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STEROIDS PART V* REACTION OF CHOLESTEROL α-EPOXIDE WITH BORON TRIFLUORIDE

I.G.Guest and B.A.Marples

The Department of Chemistry, The University of Technology,

Loughborough.

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Reaction of 3β-acetoxy-5α,6α-epoxycholestane(I) with boron trifluoride etherate in benzene solution gives high yields of the fluorohydrin(III) (60-75%) and some dimeric backbone rearranged product (V) (30% maximum) (1,2). Also, reaction of cholesterol α-epoxide(II) with boron trifluoride etherate in ether-benzene solution gives a high yield of the fluorohydrin(IV) (65%) (3). In contrast to these results, we found that cholesterol α-epoxide(II) reacted with boron trifluoride etherate in benzene solution to give a complex mixture from which a small amount of the fluorohydrin(IV) (2%), m.p. 214-216°,$[\alpha]_D$-7.5°(C,**0.25) (lit.(3) m.p.218-221°, $[\alpha]_D$+ 36°) was isolated by preparative t.l.c. Preparation of the acetate (III) m.p.213-214°, $[\alpha]_D$-26°(C, 0.15) (lit.(3)m.p. 212-214°,$[\alpha]_D$-22°) from (IV) and the ^{1}H n.m.r.spectrum confirmed the identity of (IV) despite the difference between the observed and reported specific rotations. Detailed examination of the product mixture by t.l.c. gave 3β-hydroxy-5α-cholestan-6-one(VII) (4.5%), m.p. 143-144°, $[\alpha]_D$-5.5°(C, 0.85) (lit.(4) m.p. 142-143°, $[\alpha]_D$-5.1°), 3β-hydroxy-5β-cholestan-6-one(VIII) (11%), (3-acetate (IX) m.p. 137-138°$[\alpha]_D$-25°(C, 0.5) (lit.(5) m.p. 138°, $[\alpha]_D$-26°)), the backbone rearranged product (VI) (10%), $[\alpha]_D$+ 38° (C, 0.8)(lit.(2) $[\alpha]_D$ + 38°), the Westphalen derivative (X) (7%), $[\alpha]_D$- 4.1° (C, 1.0), and an unusual $\Delta^{13,17}$-compound (XII) (17%) m.p. 174-175°, $[\alpha]_D$ + 13° (C, 0.8).

Although the Westphalen derivative (X) is not reported in the literature, it was identified by the chemical shifts of the 18- and 5β-methyl groups (τ 9.23 and 8.62 respectively) in the ^{1}H n.m.r. spectrum. These are typical of compounds in this series (6). In addition, intense end absorption (7) in the u.v. spectrum of the diacetate (XI),*** $[\alpha]_D$ + 36° (C, 0.8), (ε at 215 nm. in hexane, 5000) and Jones oxidation (8) of (X) to the diketone (XIII), $[\alpha]_D$- 46°(C, 0.8) (lit.(9) $[\alpha]_D$- 46°), confirmed the 9,10-position of the double bond.

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* Part IV, I.G.Guest, J.G.Ll.Jones, B.A.Marples and (in part) M.J.Harrington, J.Chem.Soc.(C), in press.

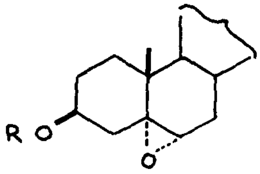
** All rotations for $CHCl_3$ solutions.

*** The acetates were more conveniently studied due to the low solubility of the diols.

Compound (XII) formed a diacetate (XIV), $[\alpha]_D + 9.1^\circ$(C, 1.1) and was oxidised to the diketone (XV), $[\alpha]_D + 27^\circ$ (C, 0.3). Intense end absorption in the u.v. spectrum of (XIV)*** (ϵ at 215 nm in hexane, 3500) suggested the presence of a tetrasubstituted double bond, and the failure of the diketone (XV) to give a Δ^7-6-ketone on treatment with sodium ethoxide in ethanol showed that the double bond was not ineither the 8,9- or the 8,14-position. The ^{1}H n.m.r. spectrum of (XIV)*** was similar to that of the normal backbone rearranged product (VI) and showed signals at τ 4.8-5.1 (m, AcOCH, $W_{\frac{1}{2}} \simeq 9$ Hz), 5.2-5.5 (t, AcOCH,J (apparent) $\simeq$ 8 Hz), 7.87 (s, 2AcO), 8.96 (s, 5β-Me), 9.0 (low field branch of 21-Me doublet), 9.1 (14-Me and up-field branch of 21-Me doublet), and 9.17 (d, side chain). Irradiation 90Hz downfield from the 21-Me doublet caused its collapse to a shoulder on the 14-Me signal as would be expected for a $\Delta^{13,17}$-compound (2). Compound (XII) is thus an isomer of the normal backbone rearranged product (VI) differing in configuration at either C-10, C-9 or C-8. In principle, 10β, 9α, and 8β-isomers of (VI) could be formed respectively by protonation of $\Delta^{9,10}$-, $\Delta^{8,9}$- and $\Delta^{8,14}$-compounds and subsequent backbone rearrangement of the resultant carbonium ions. Formation of $\Delta^{9,10}$-, $\Delta^{8,9}$- and $\Delta^{8,14}$-compounds in boron trifluoride 5α, 6α-epoxide cleavage reactions,in addition to backbone rearranged products,is well known (10)but we have only isolated the $\Delta^{9,10}$ -compound (X). Isomerisation of (X) under the epoxide cleavage conditions gives only the backbone rearranged product (VI), and it seems unlikely therefore that (XII) has the 10β-configuration. The ^{1}H n.m.r.spectrum of (XIV) confirms this since the 3-methine proton is in an equatorial conformation (4 equal vicinal spin-spin couplings $\simeq$ 2-3 Hz) and the 6-methine proton is in an equatorial conformation in a skew-boat B-ring (2 equal vicinal spin-spin couplings $\simeq$ 8 Hz). Inspection of models suggests that these data are only consistent with (XII) being the 8β-isomer of (VI) as shown.

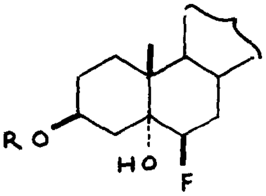
3β-Hydroxy-5β-cholestan-6-one(VIII) isomerises slowly on silica gel to the 5α-isomer(VII) and hence the isolation of some of the latter is accounted for.

Most of the products isolated (50:2) arise from C-5-oxygen bond cleavage of (II) rather than C-6-oxygen bond cleavage which is the preferred course in the reaction of the 3β-acetate(I). Although we have only accounted for 52% of the products it is clear that there is a significant difference in the two reaction courses. The reluctance of the 3β-acetate(I) to undergo C_5-oxygen bond cleavage has been ascribed (1) to the unfavourable conformational change undergone by the 3β-acetoxy-group (equatorial to axial), and to the electron withdrawing properties of 3β-acetoxy-group which would destabilise a C-5 carbonium ion. Since the conformational free



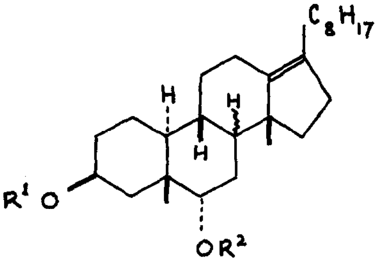
I, R = Ac

II, R = H



III, R = Ac

IV, R = H

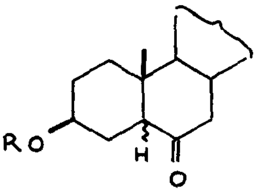


V, R^1 = Ac, R^2 = 6β-(3β-acetoxy-5α-hydroxycholestanyl-);8α-H

VI, R^1 = R^2 = H; 8α-H

XII, R^1 = R^2 = H; 8β-H

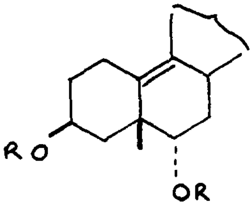
XIV, R^1 = R^2 = Ac; 8β-H



VII, R = H; 5α-H

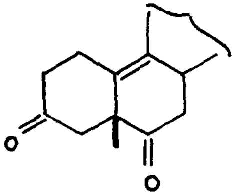
VIII, R = H; 5β-H

IX, R = Ac; 5β-H



X, R = H

XI, R = Ac



XIII

energy differences between axial and equatorial hydroxyl- and acetoxy-groups are roughly equivalent (11), it seems likely that the conformational change referred to is unimportant. The preferred C_5-oxygen bond cleavage of (II) may be in part due to the lower electron withdrawing properties of the BF_3-coordinated hydroxyl-group compared to those of the BF_3-coordinated acetoxy-group. Also, cleavage of the epoxide by a proton, released intermolecularly from a BF_3-coordinated hydroxyl-group, may be in part responsible. We are currently investigating these possibilities. The selective formation of the fluorohydrin(IV) from (II) in ether-benzene is undoubtedly due to the reduced electrophilicity of BF_3 which will be coordinated with solvent (1). Under these conditions the epoxide will be cleaved only with a concerted attack of F^-.

All compounds had satisfactory spectroscopic data and all new compounds had satisfactory elemental analyses.

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References.

1. H.B.Henbest and T.I.Wrigley, J.Chem.Soc., 4596, 4765 (1957).
2. J.W.Blunt, M.P.Hartshorn, and D.N.Kirk, Tetrahedron, 22, 3195 (1966).
3. A.Bowers and H.J.Ringold, Tetrahedron, 3, 14 (1958).
4. R.M.Dodson and B.Riegel, J.Org.Chem., 13, 424 (1948).
5. S.Julia, C.Neuville, and R.Kévorkian, Compt.rend., 258, 5900 (1964).
6. A.Fischer, M.J.Hardman, M.P.Hartshorn, D.N.Kirk and A.R.Thawley, Tetrahedron, 23,159 (1967).
7. L.Dorfmann, Chem.Rev., 53, 47 (1953).
8. C.Djerassi, R.R.Engle, and A.Bowers, J.Org.Chem., 21, 1547 (1956).
9. V.A.Petrow, O.Rosenheim, and W.W.Starling, J.Chem.Soc., 677 (1938).
10. (a) J.M.Coxon, M.P.Hartshorn, C.N.Muir, and K.E.Richards, Tetrahedron Letters, 3725 (1967); (b) J.W.Blunt, M.P.Hartshorn, and D.N.Kirk, J.Chem.Soc.(C), 635 (1968);(c)J.W.Blunt, M.P. Hartshorn, and D.N.Kirk, Tetrahedron, 25, 149 (1969).
11. E.L.Eliel, N.L.Allinger, S.J.Angyal, and G.A.Morrison, Conformational Analysis, Interscience Publishers, New York, p. 44 (1965).