

## A NOVEL METHOD OF ETHER CLEAVAGE

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ALTHOUGH ethers have become easily accessible by recently published procedures,<sup>1</sup> their widespread use as a protecting group in alicyclic chemistry still awaits satisfactory methods for their cleavage to the parent alcohols. The various methods described either use too drastic conditions<sup>2</sup> or do not lead to the desired alicyclic alcohols.<sup>3,4</sup>

<sup>1</sup> E.L. Eliel and M. Rerick, J. Org. Chem. **23**, 1088 (1958); C.E.H. Bawn and A. Ledwith, Chem. & Ind. 1329 (1958); E. Müller and W. Rundel, Ang. Chem. **70**, 105 (1958); M. Neeman, M.S. Caserio, J.D. Roberts and W.S. Johnson, Tetrahedron **6**, 36 (1959).

<sup>2</sup> E.R. Alexander, "Principles of Ionic Organic Reactions", John Wiley and Sons, New York, N.Y. 1950, pp. 214-215; H. Meerwein and H. Maier-Hüser, J. prakt. Chem. **134**, 51 (1932); G.H. Hennion, H.D. Hinton and J.A. Hieuwland, J. Amer. Chem. Soc. **55**, 2857 (1933); C.L. Wilson, J. Amer. Chem. Soc. **67** (1945); H. Stone and H. Shechter, J. Org. Chem. **15**, 491 (1950); N. Pappas, J.A. Meschino, A.A. Fournier and H.R. Mace, J. Amer. Chem. Soc. **78**, 1907 (1956); Tomiska & Spousta, Ang. Chem. **74**, 248 (1962).

<sup>3</sup> P.D. Bartlett, S. Friedman and M. Stiles, J. Amer. Chem. Soc. **75**, 1771 (1953); D.H. Gould, K.H. Shaaf and W. Ruigh, ibid. **73**, 1263 (1951).

<sup>4</sup> Treatment of methyl ethers of alicyclic alcohols with boron trichloride leads to the alicyclic chlorides; unpublished results from this laboratory. Cf. W. Gerrard and F.M. Lappert, J. Chem. Soc. 1486 (1952); T.G. Bonner E.J. Bourne and S. McNally, J. Chem. Soc. 2929 (1960).

We now wish to report a simple procedure for cleavage of aliphatic ethers. This method involves treatment of the ether in acetic anhydride with boron trifluoride-etherate and lithium halide at room temperature. When alkyl cycloalkyl ethers were subjected to these conditions the major products were cycloalkyl acetates. It is interesting to note that no ether cleavage was observed when lithium halide was not present in the reaction mixture.

Using lithium bromide, methoxycyclohexane yielded a mixture of acetoxy-cyclohexane and cyclohexene (7:1).  $\beta$ -Methoxycholestane (I)<sup>5</sup> under the same conditions was completely cleaved to give both  $\beta$ -acetoxycholestane (II) and cholest-2-ene (III) in 80-95 % yield. Using lithium chloride, lithium bromide and lithium iodide the relative ratios of II to III were 1.5:1, 3:1 and 10:1 respectively.

The following procedure is typical : A solution of I (0.5 g.) in acetic anhydride (20 cc.) was treated with boron trifluoride-etherate ( 3 cc.) and lithium bromide (2.5 g.) and kept 30 hrs at room temperature. Ice and water were added, the products isolated with ether, and washed with sodium bicarbonate. Chromatography on alumina yielded III (0.10 g.) and II (0.36 g.).

When  $\beta$ -ethoxycholestane IV, ( $83-84^{\circ}$   $[\alpha]_D^{+25^{\circ}}$ ),<sup>6</sup>  $\beta$ -isopropoxycholestane (V m.p.  $83-84^{\circ}$   $[\alpha]_D^{+23^{\circ}}$ ) and  $\beta$ -tert.-butoxycholestane (VI m.p.  $145-146^{\circ}$   $[\alpha]_D^{+23^{\circ}}$ ) were treated similarly for 3 days using lithium bromide, 15-25 % of the starting material was recovered. Whereas IV afforded both II and III (in a 2:1 ratio), V and VI gave II as the sole cleavage product.

<sup>5</sup> H.R. Nace, J. Amer. Chem. Soc. 74, 5937 (1952).

<sup>6</sup> C. Djerassi, M. Shamma and T.Y. Kan, ibid. 80, 4723 (1958).

These ether cleavages are assumed to involve formation of an oxonium ion by the addition of an acetylium ion to the ether oxygen. In this intermediate either of the alkyl-oxygen bonds may cleave by : nucleophilic attack of the halide ion on the  $\alpha$ -carbon, olefin-forming elimination and  $\alpha$ -carbon carbonium ion formation. The mechanism of these cleavages is now being studied.

When cholesteryl methyl ether<sup>5</sup> was reacted with lithium bromide acetic anhydride and boron trifluoride-etherate a mixture of cholesteryl acetate (55 %) and cholesteryl bromide (41 %) was obtained. The formation of the latter product is attributed to bromide ion attack on the available reactive site at C<sub>6</sub> and the known subsequent isomerization.<sup>7</sup>

The application of this reaction for cleavage of various cyclic and aromatic ethers is now being studied.

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<sup>7</sup> E.M. Kosower and S. Winstein, *ibid.* 78, 4354 (1956).