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THE STEREOCHEMISTRY OF ADDITION AND SUBSTITUTION IN THE REACTION OF BROMINE CHLORIDE WITH CHOLEST-5-EN-3-ONE

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The stereochemistry of electrophilic attack on Δ^5-unsaturated steroids has been investigated extensively, but the factors which determine the direction of attack are still not fully understood. Cholesterol and its derivatives (1), investigated extensively by Barton and his co-workers,[1] by Grob and Winstein,[2] and by Ziegler and Shabica,[3] are thought to be attacked by electrophilic bromine exclusively on the α-face of the molecule. Completion of reaction by a nucleophile Nu^- could then theoretically occur by anti-coordination at the 5-position to give the thermodynamically favoured 6α-Br, 5β-Nu-adduct 2, but this mode of reaction would require a major conformational change in ring A and equatorial approach to ring B. So instead the nucleophile is captured at the 6-position to give the 5α-Br, 6β-Nu-adduct 3, as was established for the case Nu = Cl . It has been assumed that this route is adopted also in the formation of the 5α,6β-dibromide.[1,2,4]

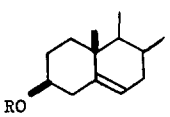
The geometry of cholest-5-en-3-one (4) differs from that of the cholesterol system (1) only through small angular distortions within the A and B rings. It was of interest, therefore, to compare the stereochemistry of addition to the two systems, now that the derivatives necessary for the establishment of structure had become available through the recognition[5] that both dibromides are susceptible to homolytic elimination.

We have now shown that the reaction of cholest-5-en-3-one with bromine chloride in deuteriochloroform in the presence of deuteriopyridine gives the 5α-bromo-6β-chloride (3; Nu = Cl), the 6β-bromo-5α-chloride (5; Nu = Cl), and 6β-bromocholest-4-en-3-one (6) in the ratio 0.56:0.36:0.06. In acetic acid in the presence of sodium acetate, the reaction mixture contains 3 (Nu = Cl; proportion 0.35) accompanied by the bromoacetates 3 (Nu = OAc; 0.19) and 5 (Nu = OAc; 0.19) and increased proportions of products of substitution (6; 0.25; and its

α-isomer; 0.02). Bromination in chloroform in the presence of deuteriopyridine gives mainly the 5α,6β-dibromide 3 (Nu = Br) with a little of its isomer 2. All these products, which have been identified through their ^{1}H n.m.r. spectra and their further reactions, are formed under kinetic control; the bases pyridine and sodium acetate are present only to inhibit rearrangements or other further reactions.

The results establish that electrophilic attack by bromine on the β-face of the cholest-5-ene system is quite accessible for the 3-one; and, in contrast with the result of attack of the α-face, gives either the "Markownikoff-oriented" adduct 5 or the product of proton-loss with double-bond rearrangement (6). Axial attack, both by the electrophile in the first stage and by the nucleophile in the second stage of attack, is clearly a favoured mode of reaction and controls the orientation of the addition. Chloride ions compete effectively with acetic acid only when coordinating with the β-face of the intermediate carbocation.

The ratio of α:β-electrophilic attack (ca. 1.3, in cholest-5-en-3-one; large, in several 3β-substituted cholest-5-enes) must evidently be critical to the exact geometric conditions in the neighbourhood of the double bond; but it seems unlikely that electrophilic attack of the α-face of cholesterol and its derivatives is entirely absent. We hope to test this, and the dependence of stereochemistry on the nature and position of the 3-substituent, by experiments currently in progress, and to extend these results to studies of chlorination.



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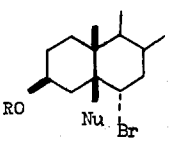

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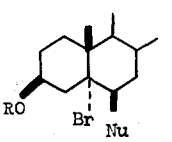

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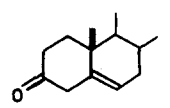

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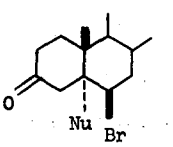

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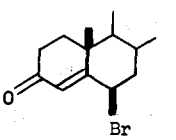

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References:

1. D.H.R. Barton and E. Miller, J. Amer. Chem. Soc., 1950, 72, 370, 1066; D.H.R. Barton, E. Miller, and H. T. Young, J. Chem. Soc., 1951, 2598.
2. C. A. Grob and S. Winstein, Helv. Chim. Acta, 1952, 35, 782.
3. J. B. Ziegler and A. C. Shabica, J. Amer. Chem. Soc., 1952, 74, 4891.
4. P.B.D. de la Mare, Progr. Stereochem., 1954, 1, 119; P.B.D. de la Mare and R. Bolton, "Electrophilic Additions to Unsaturated Systems", Elsevier, 1966, pp. 137 ff.
5. P.B.D. de la Mare and R. D. Wilson, Tetrahedron Letters, 1974, 43, 3777.