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LEWIS ACID-CATALYSED REARRANGEMENT OF STEROIDAL OXETANES: REVISION OF THE COURSE OF SOLVOLYSIS OF 3β-TOSYLOXY-5β-CHOLESTAN-5-OL-6-ONE.†

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Summary The BF_3-catalysed rearrangement of 6β-acetoxy-3α,5-epoxy-5α-cholestane gave the 3α,5β-diol, the 3α,10α-epoxide, and the 2α,5α-epoxide, and the product of solvolysis of 3β-tosyloxy-5β-cholestan-5-ol-6-one was identified as 3α,5-epoxy-A-homo-B-nor-5α-cholestan-4a-one.

The reaction of 3α,5-epoxy-5α-cholestane (1) with $BF_3.Et_2O$ was reported, by Henbest and co-workers, to give epicholesterol.[1] However, the 3β,5β-oxetan-6-one (7), which was prepared by solvolysis of 3β-tosyloxy-5β-cholestan-5-ol-6-one (5) was reported to be unreactive towards $BF_3.Et_2O$ and the 6α-acetoxy-3β,5β-oxetane (8) and its trifluoroacetoxy analogue, which were prepared from (7) by reduction and acylation, were unreactive towards a number of acidic reagents.[2] We have shown[3] that the rearrangements of some steroidal 5,6-epoxides are influenced markedly by electron withdrawing groups at C-3 and we were interested to determine whether the lack of reactivity of the 3β,5β-oxetanes related to the electron withdrawing groups at C-6 or to the configuration of the 3,5-epoxide bridge as suggested by Rowland.[2] Accordingly, we have investigated the BF_3-catalysed rearrangement of the 6β-acetoxy-3α,5α-oxetane (2).[4] Our method of preparation of (2) differed slightly from that previously reported.[4] Monoperphthalic acid oxidation of cholesteryl tosylate gave the 5ξ,6ξ-epoxides which were hydrolysed to the 3β-tosyloxy-5α,6β-diol (6).[5] Reaction of the compound (6) with Bu^tOK/Bu^tOH gave the 6β-hydroxy-3α,5α-oxetane (3) which on acetylation gave the required acetate (2).

Reaction of 6β-acetoxy-3α,5α-oxetane (2) in benzene with $BF_3.Et_2O$ gave essentially the 6β-acetoxy-3α,5β-diol(9)(26%), the 6β-acetoxy-3α,10α-epoxide (12) (16%),[6] and the 6β-acetoxy-2α,5α-epoxide (13) (10%). The structure of the 6β-acetoxy-3α,10α-epoxide (12) was confirmed by its

† Part of this work was reported at the East Midlands Meeting of the Perkin Division of The Chemical Society at Nottingham on December 18th, 1978.

spectroscopic data and its m.p. and mixed m.p. with an authentic sample.‡ The structure of the 6β-acetoxy-3α,5β-diol (9) was confirmed by its conversion via the ketol (10) into the known[7] 6β-acetoxycholest-4-en-3-one (15). The compound (15) was also prepared from 6β-acetoxy-5α-cholestane-3β,5-diol via the ketol (11)[8] which was shown to be different from the ketol (10). The structure of the 6β-acetoxy-2α,5α-epoxide (13) was established by comparison with a sample prepared by Pd/C-hydrazine debromination of the 6β-acetoxy-3ξ-bromo-2α,5α-epoxides (14).[9]

The rearrangement of the 6β-acetoxy-3α,5α-oxetane (2) (Scheme 1) presumably proceeds via cleavage of the C-5-O bond, or, to a lesser extent, the C-3-O bond leading to the C-5 or the C-3 carbonium ions.** The C-5 carbonium ion may rearrange to the C-10 carbonium ion and the 3,10-ether (12) or it may be trapped by the 6β-acetoxy-group leading to the relatively stable acetoxonium ion (6) which, on aqueous work-up, would give the 6β-acetoxy-3α,5β-diol (9). The C-3 carbonium ion could rearrange by a hydride shift to the C-2 carbonium ion and the 2,5-ether (13). The intermediacy of the acetoxonium ion (16) was supported by isolation of the dioxolane (17) when the rearrangement was carried out in ether in the presence of $NaBH_4$. The ^1H n.m.r. spectrum of the dioxolane (17) showed characteristic signals at δ5.12 (q, $MeC\underline{H}O_2$) and δ1.43 (d, $\underline{Me}CHO_2$). Similar acetoxonium ion intermediates have been reported in the rearrangements of oxiranes.[10,11]

Since the rearrangement of the 6β-acetoxy-3α,5α-oxetane (2) proceeded quite smoothly, we suspected the structural assignments of the 3β,5β-oxetanes (7)[§] and (8). A study of models and comparison of the spectroscopic data (Table) for the 3β,5β-oxetan-6-one (7) and the 3α,5α-oxetan-6-one (4) which was prepared from (3) by oxidation, led to the conclusion that the solvolysis product (7) should be formulated as the A-homo-B-nor-3α,5α-epoxide (18). This could arise by the rearrangement[12] shown in Scheme 2 which would allow normal intramolecular concerted displacement of the tosyloxy-group.

Table

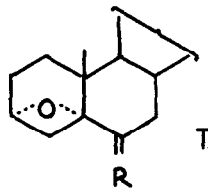
Compound	δ		ν_{max} cm^{-1}
	3-H	4-H	
4	4.45, d(br), J~7 Hz	α3.0, q, J~10 and 7 Hz; β1.86, d, J~10 Hz	1723
7/18	4.67, t(br), J~7 Hz	2.62,q, J~18 and 7 Hz; 2.08, d, J~18 Hz	1750

$NaBH_4$ reduction of the solvolysis product (18) gave a single alcohol (20)[2] and, as would be expected, the 10-Me signal in the ^1H n.m.r. spectrum was considerably downfield (δ1.05) from that in the parent ketone (δ0.73). Further support for the structure (18) was indicated by deuteriation in Et_3N/D_2O/dioxan. Even after several treatments, the 4α-monodeuterio-analogue (19) was largely

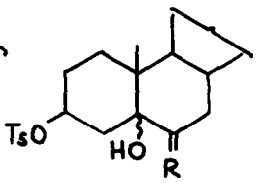
‡ Kindly provided by Professor E.Glotter.

** It is not known to what extent the subsequent rearrangements are concerted with these initial cleavages.

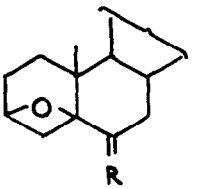
§ We are extremely grateful to Professor A.T.Rowland for a generous sample.



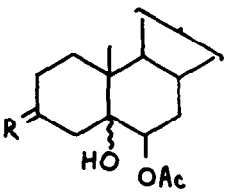
(1) R = H_2
(2) R = β-OAc, H
(3) R = β-OH, H
(4) R = O



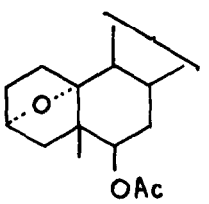
(5) 5β, R = O
(6) 5α, R = β-OH, H



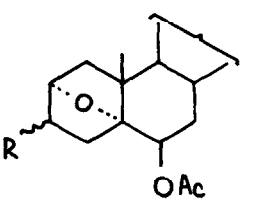
(7) R = O
(8) R = α-OAc, H



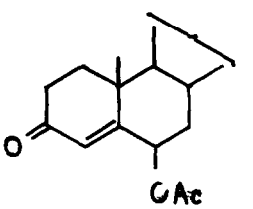
(9) 5β, R = α-OH
(10) 5β, R = O
(11) 5α, R = O



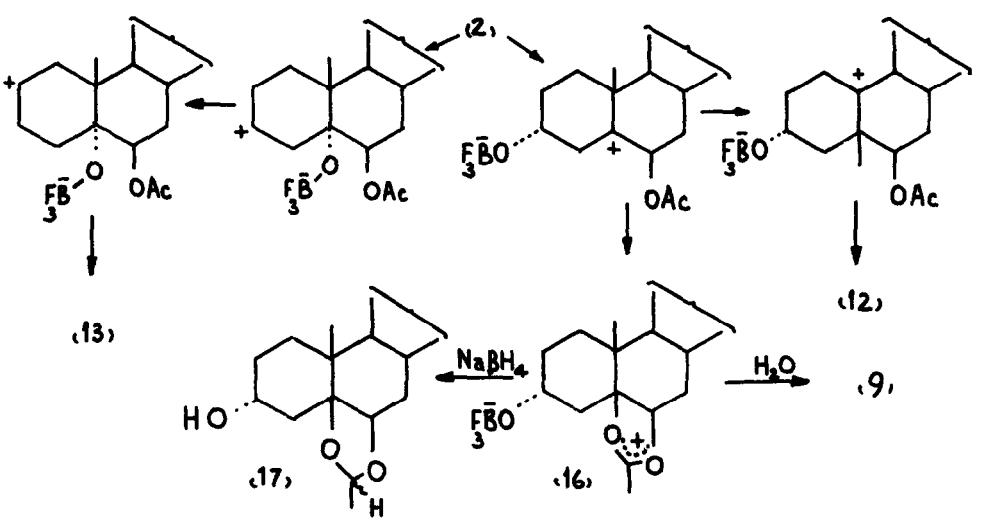
(12)



(13) R = H
(14) R = Br



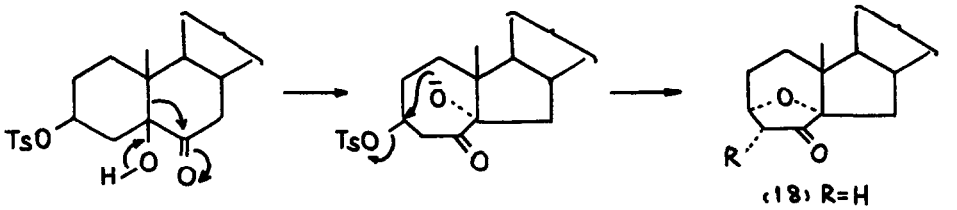
(15)



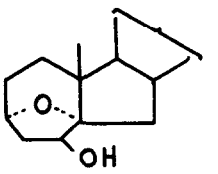
Scheme 1

obtained as indicated by the mass spectrum and by the ^1H n.m.r. spectrum in which the 3-H signal was a broadened doublet (major residual coupling to 2α-H) and the 4β-H signal (δ2.08) was a broadened singlet. As expected the signal for the 4α-H (δ2.62) had disappeared. The reluctance of the 4β-H to exchange significantly presumably relates to the hindered nature of the base and of the β-face of the 4,4a-enolate. The loss of CO and C_4H_5D in the mass spectrum of (19) gives the base peak at m/e 318 and further supports the structural assignment.

During the preparation of this manuscript an independent correction of the structure (7) has been reported. [13]



Scheme 2



(20)

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