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OPENING OF STEROID METHYL ETHERS WITH BF_3-ETHERATE

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WHEN Kamber et al.[1] published the opening up of a steroid 18,20-cyclic ether with acetic anhydride and BF_3-etherate to the 18,20-diacetate, we decided to try this reaction to regenerate a steroid alcohol after it was being protected as the methyl ether. The reaction was therefore applied[2] by us to the methyl ethers of different types of steroid alcohols. Youssefyeh and Mazur[3] have recently published some results on similar work. Their main findings are that: (a) no ether cleavage is observed with BF_3-etherate and acetic anhydride only, a lithium halide being essential for the cleavage; (b) 3β-methoxycholestane under their conditions gave cholesta-2-ene (I) and 3β-acetoxycholestane (II) in 80-85% yield; with LiCl, LiBr and LiI, the respective ratios of I and II were 1:1.5, 1:3 and 1:10 respectively; and (c) cholesteryl methyl ether under their conditions gave cholesteryl acetate (55%) and cholesteryl bromide (41%).

Our results are, however, somewhat different from the above[3]. Acetic anhydride and BF_3-etherate cleaved all the steroid ethers we tried; we had often to make the con-

ditions milder to get better product and stop further changes; the presence of lithium halides were not always very helpful; and substitution generally gave the epimeric product also.

In a typical reaction, 3β-methoxycholestane (200 mg.) in a mixture of acetic anhydride (8 ml.), dry ether (2 ml.) and BF_3-Etherate (1.4 ml.), kept at 0° for 14 hours gave I and II and 3α-acetoxycholestane (III) also. The acetates were characterised as the alcohols after hydrolysis to give I (44 mg.) cholestanol (IV), (61 mg.) and epicholestanol (V), (47 mg.). Under the same conditions 3α-methoxycholestane gave I (50%), IV (8%) and V (14%) after hydrolysis.

Cholesteryl methyl ether, under these conditions, gave cholesteryl acetate in 93% yield and no other product. With ψ-cholesteryl methyl ether (100 mg.) it required 50 hours at 0° to complete the reaction and the yield of pure ψ-cholesterol, after hydrolysis of the acetate was 54 mg. When the reaction was tried on an allylic methyl ether, 3β-methoxy-Δ^4-cholestene (m.p. 74-75°, $(\alpha)_D$ +29.6)[4] cholesta-3,5-diene was the major product. However, we could obtain 3β-acetoxy-Δ^4-cholestene in about 90% yield by conducting the reaction at -18° for 3 minutes. In these cases when the ether is cleaved from the steroid nucleus, the double bond assists to give the more stable equatorial acetates; cleavage from the other end, of course, leads to the same product.

Lupanol methyl ether, which has a strained A-ring,

under our conditions gave back only starting material, but keeping the reaction at room temp. for 14 hours, we obtained A-nor-$\Delta^{3(5)}$ lupene[5] in 63% yield, perhaps a good procedure to make this compound in a pure state.

When cleavage of 3β-methoxycholestane was repeated at 0° for 14 hours by the addition of LiBr also, the cleavage was incomplete and we got back about 55% of the starting material. On repeating the reaction under the conditions[3] of the Israeli workers with LiBr, we obtained almost the same mixture of products as we used to obtain under our conditions. The NMR spectra of the total reaction product was almost identical with that of the product we obtained under our conditions, and showed signals at τ 8.09 (equatorial C_3-acetate), τ 8.04 (axial C_3-acetate), τ 5.5 (very broad, axial C_3-proton), τ 5.1 (equatorial C_3-proton), and at τ 4.5 (C_2,C_3-vinyl protons), with intensities more or less corresponding to the above proportions. On hydrolysis and chromatography it gave I (20%), IV (31%) and V (22%). When the experiment was repeated with LiI instead of LiBr, the NMR spectra of the total product showed the approximate relative intensities of the signals of I as 19%, II as 39% and III as 20%. After hydrolysis, the mixture gave I (16%), IV (42%) and V (20%). When the reaction with 3α-methoxy cholestane was repeated with LiI under their conditions, we obtained I (45%) IV (5%) and V (16%), thus showing that LiI does not help very much to reduce the elimination or increase the proportion of alcohol with

retention of configuration.

3β-Methoxycholestane in benzene and BF_3-etherate, 3α-methoxy cholestane in acetic anhydride alone, and cholesteryl acetate and 3β-acetoxy cholestane in acetic anhydride alone, and cholesteryl acetate and 3β-acetoxy cholestane in acetic anhydride and BF_3-etherate at 0° for 14 hours gave back only starting materials showing thereby that both acetic anhydride and BF_3-etherate are essential for the ether cleavage and that the acetates once formed generally do not undergo further change under our conditions. (The allylic ester, 3β-acetoxy-Δ^4-cholestene, however, with acetic anhydride and BF_3-etherate at 0° for 14 hours was largely converted to the 3:5 diene).

The cleavage appears to involve the initial formation of an oxonium ion by the addition of BF_3-etherate to the ether oxygen and cleavage of the carbon-oxygen bond from (i) the secondary carbon to give the elimination and epimeric product, and (ii) the methoxyl methyl to give the product with retention of configuration, by the nucleophilic attack of the acetate moiety of the acetic anhydride, the BF_3-complex being subsequently replaced by the acetylium moiety of the acetic anhydride. The latter forms the predominant substitution product. Earlier observations of isolation of products by the action of BF_3-etherate and acetic anhydride on steroid ethers, with inversion of configuration (from an 18,20-epoxide[1]) and with retention of configuration (from 6,19-epoxide[6]) are in agreement with the present

results. Cholesteryl and cholestanyl tosylates under our reaction conditions gave back starting materials almost quantitatively. In these cases the BF_3 might be complexing with the electron-rich sulphoxyl oxygen which may not lead to the cleavage of the ether oxygen bond, just like in the case of cholesteryl and cholestanyl acetates. The mechanism of this cleavage is under investigation.

References

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[2]Abstract of papers (p.185) of the 50th session of the Indian Science Congress scheduled for January 1963.

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[4]It took considerable time and experimentation to get this product in a pure form. This has not been obtained pure before. See e.g. Elseviers Encyclopaedia of Organic Chemistry, Series III, Vol.14 - Supplement p.1565.

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