Neighbouring-group Participation by Ether Oxygen in Displacement Reactions of 3α-Substituted 2β,19-Oxido-androstanes

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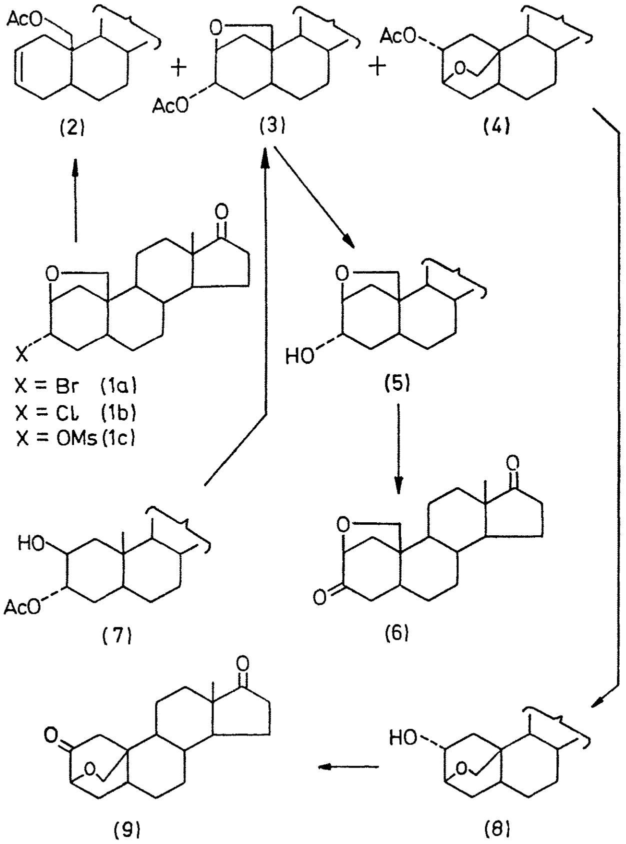
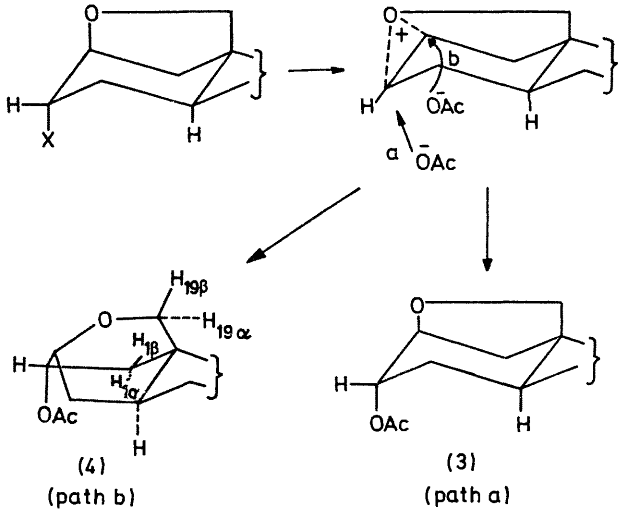
Summary A neighbouring-group participation of the ether oxygen at C-2 is observed in the displacement reactions of 3α-substituted 2β,19-oxido-androstanes.

IN the course of studies on the synthesis of C-19 functionalized steroids, we examined the displacement reactions of 3α-substituted 2β,19-oxido-androstanes with zinc and acetic acid.

Treatment of the bromo-oxide (**1a**) with zinc and acetic acid gave the corresponding elimination product (**2**) in good yield.[1] On the other hand, the chloro-oxide (**1b**) under identical conditions gave a mixture of products, and n.m.r. examination of the reaction mixture in benzene solution revealed three acetyl peaks. Chromatography of the mixture on alumina (Activity II) yielded the 19-acetoxy-olefin (**2**) (20%), and a crystalline compound consisting of a mixture of (**3**) (50%) and (**4**) (30%). The n.m.r. spectrum of this mixture in benzene solution showed the presence of two acetyl peaks and methine hydrogens attached to carbons bearing acetoxy-functions. The absence of vinyl hydrogens suggested that both (**3**) and (**4**) were acetate substitution products. Fractional crystallization of this mixture from hexane afforded a high-melting acetate, (**3**), m.p. 184—186°, and a low-melting acetate,(**4**), m.p. 152—153°.





SCHEME

The n.m.r. spectrum ($CDCl_3$) of (**3**) showed the C-19 methylene protons at δ 3·76 (dd), the C-2 proton at δ 4·26 (t, *J* 5 Hz) and the C-3 proton at δ 4·80. The fact that the C-3 proton was shifted downfield in benzene solution by 12 Hz indicated that the acetate function at C-3 was axial.† Structure (**3**) was further confirmed by conversion into the known diketone (**6**) and independent synthesis. Hydrolysis of (**3**) gave an alcohol (**5**), m.p. 216—218°, which was oxidized to (**6**),[2] m.p. 148—149°, *m/e* 302, n.m.r. signals ($CDCl_3$) at δ 3·78 (d, *J* 8 Hz) and 3·96 (d, *J* 8 Hz) (AB pattern of C-19 methylene protons) and at δ 4·00 (d, *J* 7 Hz, C-2 proton). The c.d. curve of (**6**) exhibited a positive maximum at 298 nm ($[\theta]_{298}$ + 14,400). Moreover, hypoidite oxidation of 2β,3α-hydroxy-5α-androstan-17-one 3-acetate[3] (**7**) gave (**3**) which was identical in all respects with the displacement product obtained from (**1b**).

N.m.r. ($CDCl_3$) analysis of the minor displacement product, (**4**), in which ring A exists in the quasi-boat conformation, showed a pair of doublets for the C-19 methylene protons at δ 3·88 and 4·02 (*J* 3 Hz) and a doublet at δ 3·53 (*J* 10 Hz) for the C-3 proton. In addition, a broad multiplet was seen at δ 4·86 for the C-2 proton which shifted downfield 16 Hz in benzene solution. This shift indicated that the acetate function at C-2 was axial.† Hydrolysis of (**4**) gave an alcohol (**8**), m.p. 202—203°, which was oxidized to a different diketone (**9**), m.p. 163—164°, $[\alpha]_D$ + 174°. The mass spectrum of (**9**) showed only two pertinent peaks,

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† On change of solvent from $CDCl_3$ to benzene an equatorial proton attached to a carbon bearing an axial acetoxy group suffers an appreciable downfield shift (Δ — 0·20 to —0·26 p.p.m.); whereas an axial proton suffers practically no shift.

one at m/e 302 (M^+) and the other one at m/e 258 which corresponded to loss of acetaldehyde from the molecular ion. The 100 MHz n.m.r. spectrum of (**9**) is in good agreement with the suggested 3β,19-oxido-structure. The 10-methylene group (C-19) shows an AB pattern: $\delta_{19\beta}$ 4·2, $\delta_{19\alpha}$ 3·70 p.p.m. ($J_{19\beta-19\alpha}$ 10 Hz). Moreover both 19α-H and 19β-H present an additional 4σ bond coupling:[4] one C-19 proton (19β) interacts with 1α-H ($J_{1\alpha-19\beta}$ 2 Hz) and the other C-19 proton (19α) is coupled with the 5α-H ($J_{5\alpha-19\alpha}$ 1 Hz). The C-3 proton appears at δ 3·76 (m), the 1β-H at δ 2·72 ($J_{1\alpha-1\beta}$ 19 Hz), and the 1α-H at δ 1·92 ($J_{1\alpha-1\beta}$ 19 Hz). The C-1 α-proton further interacts with 19β-H ($J_{1\alpha-19\beta}$ 2 Hz). The position of the carbonyl group in (**9**) was further confirmed by c.d. measurements.‡ Both (8) and (**9**) exhibited positive maxima; $[\theta]_{298}$ + 9450 for (8) and $[\theta]_{296}$ + 7560 for (**9**). The $[\theta]$ value of the 2-oxo-chromophore in (**9**) was thus −1890. This observed negative Cotton effect is consistent with a C-2 carbonyl function situated in the A-ring which has assumed a boat conformation.[5]

Treatment of (**1c**) with zinc and acetic acid gave rise only to displacement products (**3**) (75%) and (**4**) (20%). The same two acetates (**3**) and (**4**) were also obtained in equal amounts by the action of acetic acid and sodium acetate on the bromo-oxide (**1a**).

The bromo-oxide (**1a**) undergoes mainly elimination with zinc and acetic acid whereas under similar conditions the chloro-oxide (**1b**) undergoes both elimination and substitution and the mesylate (**1c**) only substitution. An S_N2 mechanism with neighbouring-group participation by the ether oxygen[6] is suggested as operating in the substitution reactions, since the displacement proceeded with retention of configuration. The formation of both (**3**) and (**4**) can be visualized as arising from an intermediate oxonium ion which can be cleaved by attack of acetate ion from the less hindered α-face at C-2 and C-3, respectively (Scheme).

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‡ In 2,17-dioxo- or 3,17-dioxo-steroids the distance separating the two carbonyl groups is large enough so that the "additivity rule" can be applied. (Ref. 5, p. 109).

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