Aspects of steroidal partial synthesis and rearrangements

ASPECTS OF STEROIDAL PARTIAL SYNTHESIS AND REARRANGEMENTS

BY

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SUMMARY

ASPECTS OF STEROIDAL PARTIAL SYNTHESIS AND REARRANGEMENTS

The previously reported conversion of 3β-tosyloxy-5α-cholestane-5, 6β-diol with Bu^tOK/Bu^tOH to 3β-methyl-A-nor-5β-cholestan-5-ol-6-one, is believed to arise from a novel intramolecular ene reaction of an intermediate unsaturated acyloin, 4,5-seco-cholest-3-en-6β-ol-5-one.

It was proposed to synthesise the unsaturated acyloin 4,5-seco-cholest-3-en-6β-ol-5-one to determine whether it would indeed undergo the ene reaction.

Three synthetic approaches from cholesterol through (a) 3,4-seco-4-nor-cholestan-6-ol-5-one-3-oic-acid, (b) 4,5-seco-cholest-3-en-5-one and (c) 5α-hydroxy-6β-methoxy-cholestan-3β-yl-toluene-p-sulphonate and one route to its 6-epimer through 6α-acetoxy-4,5-seco-3-cholest-n-5-one, have been investigated.

Additionally, the BF_3-catalysed rearrangement of 3α-5-epoxy 6β-methoxy-5α-cholestane gave 3α-hydroxy-5α-cholestan-6-one and β-methoxy-5β-methyl-3α, 10α-epoxy-5β-cholestane.

The formation of the BF_3-catalysed rearranged products has been rationalised in terms of a carbonium ion type mechanism.

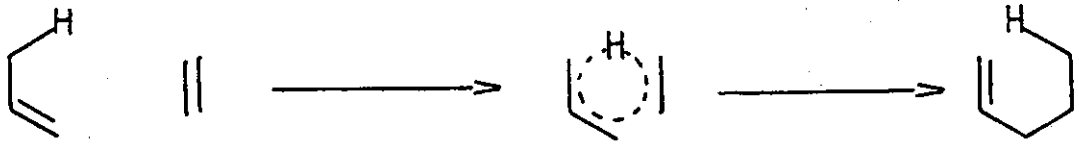
CONTENTS

PART ONE: Synthesis of the Intermediate Unsaturated Acyloin
4,5-seco-cholest-3-en-6β-ol-5-one

INTRODUCTION

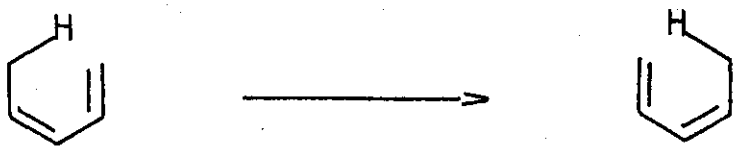
The ene reaction is one of the most simple and versatile reactions in organic chemistry and dates back to the beginning of the century. However it was in a paper by Alder in 1943 that the ene reaction began to be recognized. Several extensive reviews have recently appeared in the literature.[1-3]

The ene reaction is the indirect substituting addition of the compound with a double bond (enophile) to an olefin possessing an allylic hydrogen (ene) and involves an allylic shift of the allylic hydrogen to the enophile and bonding between the two unsaturated termini, (Scheme I).



SCHEME I

Not only is the ene reaction related to the Diels Alder addition, it can also be regarded as an intermolecular variant of the symmetry allowed 1,5 hydrogen shift (Scheme II).

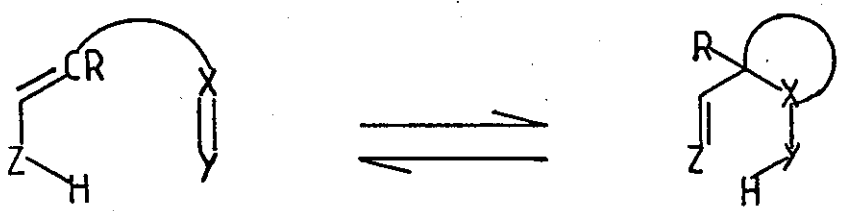


SCHEME II

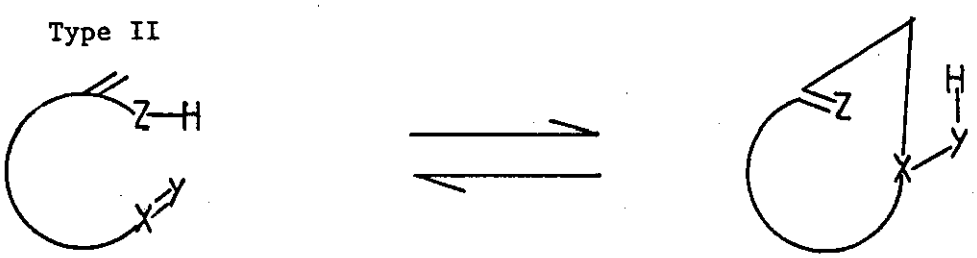
Intramolecular ene reactions are common and date back to the 1930's.

The intramolecular ene process profits from entropic advantage and exhibits preparatively useful regio- and stereo-selectivity. This applies to three different modes of thermally-induced cyclizations and cyclo-reversions in which the enophile is linked by an appropriate bridge, either to the olefinic terminal (Type I), the central atom (Type II) or the allylic terminal (Type III) of the ene unit[2], (Scheme III).

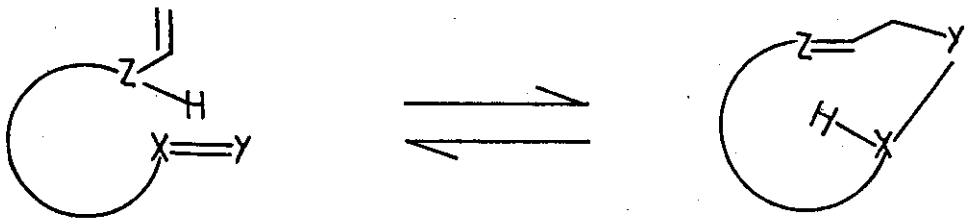
Type I



Type II



Type III



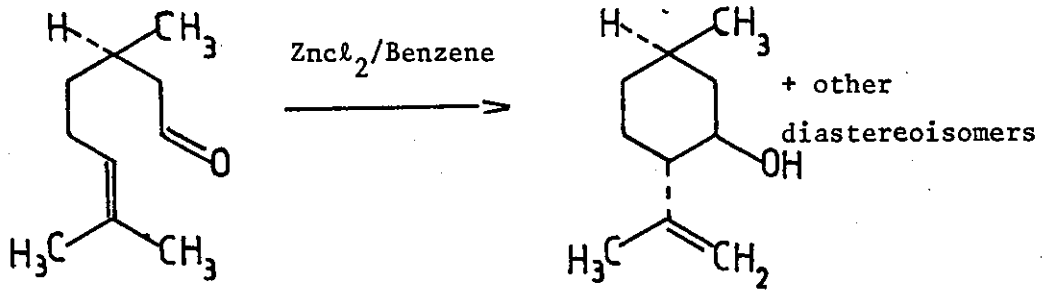
SCHEME III

Intramolecular ene reactions of enones have been widely used in the synthesis of five and six-membered ring systems[3].

The carbonyl group serves either as the enophile, or via its enol tautomer, as the ene unit.

The cyclisation of d-citronellal (1) is an acid-induced cyclisation which may be described by an intramolecular ene mechanism, when hydrogen

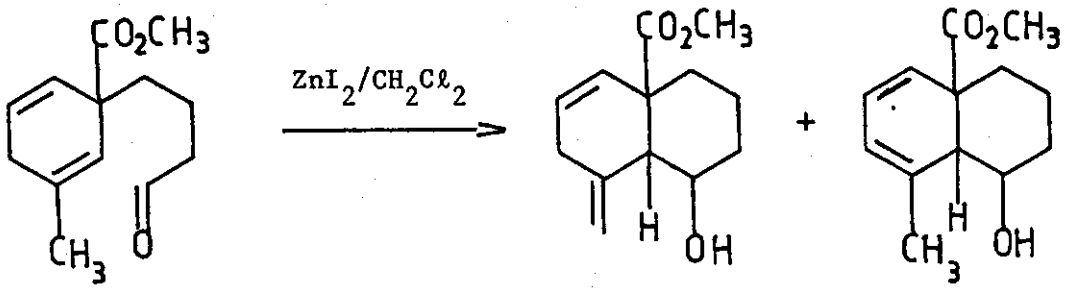
transfers from carbon to oxygen[4] (Scheme IV)



(1) (2)

SCHEME IV

A related example is the cyclisation of the diene aldehyde (3) with zinc iodide in methylene chloride. The product obtained, in quantitative yield, consisted of a 1:3 mixture of dienic alcohols (4) and (5)[5] (Scheme V).



(3) (4) (5)

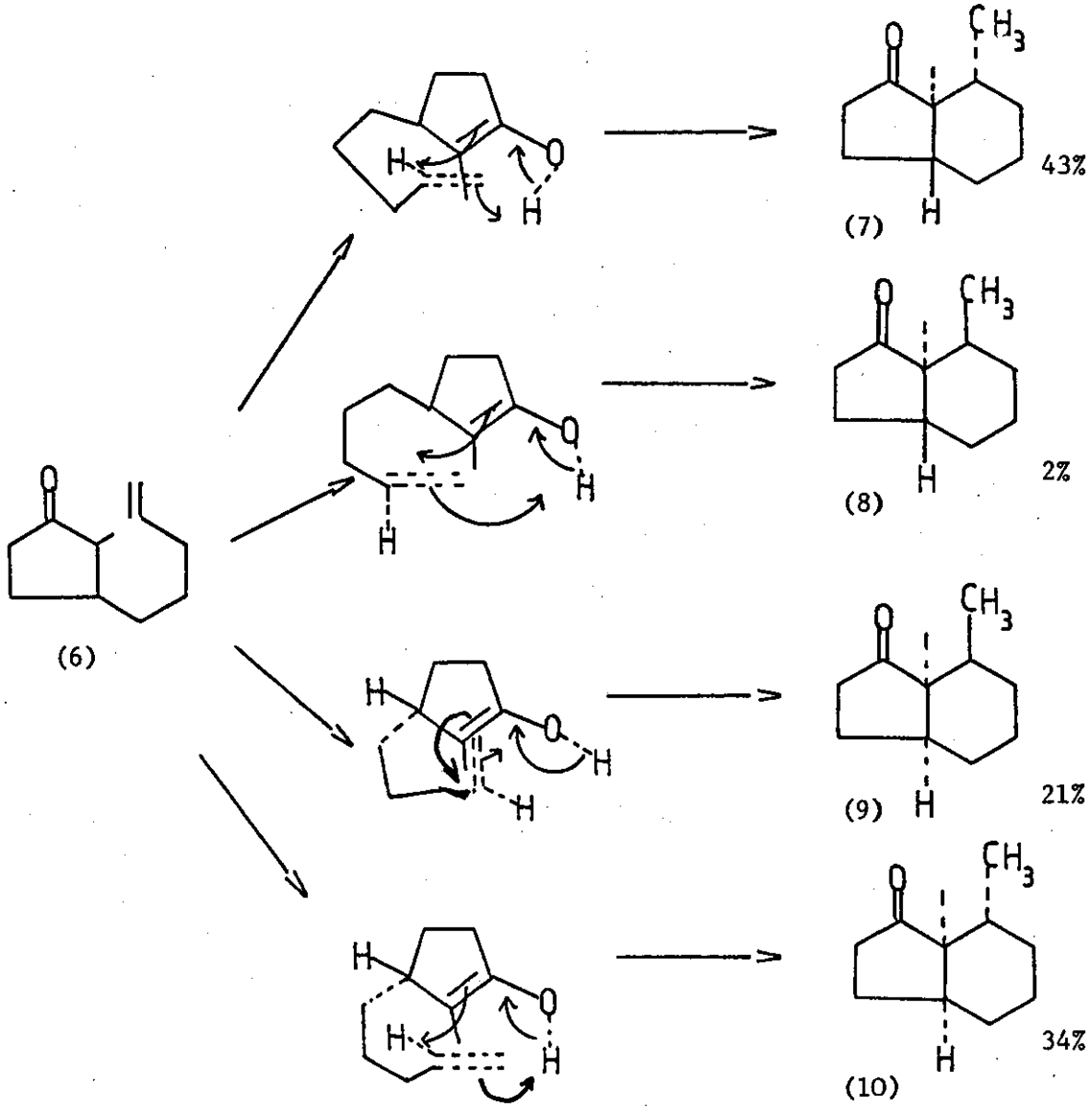
SCHEME V

There are several examples of intramolecular enone cyclizations described to date involving hydrogen transfer from an enol intermediate to an olefin enophile.[2]

As Conia et al[3] has reported, this method leads to an enormous variety of monocyclic, bicyclic and bridged systems.

Hydrindanes and related systems have been studied because of their application to steroid chemistry.[6]

When 2-methyl-3-(pent-4-enyl)-cyclopentanone (6) was heated at 350°C for 90 min, cyclization occurred quantitatively and the four possible stereoisomers of 7,7a-dimethyl-hydrindan-1-ones (7-10) were obtained[7] (Scheme VI).

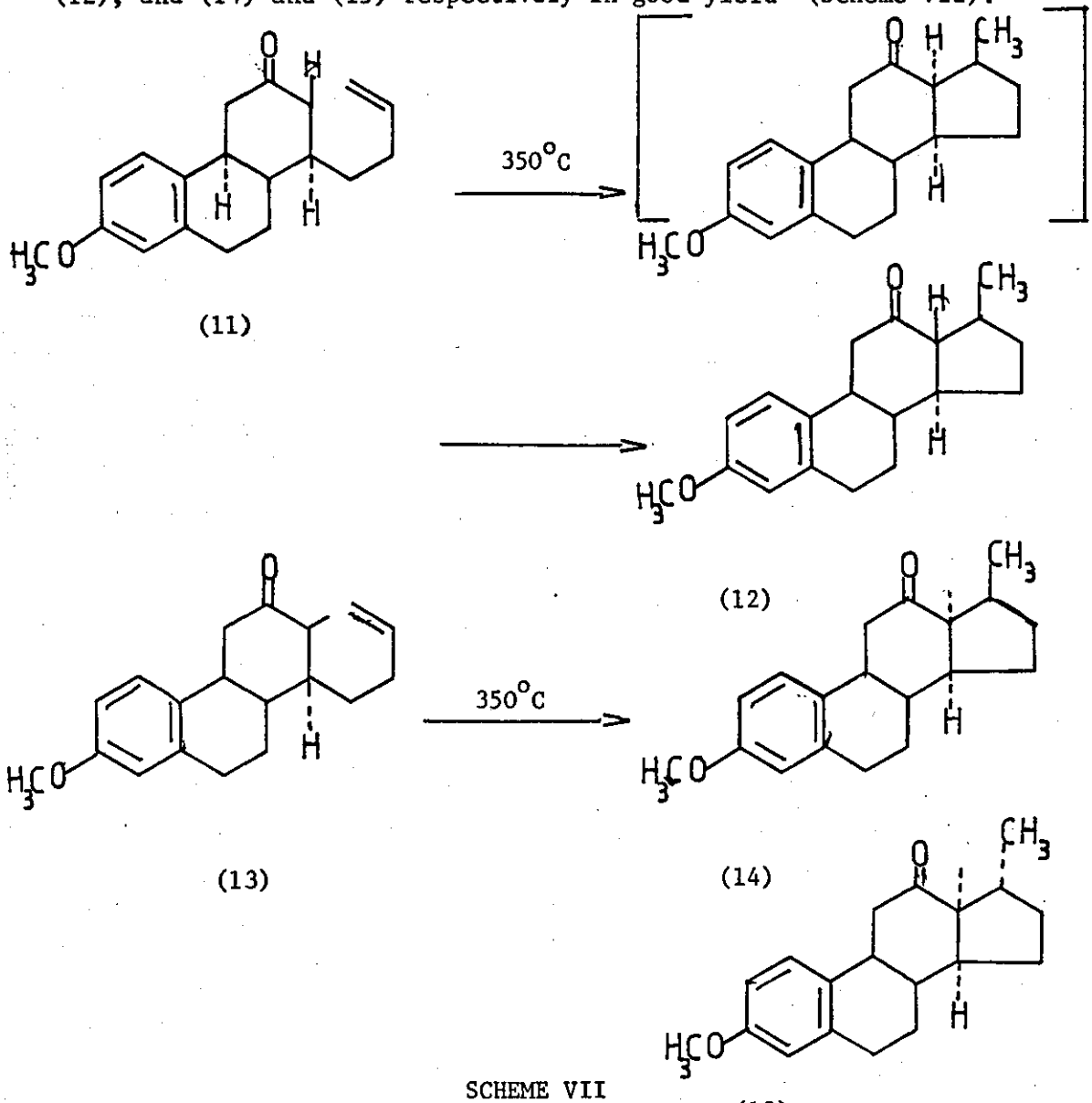


SCHEME VI

The different ratio of such unepimerisable ketones depends on whether the enol intermediate is fixed in the trans or cis configuration with respect to the enophilic bridge.[7]

An application of the process has been reported in the total synthesis of oestratriene derivatives.[8]

When compounds (11) and (13) were heated at 350°C they revealed a remarkable thermal behaviour in that they gave the tetracyclic structures (12), and (14) and (15) respectively in good yield[9] (Scheme VII).



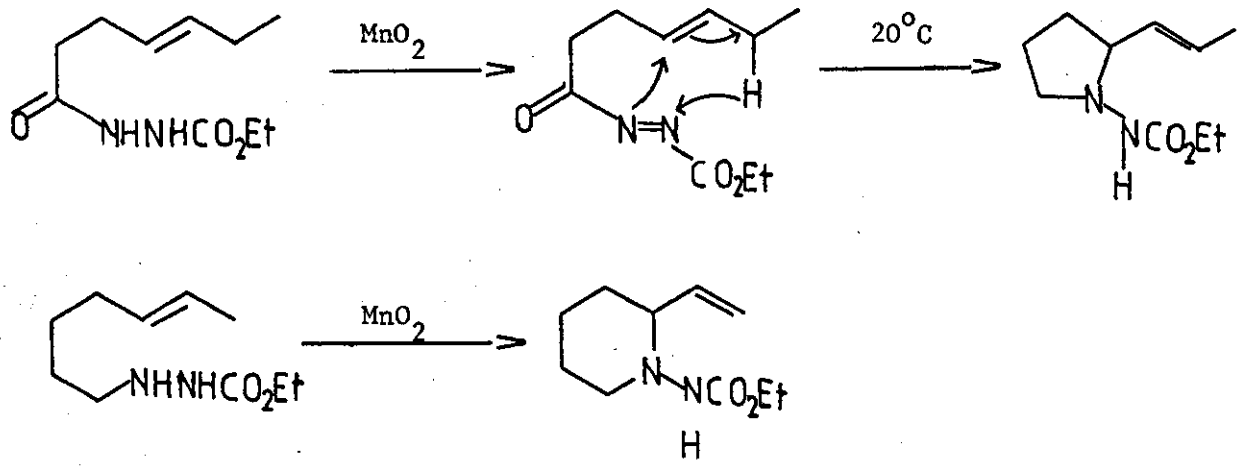
(11) (12) (13) (14) (15)

SCHEME VII

It is assumed that the trans-C/D ring junction in (12) arises from the thermal isomerisation of the initially formed and less stable compound with a C/D cis-ring junction.

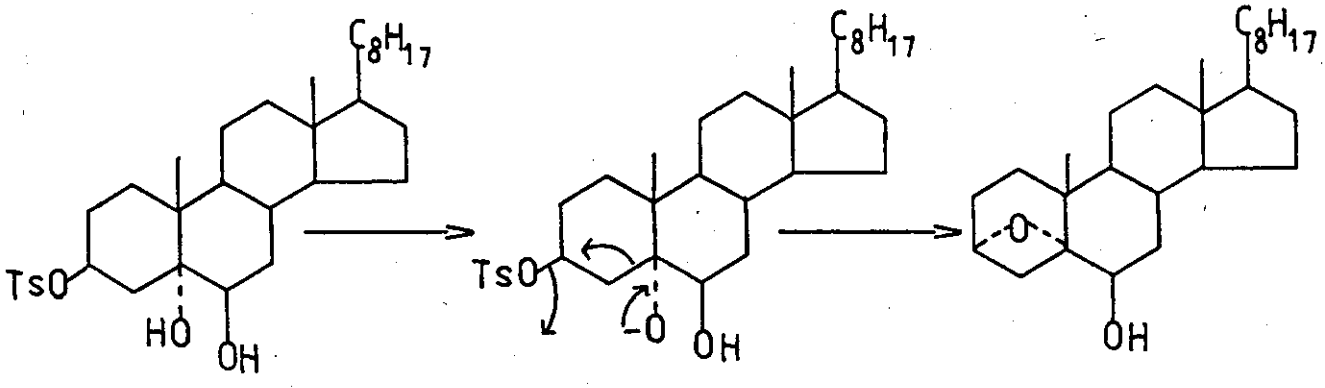
This is confirmed by the formation of the cis-fused ring junction in the cyclisation of (13), where the angular methyl group in the cyclised product prevents the formation of the Δ^{12}-enol.

It has been reported by E. Vedejs and G.P. Meier that some related ene reactions can take place at relative low temperatures[10] (Scheme VIII). There is however considerable difference between these substrates and simple unsaturated ketones.

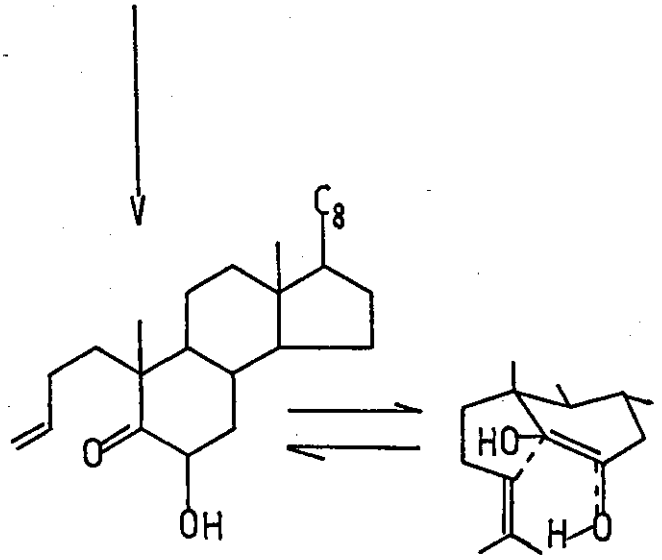


SCHEME VIII

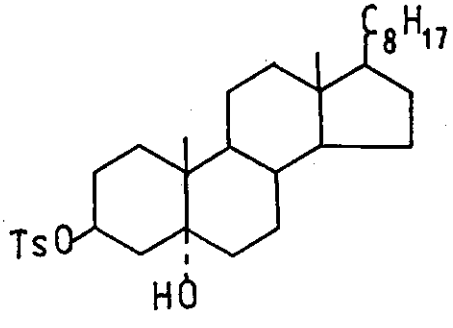
The conversion of tosyloxydiol (16) to the ketol (20) with $KOBu^t/Bu^tOH$ at 50°C has been observed in these laboratories (Marples and Foster)[11] (Scheme IX). The major product of the reaction was the oxetane (18).



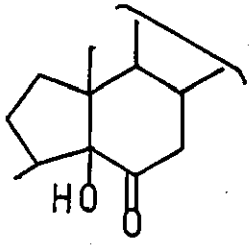
(16) (17) (18)



(19) (19A)



(21)



(20)

SCHEME IX

It is believed that (20) may be formed by an ene reaction of the unsaturated acyloin (19) which could arise by the fragmentation shown. This is analogous to that observed by Henbest *et al*[12], in the fragmentation of cholestan-3β-yl toluene-*p*-sulphonate (21).

The conversion of (19)-(20) is a novel ene reaction which has great synthetic potential, particularly in the areas of natural products and medicinal chemistry. The low temperature of the reaction is notable. It was felt necessary to synthesise the proposed intermediate (19) by an alternative route and to investigate its reactivity in the supposed ene reaction.

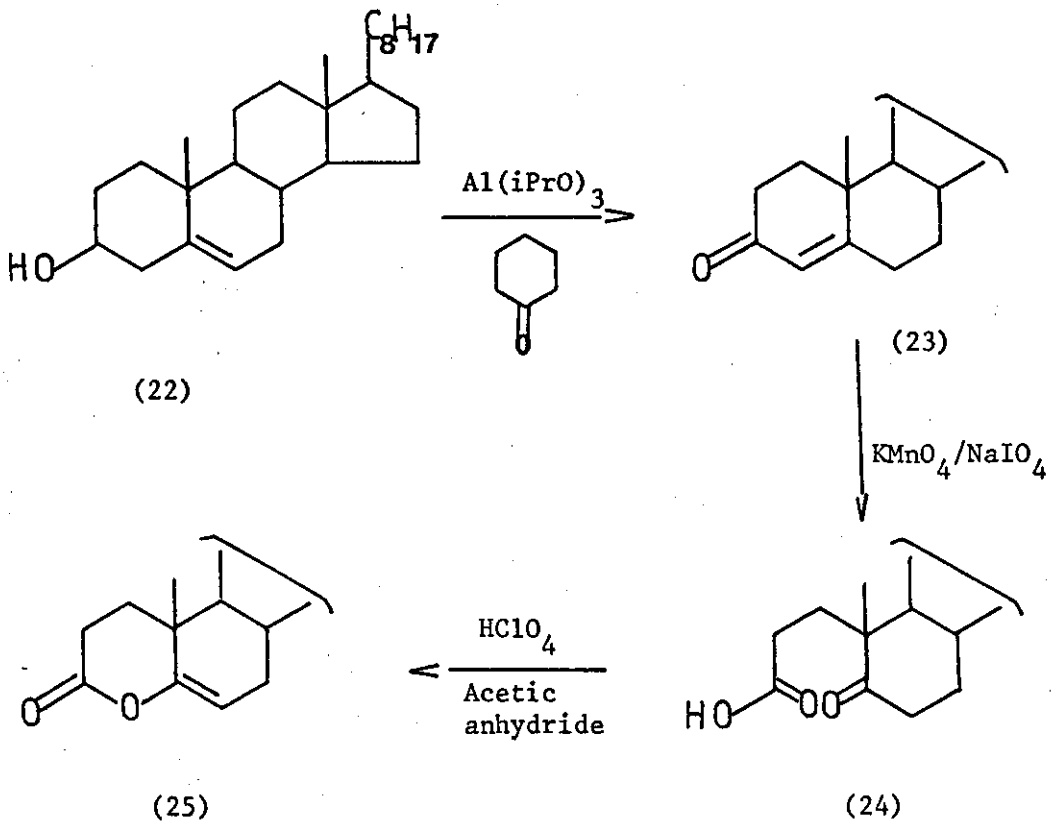
Three synthetic approaches from cholesterol to the unsaturated acyloin (19) and one route to its 6-epimer (48) have been investigated and are reported here.

Results and Discussion

The first attempted preparation of the unsaturated acyloin (19).

Cholest-4-en-3-one (23)[13] was prepared from cholesterol (22) by Oppenauer oxidation with aluminium isopropoxide and cyclohexanone. Oxidation of the enone (23) with sodium metaperiodate and 0.8% of aqueous potassium permanganate gave the keto-acid (24).[14]

The keto-acid (24) was treated with aqueous perchloric acid (10^{-3} M) and acetic anhydride giving the enol-lactone (25)[15] (Scheme X).

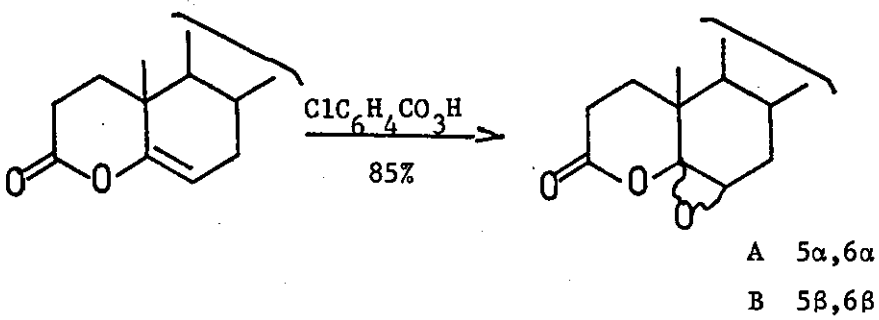


SCHEME X

The epoxide (26A) was prepared from enol-lactone (25) by oxidation with m-chloroperbenzoic acid in methylene chloride.[16]

Both 5α, 6α and 5β, 6β epoxides were obtained, as was indicated by the ^{1}H n.m.r. spectrum which showed doublets at δ3.3 and δ2.9. These were assigned to the 6β-and 6α-H respectively.

The epoxides could not be separated by preparative T.L.C. The α-epoxide was isolated in relatively low yield (45%, m.p. 150-152°C), by crystallization from acetone. (Scheme XI).

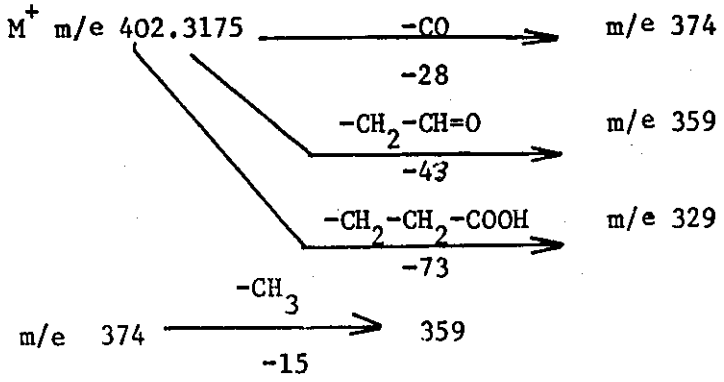


(25) (26)

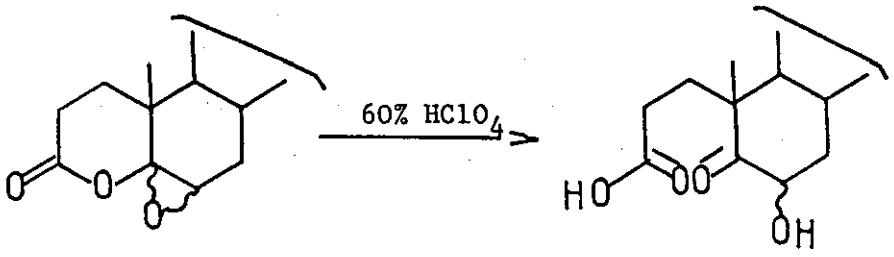
SCHEME XI

The α-epoxide (26A) had ν_{max} 1740 cm^{-1} (C=O). The 90 MHz ^{1}H n.m.r. spectrum had important peaks at δ2.7 (m, 2H, C2H), 3.3 (d, 1H, C6β-H J 5 Hz). The coupling constant is typical for 5α, 6α-epoxides.[17]

In the high resolution accurate mass spectrum, the molecular ion m/e 402.3147 ($C_{26}H_{42}O_3$), fragmented by loss of 28 (CO) to the base peak at m/e 374, and other fragmentations are shown below.



The hydrolysis of the epoxide (26A) appeared difficult. The most successful method was the use of 60% perchloric acid in ethyl methyl ketone giving the acid (27)[18] which was a white, crystalline solid having a melting point of 84-86 °C (Scheme XII).



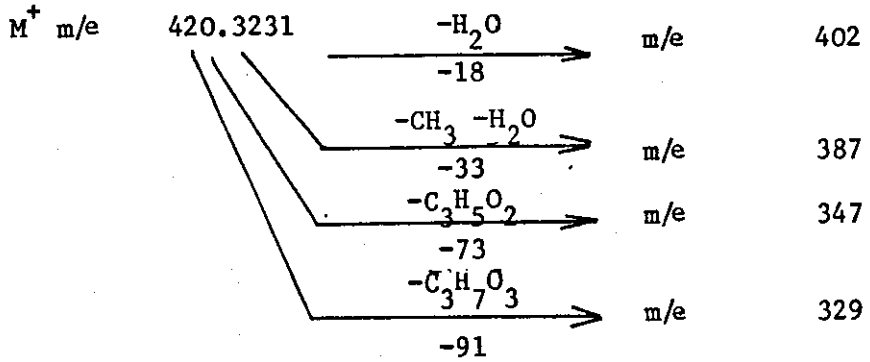
A 5α 6α
B 5β 6β

(26) (27)

SCHEME XII

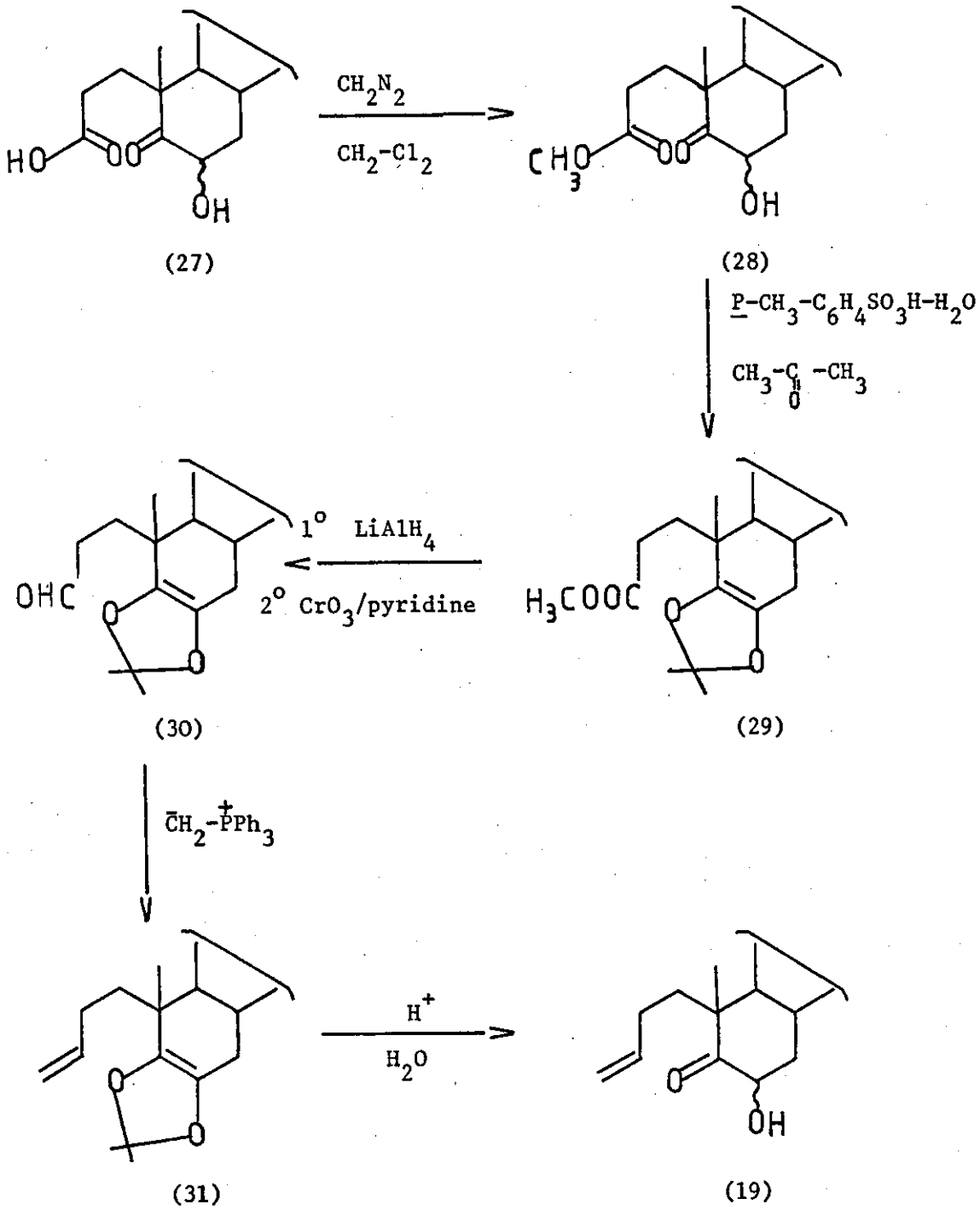
The acid (27) has not been reported in the literature. The infrared spectrum had ν_{max} 3500 cm^{-1} (OH), 1700 cm^{-1} (C=O). The 90 MHz ^1H n.m.r. spectrum had important peaks at 2.3 (m, 2H, C2H) and 4.35 (m, 1H, C6H).

The high resolution accurate mass spectrum had a molecular ion peak at m/e 420.3231 ($C_{26}H_{44}O_7$) for which main fragmentations are shown below.



Attempts to convert the acid (27) to the ester (28), by reaction with diazomethane were not successful. (Scheme XIII).

Several products were obtained and it was not possible to achieve a satisfactory purification.



(27) (28) (30) (29) (31) (19)

SCHEME XIII

It was originally proposed to convert the ester (28) to the unsaturated acyloin (19) as indicated in the (Scheme XIII). It was anticipated that the acyloin ester (28) could be converted to the

unsaturated acetal (29), possibly using the toluene-p-sulphonic acid-catalysed reaction with acetone.

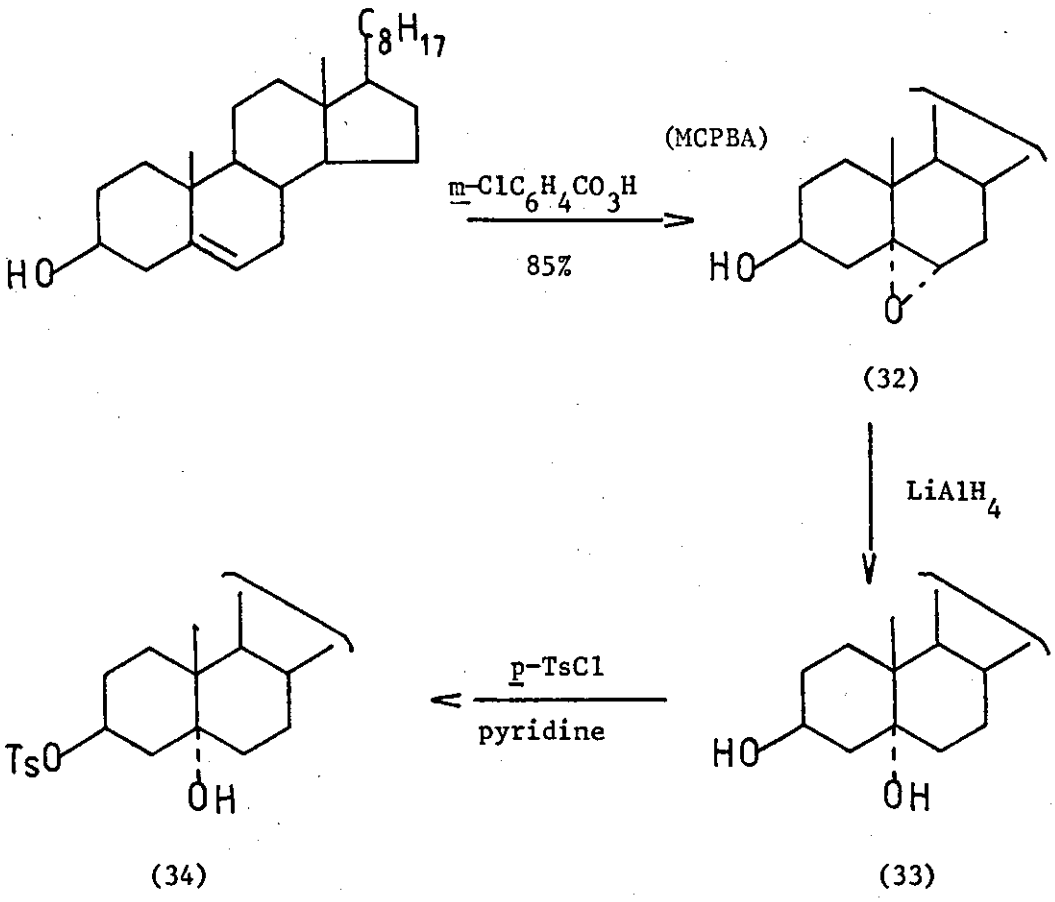
Reduction with lithium aluminum hydride followed by partial oxidation with CrO_3/pyridine was expected to yield the aldehyde (30) which by reaction with the methylene ylid $\bar{C}H_2\text{-}\overset{+}{P}Ph_3$ would give the alkene (31).

Deprotection would then be expected to give the required unsaturated acyloin (19). The conversion of acyloins into unsaturated acetals [(28)→(29)] does not appear to have literature precedent. In the event, this was not investigated since adequate supplies of the acyloin ester (28) could not be obtained as indicated above.

Similarly, it was not possible to investigate other routes to the unsaturated acyloin (19) from the acyloin-ester (28). Accordingly alternative routes of synthesis of the unsaturated acyloin (19) were explored and are described below.

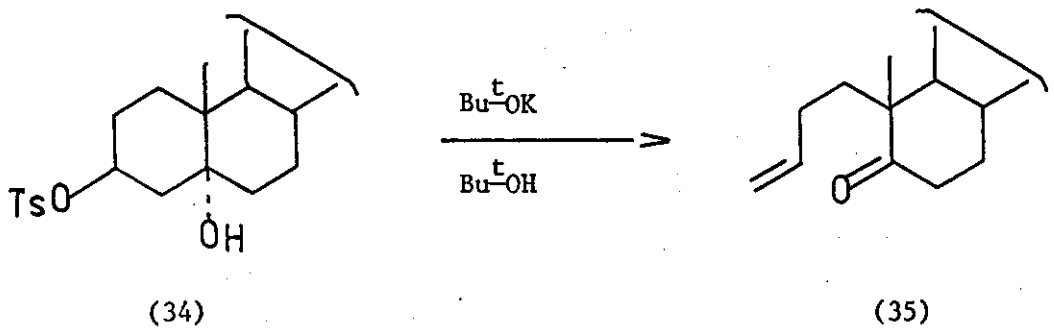
The second attempted preparation of the unsaturated acyloin (19).

Cholesterol was treated with m-chloroperbenzoic acid in diethyl ether giving the α-epoxide (32).[19] The diol (33)[20] was prepared from the epoxide (32) by reduction with lithium aluminium hydride. The diol (33) was treated with toluene-p-sulphonyl chloride in pyridine giving good yields of the tosylate (34)[21] (Scheme XIV).



SCHEME XIV

The tosylate (34) was treated with Bu ^{t}OK/Bu^{t}OH at 50°C giving the unsaturated ketone (35)[21] as an oil in low yields (30%) (Scheme XV).

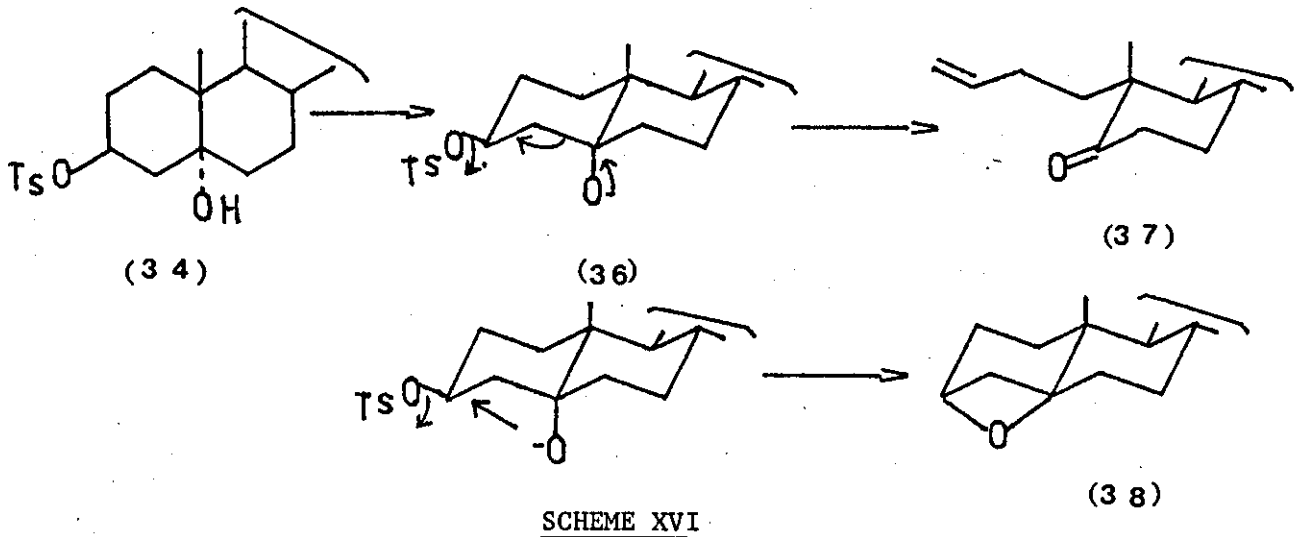


SCHEME XV

This reaction had been first reported by Henbest et al[21] to give 3α,5-epoxy-5α-cholestane (38) in 55% and the unsaturated ketone (37) in (37%).

The formation of the 3α,5-epoxide (38) and the unsaturated ketone (37) proceeds by first-order decomposition of the anion (36), which is

itself formed rapidly and reversibly from the starting material, (Scheme XVI).



SCHEME XVI

It has been suggested that the formation of the unsaturated ketone from the anion intermediate (36) occurs because of relief of steric interactions between (a) the C-9 and C-7 axial protons and the 5-oxygen anion and (b) the angular methyl group and the C-2 and C-4 axial protons.

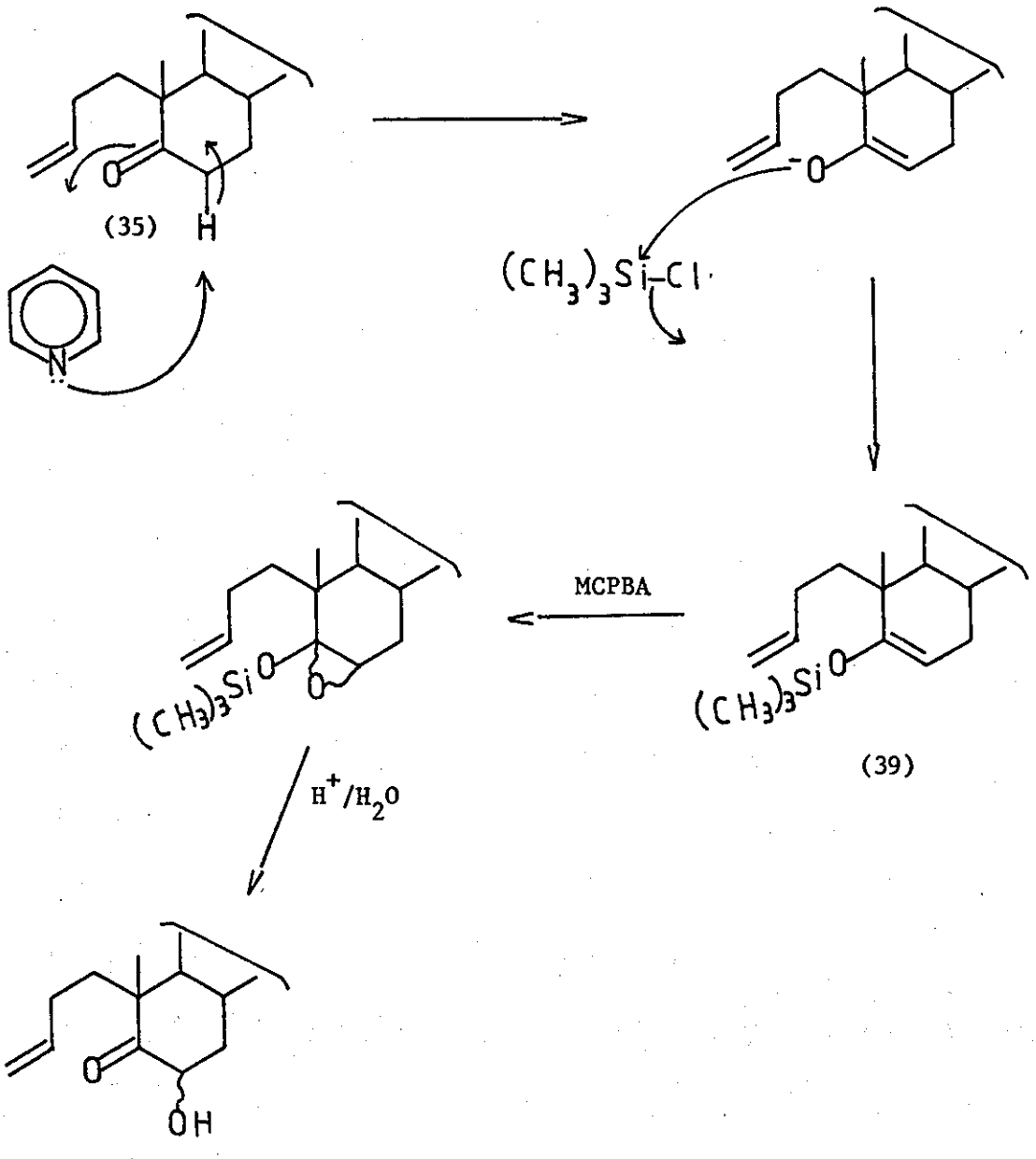
It was proposed next to synthesize the trimethylsilyl enol ether (39) and convert this by standard procedures[22] of oxidation to the unsaturated acyloin (19). (Scheme XVII).

Three methods of enolsilylation of the ketone (35) were investigated:

A. Hexamethyldisilazane, trimethyl-chlorosilane and pyridine.[23]

B. Potassium hydride, trimethyl-chlorosilane and triethylamine.[24]

C. Butyllithium, diisopropyl amine, trimethylchlorosilane and triethylamine.[25]



(39)

(19)

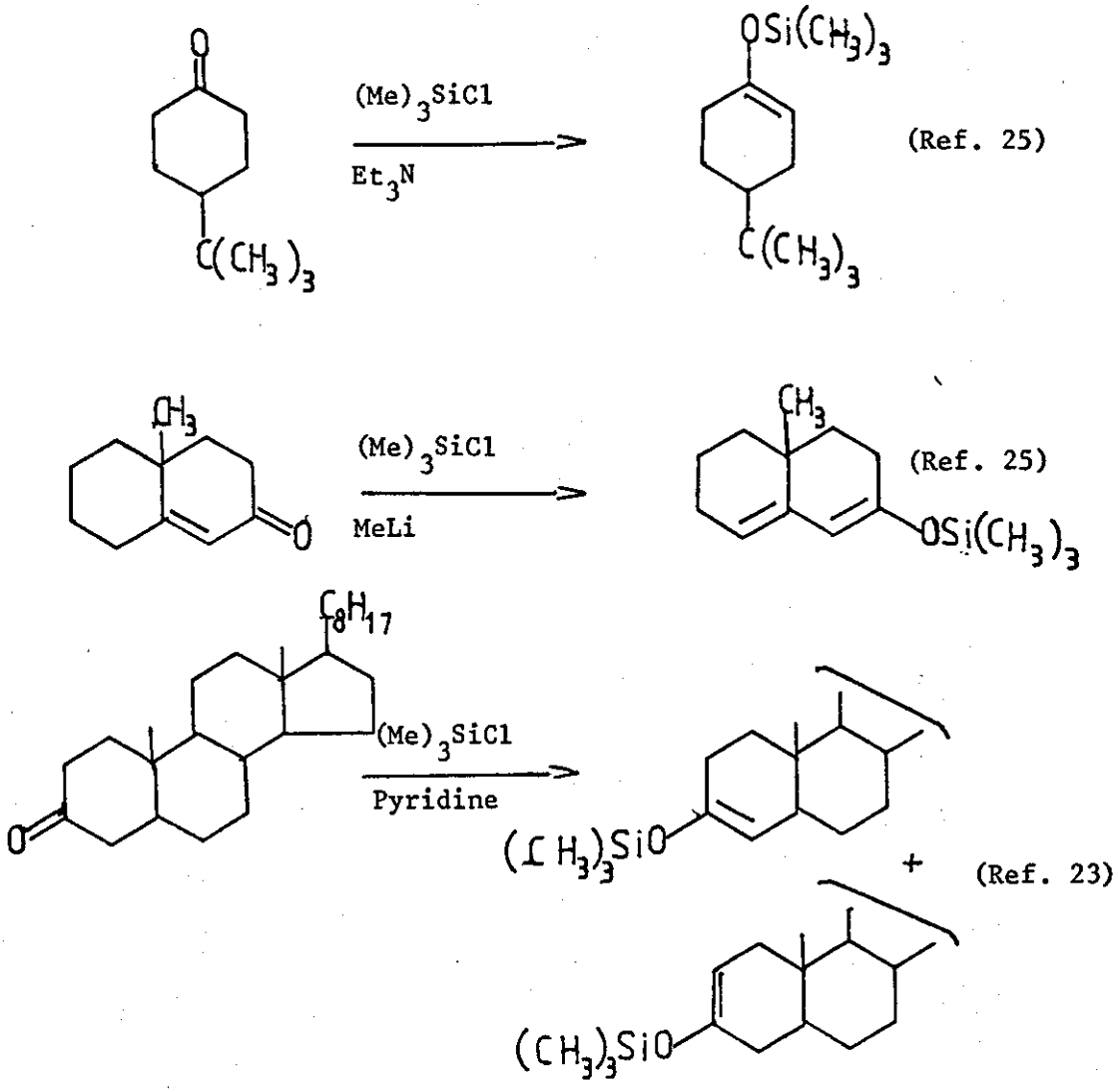
SCHEME XVII

The infrared spectrum of the reaction product indicated that it had no carbonyl band at ca 1700 cm^{-1} and it had a typical absorption of the $Si-(CH_3)_3$ group at 1020 cm^{-1}. The 90 MHz ^1H n.m.r. spectrum had important peaks at 0.02 (s, 9H, [$Si-(CH_3)_3-$]), 4.7 (m, 2H, C4-H) and 5.72 (m, 1H, C6-H).

It was assumed that the silyl-enol ether had been formed. Unfortunately this reaction could not be reproduced. Attempts using the method (B) and the method (C) were unsuccessful.

The failure of these silylations is difficult to understand in view

of the ample literature precedent[23-27] for similar reactions. Some of these are shown (Scheme XVIII).



SCHEME XVIII

Because of the unfavourable results we could not complete this synthetic sequence. Alternative routes were therefore investigated.

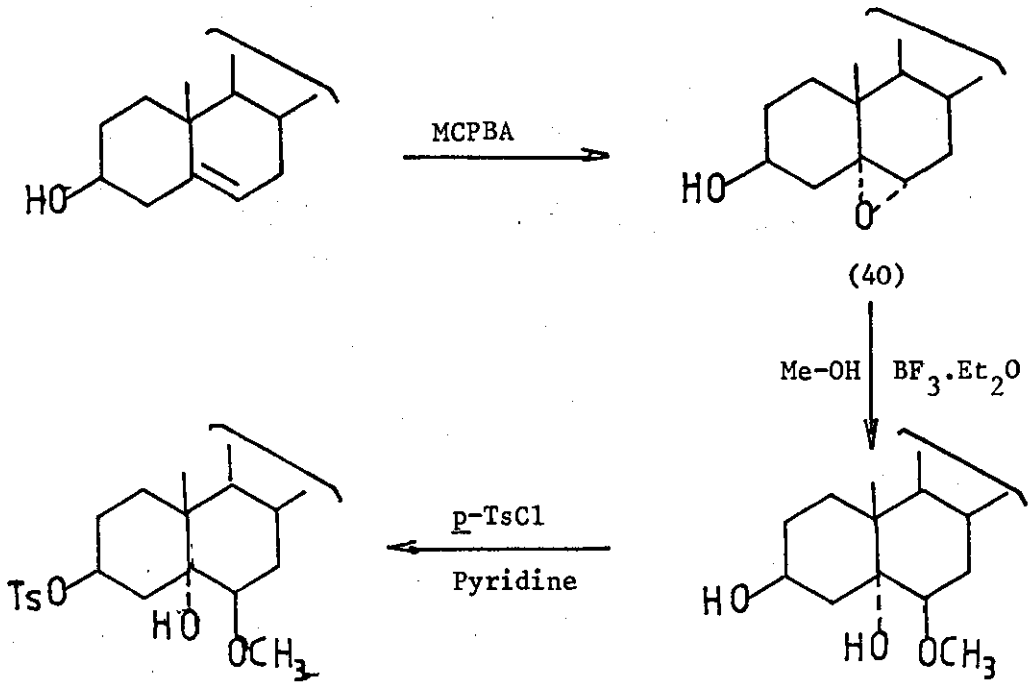
Third attempted preparation of the unsaturated acyloin (19)

Rather than attempt to introduce the 6-oxygen function into the unsaturated seco-ketone (35) as described above, it was thought that the fragmentation reaction could be induced on a 5α-hydroxy-3β -tosyloxy compound bearing an oxygen function at C-6. To this end the 6β-methoxy compound (42) was prepared.

5α,6α-Epoxy-cholestan-3β-ol (40)[16] was prepared from cholesterol.

Treatment of the α-epoxide (40) with boron trifluoride etherate in methanol gave 3β,5α-dihydroxy-6β-methoxy-cholestane (41).[21]

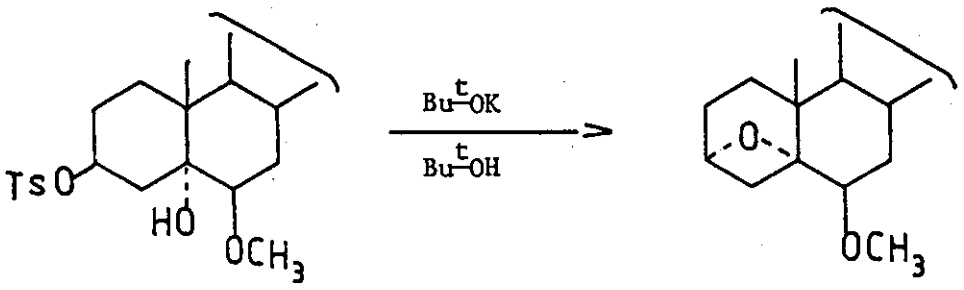
Tosylation of the methoxy-diol (41) with p-toluenesulphonyl chloride in pyridine[27] gave 5α-hydroxy-6β-methoxy-cholestan-3β-yl toluene-p-sulphonate (42) (Scheme XIX).



SCHEME XIX

Reaction of the tosylate (42) with potassium t-butoxide (2.5 mol) in t-butyl alcohol was performed.

The crude product appeared to contain only one major compound and on purification by preparative T.L.C. [solvent ether-petrol, ether (60-80), 50:50] afforded the 6β-methoxy-3α,5α-epoxy-cholestane as an oil in 69% (43) (Scheme XX).

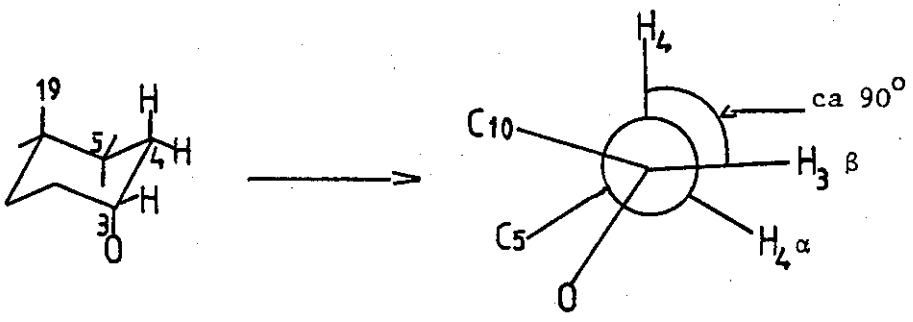


(42) (43)

SCHEME XX

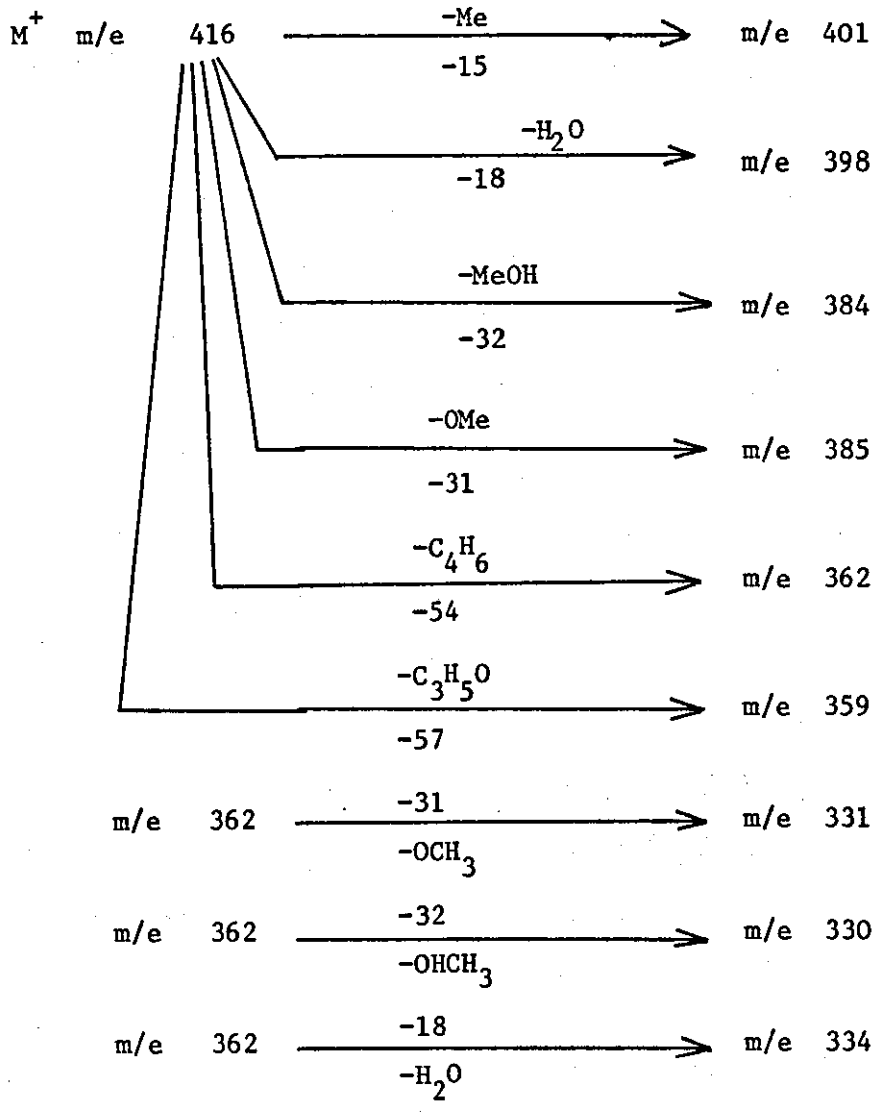
The 90 Mz 'H n.m.r. spectrum of the 3α,5α-epoxide (43) had important peaks at δ4.5 (1H,br d C3-β-H), 3.40 (1H, m, C6-αH), 3.32 (3H,s,CH_3-O-), 2.6 (1H, q, 4α-H, J 9 and 7 Hz) and 2.06 (1H, d, 4β-H, J, 9 Hz).

Confirmation of these assignments was given by double irradiation at δ4.5 which causes the signal at δ2.6 to collapse to a doublet (J 9 Hz). Similar double irradiation at δ2.6 caused the doublet at δ2.06 to collapse to a singlet and the broad doublet at δ4.5 to collapse to a broad singlet. It is evident that the 4α-H is significantly spin-spin coupled to the 4β-H (J 9 Hz) and the 3β-H (J 7 Hz) while the 4β-H is not spin-spin coupled to the 3β-H. Inspection of a model suggests this is reasonable since the dihedral angle between the 3β-H and the 4β-H is close to 90° [64] (Scheme XXI).

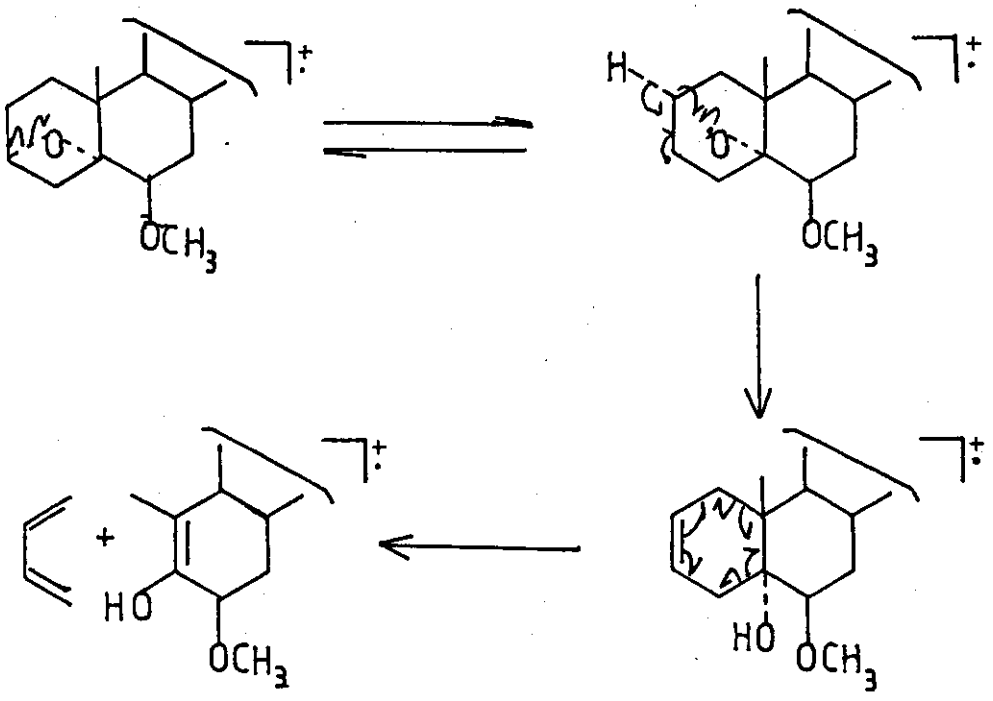


SCHEME XXI

The high resolution accurate mass spectrum had a molecular ion peak at m/e 416.3650 ($C_{28}H_{48}O_2$) for which major fragmentations are shown below.

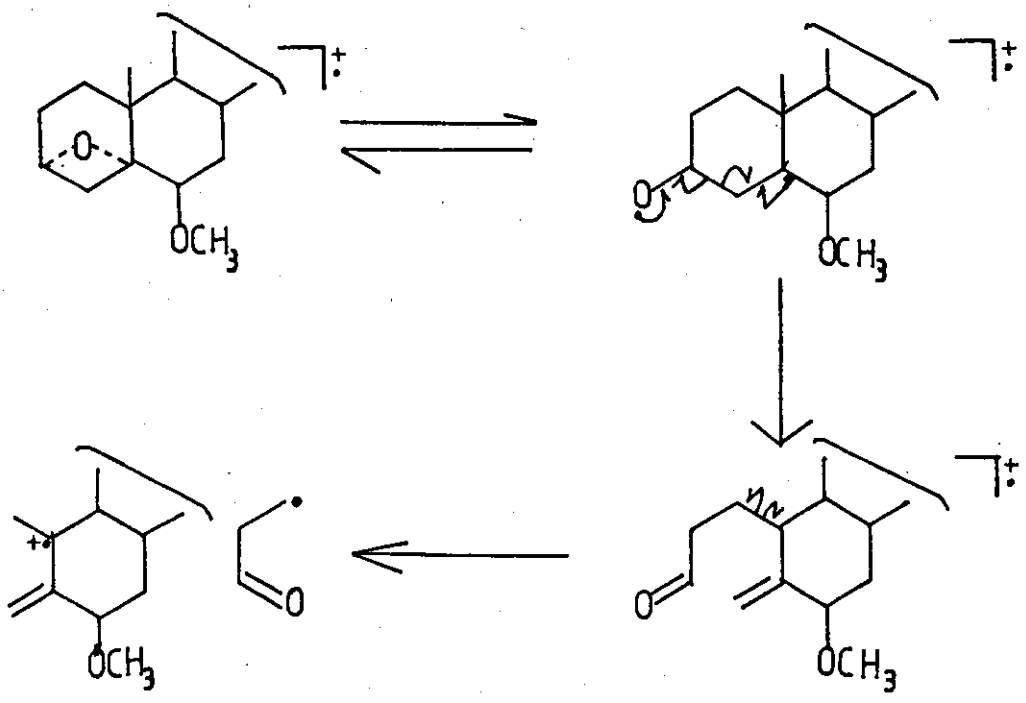


The loss of 54 (C_4H_6) from the molecular ion can be explained as indicated below. It suggests that the C-3-O bond cleaves initially and is followed by the migration of hydrogen to the oxygen radical. The final loss of C_4H_6 by cleavage of the C(1)-C(10) and C(4)-C(5) bonds is a retro-Diels-Alder reaction.



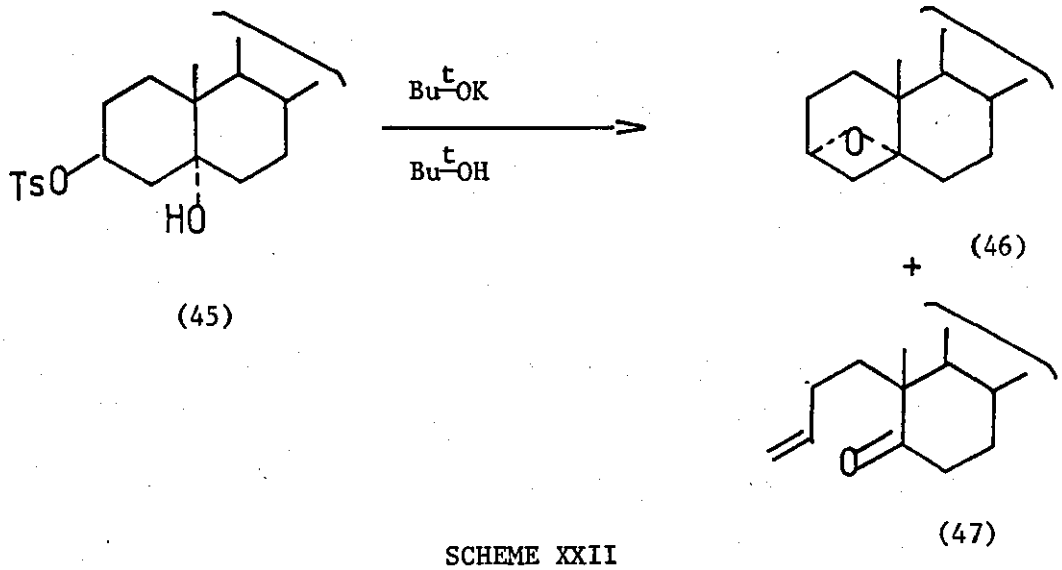
Also, in the mass spectrum, a peak at 359.3291 arose by loss of C_3H_5O from the molecular ion and was of almost equal intensity to that at m/e 362.3166.

As indicated below this fragmentation could arise by cleavage of the C5-O bond followed by cleavage by the C3-C4 bond and final cleavage of the C10-C1 bond in the intermediate unsaturated aldehyde (44).



m/e 359 (44)

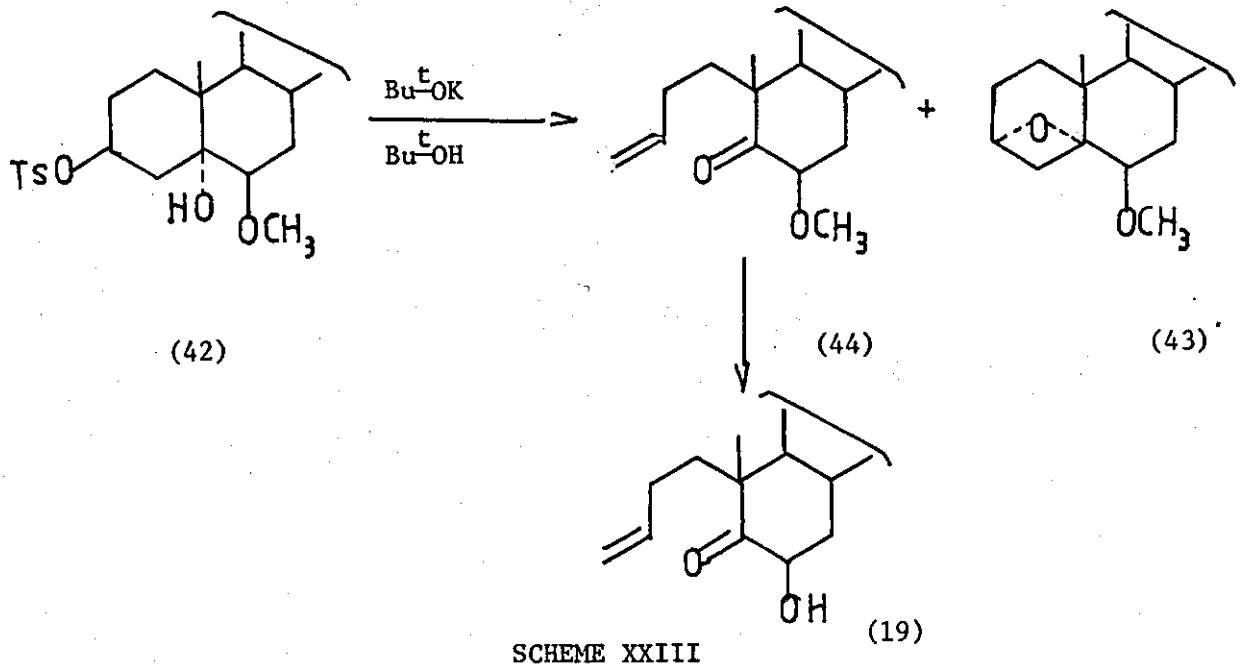
Henbest et al[21] had shown that as indicated earlier the reaction of the hydroxy toluene-p-sulphonate (45) with potassium-t-butoxide in t-butyl alcohol offered a mixture of a crystalline 3α,5-epoxide-5α-cholestane (46) in 55% and a liquid seco-ketone (47) in 37% (Scheme XXII).



(45) (46) (47)

SCHEME XXII

It was proposed to use the same conditions as Henbest to convert the methoxy-tosylate (42) to the unsaturated methoxy-ketone (44) and convert this by demethylation to the unsaturated acyloin (19) (Scheme XXIII).



(42) (44) (43) (19)

SCHEME XXIII

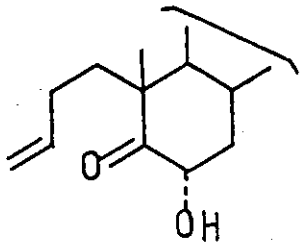
As observed, the Bu^tOK/Bu^tOH reaction of the methoxy-tosylate (42) gave only the 3α,5α-epoxide (43).

As the unsaturated ketone (44) was not obtained, the proposed synthetic sequence was not completed.

We decided to investigate the boron-trifluoride etherate catalysed rearrangement of the 6β-methoxy-3α,5α-epoxy-cholestane (43). It will be discussed in part II.

Attempted preparation of the unsaturated acyloin (48), the 6-epimer of the unsaturated acyloin (19)

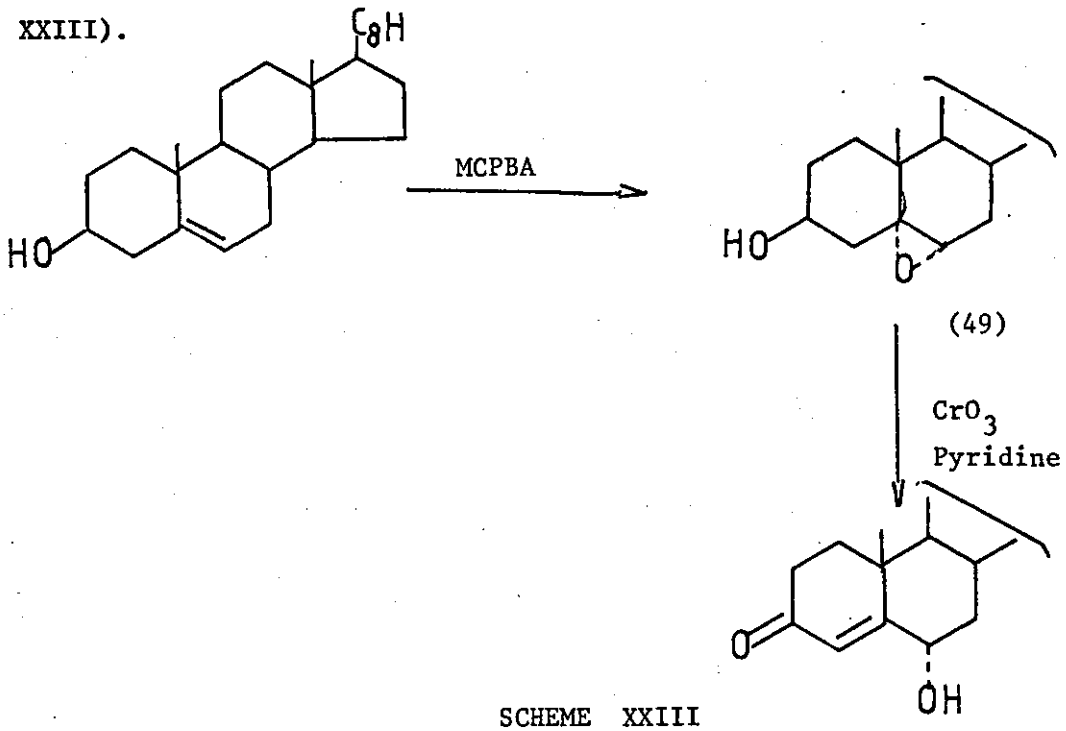
The epimer (48) was regarded as being a useful alternative to (19) to test the ene reaction, since the ene diol (58) in which the stereochemical difference at C6 is lost, is intermediate in the ene mechanism.



(48)

The epoxidation of cholesterol with m-chloroperbenzoic acid in methylene chloride gave 5,6α-epoxy-5α-cholestane 3β-ol (49)[28].

As previously observed[29] in these laboratories, oxidation of cholesterol -α-epoxide (49) with chromium trioxide in pyridine using the identical conditions employed by Ellis and Petrow,[30] gave after preparative T.L.C. (solvent ethyl acetate/benzene 50:50), 6α-hydroxy-cholest-4-en-3-one (40%) (50) (Scheme XXIII).

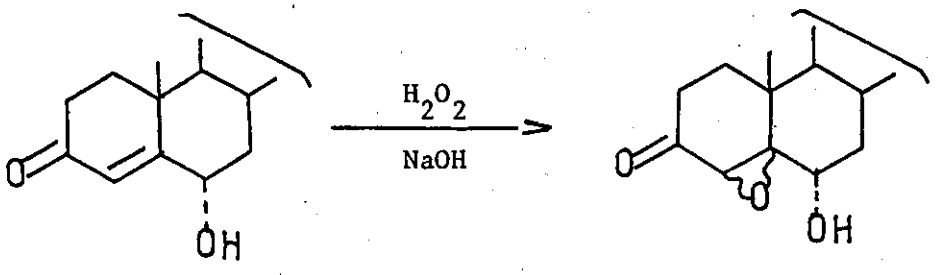


SCHEME XXIII

(49)

(50)

The hydroxy-ketone (50) on reaction with 30% hydrogen peroxide and 4N sodium hydroxide solution[31] in methanol gave a mixture containing α and β epoxides (51) (Scheme XXIV).



(50) (51)

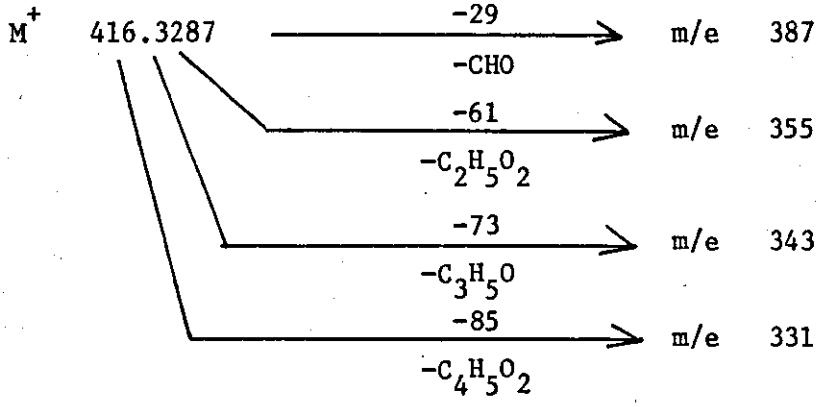
SCHEME XXIV

The α-and β-epoxides (51) which have not been reported in the literature had ν_{max} 3440 cm^{-1} (OH) and 1710 cm^{-1} (C=O).

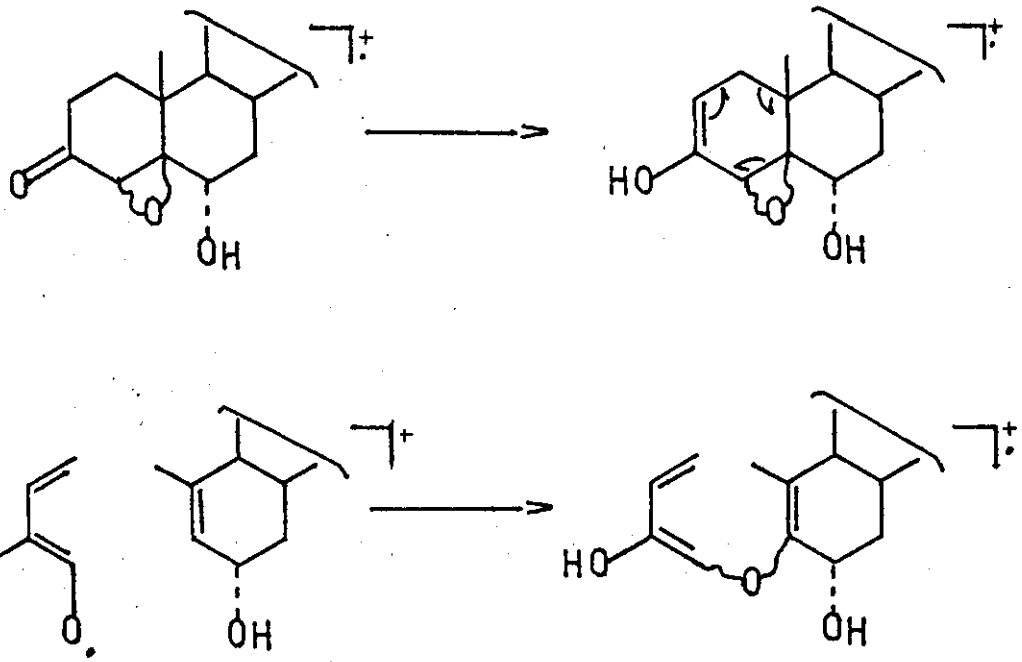
The 90 MHz ^1H n.m.r. spectrum of the mixture showed the major component gave important signals at δ 3.5 (s, 1H, C 4-H) 4.2 (q, 1H, C6-H, J11 and 4.5 Hz), 1.3 (s, 3H, C19-CH_3) 0.7 (s, 3H C18-CH_3).

As expected this confirmed the 6α-OH configuration and by analogy with the literature reports on the oxidation of other Δ^4-3-oxo-steroids,[32] it may be assumed that the major compound is the 4β,5β-epoxide. The minor 4α,5α-epoxide (< 15%) is evidently present since the ^1H n.m.r. spectrum shows singlet for the 4β-H at δ3.6.

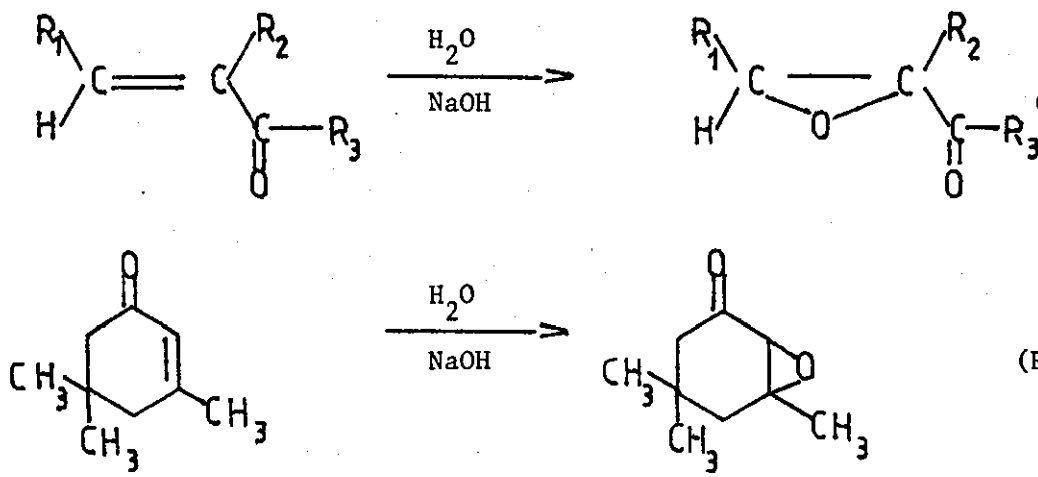
The high resolution accurate mass spectrum had a molecular ion peak at 466.3287 ($C_{27}H_{44}O_3$) for which important fragmentations are shown below.



The loss of 85 ($C_4H_5O_2$) leads to the base peak and may be explained through an internal retro-Diels-Alder fragmentation as follows.

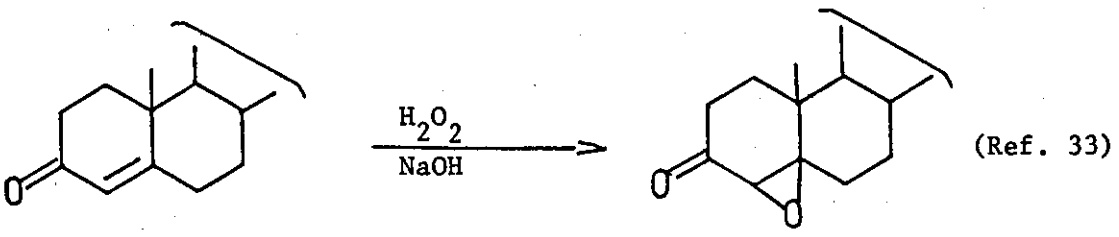


There are a number of similar preparations of α,β-epoxy-ketones involving the oxidation of conjugated ketones which alkaline hydrogen peroxide[33-39] (Scheme XXV). The normal electrophilic peracid oxidation of enones are not satisfactory for conjugated enones owing to the double bond being relatively electone deficient.

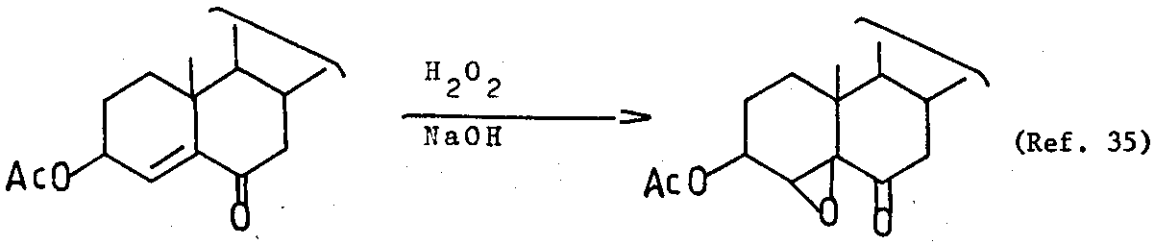


(Ref. 34)

(Ref. 36)



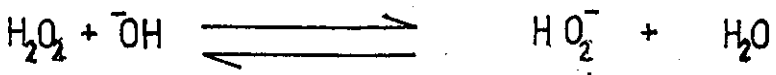
(Ref. 33)

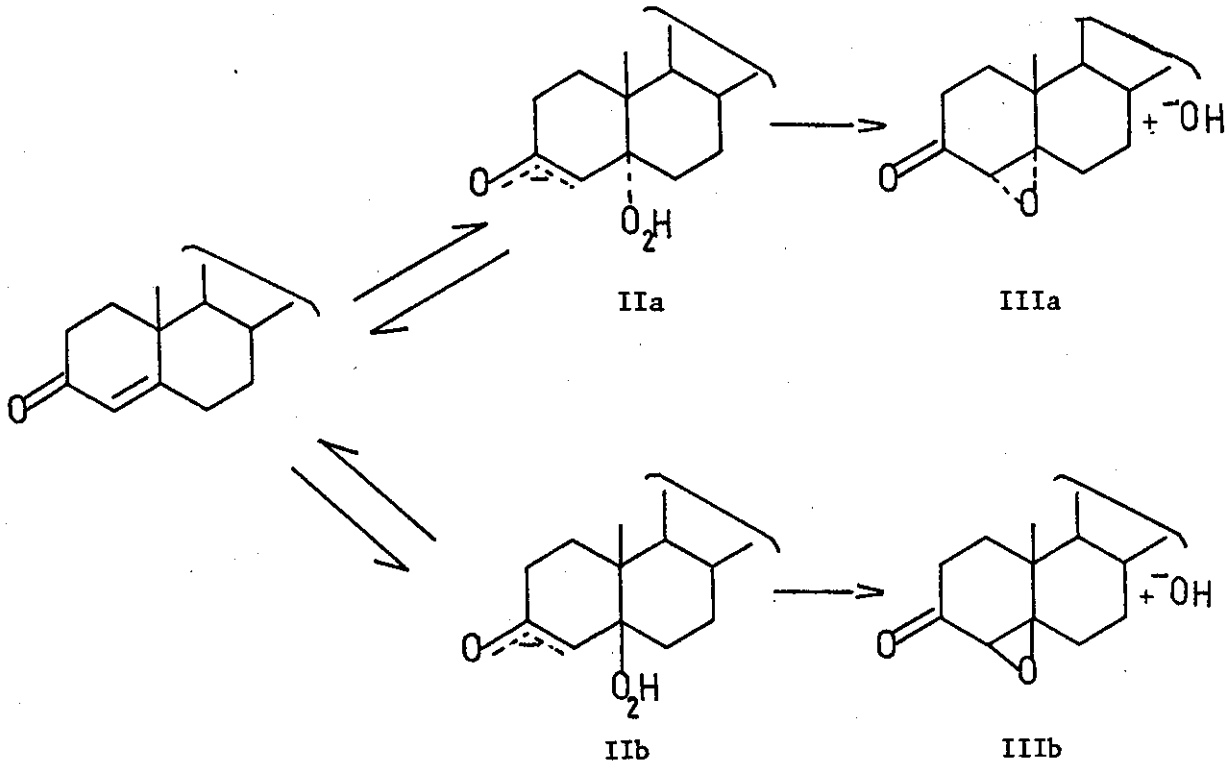


(Ref. 35)

SCHEME XXV

There is good evidence[33,34,39] to show that the mechanism of the alkaline epoxidation of conjugated unsaturated ketones first involves the reversible addition of hydroperoxide ion to the carbon-carbon double bond and that this step preceeds a slower one in which the anionic adduct is transformed into the epoxide and a hydroxide ion. For 3-oxo-Δ^4-steroids[34] the pathways are shown below.

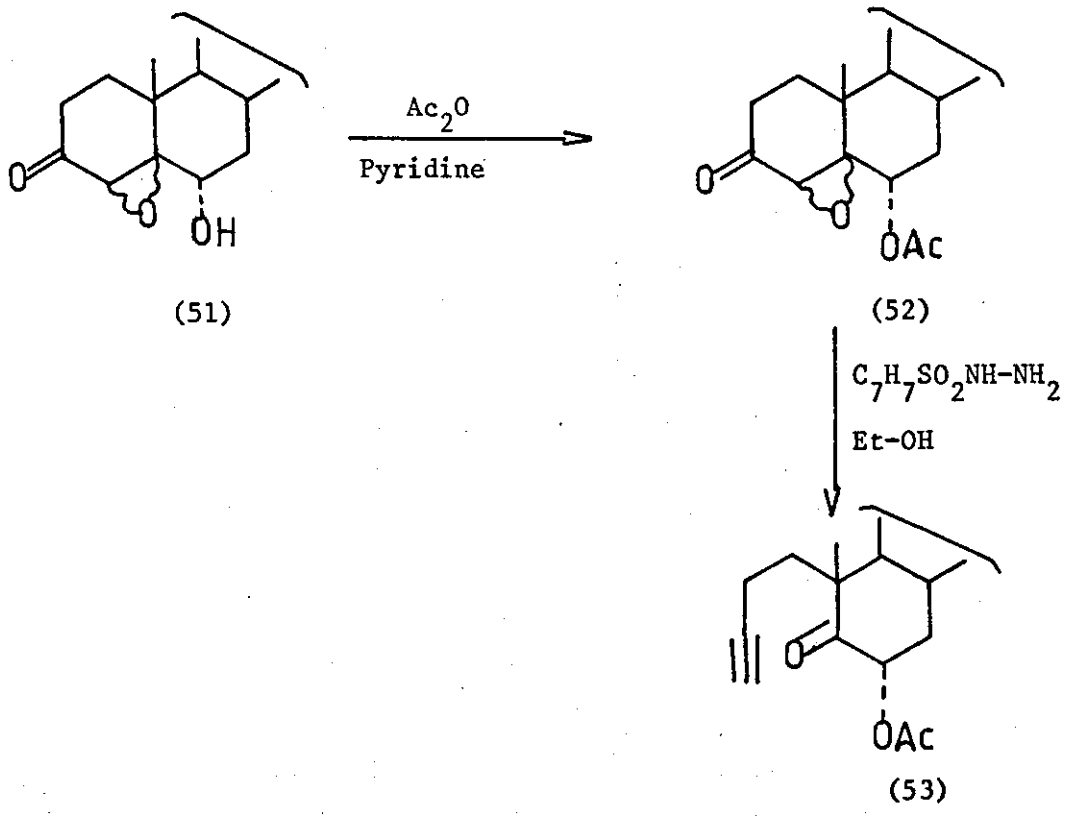




As observed earlier the 4β,5β-oxide is usually the major product. A possible, partial answer[34] may be associated with the relative relief of intramolecular and solvation compressions in the final, irreversible but alternative steps in the epoxidation. Thus the relief of compression may be greater in going to the transition state of step (IIb) → (IIIb) than for the alternative (IIa) → (IIIa). This suggestion seems reasonable from inspection of models; more exact estimates of the energy factors that could be involved in each step seem to be precluded at present by the complexity of the reaction system.

Acetylation of the epimeric mixture of 4ξ,5ξ-epoxy-cholestan-6α-hydroxy-3-one (51), gave 4ξ,5ξ-epoxy-cholestan-6α-acetoxy-3-one (52).[40]

The fragmentation of 4ξ,5ξ,-epoxy cholestan-6α-acetoxy-3-one (52) with p-toluenesulphonylhydrazine[41] in ethanol, gave 6α-acetoxy-4,5-seco-3-cholestyn-5-one (53) in (44%) (Scheme XXVI).



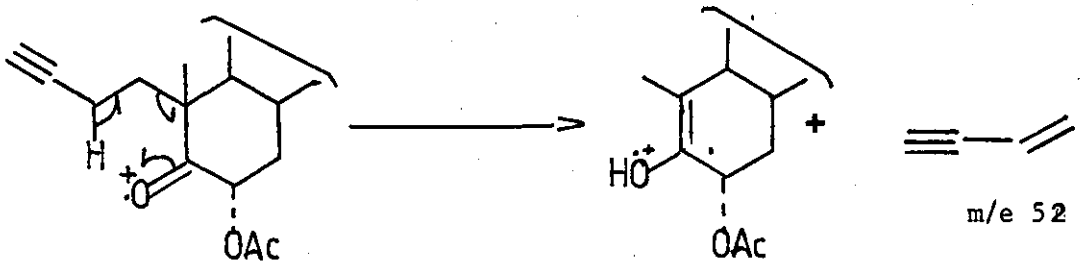
(51) (52) (53)

SCHEME XXVI

The acetylene (53) which has not been reported in the literature, had ν_{max} 3300 cm^{-1} (C≡C-H) 2120 cm^{-1} (C≡C) 1745 cm^{-1} (ester C=O), 1720 cm^{-1} (C=O) and 1240 cm^{-1} (C-O).

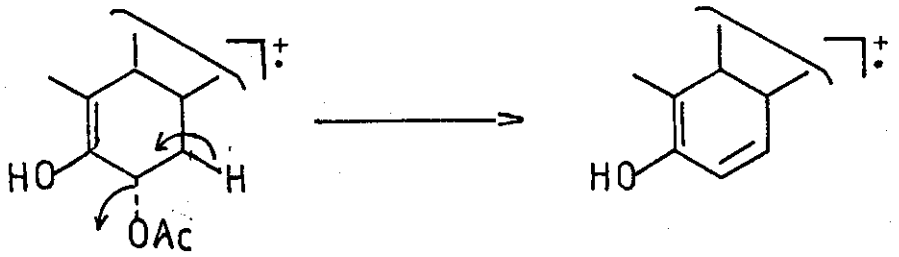
The 90 MHz ^1H n.m.r. spectrum had important peaks at δ 1.96 (m, 1H, C4-H), 2.15 (s, 3H, C6-O-C(=O)-CH_3), 5.45(q,1H,C6-H J13 and 6 Hz).

The high resolution accurate mass spectrum did not show a molecular ion, but showed an important peak at m/e 390.3134 which corresponds to the loss of C_4H_4 as indicated below; this could arise by a McLafferty rearrangement.



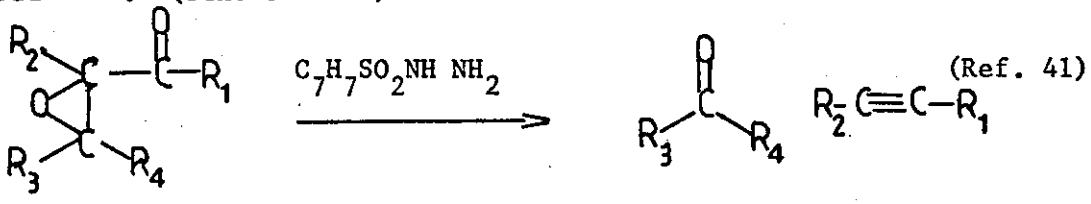
m/e 390 m/e 52

Loss of acetic acid from the m/e 390 peak to one at m/e 330 was also observed.

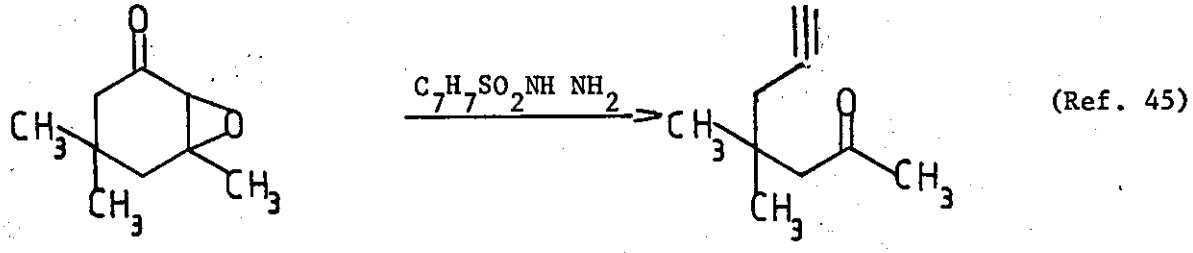


m/e 390 m/e 330

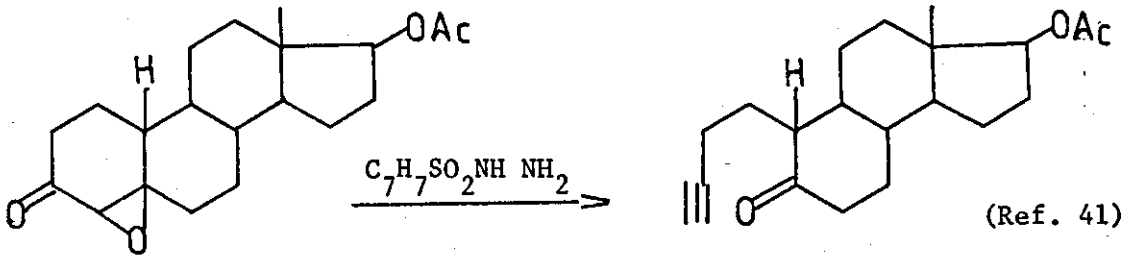
The fragmentation of α,β-epoxy-ketones by reaction with p-toluene-sulphonylhydrazine to yield acetylenic ketones has been previously described[41-45]. (Scheme XXVII).



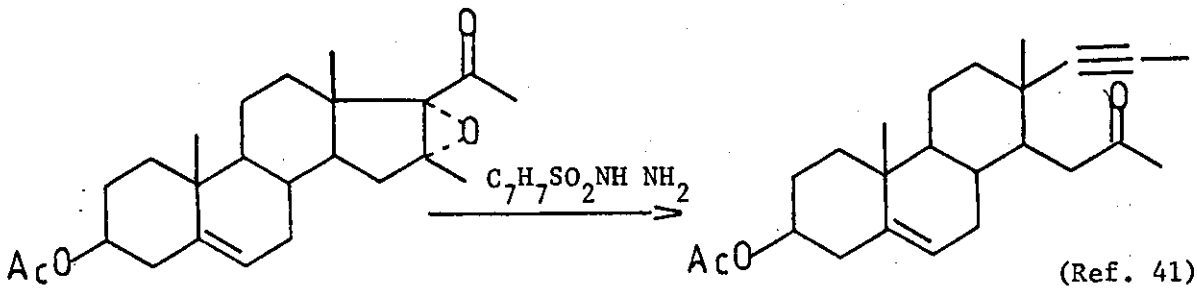
(Ref. 41)



(Ref. 45)



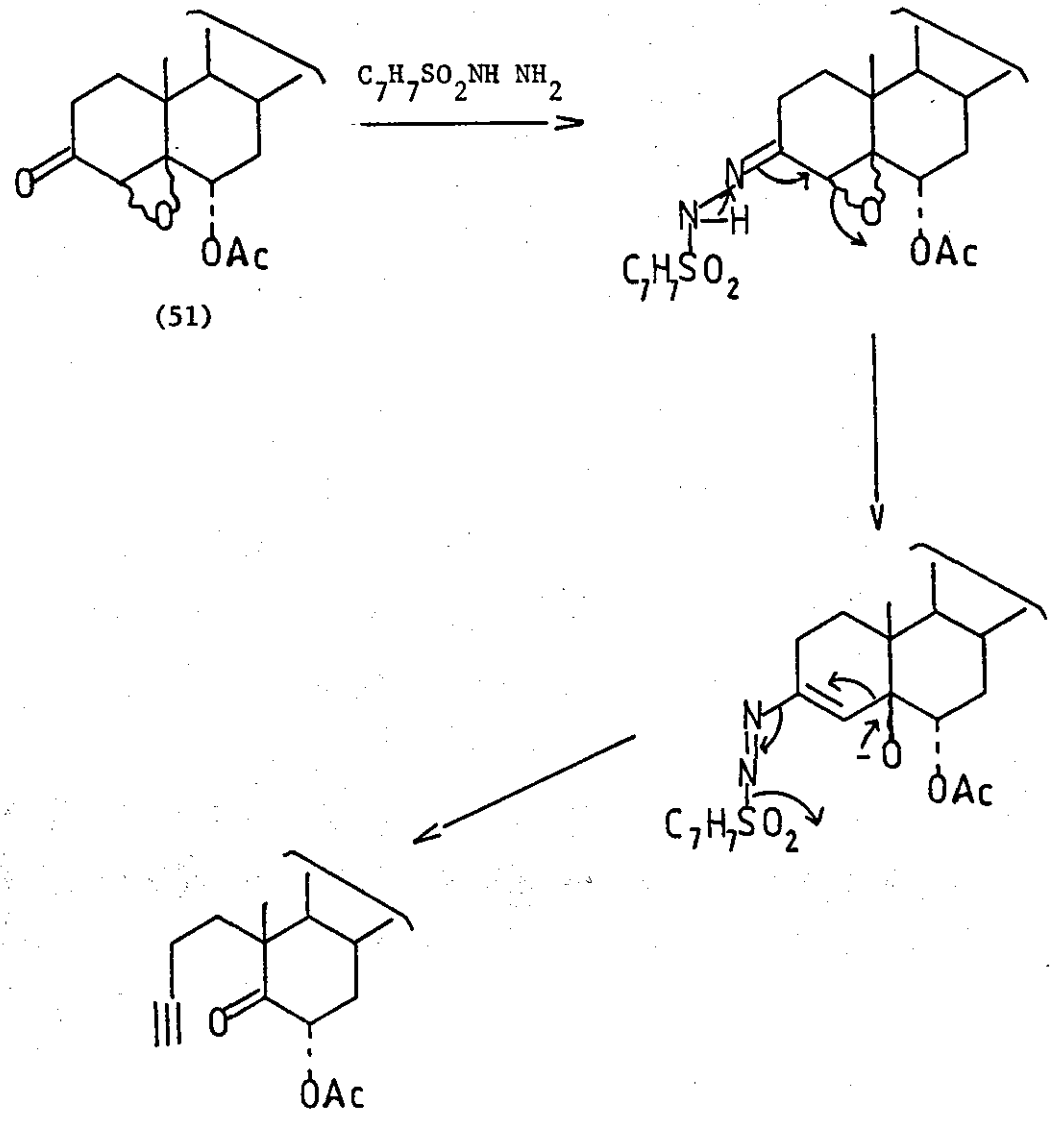
(Ref. 41)



(Ref. 41)

SCHEME XXVII

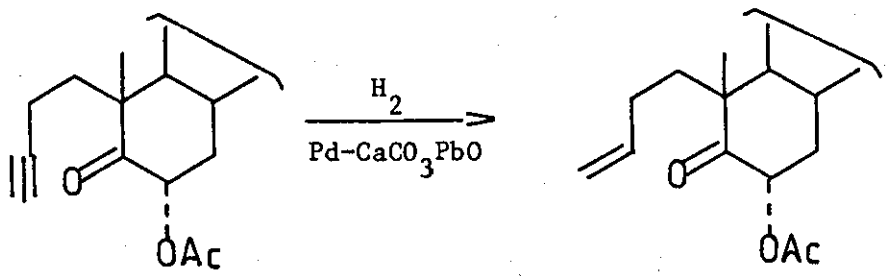
The mechanism of this applied to our acetoxy-epoxy-ketone (51) is shown below.



(51)

(53)

6α-Acetoxy-4,5-seco-3-cholestyn-5-one (53) was hydrogenated with lead-poisoned palladium on calcium carbonate (Lindlar) containing quinoline in ethyl acetate[46] to obtain 6α-acetoxy-4,5-seco-3-cholesten-5-one (54) as an oil (Scheme XXVIII).



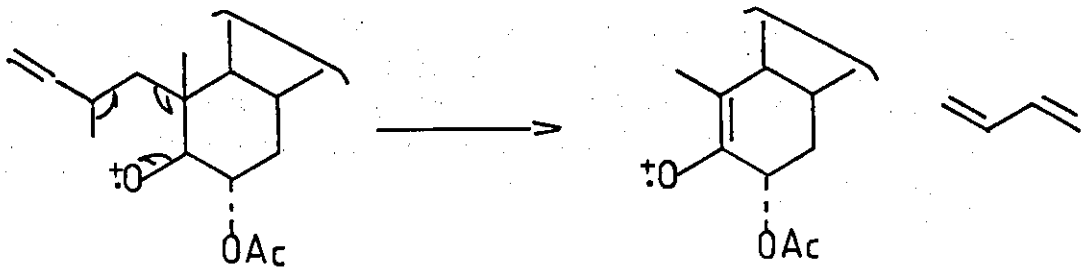
(53) (54)

SCHEME XXVIII

The seco-acetoxy-cholestanone (54) had ν_{max} 1745 cm^{-1} (ester C=O) 1725 cm^{-1} (C=O) 1640 cm^{-1} (C=C) and 1240 cm^{-1} (C-O).

The 90 MHz ^1H n.m.r. spectrum had important peaks at δ 4.96 (m, 2H C4H), 5.42 (q, 1H, C6β-H J 12 and 7 Hz) and 5.82 (m, 1H, C3-H).

The mass spectrum as in the case of the acetylene (53) showed no molecular ion, but a peak at m/e 390 arising from a similar McLafferty rearrangement is shown below.



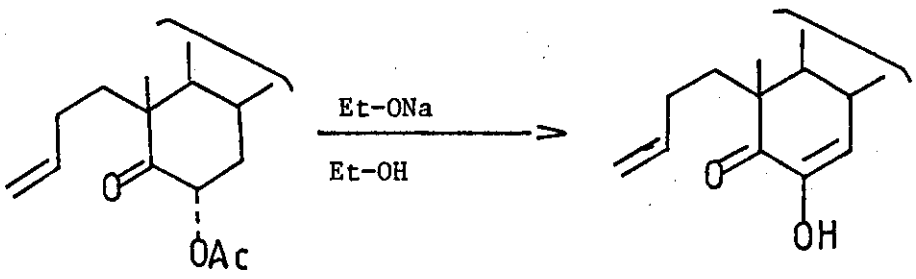
(54) m/e 390 m/e 54

Also, as in the acetylene (53) loss of acetic acid from the m/e 390 peak to one at m/e 330 was observed.

In order to test the hypothesis that the A-nor-3-methyl-5-hydroxy-6-ketone (20) arises from the ene reaction of the unsaturated acyloin (19), it was necessary to hydrolyse the seco-acetoxy-cholestanone (54) and liberate the unsaturated acyloin (48).

Treatment of the seco-acetoxy-cholestanone (54) with sodium ethoxide in ethanol gave a mixture of products from which a polar fraction could not be identified. There was no evidence of the formation of the expected A-nor-compound (20).

The only product isolated by crystallisation in (48%) was 4,5-seco-3,6-cholestadiene-6-ol-5-one (55) (Scheme XIX).



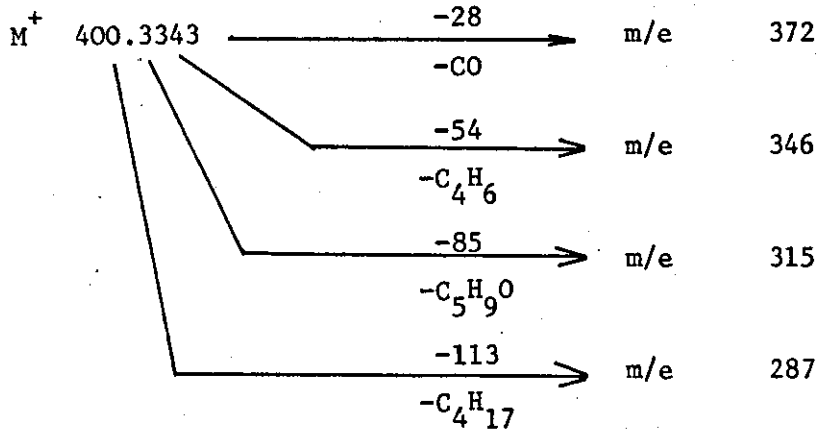
(54) (55)

SCHEME XIX

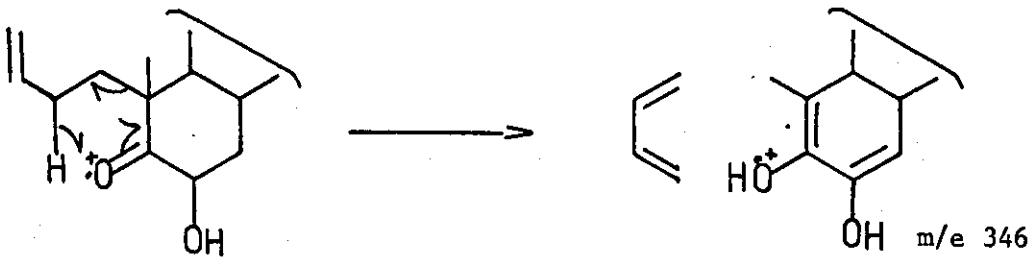
The seco-cholestadiene (55) had ν_{max} 3450 cm^{-1} (OH) 1675 (α,β unsaturated C=O) 1650 cm^{-1} (C=C). λ_{max} 268 nm. (ε 7863) λ_{max} (Et-OH with NaOH) 300 nm.

The 90 Mz 'H n.m.r. spectrum had important peaks at δ 4.98 (m, 2H, C-4-H) 5.72 (m, 1H, C3-H), 5.98 (d, 1H, C7-H J 2 Hz), 6.2 (s, 1H, OH, exchangeable with D_2O).

The high resolution accurate mass spectrum had a molecular ion peak at 400.3343 ($C_{27}H_{44}O_2$) for which important fragmentations are shown below.

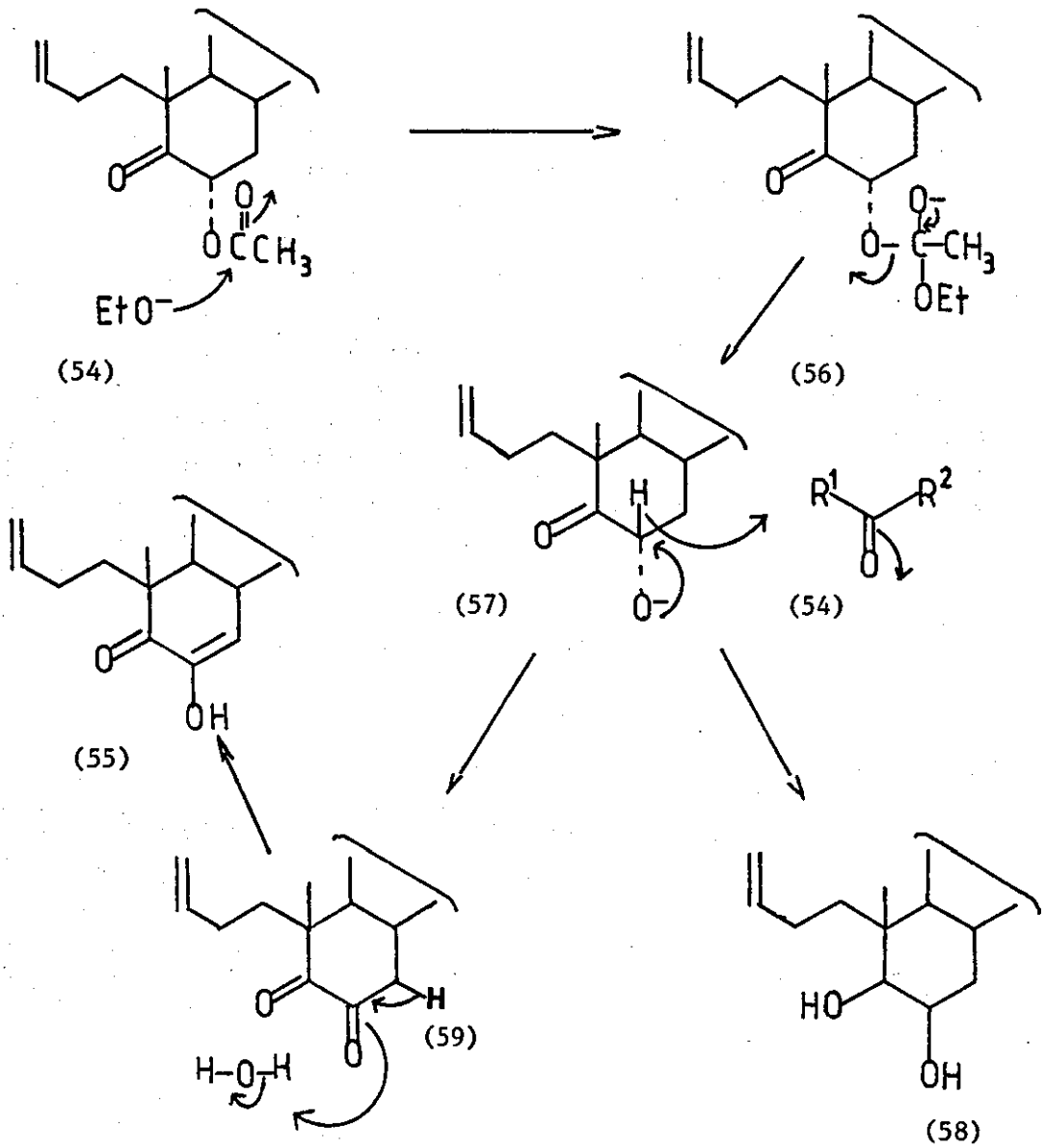


The loss of 54 (C_4H_6) leads to the base peak and may be explained by the McLafferty rearrangement shown below.



m/e 346

A possible redox mechanism leading to the formation of the seco-cholestadiene (55) is shown in Scheme XXX .



SCHEME XXX

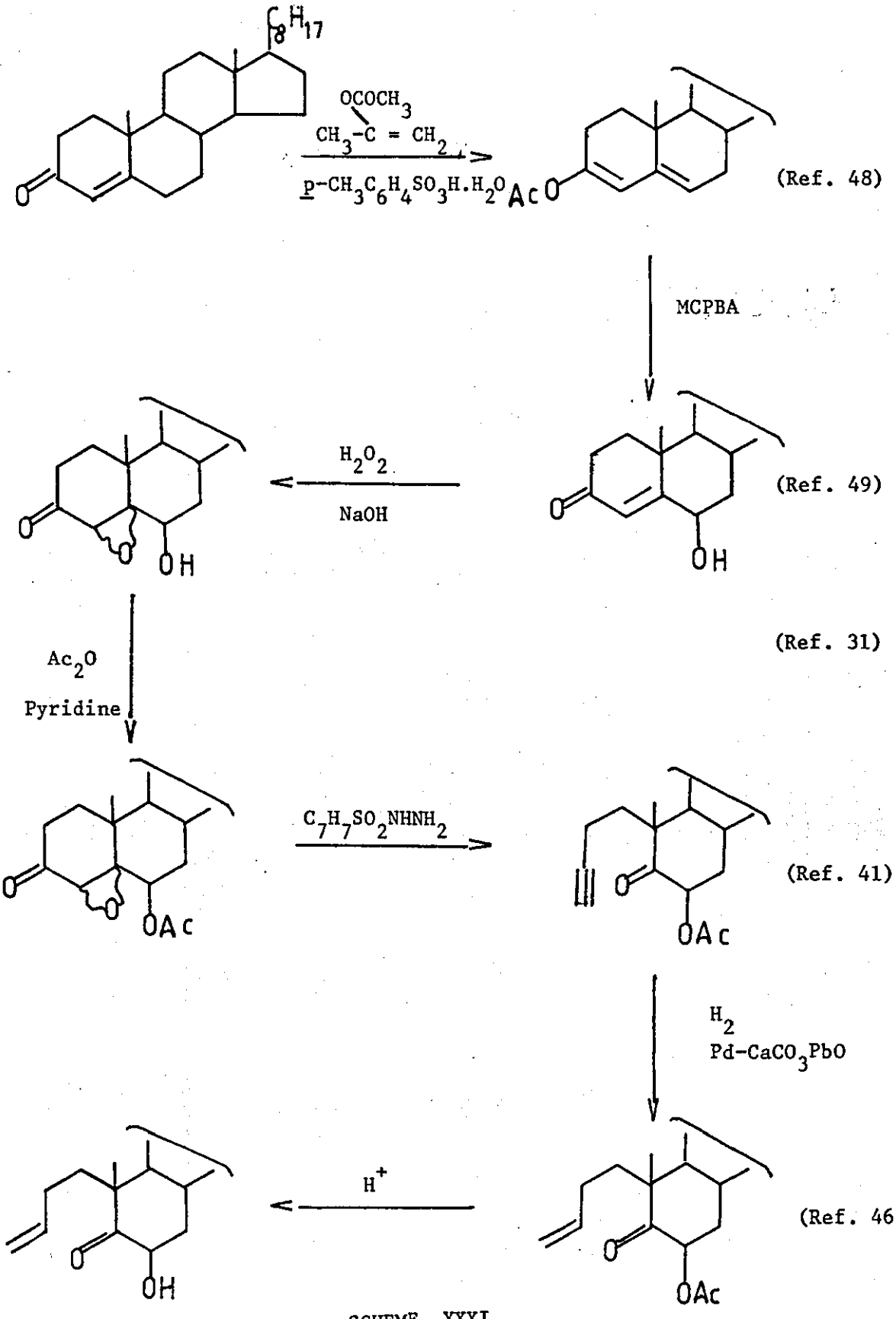
The mechanism involves the base-catalysed hydrolysis producing the ion (57). The anion (57) once formed could give the diketone (59) by loss of hydride ion to a suitable hydride aceptor R^1,R^2 C=O (59). Perhaps R^1,R^2 C=O could be the unsaturated acyloin (48) or the acetate (54) in which case the diol (58) may be a co-product in this reaction and part of the polar fraction which was not identified.

The proposed intermediate (19) in the original reaction which led to the A-nor compound (21) using Bu^tOK/Bu^tOH has a 6β-OH rather than 6α-OH as shown here.

This difference could be significant because the loss of the C6β-H would be more sterically hindered than the C6α-H.

Another difference is that the Foster and Marples[47] system uses Bu^tO^- base which is more sterically hindered than $Et\text{-}O^-$ base which is used here.

It would be of value to synthesise the unsaturated acyloin (19) by a route similar to that discussed here for its epimer (48) and thereby explore the significance of the stereochemical difference at C-6. It would be anticipated that the route shown below (Scheme XXXI) could be used.


C8H17
OCOCH3
CH3-C = CH2
p-CH3C6H4SO3H.H2O
AcO
(Ref. 48)
MCPBA
(Ref. 49)
OH
H2O2
NaOH
(Ref. 31)
Ac2O
Pyridine
OAc
C7H7SO2NHNH2
(Ref. 41)
H2
Pd-CaCO3PbO
(Ref. 46)
H+

SCHEME XXXI

The significance of the use of different bases to hydrolyse the 6ξ-OAc group and to catalyse the ene reaction would be explored in both systems (19) and (48).

If the differences between (19) and (48) and the use of different bases are insignificant then the validity of the ene mechanism is in doubt.

EXPERIMENTAL

Solutions were dried over anhydrous magnesium sulphate and solvents were removed in vacuum on a rotary evaporator. Plates (0.75 mm thick) of Kieselgel PF 254 (Merck) 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 60 MHz with a Varian FM 360A, or at 90 MHz with a Perkin-Elmer R 32 spectrometer. Ultra-violet spectra was determined in hexane, unless stated otherwise on a Pye-Unicam SP 8000 spectrophotometer. High resolution mass spectrometry was carried out on a Kratos MS50, at the P.C.M.U. by courtesy of the S.E.R.C. The important peaks are tabulated in an appendix.

Melting points were determined on a Koffler block and are uncorrected.

Optical rotations were measured for solutions in chloroform at 25°C with an Automatic Digital Polarimeter AA-10.

Cholest-4-en-3-one (23)

Distilled toluene (400 ml) was added to a 1 litre three-necked flask, equipped with a stirrer, a dropping funnel and a Dean-Stark trap. The openings of the dropping funnel and the condenser were protected with drying tubes. A portion of toluene (40 ml) was distilled off, in order to dry the system by azeotropic distillation, then cholesterol (20.0 g 0.052 M) and cyclohexanone (100 ml) was added to the flask. After additional toluene (10 ml) had been distilled off, a solution of aluminium isopropoxide* (5.6g, 0.028 m) in toluene (80 ml) was added dropwise over a period of approximately 30 min. During this time, toluene was distilled at a rate slightly greater than the rate of addition of the catalyst solution, so that when the addition was complete, about 120 ml of toluene had been distilled. After additional toluene (60 ml) had been distilled, the murky-orange coloured reaction mixture was allowed to cool to room temperature.

A saturated solution of Rochelle salt (potassium sodium tart rate, (80 ml) was added to the reaction mixture and the organic layer became of clear orange colour. The stirrer assembly was removed and the mixture was steam-distilled until 1200 ml of distillate had been collected. The residual mixture was cooled and extracted with chloroform (3 × 100 ml). The combined extract was washed with water (2 × 50 ml), dried over anhydrous magnesium sulphate, filtered and evaporated to dryness. The residual viscous oil (amber) was dissolved by heating in methanol (15 ml). When the solution had cooled to about 40 ^{o}C, seeds of cholest-4-en-3-one were added and the flask was wrapped with a small towel to ensure slow cooling. After the bulk of the material had crystallised, which required several hours, the flask was stored overnight at 0^{o}C.

The product was collected by suction filtration washed with methanol

(4-5 ml), previously cooled in an ice-salt bath, and then dried at reduced pressure at room temperature obtaining light cream coloured crystals of cholest-4-en-3-one (23) 13.59 (70%), m.p. 78-79 °C (Lit.[13] m.p.79-81 °C), ν_{max} 1673 cm^{-1} (ketone C=O), 1612 (C=C) δ 0.8 (s, 3H, C18-CH_3), 1.2 (s, 3H, C19-CH_3), 2.3 (m, 2H, C2-H), 4.3 (bs, 1H, C4-H).

*Commercial aluminium isopropoxide was taken up in dry, distilled chloroform and filtered rapidly to remove aluminium hydroxide (white gelatinous precipitate). The filtrate was evaporated to dryness and solid then employed in the reaction.

3,4-Seco-cholestan-5-one-3-oic acid (24)

Potassium carbonate (5.6 g) in water (80 ml) was added with vigorous stirring to a solution at cholest-4-en-3-one (5.0 g) in t-butanol-water azeotrope (82% R-OH, 18% water) (300 ml) followed by 50.0 ml of a solution prepared from sodium metaperiodate (20 g) and water (250 ml) and then 5 ml of 0.8% aqueous potassium permanganate. The remainder of the periodate was added at the rate of 10 ml/minute for 10 minutes and then at 3 ml/minute for the next 30 minutes. Permanganate solution was added when necessary to maintain the permanganate colour 5 ml being usually required after the first 5 minutes and a further 7.5 ml at intervals over the next 30 minutes.

After two hours the excess permagnate was destroyed with sodium bisulphite. The resultant iodine-coloured, solution was concentrated at reduced pressure to a volume of about 40.0 ml, cooled to 4 °C, acidified with ice-cold 50% sulphuric acid and extracted with ether (250 ml, 150 ml,

and 250 ml). The ethereal extract was washed with sodium bisulphite solution until free from iodine, with water until neutral, and dried with magnesium sulphate. It was then concentrated to 70 ml, diluted with hexane and further concentrated to 25 ml. After standing for 8 hours at room temperature at 4 ^{o}C, the solution yielded white needles of the keto acid (24) (3.83 g) (60%), m.p. 150-151 ^{o}C (Lit.[14] m.p. 154-155 ^{o}C), ν_{max} 3490 cm^{-1} (OH), and 1720 cm^{-1} (ketone C=O) δ 0.75 (s, 3H, C-18-CH_3), 1.1, (s, 3H, C19-CH_3), 2.2 (m, 2H, C-2H).

4-Oxa-Cholest-5-en-3-one (25)

3,4-seco-cholestan-5-one-3-oic-acid (1.0 g) was dissolved in 100 ml of reagent A* and the solution was left standing for 5 minutes at room temperature. The solution was then washed with saturated sodium bicarbonate solution (1 × 75 ml), water (1 × 75 ml), dried over anhydrous sodium sulphate and evaporated to dryness. The crude product was crystallised from aqueous acetone, giving white crystals of 4-oxa-cholest-5-en-3-one (25) (0.480 g) (50%) m.p. 92-93 ^{o}C (Lit.[15] 92-93 ^{o}C) ν_{max} 1760 cm^{-1} (C=O lactone) 1680 cm^{-1} (C=C), δ0.7 (s, 3H, C18-CH_3), 1.1 (s, 3H, C19-CH_3) 2.2 (s, 2H, C2-H) 5.2 (m, 1H, C6-H).

*Reagent A (10^{-3}M $HClO_4$) to 50 ml of absolute ethyl acetate was added (0.05 ml) of perchloric acid 75% (0.575 mmole). Ten milliliters of this solution was then added to absolute ethyl acetate (30 ml) and acetic anhydride (4.8 ml 51 mmoles) and the solution was made up to 50 ml with ethyl acetate to give a reagent 1M in acetic anhydride and 10^{-3}M in perchloric acid.

4-Oxa-5,6α-epoxy-5α-cholestan-3-one (26A)

4-oxa-cholest-5-en-3-one (5.0 g) was dissolved in methylene chloride (25 ml); m-chloroperbenzoic acid (2.75 g) in methylene chloride was added. The reaction mixture was stirred for 30 minutes at room temperature. Excess of peracid was then destroyed by addition of 10% of sodium sulfite, until a test with starch-iodine paper was negative. The reaction mixture was washed with 5% sodium bicarbonate solution (1 × 100 ml) followed by water (2 × 100 ml) and finally with saturated sodium chloride solution (1 × 100 ml), dried over anhydrous sodium sulphate and evaporated to dryness. The crude product was crystallised from acetone to obtain white crystals of 4-oxa-5,6α-epoxy-cholestan-3-one (26A), (2.25 g) (45%) m.p. 150-152 ^{o}C, $[\alpha]_D$ 36.36 ^{o}(c 11.0), ν_{max} 1740 cm^{-1} (C=O) δ 0.7 (s, 3H, C18-CH_3) 1.2 (s, 3H, C19-CH_3) 2.7 (m, 2H, C2-H) 3.3 (d, 1H, C6 -H J 5Hz). (Fond C, 77.05; H, 10.65 $C_{26}H_{42}O_3$ requires C, 77.61; H, 10.41%).

3,4-Seco-4-nor-cholestan-6-ol-5-one-3-oic acid (27)

4-oxa-5,6α-epoxy-cholestan-3-one (1.0 g) in ethyl-methyl ketone (25 ml), 60% perchloric acid (10 drops) was added. The solution was allowed to stand at room temperature for 15 minutes, and diethyl ether was added. The reaction mixture was washed with saturated sodium hydrogen carbonate solution (2 × 75 ml) and water (2 × 50 ml). The ether extract was dried over anhydrous magnesium sulphate and evaporated to dryness. The crude product which was crystallised from ether-hexane yielded white crystals of 3,4-seco-4-nor-cholestan-6-ol-5-one-3-oid acid (27), (0.700 g) (70%) m.p. 89-91 ^{o}C, $[\alpha_D]$33.93^{o} (c 8.2), ν_{max} 3500 cm^{-1} (OH) 1720 cm^{-1} (C=O) δ 0.8 (s, 3H, C18-CH_3) 1.2 (s, 3H, C19-CH_3), 2.3 (m, 2H, C2-H), 4.35 (m, 1H, C6-H).

3β-Hydroxy-5,6α-epoxy-5α-cholestane (32)

Cholesterol (10.0 g) was dissolved in methylene chloride (40 ml), m-chloroperbenzoic acid (5.5 g) in methylene chloride was added. The reaction mixture was stirred at room temperature for 30 minutes. Excess of peracid was then destroyed by addition of 10% of sodium sulfite, until a test with starch iodine paper was negative. The reaction mixture was washed with 5% sodium bicarbonate solution (1 × 100 ml) followed by water (2 × 100 ml) and finally with saturated sodium chloride solution (1 × 100 ml), dried over anhydrous sodium sulphate and evaporated to dryness. The crude product was crystallised from ethyl acetate to obtain white crystals of 3β-hydroxy-5,6α-epoxy-5α-cholestane (32), (9.5 g) (91%) m.p. 141-143 °C (Lit.[20] 141-143 °C), ν_{max} 3420 cm^{-1} (OH), δ 0.6 (s, 3H, C18-CH_3) 1.0 (s, 3H, C19-CH_3) 2.9 (d, 1H, C6β-H J 5 Hz).

3β,5α-Dihydroxy-5α-cholestane (33)

3β-hydroxy-5α,6α-epoxide-cholestane (800 mg) in dry ether (15 ml), lithiumaluminium hydride (0.550 mg) in dry ether (10 ml) was added with stirring. The solution was stirring for 2 hours at room temperature.

The reaction mixture was poured over ice-water and then added diluted sulphuric acid until separated into a clear water and ether. The reaction mixturewas then transferred to a separatory funnel, and the organic layer was washed with sodium bicarbonate solution (1 × 10 ml) and finally with water (1 × 10 ml). The ether solution was dried over anhydrous magnesium sulphate and evaporated to dryness. The crude product was crystallised from ethyl acetate to obtain white crystals of 3β,5α-dihydroxy-5α-cholestane (33), (0.550 g) (69%) m.p. 127-128 °C (Lit[20] 128-129 °C). ν_{max} 3420 (OH), δ 0.57 (s, 3H, C18-CH_3), 1.0 (s, 3H, C19-CH_3), 3.7-4.2 (m, 1H, C3αH).

5α-Hydroxy-cholestan-3β-yl-toluene-p-sulphonate (34)

3β-5α-dihydroxy-cholestane (1.7 g) and p-toluene-sulphonyl chloride (1.7 g) were kept in pyridine (20 ml) at 20 °C for 24 hours. The product was isolated with ether and chromatographed on deactivated alumina (100 g). Elution with benzene affored the 5α-hydroxy-cholestan-3β-yl-toluene-p-sulphonate (34) which crystallised from nitromethane as plates (2.1 g) (90%) m.p. 128-129 °C (Lit.[21] m.p. 128-129 °C). ν_{max} 3460 cm^{-1} (OH), 1600 cm^{-1} (C=C Aromatic), 1495, 1469, 1455, 1447, cm^{-1} (SO_2-O-) δ 0.7 (s, 3H, C18-CH_3), 1.3 (s, 3H, C19-CH_3) 2.5 (s, 3H, -C_6H_4-CH_3), 6.9 (m, 1H, 3α-H) 3.3-3.9 (4H Aromatic 8 and 9 Hz).

4,5-Seco-cholest-3-en-5-one (35)

5α-hydroxy-cholestan-3β-yl toluene-p-sulphonate (2.0 g) in tert-butyl alcohol (180 ml) and molar potassium tert-butoxide (7 ml 2.5 mol) were mixed at 50 °C (potassium-p-sulphonate began to precipitate almost immediately), and kept at 50 °C for 2 hours. The reaction mixture is transferred to a separatory funnel, added some water and extracted with ether (3 × 120 ml). The ether extracts were dried over anhydrous magnesium sulphate and evaporated to dryness. The crude product was plated (solvent, ether-petrol ether 60-80; 50/50) to obtain the 4:5-seco-cholest-3-en-5-one as an oil (35) (0.400 g) (30%), ν_{max} 1710 cm^{-1} (C=O), δ 0.8 (s, 3H, C18-CH_3) 1.1 (s, 3H, C19-CH_3) 4.95 (t, 2H, C4-H J 10 and 9 Hz), 5.8 (m, 2H, C6-H).

5-trimethylsilyloxy-4,5-seco-cholesta-3,5-diene (39)

4:5-seco-cholest-3-en-5-one (0.080 g) in dry pyridine with nitrogen passing through the reaction flask all the time was added hexamethyldisilazan (1 ml) and trimethylchlorosilan (1 ml). The reaction mixture was kept with nitrogen 120 hours at 80 °C.

On completion of the reaction, the reaction mixture was concentrated all volatile material and then added toluol (40 ml) and concentrated to dryness to yield yellow crystals of (39) (0.209 g), ν_{max} 1700 cm^{-1} (C=O), 1020 cm^{-1} [Si-$(CH_3)_3$], δ 0.02 (s, 9H, [Si-$(CH_3)_3$], 0.61 (s, 9H, [Si-$(CH_3)_3$], 0.61 (s, 3H, C18-CH_3), 0.8 (s, 3H, C19-CH_3), 4.7 (m, 2H, C4-H), and 5.72 (m, 1H, C6-H).

3β,5α-Dihydroxy-6β-methoxy-5α-cholestane (41)

5,6β-epoxy-5α-cholestan-3β-ol (1 g) was dissolved in methanol (40 ml) and boron trifluoride etherate (1 ml) was added. The solution was allowed to stand at room temperature for 4 hours. Water was added and the reaction mixture was extracted with ether (2 × 200 ml). The combined ether extract was washed with sodium bicarbonate solution (2 × 50 ml) and water (1 × 50 ml). Ether extract was dried over magnesium sulphate and evaporated to dryness. The crude product was crystallised from methanol gave white crystals of 3β,5-dihydroxy-6β-methoxy-5α-cholestane, (41) (0.900 g) (84%) m.p. 149-150 °C (Lit.[27] 150-151 °C), ν_{max} 3500 (OH), δ 0.64 (s, 3H, C18-CH_3) 1.6 (s, 3H, C19-CH_3), 2.95 (m, 1H, C6α-H), 3.7 (s, 3H, CH_3-O), 4.0 (m, 1H C3α-H).

5α-Hydroxy-6β-methoxy-cholestan-3β-yl-toluene-p-sulphonate (42)

3β,5-dihydroxy-6β-methoxy-5α-cholestane (0.5 g) and toluene-p-sulphonyl chloride (0.5 g) were kept in pyridine (20 ml) at room temperature for 24 hours. The reaction mixture was poured into ice-water and extracted with ether (3 × 50 ml). The combined ether extract was washed with hydrochloric acid (2 × 25 ml) followed by ice-cold water (2 × 50 ml). Ether extract was dried over magnesium sulphate and evaporated to dryness. The crude product (690 mg) was crystallized from 60-80 petrol ether-acetone to obtain white crystals of 5α-hydroxy-6β-methoxy-cholestan-3β-yl toluene-p-sulfonate (42) (2.1 g) (97%) m.p. 123-125 °C, [α] - 24° (C 10.0), ν_{max} 3500 cm^{-1} (OH), 1600 cm^{-1} (C=C) Aromatic) 1455, 1355, 1160, 1100 cm^{-1} (-SO_2-O-) δ 0.63 (s,

3H, C18-CH_3) 1.2 (s, C19-CH_3), 2.42 (s, 3H, -C_6H_4-CH_3), 2.9 (m, 1H, C6α-H), 4.8 (m, 1H, C3α-H), 7.20-7.84 (4H, Aromatic J 8 and 7 Hz), (Found C, 71.30; H, 9.8; S, 5.44 $C_{35}H_{56}O_5S$ requires C, 71.42; H, 9.52; S, 5.2%).

6β-Methoxy-3α,5-epoxy-5α-cholestane (43)

The hydroxy-tosylate (42) (0.5g) in tert-butyl alcohol (30 ml) and molar potassium tert-butoxide (7 ml 2.5 mol) were kept at 50°C for 2 hours. The reaction mixture was extracted with ether (3 × 100 ml). The combined ether extract was evaporated to dryness. The crude product was plated (solvent ether-petrol ether (60-80), 50:50) to obtain the 6β-methoxy-3α,5α-epoxy-5α-cholestane (43) as an oil (1.80 g) (68%), $[\alpha]_D$ 24° (C 10.0). δ 0.69 (s, 3H, C18-CH_3), 1.4 (s, 3H, C19-CH_3), 4.5 (brd, 1H, C3-β-H), 3.40 (m, 1H, C6α-H), 3.32 (s, 3H, CH_3-O-), 2.6 (q, 1H, 4α-H, J, 9 and 7 Hz), 2.06 (d, 1H, 4β-H J, 9 Hz), (Found C, 80.45°, H, 11.61, $C_{28}H_{40}O_2$ requires C, 80.71; H, 11.61).

6α-hydroxy-cholest-4-en-3-one (50)

A solution of 5,6α-epoxy-5α-cholestan-3β-ol (200 mg) in pyridine (2.0 ml) was added to a solution of chromium trioxide (200 mg) in pyridine (2.0 ml) and the reaction mixture was stirred at room temperature for 12 hours. The resultant mixture was poured into water and extracted with ether (2 × 100 ml). The ether extract was eashed with dilute acetic acid (1 × 50 ml), aqueous sodium bicarbonate solution (1 × 50 ml) water (1 × 50 ml) and dried over magnesium sulphate and evaporated to dryness. The crude product was plated (solvent:ethyl acetate-benzene 60/40) to obtain white crystals of 6α-hydroxy-cholest-4-en-3-one (50) (0.088) (45%) m.p. 154-155°C (Lit.[73] 156°C) ν_{max} 3400 cm^{-1} (OH), 1665 cm^{-1} (α,β-enone), 1620 cm^{-1} (C=C), δ 0.6 (s, 3H, C18-CH_3) 1.1 (s, 3H, C19-CH_3) 4.2 (m, 1H, C6βH), 6.1 (s, 1H, C4-H).

4ξ,5ξ-Epoxy-cholestan-6α-ol-3-one (51)

6α-hydroxy-cholest-4-en-3-one 1.700 g) in methanol (70 ml) was added to a solution of sodium hydroxide 4N (2.8 ml) and solution of hydrogen peroxide 30% (1.6 ml). The reaction mixture was stirred at room temperature for 3 hours, then diluted with water and extracted with ether (2 × 100 ml). The organic layer was washed successively with dilute sulphuric acid solution (1 × 50 ml), sodium hydrogen carbonate solution (1 × 50 ml) and water (1 × 50 ml). The ether solution was dried over anhydrous magnesium sulphate and evaporated to dryness to obtain 6α-hydroxy-4ξ,5ξ-epoxy-cholestan-3-one (51) as an oil (0.550 g) (75.5%). ν_{max} 3440 cm^{-1} (OH), 1710 cm^{-1} (C=O) δ 0.6 (s, 3H, C18-CH_3), 1.1 (s, 3H C19-CH_3), 3.5 (s, 1H C4α-H) 4.2 (q, 1H, C6β-H J. 11 and 4.5 Hz).

4ξ5ξ-Epoxy-cholestan-6α-acetoxy-3-one (52)

To a solution of 4,5-epoxy-cholestan-6α-hydroxy-3-one(120 mg) in pyridine (10 ml), acetic anhydride (6 ml) was added. The solution was left to stand overnight at room temperature.

The reaction mixture was poured over ice-water and extracted with ether (3 × 50.0 ml). The combined ether extract was washed with water (2 × 50 ml), dried over anhydrous magnesium sulphate and evaporated to dryness, to give 4ξ,5ξ-epoxy-cholestan-3α-acetoxy-3-one as an oil, (52), (0.125 g) (94.6%) $[\alpha]_D$ 24° (C 10.0), ν_{max} 1745 cm^{-1} (ester C=O) 1710 cm^{-1} (C=O), 1240 cm^{-1} (C-O) δ 0.6 (s, 3H, C18-CH_3), 1.1 (s, 3H, C19-CH_3) 1.85 (s, 3H, C6-O-$\overset{O}{\overset{\|}{C}}$-$CH_3$) 3.32 (s, 1H, C4-H), 5.3 (m, 1H (C6β-H).

3α-acetoxy-4,5-seco-3-cholestyn-5-one (53)

To a solution of 4ξ5ξ-epoxy-cholestan-3α-acetoxy-3-one(0.442 g) in

ethanol (10 ml), p-toluenesulfonyl hydrazine (64.35 mg) was added. The solution was kept at 50°C for 2 hours, then diluted with water and extracted with ether (2 × 75 ml).

The organic layer was washed with dilute hydrochloric acid (1 × 25 ml), sodium hydrogen carbonate solution (1 × 25 ml) and water (1 × 25 ml), and evaporated to dryness. The crude product (0.399g) was plated (solvent: ethyl acetate-benzene 5/95) to obtain 3α-acetoxy-4,5-seco-3-cholestyn-5-one as an oil (0.186 g). (43.6%). $[\alpha]_D$ -15° (C 5.25) ν_{max} 3300 cm^{-1} (C-H), 2120 cm^{-1} (C≡C), 1745 cm^{-1} (ester C=O) 1720 cm^{-1} (C=O) and 1240 cm^{-1} (C-O) δ 0.74 (s, 3H, C-18-CH_3) 1.16, (s, 3H, C19-CH_3) 2.15 (s, 3H, C6-O-C-CH_3), δ 5.45 (q, 1H, C6-H J 13 and 6 Hz), 1.96 (br. s, 1H, C4-H).

Hydrogenation of 6α-acetoxy-4,5-seco-3-cholestyn-5-one (53)

3α-acetoxy-4,5-seco-3-cholestan-5-one (206) was taken up in ethyl acetate (10 ml) and hydrogenated using palladium on calcium carbonate poisoned with lead (palladium content 5%) (25 mg) and 1 ml of quinoline solution (ethyl acetate-quinoline 4/1), until 1 mol of hydrogen was consumed. The solution was filtered and the flask was washed with ethyl acetate (10 ml). The combined ethyl acetate was washed with dilute hydrochloric acid (1 × 25 ml), sodium bicarbonate solution (1 × 25 ml) and water (1 × 25 ml), and evaporated to dryness. The crude product was plated (solvent:benzene-ethyl acetate 95/5) to obtain a product which was identified as 3α-acetoxy-4,5-seco-3-cholesten-5-one as an oil (54) (0.160 g) (86.5%), ν_{max} 1745 cm^{-1} (ester C=O), 1725 cm^{-1} (C=O), 1640 cm^{-1} (C=C) and 1240 cm^{-1} (C-O), δ 0.74 (s, 3H, C-18-CH_3), 1.16 (s, 3H, C19-CH_3), 2.15 (s, 3H, C6-O-C-CH_3) 4.96 (m, 2H, C4-H), 5.42 (q, 1H, C6β-H 12 and 7 Hz), 5.82 (m, 1H, C3-H).

Reaction of 3α-acetoxy-4,5-seco-3-cholesten-5-one (54) with sodium ethoxide

3α-acetoxy-4,5-seco-3-cholesten-5-one (0.160 g) in absolute ethanol (5 ml) and molar sodium ethoxide (5 ml ethanol 2.5 ml) were kept at 50 °C for 2 hours under nitrogen atmosphere. The reaction mixture was extracted with ether (3 × 20 ml). The combined ether extract was washed with diluted hydrochloric acid (1 × 10 ml), sodium bicarbonate (2 × 10 ml), and finally with water (2 × 20 ml), dried over anhydrous magnesium sulphate and evaporated to dryness. The crude product was crystallised from methanol to yield white crystals of 4,5-seco-3,6-cholestadiene (55) (0.623 g) (48%). The mother liquors (30 mg) were plated, but we could not isolate the polar product.

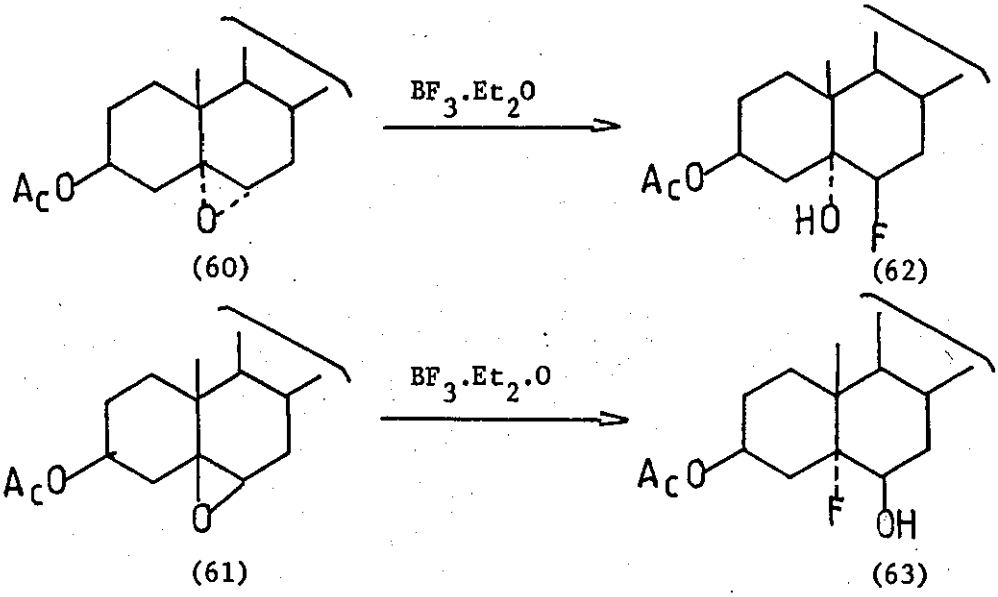
The diol (55) $[\alpha]_D$ 8.45 (C 14.2), ν_{max} 3450 cm^{-1} (OH), 1675 cm^{-1} (α,β unsaturated C=O) 1650 cm^{-1} (C=C) λ_{max} 268 nm. (ε 7863) λ_{max} (Et-OH with NaOH) 300 nm., δ 0.76 (s, 3H, C18-CH_3) 1.4 (s, 3H, C19-CH_3) 4.98 (m, 2H, C4-H), 5.72 (m, 1H, C3-H), 5.98 (d, 1H, C6-H J 2 Hz), 6.2 (s, 1H, OH, exchangeable with D_2O).

PART TWO: Rearrangement of 3,5-epoxy steroids

INTRODUCTION

The boron trifluoride-catalysed reactions of steroidal 5,6-epoxides in benzene have been widely reported.[50-60]

Henbest et al[50] in 1957 examined the reaction of 3β-acetoxy-5α,6α-epoxide (60) and the 3β-acetoxy-5β,6β-epoxide (61) with boron trifluoride ether-complex in benzene solution, and reported the isolation of the fluorohydrins (62) and (63) as the major products, accompanied by starting material and a polar fraction which was not examined (Scheme XXXII).

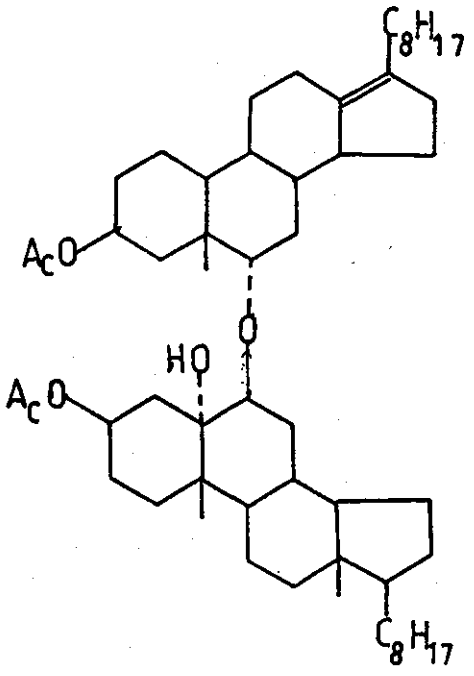


(60) (62)

(61) (63)

SCHEME XXXII

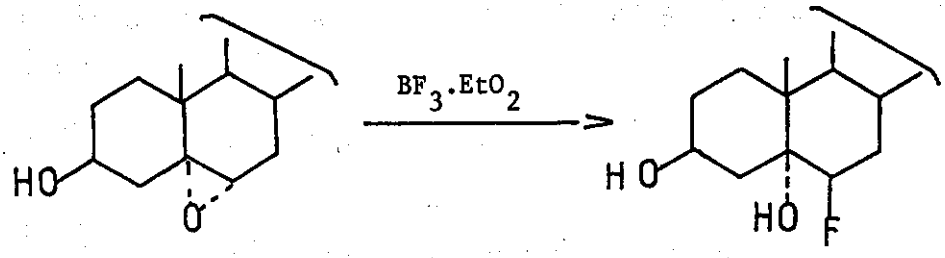
Hartshorn et al,[51] re-examined the reaction of 3β-acetoxy-5,6α-epoxy-5α-cholestane (60) with boron trifluoride ether-complex and found that, depending, upon the reaction conditions a yield of up to 32% of a dimer (64) was obtained in addition to the fluorohydrin (62).



(64)

They found that BF_3-etherate freed from HBF_4 must be used in order that the BF_3 may exert its full effect as a Lewis acid.

Also, the reaction of the 3β-acetoxy-5α,6α-epoxide(60) and the 3β-hydroxy 5α,6α-epoxide (65) with boron-trifluoride-ether complex in ether-benzene (1:1) solution was reported to give good yields of fluorohydrins (62) and (63) respectively[52] (Scheme XXXIII).

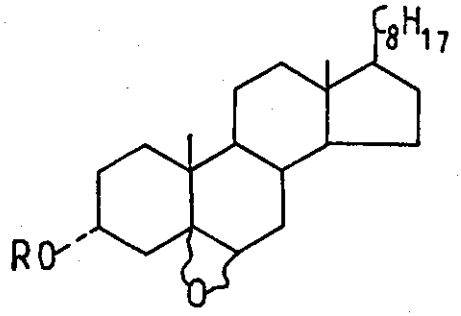


(65) (66)

SCHEME XXXIII

It was reported in 1969 by Bowers[53] et al than an increase in fluoroboric acid concentration (as added HF) caused an enhancement in the yield of the fluorohydrin compounds. Coxon et al[54] studied the boron trifluoride-catalysed

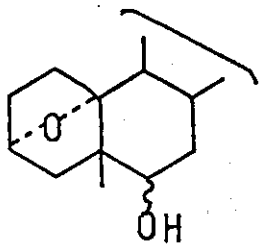
rearrangements of the 5,6-epoxides of epicholesterol (67A) and (67B) and epicholesterol acetate (67C).



(67)

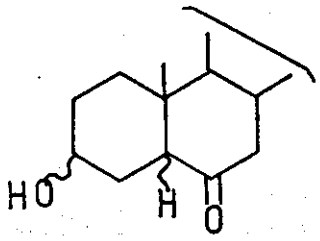
A R=H 5α,6α
B R=H 5β,6β
C R=Ac 5β,6β

The BF_3-catalysed rearrangement of the 3α-hydroxy-5β,6β-epoxide (67B) gave a 3α,10α-epoxide (68A) in (28%), a ketone (66A) in (19%), a backbone rearrangement product (70A) (36%) and starting material (67B) (7%).



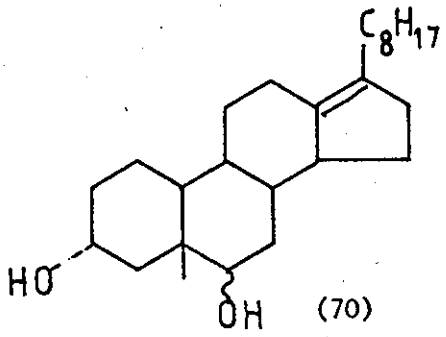
(68)

A 6β-OH
B 6α-OH



(69)

A 5αH, 3αOH
B 5βH, 3αOH
C 5αH, 3βOH
D 5βH, 3βOH



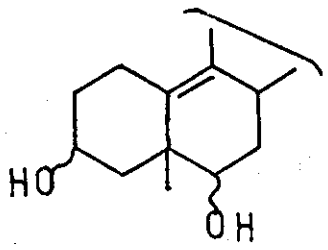
(70)

A 3αOH, 6βOH
B 3αOH, 6αOH
C 3βOH, 6αOH
D 3βOH, 6βOH

Extended treatment of the epoxide (67B) with BF_3-etherate in benzene gave a backbone rearrangement product (70A) (41%) and Δ^9-olefin (71A) (22%).

It was suggested that, over a long term reaction, the intermediate 3,10-

epoxide (68A) was rearranged further to the compounds (70A) and (71A) respectively.



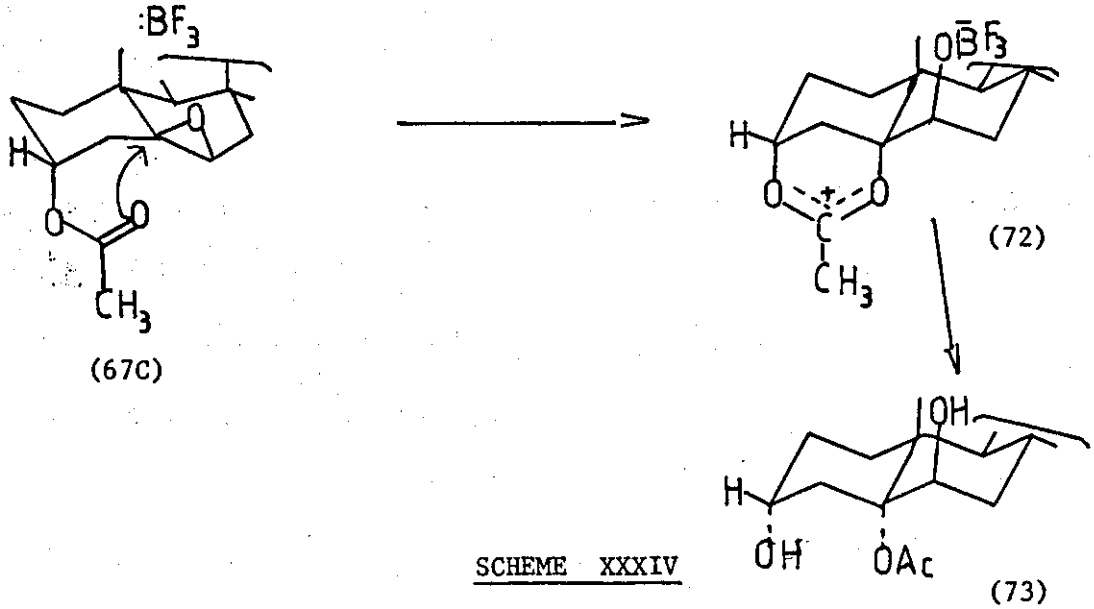
(71)

A 3αOH, 6βOH

B 3βOH, 6αOH

Reaction of epoxide (67A) with BF_3-etherate[54] gave the compounds (68B) (13%), a fluorohydrin (62) (47%), a 6-ketone (69B) (14%), and a backbone rearranged product (70B) (10%). Again treatment of the epoxide (68B) gave the backbone rearranged product (70B).

Treatment of the 3α-acetoxy-epoxide (67C) with BF_3-etherate in methylene chloride gave the 5α-acetoxy-diol (73) as a single product. The acetoxy-diol (73) is considered to arise from the acetoxy-epoxide (67C) via the 3α,5α-acetoxonium ion (72) which on treatment with aqueous $NaHCO_3$ gives the 3α-hydroxy-5α-acetate (73) (Scheme XXXIV).



(67C) (72) (73)

SCHEME XXXIV

Guest and Marples[55] re-examined the reaction of 5,6α-epoxy-3β-hydroxy 5α-cholestane (65) with BF_3-etherate complex in benzene solution and found very poor yields of fluorohydrin (66) (2%).

The reaction gave mixtures of rearrangement products which were identified as 6-ketones (69C) (45%) and (69D) (11%), a backbone rearranged product (70C) (10%), a Δ^9-olefin (71B) (7%), and a polar fraction which was identified as a second backbone rearranged product (70D) (17%).

The Bowers and Ringold[53] reaction system used a mixture of benzene-ether (1:1), Guest and Marples[55] used BF_3-etherate solely in benzene. This considerably increases the Lewis acid nature of the boron trifluoride by effectively releasing it from the ether ligand.

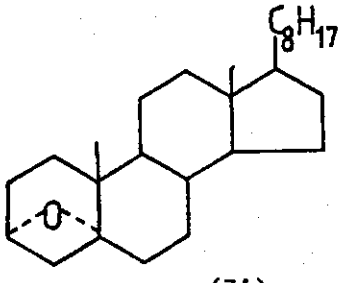
Guest and Marples[55,56] reported that the change of the 3β-substituent in 5,6-epoxy cholestanes, androstanes and pregnanes from OAc to OH or OMe suppressed BF_3-catalysed C(5)-O-cleavage.

Also it was suggested that the electronegativity not only of the C-3 substituent, but also of the C-17 substituent has a considerable effect on the epoxide cleavage.

Rearrangements of 5,6-epoxides with BF_3-etherate complex have been widely reported[50-60] and these have been briefly reviewed above.

However, there have been few similar studies of the rearrangements of steroidal 3,5-epoxides which should be similarly suceptible to Lewis acid-catalysed cleavage rearrangement.

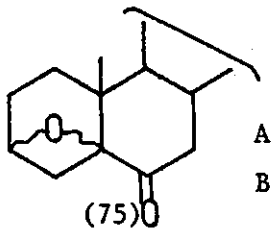
The reaction of 3α,5-epoxy-5α-cholestane (74) with $BF_3.Et_2O$ was reported by Henbest[11] and co-workers to give epicholesterol.



(74)

However, Rowland[62] reported that a compound formulated as 3β,5-epoxy-5β-cholestan-6-one (75B) did not react with boron trifluoride etherate in benzene at room temperature within 48 hr. and did not react with periodic acid and water.

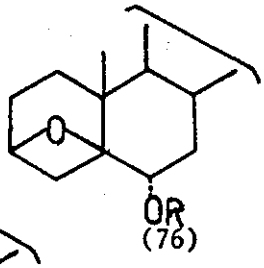
Also the 6α-acetate (76A) and its trifluoroacetoxy analogue (76B), were reported to be unreactive towards a number of acidic reagents.



(75)

A 3α,5α

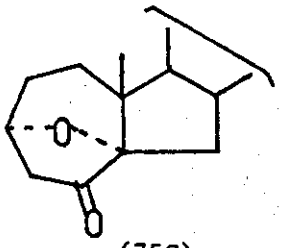
B 3β,5β



(76)

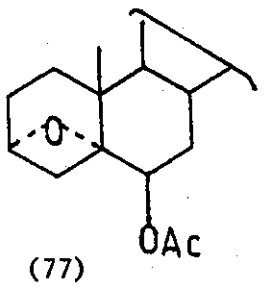
A R=MeCO

B R=CF_3CO

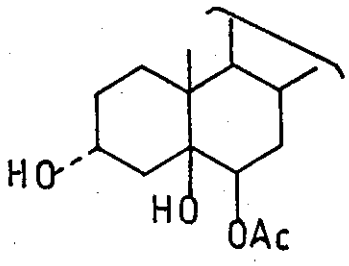


(75C)

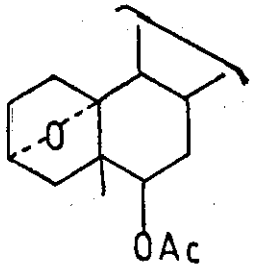
Foster and Marples[63] investigated the BF_3-catalysed rearrangement of the 6β-acetoxy-3α,5α-oxetan (77), and reported the isolation of the 6β-acetoxy-3α,5β-diol (78) (26%), the 6β-acetoxy-3α,10α-epoxide (79A) (16%) the 6β-acetoxy-2α,5α-epoxide (79B) (10%) and observed that the compound previously formulated as 3β,5-epoxy-5β-cholestan-6-one (75B) was in fact 3α,5-epoxy-A-homo-B-nor-5α-cholestan-4a-one (75C).



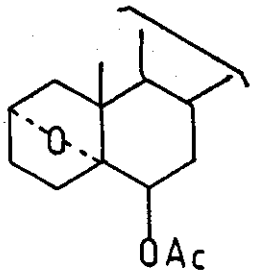
(77)



(78)

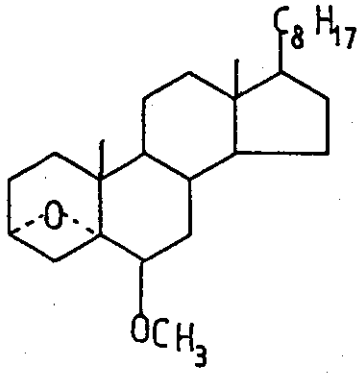


(79A)



(79B)

We decided to investigate the boron trifluoride etherate-catalysed rearrangement of the 6β-methoxy-3α, 5-epoxy-5α-cholestane (43) to determine whether the 6β-methoxy-group would significantly change the course of rearrangement.



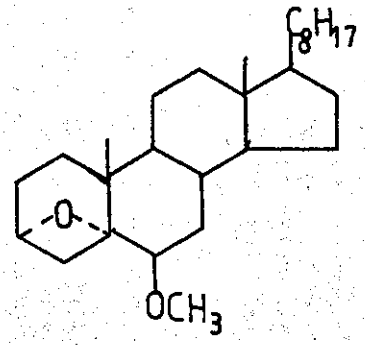
(43)

Results and Discussion

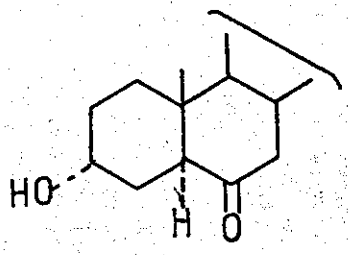
Reaction of 6β-methoxy-3α,5-epoxy-5α-cholestane (43) with boron trifluoride diethyl etherate

The preparation of the required 6β-methoxy-3α,5-epoxy-5α-cholestane (43) was discussed in part one.

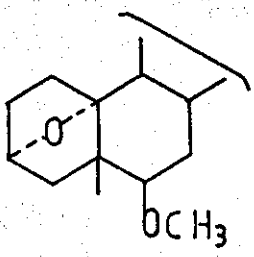
Treatment of the 3α,5α-epoxy (43) with boron trifluoride etherate in benzene solution at room temperature for fifteen minutes revealed a variety of products of which the major two have been isolated and identified.



(43)



(80)

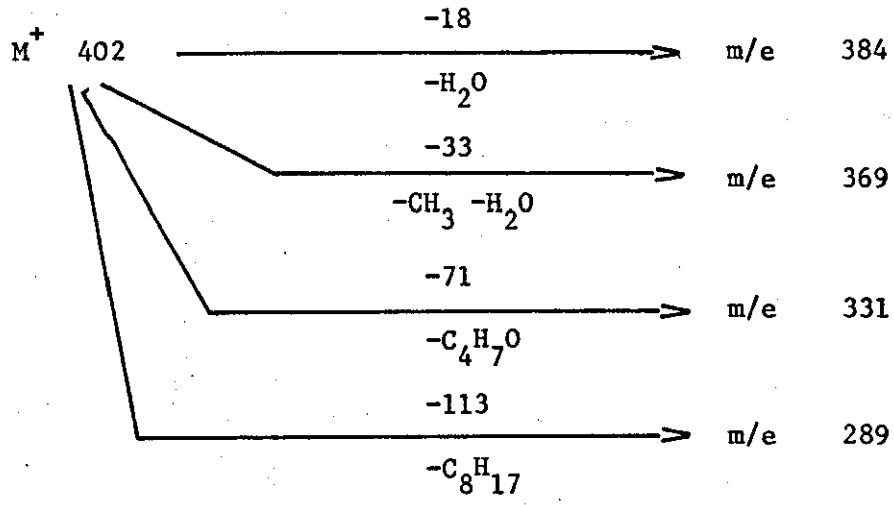


(81)

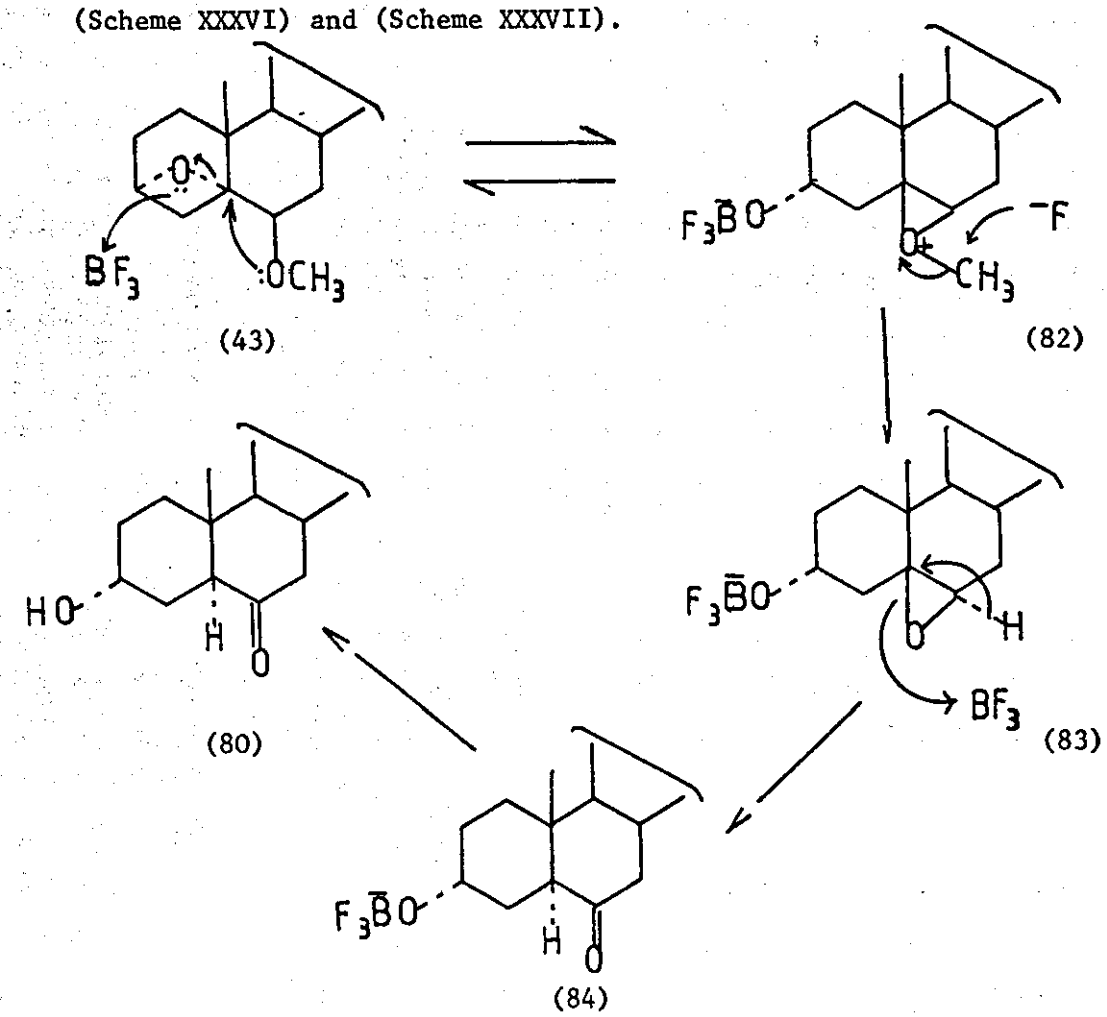
The pure products were isolated by preparative T.L.C. on silica gel and identified by spectroscopic analysis.

The most polar product (80) was isolated in (26%) yield as a white crystalline solid having a melting point of 160-162 °C (Lit.[72] 159-160.5 °C). Its infrared spectrum had ν_{max} 3440 cm^{-1} (OH) and 1710 cm^{-1} (C=O). The 90 MHz ^{1}H.n.m.r. had important peaks at δ 4.16 (m, 1H C3-H $W_{\frac{1}{2}}$ 9 Hz).

The high resolution accurate mass spectrum had a molecular ion peak at m/e 402.3497 ($C_{27}H_{46}O_2$) for which fragmentations are shown below.

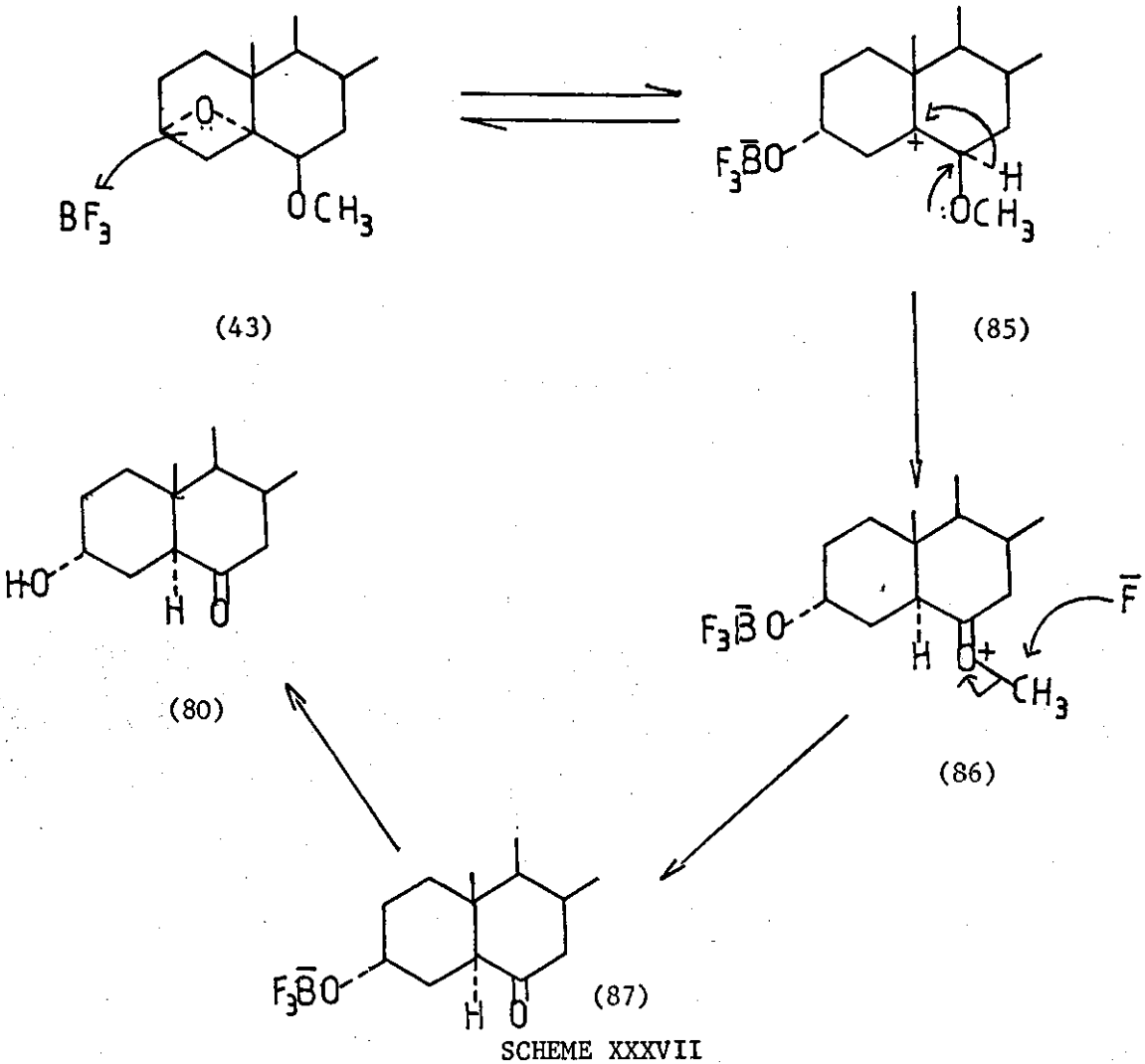


To explain the isolation of the hydroxy ketone (80), two possible mechanisms may be involved which proceed via C(5)-O bond cleavage (Scheme XXXVI) and (Scheme XXXVII).



SCHEME XXXVI

The cleavage of the C(5)-O bond is assisted by attack of the lone pair of electrons on the O-Me giving the species (82), which could be attacked by fluorine ion to give the species (83). Hydride transfer from C-6 to C-5 occurs giving the species (84) which by loss of BF_3 leads to the product (80).



SCHEME XXXVII

Alternatively the mechanism involves the formation of the carbonium ion at C(5), giving the species (85).

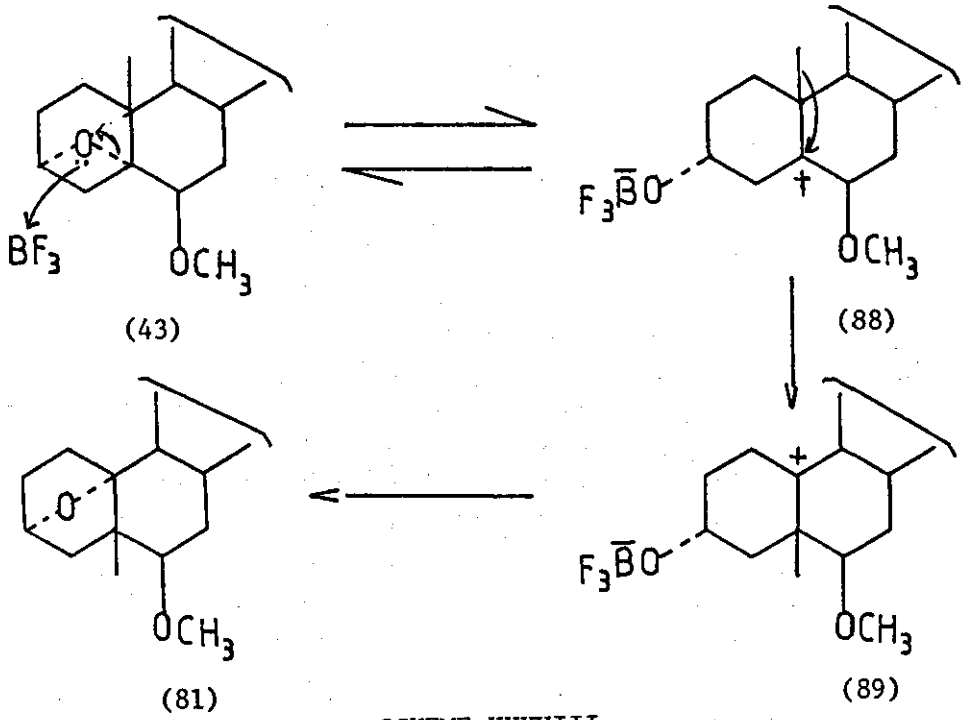
Hydride transfer from C-6 to C-5 occurs giving the species (86) which by a nucleophilic attack by fluoride ion would give the species (87).

The second product (22%) was 3,10-epoxide (81) which was isolated as an oil.

The 90 MHz ^{1}H n.m.r. spectrum had peaks at δ 3.72 (s, 3H, -O-CH_3), 4.34 (m, 1H, C6-H) and compared favourably with that of the similar 3,10-epoxide (79).[63]

The high resolution accurate mass spectrum had a molecular ion peak at m/e 416.3656 ($C_{28}H_{48}O_2$), which fragmented by loss of 15 (-CH_3) to m/e 401.3419 ($C_{27}H_{45}O_2$). Other fragmentations were loss of 32 (-CH_4O) to m/e 384 and loss of 50 (-CH_3-OH -H_2O) from the molecular ion.

To explain the isolation of the epoxide (81) a possible mechanism involves C(5)-O bond cleavage and rearrangement (Scheme XXXVIII).



(43) (88) (89) (81)

SCHEME XXXVIII

The cleavage of the C(5)-O bond occurs initially producing a carbonium ion at C-5.

The species (88) can rearrange by a C-10 to C-5 methyl transfer giving (89) followed by ring closure to (81).

The previously mentioned BF_3-catalysed rearrangement of 6β-acetoxy-3α,5α-epoxide (77) gave (78), (79) and (80).[63]

It is believed that the acetoxy-diol (78) arose from participation of

the neighbouring 6β-acetoxy group in the C(5)-O cleavage process. Similar participation appears to be involved for the 6β-methoxy group in the 6β-methoxy-3α,5α oxetane (43) leading to the hydroxy-ketone (80). The competing rearrangement of the 10-methyl group to give the 5β-methyl-3α,10α-epoxide (81) is analogous to that involved in the formation of the similar epoxide (79). The relative yields (78):(79); 26:16 are not dissimilar from those of (80):(81); 26:22 suggesting that the OMe is as effective as OAc in its participation.

EXPERIMENTAL

Reaction of 6β-methoxy-3α,5α-epoxy cholestane (43) with boron trifluoride diethyl etherate

6β-methoxy-3α,5α-epoxy-cholestane (1.0 g) in dry benzene (40 ml) was treated with freshly distilled boron trifluoride etherate (1.2 ml) at 20 °C for 15 minutes. The reaction mixture was poured into a saturated solution of sodium hydrogen carbonate and extracted with ether (2 × 150 ml). Ether extract was washed with water and dried over magnesium sulphate and evaporated to dryness to give the crude product mixture. The crude product was plated (solvent: ethyl acetate-benzene; 30:70) to obtain two major products.

The first, non-polar fraction was plated again (solvent; ether-petrol, ether (60-80) 50/50) to obtain 3β-methoxy-5β-methyl-3α,10α-cholestane as an oil (81), (0.126 g) (22%) $[\alpha]_D$ -37.6° (c 12.7), δ 0.66 (s, 3H, C18-CH_3) 1.17 (s, 3H, C19-CH_3) 3.72 (s, 3H, O-CH_3), 4.34 (m, 1H, C6-H).

The second fraction was crystallized from pentane to obtain white crystals of 3α-hydroxy-5α-cholestan-6-one (80) (0.250 g) (26%), m.p. 160-162°C (Lit.[62] 159-160.2 °C). ν_{max} 3440 cm^{-1} (OH), 1710 cm^{-1} (C=O), δ 0.66 (s, 3H, C18-CH_3) 0.9 (s, 3H, C19-CH_3), 4.16 (m, 1H, C3 -H. Wi 9 Hz).

APPENDIX

Mass Spectral Data

COMPOUND	IMPORTANT IONS		RELATIVE INTENSITY %	FORMULA	REQUIRES
26	$M^{+}\cdot$	402.3137	47.19	$C_{19}H_{42}O_3$	402.3134
	M-CO	374.2866	100.00	$C_{24}H_{38}O_3$	374.2821
	$M-C_2H_3O$	359.2941	3.08	$C_{24}H_{39}O_2$	359.2932
	$M-C_3H_5O_2$	329.2849	41.11	$C_{23}H_{31}O$	329.2844
27	$M^{+}\cdot$	420.3231	6.83	$C_{26}H_{44}O_4$	420.3223
	$M-H_2O$	402.3160	93.51	$C_{26}H_{42}O_3$	402.3133
	$M-CH_3-H_2O$	387.2937	12.57	$C_{25}H_{39}O_3$	387.2899
	$M-C_3H_5O_2$	347.2957	47.19	$C_{23}H_{39}O_2$	347.2950
	$M-C_3H_7O_3$	329.2865	49.39	$C_{23}H_{37}O$	329.2844
43	$M^{+}\cdot$	416.3650	26.53	$C_{28}H_{48}O_2$	416.3643
	$M-CH_3$	401.3409	79.93	$C_{27}H_{45}O_2$	401.3399
	$M-H_2O$	398.3546	12.45	$C_{28}H_{46}O$	398.3544

COMPOUND	IMPORTANT IONS		RELATIVE INTENSITY %	FORMULA	REQUIRES
43	M-CH_3O	385.3438	15.99	$C_{27}H_{45}O$	385.3405
	M-CH_4O	384.3381	44.80	$C_{27}H_{44}O$	384.3370
	M-C_4H_6	362.3166	52.31	$C_{24}H_{42}O_2$	362.3148
	M-C_3H_5O	359.3291	82.64	$C_{25}H_{43}O$	359.3268
51	$M^{+\cdot}$	416.3287	18.82	$C_{27}H_{44}O_3$	416.3284
	M-CHO	387.3246	17.53	$C_{26}H_{43}O_2$	387.3229
	M-$C_2H_5O_2$	355.3009	7.45	$C_{25}H_{39}O$	355.3001
	M-C_3H_5O	343.3015	13.98	$C_{24}H_{39}O$	343.3001
	M-$C_4H_5O_2$	331.292	100.00	$C_{23}H_{39}O$	331.2983
53	M-C_4H_4	390.3143	30.49	$C_{25}H_{42}O_3$	390.3134
	M-$C_2H_3O_2$	330.2914	100.00	$C_{23}H_{38}O$	330.2905
55	$M^{+\cdot}$	400.3343	28.95	$C_{27}H_{44}O_2$	400.3341
	M-CO	372.3386	5.64	$C_{26}H_{44}O$	372.3380

COMPOUND	IMPORTANT IONS	RELATIVE INTENSITY %	FORMULA	REQUIRES
55	$M-C_4H_6$ 346.2883	100.00	$C_{23}H_{38}O_2$	346.2871
	$M-C_5H_9O$ 315.2686	5.79	$C_{22}H_{35}O$	315.2684
	$M-C_8H_{17}$ 287.2006	7.73	$C_{19}H_{27}O$	287.2001
80	M^{+} 402.3497	83.11	$C_{27}H_{46}O_2$	402.3497
	$M-H_2O$ 384.3381	11.55	$C_{27}H_{44}O$	384.3370
	$M-CH_3-H_2O$ 369.3140	12.83	$C_{26}H_{44}O$	369.3122
	$M-C_4H_7O$ 331.2976	3.21	$C_{23}H_{39}O$	331.2951
	$M-C_8H_{17}$ 289.2168	17.42	$C_{19}H_{29}O_2$	289.2167
81	M^{+} 416.3656	59.73	$C_{28}H_{48}O_2$	416.3654
	$M-CH_3$ 401.3419	89.80	$C_{27}H_{45}O_2$	401.3419
	$M-CH_4O$ 384.3380	100.00	$C_{27}H_{44}O$	384.3368
	$M-CH_6O_2$ 366.3284	11.62	$C_{27}H_{42}O$	366.3281

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