side chain methyls), δ1.03 (3H, s, 10β-Me), δ0.69 (3H, s, 13β-Me). M^+ 444. Base peak m/e 384.

Reaction of 6β-acetoxy-3α,5-epoxy-5α-cholestane (83A) with boron
trifluoride diethyl etherate.

6β-Acetoxy-3α,5-epoxy-5α-cholestane (400mg) was dissolved in dry benzene
($20cm^3$) and boron trifluoride diethyl etherate ($0.08cm^3$) added. The
mixture was allowed to stand at room temperature for ten minutes, then
diluted with ether, washed with water, the ether phase dried and
evaporated in vacuo to a colourless oil. Preparative t.l.c. eluting in
ether gave essentially three fractions of which the most polar, Rf 0.11,
was pure cholestan-3α,5β,6β-triol-6-acetate (88) (26%). Repeat preparative
t.l.c. of the least polar fraction, Rf 0.7, in 95% 40:60 pet.-ether, 5%
acetone gave four fractions of which the fractions having Rf 0.54 and
0.66 were identified as 6β-acetoxy-3α,10-epoxy-5-methyl-5β-cholestane (96)
and 6β-acetoxy-2α,5-epoxy-5α-cholestane (99) respectively.

Compound (88) had v_{max} $1740cm^{-1}$ (ester C=O), $3400cm^{-1}$ (br., O-H), δ3.95
(1H, m, W½ 20Hz, 3β-H), δ4.69 (1H, m, W½ 5Hz, 6α-H), δ2.08 (3H, s, $MeCO_2$),
δ0.98 (3H, s, 10β-Me), δ0.9 and δ0.81 (side chain methyls) and δ0.67 (3H,
s, 13β-Me). M^+ 462. Base peak m/e 384. (Found 402.3531 $C_{27}H_{46}O_2$ (M^+-
$MeCO_2$) requires 402.3498, 390.3150 $C_{25}H_{42}O_3$ requires 390.3134, 384.3386
$C_{27}H_{44}O$ requires 384.3392 and 330.2938 $C_{23}H_{38}O$ requires 330.2923 . No
M^+ at m/e 462). The 3,5-dinitrobenzoate of (88) had m.p. 156-8°C. (ether).
(Found C, 65.8; H, 8.0; N, 4.0 $C_{36}H_{52}O_9N_2$ requires C, 65.83, H, 7.98;
N, 4.26%).

Compound (96) had v_{max} $1745cm^{-1}$ (ester C=O), δ4.84 (1H, t, W½ 20Hz, 6α-H),
δ4.29 (1H, t, W½ 12Hz, 3β-H), δ2.02 (3H, s, $MeCO_2$), δ1.15 (3H, s, 5β-Me),
δ0.92 and δ0.81 (side chain methyls) and δ0.65 (3H, s, 13β-Me). M^+ 444.
Base peak m/e 384. Metastable peak at m/e 332.1 corresponding to the loss
of 60 ($MeCO_2H$) (444-384). (Found M^+ 444.3591 $C_{29}H_{48}O_3$ requires 444.3603
and 384.3390 $C_{27}H_{44}O$ (M^+-$MeCO_2H$) requires. 384.3392). m.p. 118-20°C.
(methanol) (lit.[39] 118-19°C. No depression with an authentic sample.).

Compound (99) had v_{max} 1750cm^{-1} (ester C=O), δ5.2 (1H, m, W½ 5Hz, 6α-H),

δ4.4 (1H, t, J 5Hz, 2β-H), δ2.03 (3H, s, MeCO$_2$), δ1.08 (3H, s, 10β-Me),

δ0.9 and δ0.84 (side chain methyls) and δ0.68 (3H, s, 13β-Me). M^{+} 444.

Base peak m/e 384. Metastable peak at m/e 332.1 corresponding to the loss

of 60 (MeCO$_2$H) (444-384). (Found 444.3610 $C_{29}H_{48}O_3$ requires 444.3603 and

384.3394 $C_{27}H_{44}O$ (M^{+}-MeCO$_2$H) requires 384.3392). m.p. 77-80°C. (methanol).

3α,6β-Diacetoxy-5-hydroxy-5β-cholestane (89)

Acetylation of (88) in acetic anhydride and pyridine gave (89) an oil,

having v_{max}1735cm^{-1} (ester C=O), 3480cm^{-1} (O-H), δ4.97 (1H, m, W½ 20Hz,

3β-H), δ4.63 (1H, m, W½ 5Hz, 6α-H), δ2.06 and δ1.98 (6H, 2xs, 2xMeCO$_2$),

δ0.98 (3H, s, 10β-Me), δ0.9 and δ0.8 (side chain methyls) and δ0.66 (3H,

s, 13β-Me). M^{+} 504. Base peak m/e 43.

6β-Acetoxy-5-hydroxy-5β-cholestan-3-one (91)

Compound (88) (25mg) was dissolved in acetone (2cm^3), cooled to 0°C. and

Jones reagent (4 drops) added. The mixture was stirred for fifteen minutes,

diluted with water and extracted with ether. The ether extract was dried

and evaporated in vacuo giving 6β-acetoxy-5-hydroxy-5β-cholestan-3-one (91)

(20mg) (80%) having v_{max} 1710cm^{-1} (ketone C=O), 1750cm^{-1} (ester C=O) and

3450cm^{-1} (O-H), δ4.65 (1H, m, W½ 5Hz, 6α-H), δ2.79 (1H, d, J$_{gem}$(4β) 15Hz,

4α-H), δ2.08 (3H, s, MeCO$_2$), δ1.08 (3H, s, 10β-Me), δ0.7 (3H, s, 13β-Me),

δ0.9 and δ0.8 (side chain methyls). M^{+} 460. Base peak m/e 400. Recrystall-

isation from ether, 40:60 pet.-ether gave 13mg of white crystals m.p.

184-8°C.

6β-Acetoxy-cholest-4-en-3-one (90)

Compound (91) (13mg) was dissolved in pyridine (0.5cm^3) and thionyl chloride

(5 dm^3). The solution was heated gently under reflux for fifteen minutes,

then ice added and extracted with ether. The ether extract was dried and

evaporated in vacuo to a colourless, oily solid (10mg) having $\delta 5.9$ (1H, s, 4-H), $\delta 5.38$ (1H, m, W½ 5Hz, 6α-H), $\delta 2.04$ (3H, s, $MeCO_2$), $\delta 1.29$ (3H, s, 10β-Me), $\delta 0.76$ (3H, s, 13β-Me), $\delta 0.91$ and $\delta 0.81$ (side chain methyls). Purification by preparative t.l.c. followed by recrystallisation from acetone, methanol gave 6β-acetoxy-cholest-4-en-3-one (90) (2mg) m.p. 104-6°C. (lit.[34] m.p. 103.5-104.5°C), v_{max} 1683cm^{-1} (α,β-unsaturated C=O), 1630cm^{-1} (C=C), 1740cm^{-1} (ester C=O). M$^+$ 442.

3β,5α,6β-Cholestane triol (92)

Cholesterol (1g) was suspended in 88% formic acid (10cm^3) and warmed to 70-80°C. for ten minutes, whereupon an oily, upper layer separated. The mixture was allowed to cool then 30% hydrogen peroxide (1cm^3) added. It was stirred at room temperature for eight hours then boiling water (15cm^3) added. On cooling, a white solid separated. The supernatent liquid was decanted, the solid residue washed with water then dissolved in methanol (30cm^3) and 25% w/w aqueous sodium hydroxide solution (1cm^3) added to the mixture which was then warmed on a steam bath for thirty minutes. The mixture was filtered, the filtrate diluted with water, acidified with dilute hydrochloric acid and extracted with chloroform. The organic phase was dried and evaporated in vacuo to a white, crystalline solid. The product was pure by t.l.c. and was used as such in the next stage. (lit.[35] m.p. 237-239°C.).

3β,5α,6β-Cholestane triol-3,6-diacetate (93)

The crude triol (92) was dissolved in pyridine (30cm^3) and acetic anhydride (2.5cm^3). The mixture was heated under reflux for one hour, allowed to cool, ice added and extracted with ether. The organic phase was dried and evaporated in vacuo. Excess pyridine was removed as an azeotrope in benzene and the product was recrystallised from methanol giving (93) (0.62g) m.p. 171-4°C. (lit.[36] m.p. 165°C.).

3β,5α,6β-Cholestane triol-6-acetate (94)

Diacetate (93) (300mg) was dissolved in methanol (30cm^3). Sodium bicarbonate (380mg) was added and the mixture stirred for eight days at room temperature. It was diluted with ether, washed with water, the organic phase dried and evaporated in vacuo. Preparative t.l.c. eluting in 60% chloroform, 30% ethyl acetate, 10% methanol followed by recrystallisation from methanol gave (94) m.p. 147-8°C. (lit.[37] m.p. 143-4°C.).

6β-Acetoxy-5-hydroxy-5α-cholestan-3-one (95)

Acetoxy-diol (94) (30mg) was dissolved in acetone (3cm^3) and cooled to 0°C. Jones reagent (4 drops) was added, the mixture stirred for fifteen minutes, then diluted with water and extracted with ether. The ether extract was dried and evaporated in vacuo. Recrystallisation from ether, 40:60 pet.-ether gave (95) (25mg) (83%) m.p. 165-9°C. (lit.[38] m.p. 161-2°C.) δ4.64 (1H, m, W½ 4Hz, 6α-H), δ2.85 (1H, d, J 15Hz, 4-H), δ2.05 (3H, s, MeCO$_2$), δ1.3 (3H, s, 10β-Me), δ0.7 (3H, s, 13β-Me), δ0.9 and δ0.8 (side chain methyls).

6β-Acetoxy-cholest-4-en-3-one (90)

Compound (95) (21mg) was dissolved in pyridine (0.75cm^3) and thionyl chloride (7.5μdm^3). The solution was heated under reflux for fifteen minutes, poured onto ice and extracted with ether. The ether layer was dried and evaporated in vacuo. Its ^{1}H n.m.r. spectrum indicated approximately 50% starting material remained. It was therefore retreated with a further 5μdm^3 of thionyl chloride and worked up as before giving (90) (19mg). The crude product was purified by preparative t.l.c. eluting in chloroform. Its infrared and ^{1}H n.m.r. spectra were identical to those of (90) obtained by oxidation and dehydration of (88). Recrystallisation from acetone, methanol gave m.p. 101-4°C. Mixed m.p. 100-3°C. (lit.[34] m.p. 103.5-104.5°C.).

3α,10-Epoxy-6β-hydroxy-5-methyl-5β-cholestane (97)

Acetate (96) (21mg) was dissolved in 1% methanolic potassium hydroxide solution (2cm^3) and allowed to stand at room temperature. After two and a half hours t.l.c. indicated that little reaction had occurred. 5% Methanolic potassium hydroxide solution (2cm^3) was added and after a total of eight and a half hours t.l.c. indicated complete reaction. The methanol was removed in vacuo, water was added to the residue which was extracted with ether. The ether phase was dried and evaporated in vacuo giving (97)[25] (19mg) having ν_{max} 3480cm^{-1} (O-H), δ4.32 (1H, t, W½ 12Hz, 3β-H), δ3.74 (1H, t, W½ 20Hz, 6α-H), δ1.07 (3H, s, 5β-Me), δ0.66 (3H, s, 13β-Me), δ0.91,δ0.86 and δ0.82 (side chain methyls).

3α,10-Epoxy-5-methyl-5β-cholestan-6-one (98)

Alcohol (97) (19mg) was dissolved in acetone (4cm^3) and cooled to 0°C. Jones reagent (four drops) was added, the mixture stirred for fifteen minutes, diluted with water and extracted with ether. The ether extract was dried and evaporated in vacuo giving (98) (17mg). Preparative t.l.c. gave (13mg) as white crystals m.p. 75-85°C. (lit.[25] m.p. 94-5°C.) having ν_{max} 1718cm^{-1} (C=O), δ4.27 (1H, t, W½ 10Hz, 3β-H), δ1.13 (3H, s, 5β-Me), δ0.72 (3H, s, 13β-Me), δ0.9 and δ0.8 (side chain methyls). M$^+$ 400. Base peak m/e 43.

2α,5-Epoxy-6β-hydroxy-5α-cholestane (100)

Acetate (99) (16mg) was hydrolysed according to the procedure adopted for (96). The product (100) (16mg) had ν_{max} 3460cm^{-1} (O-H), δ4.36 (1H, t, W½ 12Hz, 2β-H), δ4.01 (1H, m, W½ 5Hz, 6α-H), δ1.1 (3H, s, 10β-Me), δ0.68 (3H, s, 13β-Me), δ0.9 and δ0.81 (side chain methyls).

2α,5-Epoxy-5α-cholestan-6-one (101)

Alcohol (100) (16mg) was oxidised according to the procedure adopted for

(97). The product (101) (17mg) had ν_{max} 1717cm^{-1} (C=O), δ4.59 (1H, t, J 5Hz, 2β-H), δ0.96 (3H, s, 10β-Me), δ0.65 (3H, s, 13β-Me), δ0.9 and δ0.8 (side chain methyls). M^{+} 400. Preparative t.l.c. eluting in 90% 40:60 pet.-ether, 10% ether followed by recrystallisation twice from methanol gave m.p. 136-40°C.

Reaction of epoxy-acetate (99) with boron trifluoride diethyl etherate/ acetic acid/acetic anhydride mixture

(99) (45mg) was dissolved in glacial acetic acid (1.1cm^{3}) and acetic anhydride (0.75cm^{3}) and cooled to 0°C. Boron trifluoride diethyl etherate (0.38cm^{3}) in glacial acetic acid (1.1cm^{3}) was added and the mixture allowed to stand overnight in the refrigerator. It was diluted with ether, poured onto 1M sodium hydroxide solution, the ether layer washed with water, dried and evaporated in vacuo to a yellow oil (ca. 50mg). Preparative t.l.c. eluting in 94% 40:60 pet.-ether, 6% acetone gave (102) as an oil (40mg). $[\alpha]_D^{23}$ -6° (c 1.1), ν_{max} 1738cm^{-1} (ester C=O), δ5.08 (1H, m, W½ 8Hz, 6α-H), δ4.66 (1H, q, J_{inner} 4Hz, J_{outer} 7Hz, 2β-H), δ2.06 (3H, s, MeCO$_2$), δ2.03 (3H, s, MeCO$_2$), δ0.81 (3H, s, 14β-Me), δ0.87 (3H, s, 5β-Me), δ0.91 and δ0.92 (25-Me's) and δ0.99 (left hand branch of the 20-Me doublet). Double resonance irradiating 134Hz downfield of the peak at δ0.99 caused it to collapse to a shoulder at δ0.96 (C-21 Me doublet, low field branch). M^{+} 486. Base peak m/e 373 owing to loss of the side chain.

5,6β-Dihydroxy-5α-cholest-2-ene (105)

3β,5α,6β-Cholestane triol-3-tosylate (86) (95mg) was heated under reflux for one hour in 2,6-lutidine (1cm^{3}). The solution was cooled, ice and dilute hydrochloric acid added and the mixture extracted with ether. The ether phase was washed with dilute hydrochloric acid, water, saturated sodium bicarbonate solution, water, then dried and evaporated in vacuo to a white, crystalline solid (105) (66mg). The crude product was

acetylated as described below. (lit.[44] m.p. 133-34°C.).

6β-Acetoxy-5-hydroxy-5α-cholest-2-ene (106)

Crude diol (105) (127mg) was acetylated in pyridine ($1.5cm^3$) and acetic

anhydride (320mg, 10 mole equiv.) heated under reflux for two hours. Work

up in the usual manner gave a yellow oil. Preparative t.l.c. eluting in

50% 60:80 pet.-ether, 50% ether gave (106) (100mg) having ^{1}H n.m.r.

spectrum identical with that in the literature.[33]

6β-Acetoxy-3ξ-bromo-2α,5-epoxy-5α-cholestane (108)

The unsaturated compound (106) (100mg) was dissolved in dioxane ($4.5cm^3$)

and water ($0.9cm^3$). The solution was treated with 10% perchloric acid

($0.225cm^3$) and N-bromoacetamide (37mg, 1.2 mole equiv.) and left to stand

at room temperature for one hour. It was diluted with water and extracted

with ether. The ether phase was washed with water, aqueous sodium

thiosulphate solution, saturated sodium bicarbonate solution, water, then

dried and evaporated in vacuo to a pale yellow oil. The oil contained one

polar fraction, 6β-acetoxy-3α-bromo-2β,5-dihydroxy-5α-cholestane (107)

and a poorly resolved non-polar fraction, 6β-acetoxy-3ξ-bromo-2α,5-epoxy-

5α-cholestane (108). Preparative t.l.c eluting in 96% benzene, 4% ether

gave a mixture of the epimeric bromides (108) (47mg) (38%) having ν_{max}

$1745cm^{-1}$ (ester C=O), $1240cm^{-1}$ (C-O), δ0.7 (3H, s, 13β-Me), δ1.16 (3H, s,

10β-Me), δ0.82, δ0.9, δ1.03 (side chain methyls), δ2.04 (3H, s, $MeCO_2$),

δ3.87-4.57 (3H, m, 2β,3β and 3α methines), δ5.19 (1H, m, W½ 5Hz, 6α-H

for 3β-bromide), δ5.37 (1H, m, W½ 5Hz, 6α-H for 3α-bromide). M^+ 522/524

containing one bromine atom. Base peak m/e 443 owing to the loss of Br

from M^+. (Found 480.2586 $C_{27}H_{45}O_2Br$ requires 480.2602, 463.2543 $C_{27}H_{44}OBr$

requires 463.2564, 462.2500 $C_{27}H_{43}OBr$ requires 462.2486, 447.2268 $C_{26}H_{40}OBr$

requires 447.2332, 443.3523 $C_{29}H_{47}O_3$ requires 443.3513, 444.3562 $C_{29}H_{48}O_3$

requires 444.3591, 384.3379 $C_{27}H_{44}O$ requires 384.3381, 383.3324 $C_{27}H_{43}O$

requires 383.3303. No M^+ at 522.).

6β-Acetoxy-2α,5-epoxy-5α-cholestane (99)

Bromide (108) (16mg) was dissolved in ethanol (1cm^3) containing 5% palladium on charcoal (11mg) and hydrazine hydrate (four drops). The mixture was heated under reflux for two hours then retreated with hydrazine hydrate (three drops) and heating continued for a further one and a half hours. It was treated again with hydrazine hydrate (two drops) and 5% palladium on charcoal (3mg) and heated under reflux for a further ten minutes. The mixture was filtered through hyflo, the filtrate evaporated in vacuo and the residue taken up in ether, washed with water, dilute hydrochloric acid, water, saturated sodium bicarbonate solution, water, then dried and evaporated in vacuo to an oil. The oil was acetylated in pyridine (1cm^3) and acetic anhydride (ten drops) heating at 100°C. for three quarters of an hour then under reflux for half an hour. Work up in the usual manner gave an impure oil (8mg). Preparative t.l.c. eluting in 75% 40:60 pet.-ether, 25% ether gave (99) as an oil. Spectroscopic data and t.l.c. Rf value were identical to those of (99) isolated from the BF$_3$-etherate catalysed rearrangement of (83A). m.p. 75-7°C. (methanol). Mixed m.p. 75-8°C.

6β-Acetoxy-5-methyl-5β-cholest-9-en-3-one (111)

6β-Acetoxy-3β-hydroxy-5-methyl-5β-cholest-9-ene (50mg) was dissolved in acetone and cooled to 0°C. Jones reagent (six drops) was added, the solution stirred for fifteen minutes, diluted with ether, washed with water, dried and evaporated in vacuo to a colourless oil (ca. 50mg) having ν_{max} 1740cm^{-1} (ester C=O), 1715cm^{-1} (ketone C=O), δ4.82 (1H, q, J 4Hz, 6α-H), δ2.04 (3H, s, MeCO$_2$), δ1.06 (3H, s, 5β-Me), δ0.91 and δ0.81 (side chain methyls and 13β-Me). (lit.[45] m.p. 79-80°C.).

6β-Acetoxy-3ξ-hydroxy-5-methyl-5β-cholest-9-ene (110)

Ketone (111) (50mg) was dissolved in ethanol (1cm^3) and sodium borohydride (12mg) added. The solution was allowed to stand at room temperature and the reaction monitored by t.l.c. After one and a half hours glacial acetic acid (three drops) was added, followed by water and ether extraction. The ether extract was washed with saturated sodium bicarbonate solution, water, dried and evaporated in vacuo giving (110) (50mg). Extensive chromatography eluting in 15% acetone, 85% 40:60 pet.-ether separated the isomers giving (110A) (8mg) and (110B) (39mg).

(110A) had δ4.79 (1H, q, J_{inner} 4Hz, J_{outer} 6Hz, 6α-H), δ3.93 (1H, m, W½ 20Hz, 3β-H), δ2.05 (3H, s, MeCO$_2$), δ1.1 (3H, s, 5β-Me), δ0.91, δ0.82 and δ0.8 (side chain methyls and 13β-Me), (lit.[46] m.p. 57°C.).

(110B) had δ4.72 (1H, q, J 5Hz, 6α-H), δ4.07 (1H, t, J 4Hz, 3α-H), δ2.04 (3H, s, MeCO$_2$), δ1.27 (3H, s, 5β-Me), δ0.9 and δ0.79 (side chain methyls and 13β-Me). (lit.[45] m.p. 148-49°C.).

Reaction of 6β-acetoxy-3α,5-epoxy-5α-cholestane (83A) with boron trifluoride diethyl etherate containing sodium borohydride

6β-Acetoxy-3α,5-epoxy-5α-cholestane (83A) (100mg) was dissolved in dry ether (1cm^3). Sodium borohydride (0.33g) was added followed by boron trifluoride diethyl etherate (0.05cm^3). The mixture was stirred at room temperature overnight, diluted with ether, washed with sodium bicarbonate solution, the ether layer dried and evaporated in vacuo to an oil (96mg). Preparative t.l.c. gave 5β,6β-ethylidenedioxy-cholestan-3α-ol (117) (21mg) (21%) as an oil having v_{max} 3440cm^{-1} (O-H), δ5.12 (1H, q, J 5Hz, MeCHO$_2$), δ3.58 (1H, d, J 5Hz, 3β-H), δ1.43 (3H, d, J 5Hz, MeCHO$_2$), δ0.87 (6H, d, J 6Hz, 25-Me's), δ0.92 (3H, d, J 6Hz, 20-Me), δ0.97 (3H, s, 10β-Me), δ0.65 (3H, s, 13β-Me). Double resonance irradiating at δ5.12 caused the doublet at δ1.43 to collapse to a singlet. M$^+$ 446.

Rearrangement of 3α,5-epoxy-6β-hydroxy-5α-cholestane (87A) in

deuteriochloroform

Epoxide (87A) (50mg) was dissolved in deuteriochloroform and allowed to

stand at 35°C. The progress of the rearrangement was followed daily by

recording the ^{1}H n.m.r. spectrum. After four days the epoxide (87A) had

almost completely rearranged to epicholesterol-5β,6β-epoxide (71A) having

δ4.08 (1H, m, W½ 8Hz, 3β-H), δ2.98 (1H, d, J 2Hz, 6α-H), δ0.99 (3H, s,

10β-Me), δ0.63 (3H, s, 13β-Me), δ0.9 and δ0.8 (side chain methyls). A

comparison with spectra of an authentic sample indicated it was

epicholesterol-5β,6β-epoxide.[33]

3α,5-Epoxy-4aβ-hydroxy-A-homo-B-nor-5α-cholestane (123)

Ketone (122) (30mg) was dissolved in ethanol (0.5cm^3) and tetrahydrofuran

(0.5cm^3) and treated with a solution of sodium borohydride (6mg) in ethanol

(0.5cm^3). After five and a half hours acetic acid (one drop) was added,

the mixture diluted with water and extracted with ether. The dried ether

extract was evaporated in vacuo. Recrystallisation from 40:60 pet.-ether

gave (123) (18mg) (60%) m.p. 152-4°C. (lit.[29] m.p. 151.5-153°C.) having

v_{max} 3470cm^{-1} (O-H), δ4.06-4.34 (2H, m, 3β-H and 4aα-H), δ1.04 (3H, s,

10β-Me), δ0.9 and 0.81 (side chain methyls), δ0.66 (3H, s, 13β-Me). M$^+$

402. Base peak m/e 318.

Oxidation with Jones reagent (six drops) in acetone (6cm^3) at 0°C. over

fifteen minutes gave back the original ketone (122).

Monodeuteriation of (122).

Ketone (122) (30mg) was dissolved in 5% w/v triethylamine in dioxane

(3cm^3). Deuterium oxide (twenty drops) was added and the solution heated

under reflux overnight. It was evaporated in vacuo, the residue taken up

in ether, washed with dilute hydrochloric acid and water, the ether layer

dried and evaporated in vacuo to a white crystalline solid (124) having

$\delta 4.67$ (1H, br. d, J 7Hz, 3β-H), $\delta 2.11$ (1H, m, 4β-H), $\delta 0.92$ (3H, d, J 7Hz, 20-Me), $\delta 0.88$ (6H, d, J 7Hz, 25-Me's), $\delta 0.75$ (3H, s, 10β-Me), $\delta 0.66$ (3H, s, 13β-Me). M^+ 401.

Dideuteriation of (122)

Ketone (122) (30mg) was dissolved in dioxane ($3cm^3$) and added to a mixture of sodium (70mg) in deuterium oxide ($1cm^3$) and dioxane ($2cm^3$) under nitrogen. The mixture was heated under reflux for twenty five hours, then diluted with ether, washed with deuterium oxide, the ether layer dried and evaporated in vacuo to a white crystalline solid (125) having $\delta 4.63$ (1H, d, J 7Hz, 3β-H). M^+ 402.

6β-Acetoxy-5-hydroxy-5β-epicholesteryl tosylate (126)

Acetoxy-diol (88) (2.3g) was dissolved in pyridine ($20cm^3$) and p-toluene-sulphonyl chloride (5.0g) added. The solution was allowed to stand at room temperature for forty eight hours, then ice added, the mixture extracted with ether, the ether layer washed with dilute hydrochloric acid, water, dried and evaporated in vacuo. Recrystallisation from ether, 40:60 pet.-ether gave (126) (2.06g) (67%) m.p. 133-5°C. having v_{max} $3550cm^{-1}$ (O-H), $1753cm^{-1}$ (ester C=O), $\delta 7.5$ (aromatic-H's), $\delta 4.73$ and $\delta 4.59$ (two unresolved multiplets, 3β-H, 6α-H), $\delta 2.53$ (3H, s, $\underline{Me}C_6H_4$-), $\delta 2.06$ (3H, s, $MeCO_2$), $\delta 0.93$ (3H, s, 10β-Me), $\delta 0.9$ and $\delta 0.8$ (side chain methyls), $\delta 0.65$ (3H, s, 13β-Me). No molecular ion at m/e 616.

3β,5-Dihydroxy-5α-cholestan-6-one (127C)

Triol (92) (2.3g) was dissolved in ether ($45cm^3$), methanol ($7.5cm^3$) and water ($7.5cm^3$). N-bromosuccinimide (1.08g, 1.05 molar equiv.) was added and the mixture shaken for ten minutes giving an orange solution. Water was added causing the diolone to separate into the upper layer. The lower layer was drained, the ethereal suspension washed with sodium

metabisulphite solution, water, saturated sodium bicarbonate solution, water, then filtered giving (127C) as a white crystalline solid. (lit.[35] m.p. 231-2°C.).

3β,5-Dihydroxy-5β-cholestan-6-one (127B)

Dihydroxy-ketone (127C) (6g) was heated under reflux for twelve hours in 10% methanolic potassium hydroxide solution ($250cm^3$). The methanol was removed in vacuo, water added and extracted with ether. The ether extract was dried and evaporated in vacuo giving a yellow solid which was passed down a column of alumina (200g grade 3) eluting initially with ether giving (127B) (1.6g) and finally with ethyl acetate giving (127C) (2.5g) (lit.[47] m.p. 62°C.).

5-Hydroxy-3β-tosyloxy-5β-cholestan-6-one (129)

Dihydroxy-ketone (127B) (1.6g) and p-toluenesulphonyl chloride (3.6g) were dissolved in pyridine ($18cm^3$). The solution was allowed to stand at room temperature for three days, then poured onto ice and extracted with ether. The ether layer was dried and evaporated in vacuo. Residual pyridine was removed as an azeotrope with benzene yielding (129) as a pale yellow solid (2.3g). (lit.[48] m.p. 144-45°C.).

3α,5-Epoxy-A-homo-B-nor-5α-cholestan-4a-one (122)

Hydroxy-tosylate (129) (2.3g) was heated under reflux for six hours in dry ethanol ($110cm^3$). The ethanol was removed in vacuo yielding a dark brown oil, which when chromatographed on alumina (100g grade 3) eluting with 40:60 pet.-ether gave (122) (0.88g) having δ4.66 (1H, t, J 8Hz, 3β-H), δ2.62 (1H, q, J 8Hz, 4aα-H), δ0.91 and δ0.82 (side chain methyls), δ0.75 (3H, s, 10β-Me), δ0.64 (3H, s, 13β-Me), identical to a ^{1}H n.m.r. spectrum of a sample donated by Alex T. Rowland.

3α,5-Dihydroxy-5β-cholestan-6-one (127A)

Epoxy-ketone (122) (880mg) was dissolved in THF (44cm^3) and treated with 60% perchloric acid (7cm^3). The solution was heated under reflux for four hours, then diluted with ether, washed with water, saturated sodium bicarbonate solution, water, then dried and evaporated in vacuo giving a brown, oily solid. Preparative t.l.c. eluting with 50% benzene, 50% ether gave (127A) (475mg) (52%) having δ3.94 (1H, s, O-H, exchangeable with D$_2$O), δ3.93 (1H, m, W½ 8Hz, 3β-H), δ1.68 (1H, s, O-H, exchangeable with D$_2$O), δ0.9 and δ0.82 (side chain methyls), δ0.69 and δ0.64 (6H, 2xs, 10β-Me and 13β-Me). m.p. 123-4°C. (ether: pet.-ether) (lit.[34] 121-123.5°C.).

5-Hydroxy-3α-tosyloxy-5β-cholestan-6-one (130)

Dihydroxy-ketone (127A) (475mg) was dissolved in pyridine (20cm^3) and treated with p-toluenesulphonyl chloride (1.0g). After two days at room temperature water was added and the mixture extracted with ether. The ether layer was dried and evaporated in vacuo. Residual pyridine was removed as an azeotrope with benzene giving (130) (330mg) (51%) having δ7.53 (m, aromatic protons), δ4.70 (1H, m, W½ 16Hz, 3β-H), δ3.85 (1H, s, O-H), δ2.42 (3H, s, MeC$_6$H$_4$SO$_3$-), δ0.9 and δ0.81 (side chain methyls), δ0.64 and δ0.62 (6H, 2xs, 10β-Me and 13β-Me). (lit.[48] m.p. 137-38°C.).

3α,5β,6β-Cholestane triol-3-tosylate (131)

Ketone (130) (330mg) was dissolved in tetrahydrofuran (10cm^3) and treated with sodium borohydride (20mg). After two days at room temperature the mixture was diluted with water, extracted with ether, the ether layer dried and evaporated in vacuo. Preparative t.l.c. eluting in 50% ether, 50% 40:60 pet.-ether gave (131) (164mg) (50%) having δ4.7 (1H, m, W½ 16Hz, 3β-H), δ3.45 (1H, m, W½ 7Hz, 6α-H), δ7.49 (m, aromatic protons), δ2.42 (3H, s, MeC$_6$H$_4$SO$_3$-), δ0.97 (3H, s, 10β-Me), δ0.9 and δ0.81 (side chain methyls), δ0.65 (3H, s, 13β-Me).

3β,5-Epoxy-6β-hydroxy-5β-cholestane (87B)

A. From potassium t.-butoxide and (126)

Hydroxy-tosylate (126) (75mg) was dissolved in t.-butyl alcohol ($9cm^3$) and potassium t.-butoxide (3 mole equiv.) in t.-butyl alcohol ($1cm^3$) added which immediately formed a precipitate. The mixture was kept at 50°C. for two hours, then acidified with dilute hydrochloric acid, extracted with ether, the ether extract washed with water, dried and evaporated in vacuo. Preparative t.l.c. on alumina, eluting twice with 60% 40:60 pet.-ether, 40% ether gave (87B) (8mg) (16%) and the corresponding acetate (83B) (6mg) (11%).

B. From sodium hydride and (126)

Hydroxy-tosylate (126) (100mg) was dissolved in dry DMF ($3cm^3$) and sodium hydride (4mg, 1 mole equiv.) added under nitrogen. The mixture was stirred at 70°C. for four hours, then poured onto water, acidified with dilute hydrochloric acid, extracted with ether, the ether layer washed with water, dried and evaporated in vacuo. Preparative t.l.c. eluting in 60% ether, 40% 40:60 pet.-ether gave (87B) (50mg) (77%) m.p. 145-50°C. (methanol).

C. From sodium hydride and (131)

Hydroxy-tosylate (131) (82mg) was dissolved in dry DMF ($2cm^3$) under nitrogen and to the stirred solution was added sodium hydride (20mg, 6 mole equiv.). The mixture was stirred at 70°C. for five hours, then water added and extracted with ether. The ether layer was dried and evaporated in vacuo. Preparative t.l.c eluting in 60% ether, 40% 40:60 pet.-ether gave (87B) (28mg) (52%).

(87B) had ν_{max} $3440cm^{-1}$ (O-H), $\delta4.45$ (1H, d, J 6Hz, 3α-H), $\delta3.85$ (1H, m, W½ 4Hz, 6α-H), $\delta1.24$ (3H, s, 10β-Me), $\delta0.9$ and $\delta0.81$ (side chain methyls), $\delta0.68$ (3H, s, 13β-Me). M^+ 402. $[\alpha]_D$ + 26.8 (c 4.2). (Found C, 80.6; H, 11.3 $C_{27}H_{46}O_2$ requires C, 80.54; H, 11.52%).

6β-Acetoxy-3β,5-epoxy-5β-cholestane (83B)

Epoxy-alcohol (87B) (50mg) was dissolved in pyridine (1cm^3) and acetic anhydride (120mg) and heated under reflux for two hours, left to stand at room temperature overnight, then ice added and extracted with ether. The ether layer was dried and evaporated in vacuo. Residual pyridine was removed as an azeotrope with benzene giving (83B) (36mg) having ν_{max} 1745cm^{-1} (ester C=O), δ5.0 (1H, m, W½ 5Hz, 6α-H), δ4.42 (1H, d, J 6Hz, 3α-H), δ2.01 (3H, s, MeCO$_2$), δ1.21 (3H, s, 10β-Me), δ0.9 and δ0.8 (side chain methyls), δ0.68 (3H, s, 13β-Me). (Found 402.3500 C$_{27}$H$_{46}$O$_2$ (M$^+$- C$_2$H$_2$O) requires 402.3486 and 330.2921 C$_{23}$H$_{38}$O requires 330.2913). $[\alpha]_D$+5.1 (c 1.94).

Reaction of 6β-acetoxy-3β,5-epoxy-5β-cholestane (83B) with boron trifluoride diethyl etherate

Epoxide (83B) (150mg) was dissolved in benzene (5cm^3) and to the stirred solution was added boron trifluoride diethyl etherate (0.02cm^3). After ten minutes at room temperature ether was added, the solution washed with water, dried and evaporated in vacuo giving an oil. Preparative t.l.c. eluting with 25% ethyl acetate, 75% benzene gave several fractions, one of which was identified as 6β-acetoxy-3β,5-dihydroxy-5β-cholestane (132) (94mg) (60%), the remaining fractions were impure and unidentified. (132) had ν_{max} 3430cm^{-1} (br. O-H), 1740cm^{-1} (ester C=O), δ4.69 (1H, m, W½ 6Hz, 6α-H), δ3.92 (1H, m, W½ 5Hz, 3α-H), δ3.35 (1H, s, O-H, exchanged with D$_2$O), δ3.83 (1H, s, O-H, exchanged with D$_2$O), δ2.06 (3H, s, MeCO$_2$), δ1.02 (3H, s, 10β-Me), δ0.88 and δ0.8 (side chain methyls), δ0.66 (3H, s, 13β-Me). (Found C, 75.7; H, 11.1 C$_{29}$H$_{50}$O$_4$ requires C, 75.28; H, 10.89%) m.p. 184-6°C. $[\alpha]_D$ +5.1 (c 2.94).

6β-Acetoxy-5-hydroxy-5β-cholestan-3-one (91)

Diol (132) (15mg) was dissolved in acetone (1cm^3), the solution cooled to

0°C. and Jones reagent (two drops) added. The mixture was stirred for five minutes, then diluted with water, extracted with ether, dried and evaporated in vacuo to a white crystalline solid (12mg) having a ^{1}H n.m.r. spectrum identical to that of (91) prepared by oxidation of (88). Recrystallisation from ether, 40:60 pet.-ether gave 6mg m.p. 184-8°C.

PART THREE.   Photolysis of 3ξ,5ξ-epoxy steroids

INTRODUCTION

Following our interest in the photolysis of β,γ-epoxy ketones and the

ready availability of the 3ξ,5ξ-epoxy-6-keto steroids (81A) and (81B)

it was decided to investigate the photochemical reactivity of these

epimers.

RESULTS AND DISCUSSION

Preparation of 3α,5-epoxy-5α-cholestan-6-one (81A)

Oxidation of (87A) with chromium trioxide gave the epoxy-ketone (81A) in 68% yield.
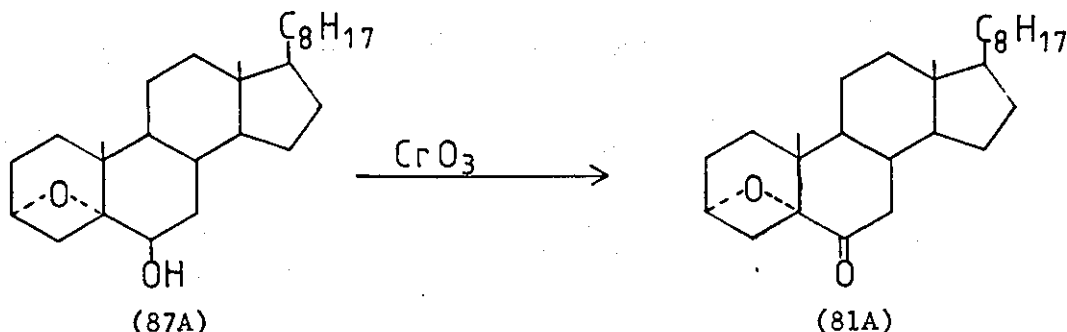
The epoxy-ketone (81A) had v_{max} 1725cm^{-1} (C=O). The 90MHz ^{1}H n.m.r. spectrum had important peaks at δ3.0 (1H, q, J_{gem} 10Hz, J_{vic} 7Hz, 4α-H), δ4.45 (1H, d, J 7Hz, 3β-H) and δ1.86 (1H, d, J 10Hz, 4β-H). Double irradiation experiments irradiating initially at δ4.45 caused the quartet at δ3.0 to collapse to a doublet (J 10Hz). Similarly, irradiation at δ3.0 caused the doublet at δ4.45 to collapse to a broad singlet, indicating vicinal coupling of 7Hz between the 3β- and 4α-protons. The irradiation at δ3.0 also caused the doublet at δ1.86 to collapse to a singlet and similar irradiation at δ1.86 caused the quartet at δ3.0 to collapse to a doublet (J 7Hz), indicating geminal coupling of 10Hz between the 4α- and 4β-protons. The irradiation at δ4.45 had no effect on the doublet at δ1.86 indicating lack of coupling between the 3β- and 4β-protons, which, as models indicate, are at 90° to each other. The mass spectrum confirmed the molecular weight having a molecular ion peak at m/e 400.

Preparation of 3β,5-epoxy-5β-cholestan-6-one (81B)

Oxidation of (87B) with Jones reagent gave the corresponding ketone (81B).
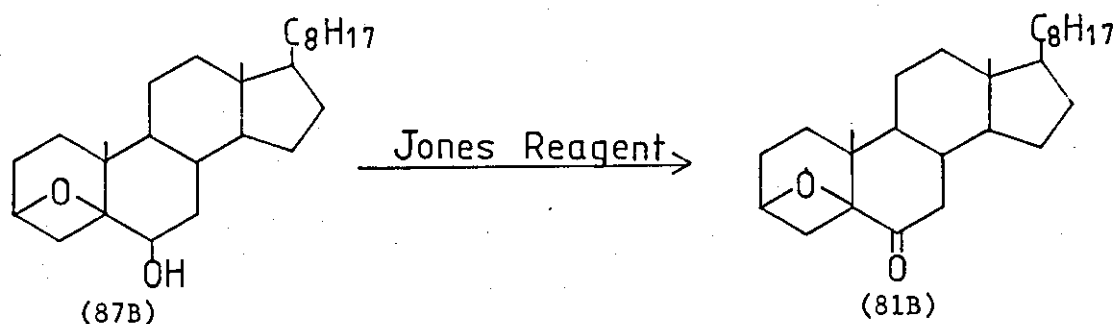
The epoxy-ketone (81B) had ν_{max} 1715cm^{-1} (C=O). In the 60MHz ^{1}H n.m.r. spectrum a triplet (J 7Hz) centred at δ2.8 was assigned to the 4β-proton, and a broad doublet (J 7Hz) centred at δ4.41 was assigned to the 3α-proton. The mass spectrum had a molecular ion peak at m/e 400 which was also the base peak. Other fragmentations are shown below:
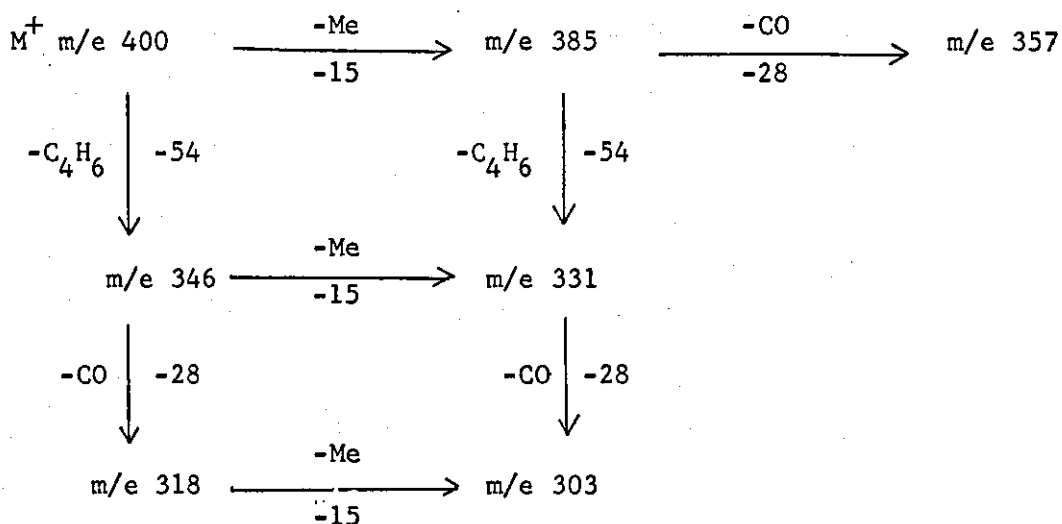
Photolysis of 3α,5-epoxy-5α-cholestan-6-one (81A) in ether

The epoxy-ketone (81A) was photolysed in ether. Preparative t.l.c. gave several fractions, one of which was unreacted starting material (42%). The remaining fractions were still complex mixtures although the major fraction did contain an aldehydic species as indicated by the ^{1}H n.m.r spectrum. However, attempts to purify this aldehyde by preparative t.l.c. resulted only in its decomposition.

Photolysis of 3α,5-epoxy-5α-cholestan-6-one (81A) in benzene

The epoxy-ketone (81A) was photolysed in benzene and the reaction was monitored by t.l.c. The rearrangement proceeded rapidly and smoothly to give a mixture, containing largely one component by t.l.c. The spectra of the crude product suggested that this major component was compound (134).

(134)
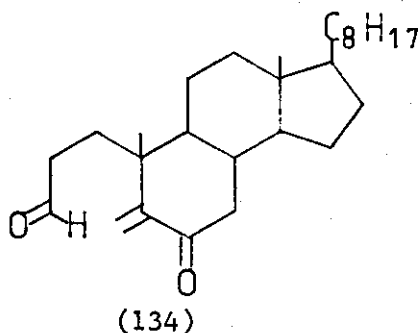
Initial excitation causes a n→π* transition of one of the lone pair electrons of the carbonyl oxygen resulting in a weakening of the α and β bonds adjacent to the carbonyl group. The C-O bond is a weaker bond than the C-C bond and hence the excitation results in C(5)-O bond cleavage giving a diradical species which rearranges giving compound (134), having ν_{max} 1604cm^{-1} (C=C), 1694cm^{-1} (α,β-unsaturated C=O), 1726cm^{-1} (aldehydic C=O) and 2725cm^{-1} (aldehydic C-H). The 60MHz ^{1}H n.m.r. spectrum had important peaks at δ9.71 (1H, m, W½ 4Hz, CHO) and δ5.81 and δ5.04 (2H, 2xm, W½ 3Hz, C=CH$_2$). The signal at δ5.81 arises from the exocyclic methylene group proton which is nearest to the carbonyl group oxygen atom.

However, it soon became apparent that (134) was inherently unstable. It could not be kept for any great length of time under nitrogen in the freezer, nor could it be purified by preparative t.l.c. It could not be crystallised and attempts to prepare the dimedone derivative again caused it to decompose to a mixture. Reduction of the crude product, however, with sodium borohydride in ethanol and tetrahydrofuran gave a mixture containing the hydroxy-ketone (135). Acetylation of (135) gave (136) which was purified by preparative t.l.c.

The overall sequence, including photolysis and characterisation of the

crude product, is shown below. (Scheme XXII):

(81A)   (134)

(136)   (135)
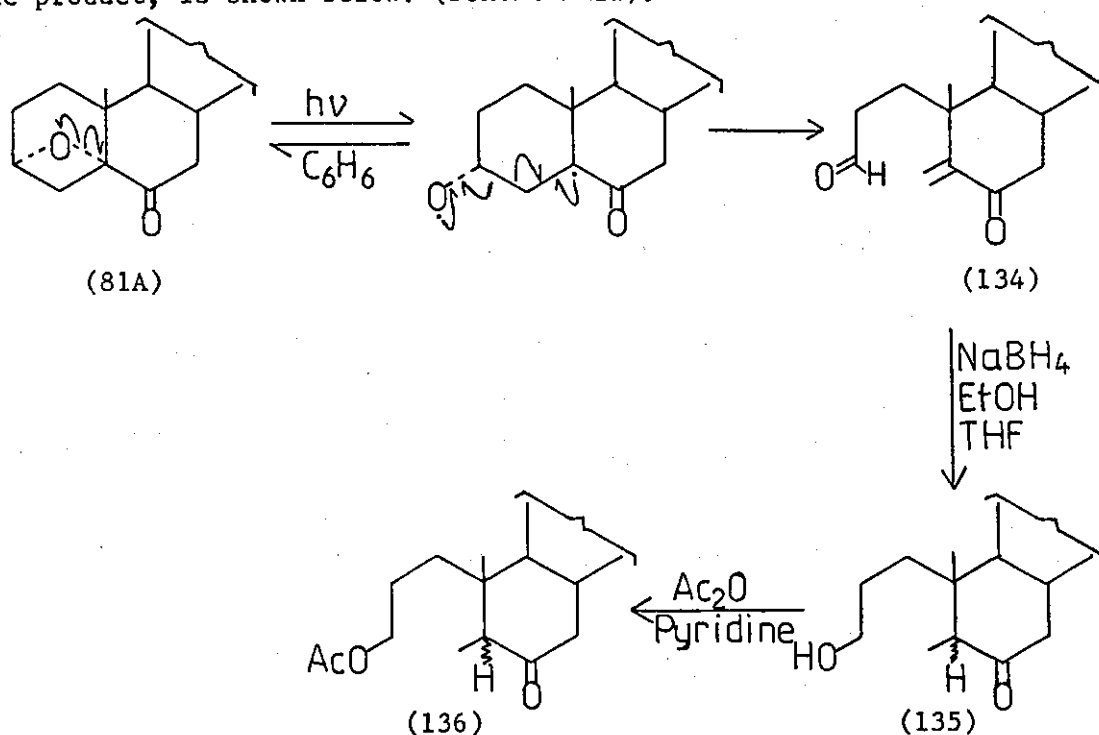
Scheme XXII

The product of reduction (135) had a carbonyl stretching frequency in the

infrared spectrum at 1705cm^{-1}, indicating that reduction of the α,β-

unsaturated ketone system had proceeded via 1,4-addition effectively

reducing the exocyclic olefinic bond. The presence of a hydroxyl absorption

band (v_{max} 3400cm^{-1}) indicated that the reduction of the aldehyde moiety

proceeded smoothly. The 60MHz ^{1}H n.m.r. spectrum of the crude reduction

product clearly indicated an impurity containing olefinic protons as seen

by a series of small peaks between δ4.7-5.2. A broad multiplet at δ3.6

was assigned to the methylene adjacent to the hydroxyl function and the

extra methyl at C-5 was a doublet (J 7Hz) centred at δ0.91.

Acetylation gave a product (136) which had a similarly patterned ^{1}H n.m.r.

spectrum differing only in a distinct downfield shift of the 3-methylene

signal. The ^{1}H n.m.r. spectrum of the major fraction which was separated

by chromatography on silica gel had peaks at δ4.04 (2H, m, W½ 10Hz, CH_2OAc)

and δ2.05 (3H, s, MeCO). The infrared spectrum had v_{max} 1717cm^{-1} (ketone

C=O) and 1746cm^{-1} (ester C=O). The mass spectrum confirmed the molecular

weight of (136) having a molecular ion peak at m/e 446 which fragmented

to m/e 345, probably owing to the loss of $CH_3CO_2(CH_2)_3$.

The second fraction after chromatography containing olefinic protons was

still clearly a mixture and was not further investigated.

On the basis of the weight of (136) obtained from the photolysis of (81A)

the yield of (134) was 38%. However, the instability of (134) will rapidly

decrease the amount available for characterisation and hence the actual

yield is probably somewhat higher.

Photolysis of 3β,5-epoxy-5β-cholestan-6-one (81B) in benzene

The epoxy-ketone (81B) was photolysed in benzene and the reaction was

monitored by t.l.c. After five and a half hours photolysis time the epoxy-

ketone was largely unchanged. It was therefore rephotolysed for a further

twenty hours, but still remained largely unchanged at the end of this

period as denoted initially by t.l.c. and later by its [1]H n.m.r. spectrum.

No further investigation was carried out.

Photolysis of 3α,5-epoxy-A-homo-B-nor-5α-cholestan-4a-one (122) in benzene

The epoxy-ketone (122) was photolysed in benzene and the reaction was

monitored by t.l.c. After five hours photolysis time the epoxy-ketone was

unchanged. It was not further investigated.

It is not known whether the photochemical rearrangement of (81A) proceeds

via an excited singlet or triplet diradical species. A long lived triplet

species may allow sufficient time for conformational rearrangement to

occur which may be necessary before further bond formation or cleavage

is possible. On the other hand, recombination to give starting material

may be the preferred route for a relatively short lived singlet species,

as perhaps in the case of (81B) or (122). However, this is purely

speculative and requires further investigation..

The photochemical stability of the β-epoxide (81B), compared to that of the

α-epoxide (81A), may also arise as a result of the relative configurations

of the A-rings. An inspection of models shows that in the case of the

α-epoxide the A-ring will adopt a boat conformation which incorporates the

oxygen atom with the 3β,5β-methylene bridge as a substituent. In contrast,

the A-ring of the β-epoxide, incorporating the oxygen atom, will adopt

a more stable chair conformation with a substituent 3α,5α-methylene bridge.
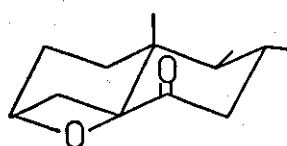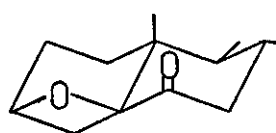
(81A)   (81B)

However, an inspection of models also shows that the oxygen atom of (122)

will be incorporated in a 6-membered ring which will adopt the less stable

boat conformation. The photochemical stability of (122) may arise as a

result of the stability of the cycloheptanone ring which will adopt a chair

conformation.

EXPERIMENTAL

3α,5-Epoxy-5α-cholestan-6-one (81A)

Chromium trioxide (2.15g, 0.0215moles) was added to a mixture of pyridine (3.39g, 0.043moles) and dichloromethane ($53.5cm^3$) and allowed to stir at room temperature for fifteen minutes, during which time a deep burgundy colour appeared. 6β-Hydroxy-3α,5-epoxy-5α-cholestane (1.43g, 3.55mmoles) in a small volume of dichloromethane was added and the mixture stirred at room temperature for a further fifteen minutes. The dichloromethane was decanted, the black, tarry residue washed with dichloromethane and the combined extracts evaporated in vacuo. The residue was taken up in ether, filtered, washed with 4%w/w sodium bicarbonate solution and brine, then dried and evaporated in vacuo to a white, crystalline solid. Excess-pyridine was removed as an azeotrope in benzene. Recrystallisation from methanol gave 3α,5-epoxy-5α-cholestan-6-one (0.96g) (68%) m.p. 120-2°C. $[\alpha]_D$ +5.6° (c 5.7), ν_{max} $1725cm^{-1}$ (C=O), δ0.66 (3H, s, 13β-Me), δ0.77 (3H, s, 10β-Me), δ0.92 (3H, d, J 7Hz, 20-Me), δ0.86 (6H, d, J 7Hz, 25-Me's), δ3.0 (1H, q, J 10Hz, 7Hz, 4α-H), δ4.45 (1H, br. d, J 7Hz, 3β-H), δ1.86 (1H, d, J 10Hz, 4β-H). Double irradiation at δ4.45 caused the quartet at δ3.0 to collapse to a doublet (J 10Hz) but caused no change in the doublet (J 10Hz) at δ1.86. Double irradiation at δ3.0 caused the doublet at δ4.45 to collapse to a broad singlet, and the doublet at δ1.86 also to collapse to a singlet. Double irradiation at δ1.86 caused the quartet at δ3.0 to collapse to a doublet (J 7Hz). M^+ 400. Base peak m/e 400. (Found C, 81.0; H, 11.2 $C_{27}H_{44}O_2$ requires C, 80.94; H, 11.07%).

3β,5-Epoxy-5β-cholestan-6-one (81B)

Alcohol (87B) (50mg) was dissolved in acetone ($10cm^3$), cooled to 0°C. and treated with Jones reagent (5 drops) over five minutes. The mixture was diluted with water and extracted with ether giving (81B) (49mg). Recrystallisation from methanol gave (28mg) m.p. 166-71°C. (analytical

sample m.p. 167-72°C.), ν_{max} 1715cm^{-1} (C=O), δ4.41 (1H, d, J 7Hz, 3α-H),

δ2.8 (1H, t, J 7Hz, 4β-H), δ0.98 (3H, s, 10β-Me), δ0.9 and δ0.81 (side

chain methyls), δ0.66 (3H, s, 13β-Me). M$^+$ 400. Base peak m/e 400. (Found

C, 80.8; H, 10.9 $C_{27}H_{44}O_2$ requires C, 80.94; H, 11.07%).

Photolysis of 3α,5-epoxy-5α-cholestan-6-one (81A) in benzene

3α,5-Epoxy-5α-cholestan-6-one (50mg) was photolysed in dry benzene (130cm^3)

for two hours. The benzene was removed in vacuo, the residue (134) dissolved

in dry tetrahydrofuran (2cm^3) and a solution of sodium borohydride (5mg)

in ethanol (0.5cm^3) added. The reaction was monitored by t.l.c. After

forty five minutes the solution was diluted with water, brought to pH 5

with dilute acetic acid and a faint white precipitate extracted into ether.

The ether layer was washed with saturated sodium bicarbonate solution and

water, dried and evaporated in vacuo giving a colourless oil (135). This

oil was dissolved in pyridine (1cm^3) and acetic anhydride (30 drops)

added. It was allowed to stand at room temperature overnight, then ice

added and extracted with ether. The ether extract was dried and evaporated

in vacuo and excess pyridine was removed as an azeotrope with benzene.

Preparative t.l.c. on silica gel eluting with 60% 40:60 pet.-ether, 40%

ether gave (136) (21mg).

Compound (134) had ν_{max} 1604cm^{-1} (C=C), 1694cm^{-1} (α,β-unsaturated C=O),

1726cm^{-1} (aldehydic C=O) and 2725cm^{-1} (aldehydic C-H), δ9.71 (1H, m, W½

4Hz, CHO), δ5.81 and δ5.04 (2H, 2xm, W½ 3Hz, C=CH$_2$).

Compound (135) had ν_{max} 1705cm^{-1} (C=O) and 3400cm^{-1} (O-H), δ3.6 (2H, m,

CH$_2$OH), δ0.65 and δ0.68 (6H, 2xs, 10β-Me and 13β-Me), δ0.81 and δ0.9

(side chain methyls) and δ0.91 (3H, d, J 7Hz, 5-Me).

Compound (136) had ν_{max} 1717cm^{-1} (ketone C=O) and 1746cm^{-1} (ester C=O),

δ4.04 (2H, m, W½ 10Hz, CH$_2$OAc), δ2.05 (3H, s, MeCO$_2$), δ0.9 and δ0.81

(side chain methyls), δ0.67 and δ0.69 (6H, 2xs, 10β-Me and 13β-Me) and

δ0.91 (3H, d, J 7Hz, 5-Me). M$^+$ 446. Base peak m/e 43.

PART FOUR. Structure Elucidation of 3β-Methyl-A-nor-5β-cholestan-5-ol-6-one

RESULTS AND DISCUSSION

During our investigation of the ring-closure of 5,6β-dihydroxy-5α-cholesteryl tosylate (86) with potassium t.-butoxide in t.-butanol, a by-product, namely 3β-methyl-A-nor-5β-cholestan-5-ol-6-one (137) (23%) was isolated. Structure elucidation was supported by spectroscopic analysis. The hydroxy-ketone (137) had ν_{max} 3480cm^{-1} (H-bonded O-H) and 1695cm^{-1} (H-bonded C=O). Evidence for the intra-molecular nature of the hydrogen bonding was obtained from solution infrared spectra which did not change on dilution, and from the ^{1}H n.m.r. spectrum where the signal owing to the hydroxyl proton exchanged only slowly with D_2O. The 300MHz ^{1}H n.m.r. spectrum had important peaks at δ0.63 (3H, s, 13β-Me), δ0.83 and δ0.84 (6H, 2xd, J 7Hz, 25-Me's), δ0.86 (3H, s, 10β-Me), δ0.88 (3H, d, J 7Hz, 20-Me) and δ3.8 (1H, s, O-H). The presence of an extra methyl at C-3 was clearly seen by the doublet (J 7Hz) at δ0.79.

The high resolution accurate mass spectrum indicated a molecular ion at m/e 402.3487 ($C_{27}H_{46}O_2$). Fragmentations from the molecular ion were measured at m/e 374.3546 ($C_{26}H_{46}O$) and m/e 318.2918 ($C_{22}H_{38}O$).

Further support for the extra methyl group was obtained from the noise decoupled ^{13}C n.m.r. spectrum having a singlet at δ13.0, a quartet in the off-resonance decoupled spectrum.

Lead tetraacetate oxidation of (137) gave a complex mixture. No acidic material, which may have been expected from an α-hydroxy ketone, was isolated. When photolysed in ether (137) gave a complex mixture from which 48% recovered starting material was obtained. Attempted dehydration with thionyl chloride in pyridine resulted only in a quantitative recovery of starting material.

Reduction, on the other hand, either with sodium borohydride or with lithium aluminium hydride (see table V) gave a mixture of 6α- and 6β- diols, (138A) and (138B) respectively.

(137)
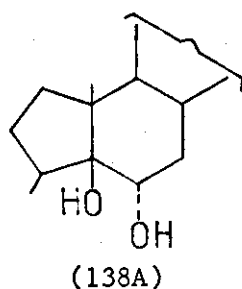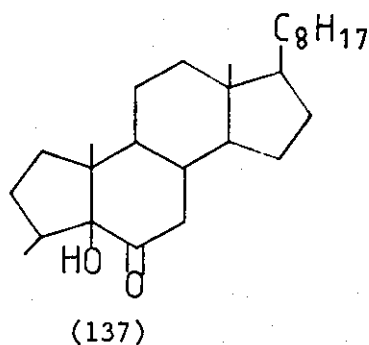
(138A)
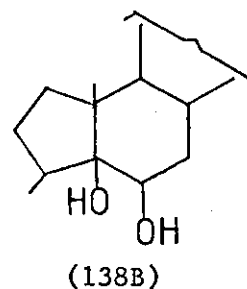

(138B)

Table V

Reduction of	% Yield	
(137) with:	(138A)	(138B)
1) NaBH$_4$	48	45
	57	39
2) LiAlH$_4$	32	60
	34	56

The configuration of the 6-OH was determined from a comparison of the 6-methine splitting pattern and from the chemical shift of the 10β-Me group. The diol (138A) had v_{max} 3430cm^{-1} (O-H). The 90MHz ^{1}H n.m.r. spectrum showed important peaks at δ1.08 (3H, d, J 7Hz, 3β-Me) and δ3.54-3.92 (1H, m, W½ 18Hz, 6β-H).

The diol (138B) had v_{max} 3560cm^{-1} (O-H). The 60MHz ^{1}H n.m.r. spectrum had important peaks at δ0.9 (3H, d, J 7Hz, 3β-Me), δ1.03 (3H, s, 10β-Me), δ3.76 (1H, m, W½ 6Hz, 6α-H) and δ4.62 (1H, br. s, W½ 2Hz, O-H).

The 5β-acetate (139) was obtained by the acid-catalysed acetylation of (137).

(139)
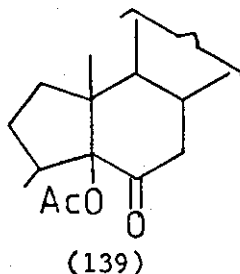
(139) had ν_{max} 1715cm^{-1} (ketone C=O) and 1750cm^{-1} (acetate C=O). In the

60MHz ^{1}H n.m.r. spectrum the acetate methyl appeared as a singlet at δ2.09.

The high resolution accurate mass spectrum gave no molecular ion at m/e 444,

but a fragmentation of the molecular ion was detected at m/e 401.3407

($C_{27}H_{45}O_2$) owing to the loss of 43(CH$_3$CO) from the molecular ion.

Treatment of (138A) or (138B) with lead tetraacetate or periodic acid gave

the same oxidation product, the keto-aldehyde (140), having ν_{max} 1710cm^{-1}

(aldehydic C=O) and 1735cm^{-1} (5-ring ketone C=O). The 90MHz ^{1}H n.m.r.

spectrum had important peaks at δ2.59 (2H, m, W½ 7Hz, CH$_2$CHO) and δ9.78

(1H, m, W½ 3Hz, CHO). Reduction of (140) prepared from either (138A) or

(138B) gave the same ketol (141) having ν_{max} 1735cm^{-1} (5-ring C=O) and

3400cm^{-1} (br. O-H). In the 90MHz ^{1}H n.m.r. spectrum a triplet (J 8Hz) at

δ3.74 was assigned to the methylene adjacent to the alcohol function. A

molecular ion at m/e 404 was apparent in the mass spectrum.

The 3,5-dinitrobenzoate of (141) had a ^{1}H n.m.r spectrum similar to that

of the parent alcohol, except for a downfield shift to δ4.45 for the 7-

methylene, and the appearance of an extra peak at δ9.04 owing to the

aromatic protons of the benzoate ring. A molecular ion could not be

detected in the mass spectrum.
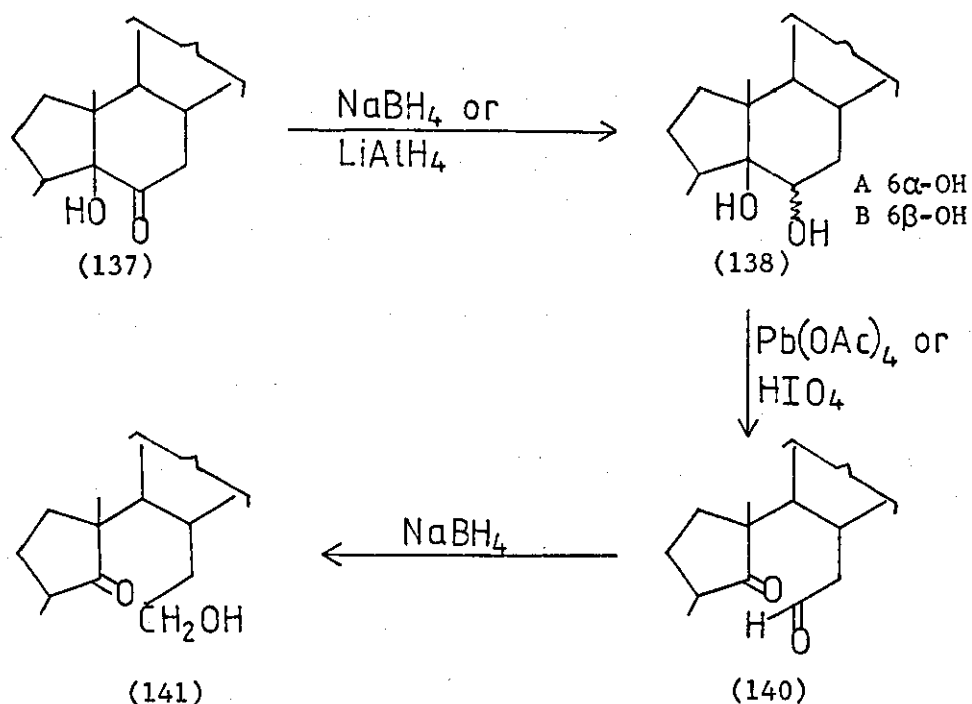
Periodic acid oxidation of the hydroxy-ketone (137) gave the keto-acid (142).
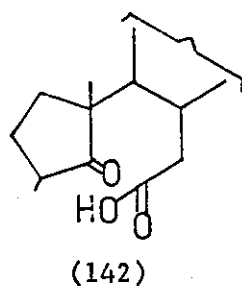
The keto-acid (142) had ν_{max} 1705cm^{-1} (acid C=O), 1735cm^{-1} (5-ring C=O) and 3000cm^{-1} (br. O-H). The 60MHz ^{1}H n.m.r. spectrum had important peaks at δ2.52 (2H, m, W½ 6Hz, $\underline{CH_2}$COOH) and δ1.05 (3H, s, 10β-Me). An acidic proton was not detected in the ^{1}H n.m.r. spectrum. However, the spectrum was very similar to that of the aldehyde (140). A molecular ion peak at m/e 418 confirmed the molecular weight and further support for the structure of (142) was gained from the loss of 44(CO_2) from the molecular ion to m/e 374.

Final proof of the structure (137),[49] including the establishment of the 3β,5β-configuration was achieved through X-ray chrystallography. Direct methods were employed using MULTAN and the present conventional R is 0.089 from the 1459 observed reflections (diffractometer data).
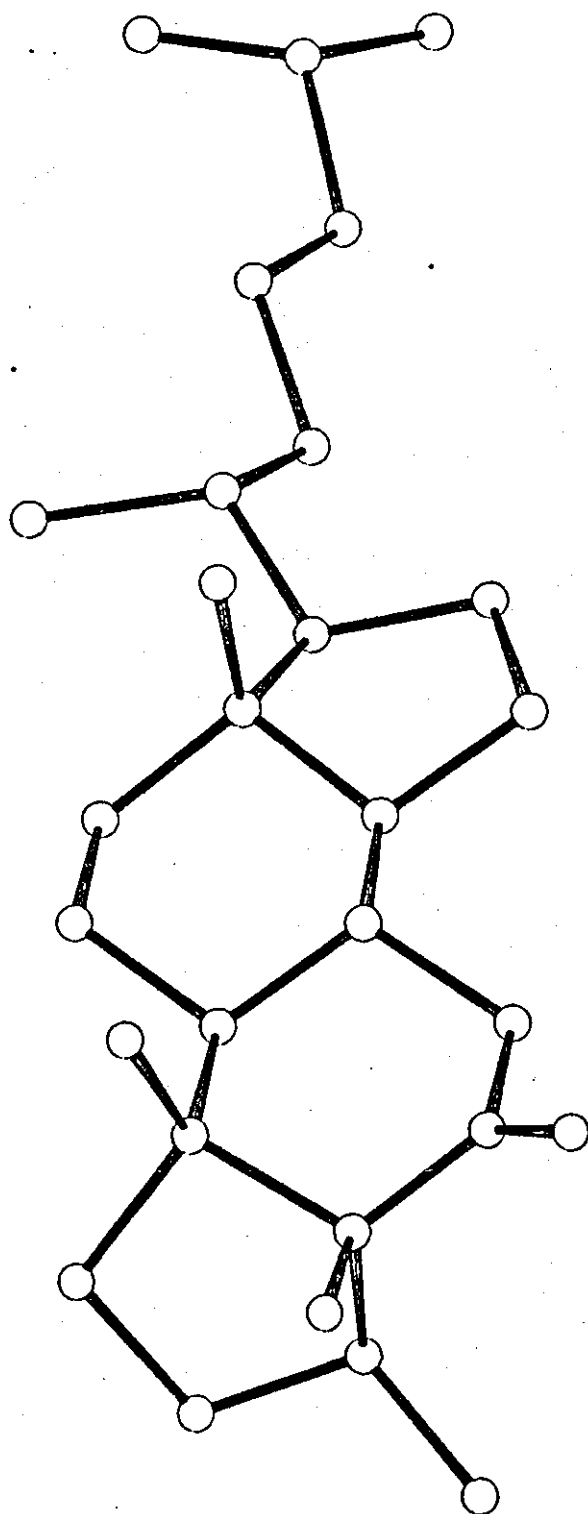
The hydroxy-ketone (137) is thought to arise via acyloin (143) formed from alkoxide (144) (Scheme XXIII).
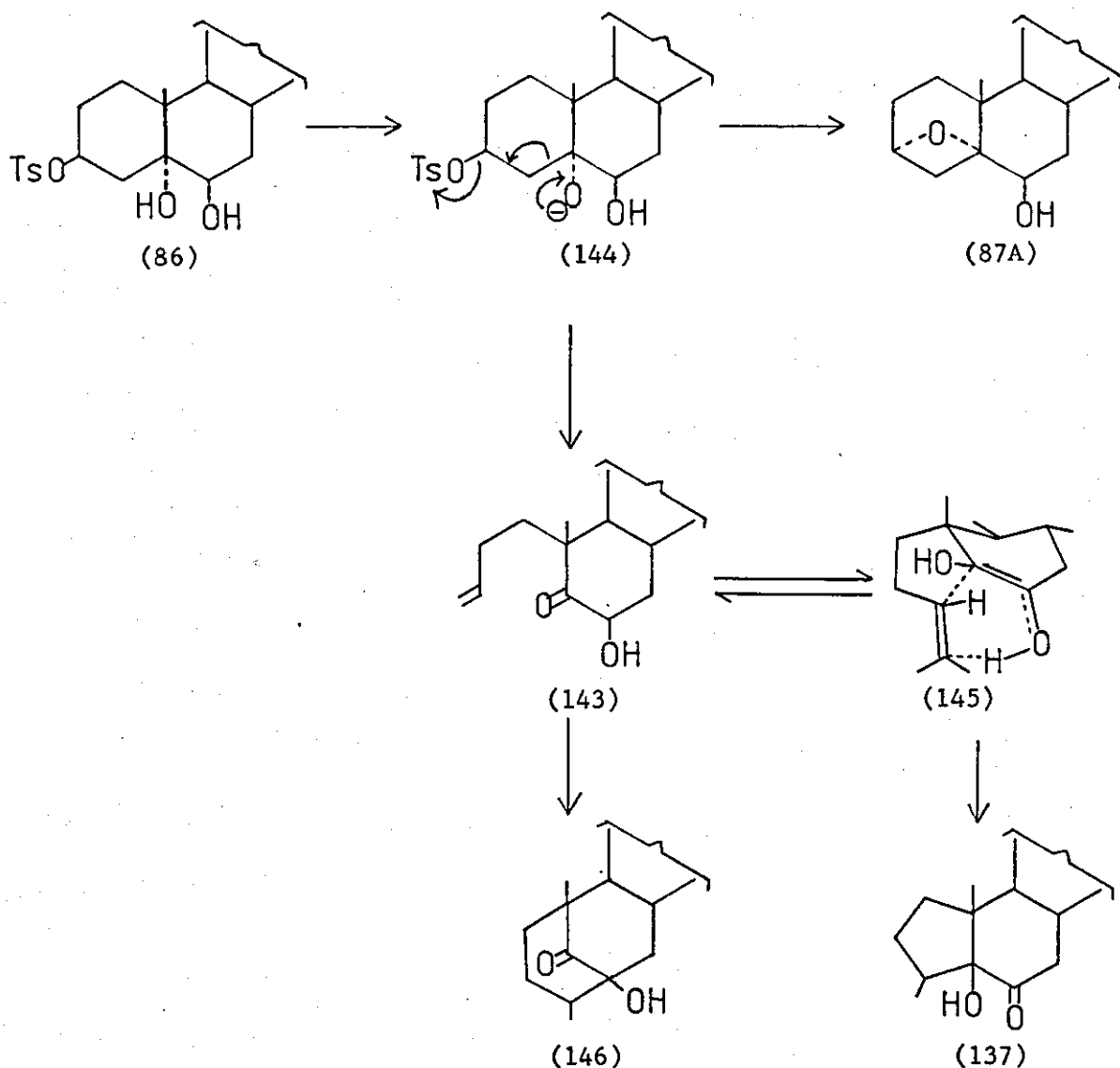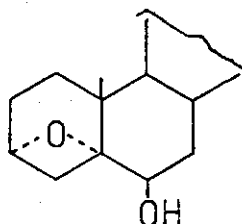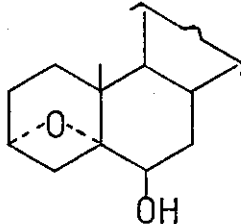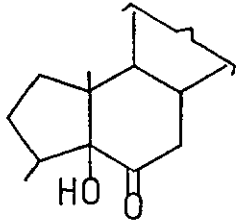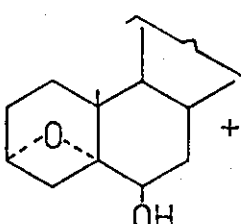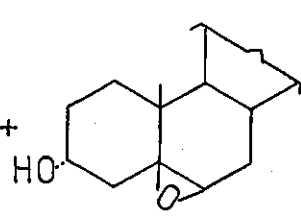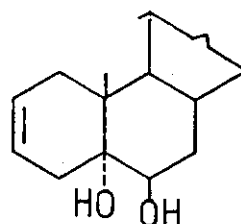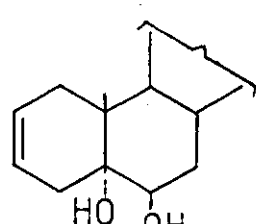
Scheme XXIII

Treatment of (86) with base leads to the formation of alkoxide (144) which then can either undergo ring-closure to epoxide (87A), or ring-opening to acyloin (143). The acyloin (143) is then capable of an ene reaction via intermediate (145) giving the ketol (137). Intermediate (145) is the most favourable transition state and would lead to the observed stereochemistry. The alternative ene reaction to the hydroxy-ketone (146) is not observed.

The acyloin (143) could not be isolated although the effect of different

bases on (86) was studied. The results are shown in table VI.

Table VI

BASE	MOLE RATIO (137): BASE	RESULT
NaH	1:1.1	
K⊕ t.-BuO⊖	1:1	S.M. + others
K⊕ t.-BuO⊖	1:2	
Dimsyl	1:1.1	
Li$_2$CO$_3$ in a) DMF	1:5	
b) t.-BuOH	1:5	S.M.
c) MeOH/H$_2$O	1:5	S.M. +

Acetylation of (86) at the 6β-OH gave (147) which when treated with potassium t.-butoxide gave a mixture, as indicated by its [1]H n.m.r. spectrum, consisting mainly of the epoxide (87A), some epicholesterol epoxide (71A) and some unknown olefinic material. The splitting pattern of the olefinic material however, was not consistent with that expected for the acyloin (143) which should show a distinct ABX splitting pattern. Similarly, residual olefinic material formed during the cyclisation of (86) with base was not consistent with that expected.

EXPERIMENTAL

3β-Methyl-A-nor-5β-cholestan-5-ol-6-one (137)

5,6β-Dihydroxy-5α-cholesteryl tosylate (12.3g, 0.021moles) was dissolved

in dry t.-butyl alcohol ($1dm^3$), the solution warmed to 50°C. and, under

nitrogen, a solution of potassium t.-butoxide (4.65g, 0.042moles) in

t.-butyl alcohol ($40cm^3$) added. The solution was kept at 50°C. for two

hours, then poured onto ice, acidified with dilute hydrochloric acid and

extracted with ether. The combined ether extracts were washed with

saturated sodium bicarbonate solution, dried and evaporated in vacuo to

a colourless oil. The oil was passed down a column of grade three alumina

(450g) and eluted with benzene. The first major fraction was 3β-methyl-

A-nor-5β-cholestan-5-ol-6-one (2g) (23%). Partial purification by prep-

arative t.l.c. eluting with 25% ether, 75% 40:60 pet.-ether followed by

recrystallisation from methanol gave the pure product (1.2g) m.p. 116-

118°C. $[\alpha]_D$ -12.2° (c 3.28), v_{max} $1695cm^{-1}$ (C=O), $3480cm^{-1}$ (O-H). The

300MHz ^{1}H n.m.r. spectrum had δ0.63 (3H, s, 13β-Me), δ0.79 (3H, d, J 7Hz,

3β-Me), δ0.83 and δ0.84 (6H, 2xd, J 7Hz, 25-Me's), δ0.86 (3H, s, 10β-Me),

δ0.88 (3H, d, J 7Hz, 20-Me), δ3.8 (1H, s, O-H, exchanged slowly with D_2O).

M^{+} 402. Base peak m/e 318. M^* 270.4 (374-318 C_4H_8), M^* 347.9 (402-374 CO).

(Found M^{+} 402.3487 $C_{27}H_{46}O_2$ requires 402.3497, 374.3546 $C_{26}H_{46}O$ requires

374.3548 and 318.2918 $C_{22}H_{38}O$ requires 318.2913). (Found C, 80.8; H, 11.75

$C_{27}H_{46}O_2$ requires C, 80.54; H, 11.51%).

5,6ξ-Dihydroxy-3β-methyl-A-nor-5β-cholestane (138) by reduction of (137)

a) with sodium borohydride

Ketol (137) (155mg) in ethanol ($2.5cm^3$) and tetrahydrofuran ($3cm^3$) was

treated with a solution of sodium borohydride (36mg) in ethanol ($2.5cm^3$).

After standing at room temperature overnight it was retreated with sodium

borohydride (20mg) and heated under reflux for half an hour. Water was

added and the mixture extracted with ether, dried and evaporated in

vacuo. Preparative t.l.c. eluting in 50% ether, 50% 40:60 pet.-ether gave

5,6α-dihydroxy-3β-methyl-A-nor-5β-cholestane (138A) (75mg) (48%) and 5,6β-

dihydroxy-3β-methyl-A-nor-5β-cholestane (138B) (70mg) (45%).

b) with lithium aluminium hydride

Ketol (137) (100mg) in dry ether ($2cm^3$) was added, under nitrogen, to a

stirred suspension of lithium aluminium hydride (24mg) in ether ($1cm^3$).

The mixture was stirred at room temperature for fifteen minutes, ethyl

acetate added followed by water and extraction with ether. The ether

extract was dried and evaporated in vacuo to an oil. Preparative t.l.c.

eluting in 50% ether, 50% 40:60 pet.-ether gave (138A) (34mg) (34%) and

(138B) (56mg) (56%).

(138A) had v_{max} $3430cm^{-1}$ (O-H), $\delta 0.65$ (3H, s, 13β-Me), $\delta 0.9$ (3H, s, 10β-Me),

$\delta 1.08$ (3H, d, J 7Hz, 3β-Me), $\delta 0.82$ and $\delta 0.9$ (side chain methyls), $\delta 3.54$-

3.92 (1H, m, 6β-H). M^{+} 404. m.p. 142-3°C. (methanol), $[\alpha]_D$ +50.6 (c 3.045).

(Found C, 79.8; H, 11.9 $C_{27}H_{48}O_2$ requires C, 80.14; H, 11.96%). ^{13}C n.m.r.

data in table VII.

(138B) had v_{max} $3460cm^{-1}$ (O-H), $\delta 0.67$ (3H, s, 13β-Me), $\delta 1.03$ (3H, s, 10β-Me),

$\delta 0.9$ (3H, d, J 7Hz, 3β-Me), $\delta 0.81$ and $\delta 0.9$ (side chain methyls), $\delta 3.76$

(1H, m, W½ 6Hz, 6α-H), $\delta 4.62$ (1H, br. s, W½ 2Hz, O-H). M^{+} 404. m.p. 130-

1°C. (methanol), $[\alpha]_D$ +37.4 (c 3.26). (Found M^{+} 404.3658 $C_{27}H_{48}O_2$ requires

404.3653).

3β-Methyl-A-nor-5,6-seco-cholestan-5-one-6-al (140)

1) by oxidation of (138A)

a) with periodic acid

Diol (138A) (30mg) in ether ($1cm^3$) was treated with a solution of periodic

acid in ether ($1.25cm^3$). After half an hour at room temperature the

mixture was filtered, the filtrate diluted with ether, washed with water,

sodium bicarbonate solution and water, dried and evaporated in vacuo

giving (140) (30mg).

b) with lead tetraacetate

Diol (138A) (50mg) was dissolved in dry benzene (2cm^3) and, under nitrogen, lead tetraacetate (60mg) added. After one and a half hours water was added and the mixture extracted with ether. The ether layer was dried and evaporated in vacuo to a colourless oil (140) (ca. 54mg).

2) by oxidation of (138B) with periodic acid

Diol (138B) (30mg) was oxidised as in 1a) above giving (140) (29mg). The aldehydo-ketone (140) had v_{max} 1710cm^{-1} (aldehydic C=O) and 1735cm^{-1} (5-ring ketone C=O), δ9.78 (1H, m, W½ 3Hz, CHO), δ2.59 (2H, m, W½ 7Hz, CH$_2$CHO), δ1.09 (3H, d, J 7Hz, 3β-Me), δ1.03 (3H, s, 10β-Me), δ0.88 and δ0.81 (side chain methyls) and δ0.67 (3H, s, 13β-Me). Double irradiation at δ2.03 caused the doublet at δ1.09 to collapse to a singlet.

3β-Methyl-A-nor-5,6-seco-cholestan-6-ol-5-one (141)

Aldehyde (140) (30mg) in ethanol (1cm^3) was treated with sodium borohydride (1.6mg) in ethanol (1cm^3). After half an hour the mixture was diluted with ether, washed with water, dried and evaporated in vacuo giving (141) (26mg), v_{max} 1735cm^{-1} (5-ring C=O) and 3400cm^{-1} (br. O-H), δ3.74 (2H, t, J 8Hz, CH$_2$OH), δ1.15 (3H, s, 10β-Me), δ1.12 (3H, d, J 6Hz, 3β-Me), δ0.91 and δ0.83 (side chain methyls), δ0.67 (3H, s, 13β-Me). Double irradiation at δ2.08 caused the doublet at δ1.12 to collapse to a singlet. M$^+$ 404. Base peak m/e 112. The 3,5-dinitrobenzoate had m.p. 135-41°C. (40:60 pet.-ether).

5-Acetoxy-3β-methyl-A-nor-5β-cholestan-6-one (139)

Hydroxy-ketone (137) (50mg) was dissolved in glacial acetic acid (1.5cm^3) containing acetic anhydride (0.2cm^3) and p-toluenesulphonic acid (5mg). The solution was allowed to stand at room temperature for forty eight hours, warmed to 50-70°C. for one hour, then diluted with ether, washed with water, saturated sodium bicarbonate solution, and water, dried and

evaporated in vacuo giving a light brown oil (64mg). Preparative t.l.c. eluting in 75% 40:60 pet.-ether, 25% ether gave 5-acetoxy-3β-methyl-A-nor-5β-cholestan-6-one (139) (30mg), v_{max} 1715cm^{-1} (ketone C=O) and 1750cm^{-1} (acetate C=O), δ2.09 (3H, s, MeCO$_2$), δ0.97 (3H, s, 10β-Me), δ0.91 and δ0.82 (side chain methyl), δ0.87 (right hand branch of the 3β-Me doublet), δ0.68 (3H, s, 13β-Me). (Found 401.3407 $C_{27}H_{45}O_2$ (M$^+$-CH$_3$CO) requires 401.3408. No M$^+$ at 444.). m.p. 119-21°C. (methanol).

3β-Methyl-A-nor-5,6-seco-cholestan-5-one-6-carboxylate (142)

Hydroxy-ketone (137) (35mg) in ether (1cm^3) was treated with a solution of periodic acid in ether (1.25cm^3). After standing at room temperature overnight it was further treated with ethereal periodic acid (1.25cm^3) and allowed to stand at room temperature for seven days. It was washed with water, saturated sodium bicarbonate solution and water, dried and evaporated in vacuo to an oil (37mg).

When repeated with (137) (10mg) in ether (0.5cm^3) and ethereal periodic acid (0.8cm^3) containing perchloric acid (1 drop) a similar result was obtained.

The products were combined and preparative t.l.c. eluting in 50% ether, 50% 40:60 pet.-ether gave (142) (22mg) having v_{max} 1705cm^{-1} (acid C=O), 1735cm^{-1} (5-ring C=O) and 3000cm^{-1} (acid O-H), δ2.52 (2H, m, W½ 6Hz, CH$_2$COOH), δ1.05 (3H, s, 10β-Me), δ0.9 and δ0.8 (side chain methyls), δ0.66 (3H, s, 13β-Me), δ1.19 (3H, d, J 6Hz, 3β-Me). M$^+$ 418. Base peak m/e 112.

Reaction of 5,6β-dihydroxy-5α-cholesteryl tosylate (86) with:

a) sodium hydride

Dihydroxy-tosylate (86) (100mg) in DMF (2cm^3) was treated with 50% sodium hydride oil dispersion (4.5mg, 1.1mole equiv.) under nitrogen. The mixture was warmed to 70°C. for four hours, left to stand for one week at room temperature, then diluted with water and washed with ether. The

aqueous layer was acidified with dilute hydrochloric acid and extracted
with chloroform giving (87A) (49mg).

b) 1mole of potassium t.-butoxide

Dihydroxy-tosylate (86) (200mg) in t.-butanol (15cm^3) was treated with
potassium t.-butoxide (from 12mg potassium in 0.3cm^3 t.-butanol) at 50°C.
for two hours. The mixture was poured onto ice and extracted with ether.
The ether layer was dried and evaporated in vacuo to an oil (90mg). The
aqueous layer was acidified and extracted with ether which was dried and
evaporated in vacuo to an oil (70mg). Preparative t.l.c. of the combined
ether extracts eluting with 50% ether, 50% 40:60 pet.-ether gave
epicholesterol epoxide (71A) (43mg), starting material (86) (63mg) and
some unidentified olefinic material (30mg) plus several other minor
components.

c) sodium methylsulphinylmethylide

Dimethylsulphoxide (40cm^3) and sodium hydride (200mg) were heated under
nitrogen at 60°C. until evolution of hydrogen had ceased.
The above solution (0.9cm^3; 1.1mole equiv.) was added under nitrogen to a
solution of dihydroxy-tosylate (86) (100mg) in DMSO (1cm^3). The mixture
was warmed to 50°C. for two hours then water added, acidified with dilute
hydrochloric acid and extracted with ether. The ether layer was dried and
evaporated in vacuo to a colourless oil (80mg). The 60MHz ^{1}H n.m.r. spectrum
indicated that it was a mixture consisting mainly of epicholesterol epoxide
(71A), epoxide (87A) and some starting material (86). No olefinic material
was detected.

d) lithium carbonate in DMF

Dihydroxy-tosylate (86) (100mg) was treated with lithium carbonate (63mg)
in DMF (2cm^3) heated under reflux for one hour. The mixture was acidified
with dilute hydrochloric acid and extracted with ether. The ether extract
was dried and evaporated in vacuo giving 5,6β-dihydroxy-5α-cholest-2-ene
(105) (67mg).

e) lithium carbonate in t.-butanol

Similar conditions to d) above gave no reaction and (86) was recovered unchanged.

f) lithium carbonate in methanol/water

Similar conditions to d) above gave mostly unchanged starting material plus some (105) as detected by the [1]H n.m.r. spectrum.

6β-Acetoxy-5-hydroxy-3β-tosyloxy-5α-cholestane (147)

Dihydroxy-tosylate (86) (0.5g) in pyridine (5cm^3) was treated with acetic anhydride (0.4g) and left to stand for four days at room temperature. Normal work up gave 6β-acetoxy-5-hydroxy-3β-tosyloxy-5α-cholestane (147) (0.5g) having δ7.46 (aromatic protons), δ4.84 (1H, m, W½ 28Hz, 3α-H), δ4.63 (1H, m, W½ 5Hz, 6α-H), δ2.4 (3H, s, $CH_3C_6H_4SO_2$-), δ2.02 (3H, s, CH_3CO_2), δ1.11 (3H, s, 10β-Me), δ0.9 and δ0.81 (side chain methyls), δ0.67 (3H, s, 13β-Me).
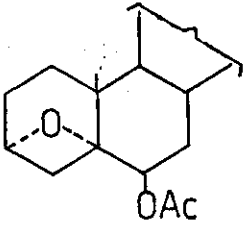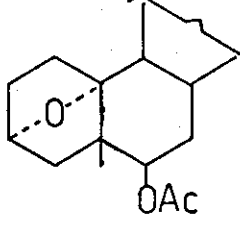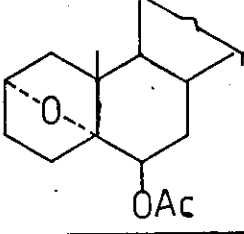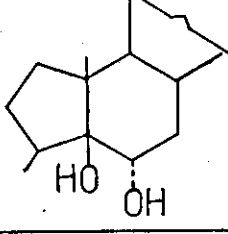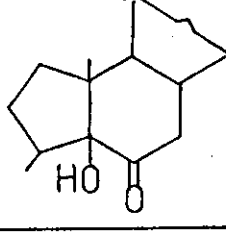
Reaction of (147) with potassium t.-butoxide

(147) (100mg) in t.-butanol (1cm^3) was treated under nitrogen with potassium t.-butoxide in t.-butanol (from 20mg potassium in 1.5cm^3 t.-butanol) at 50°C. for two hours. The mixture was poured onto ice, acidified and extracted with ether. The ether layer was dried and evaporated in vacuo to an oil. The [1]H n.m.r. spectrum indicated that it was mostly starting material (147). It was therefore retreated as above. Work up gave a product consisting mainly of the epoxide (87A), some epicholesterol epoxide (71A) and some unidentified olefinic material (42mg).

Table VII ^{13}C-Data

COMPOUND CARBON NO.	OAc	OAc	OAc	HO OH	HO O
1	31.181	46.634	47.125	36.084	35.537
2	27.984	25.392	73.664	35.401	39.529
3	75.038	75.794	31.835	35.156	42.619
4	34.621	33.364	33.856	16.280	13.006
5.	88.857	unassigned	86.933	84.270	89.484
6	78.371	76.558	78.251	74.791	210.696
7	30.829	31.726	30.634	33.489	41.826
8	30.612	30.688	30.306	29.446	30.724
9	45.782	41.228	49.528	46.738	47.786
10	38.711	91.520	45.050	50.835	57.876
11	22.051	unassigned	21.460	22.754	22.932
12	40.094	39.753	40.299	40.154	39.884
13	42.857	42.593	43.030	42.831	43.220

14	55.698	56.244	56.408	56.353	57.220
15	24.083	24.026	24.026	24.174	24.080
16	28.255	unassigned	28.340	28.217	28.099
17	56.239	58.319	56.190	56.271	56.235
18	12.217	12.013	12.177	12.128	12.104
19	18.854	19.385	16.928	14.668	14.565
20	35.813	35.985	35.931	35.756	35.728
21	18.665	18.839	18.784	18.656	18.693
22	36.192	36.368	36.368	36.166	36.166
23	23.920	24.299	24.299	23.847	23.889
24	39.523	39.589	39.699	39.526	39.638
25	28.038	28.122	28.122	27.999	28.017
26	22.539	22.661	22.880	22.535	22.576
27	22.810	22.880	22.661	22.699	22.795
$\underline{C}H_3CO$	21.184	21.296	21.242	———	———
$CH_3\underline{C}O$	169.938	171.465	170.32	———	———

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