Improved Synthesis of 4,4-Dimethyl-6-oxosteroids

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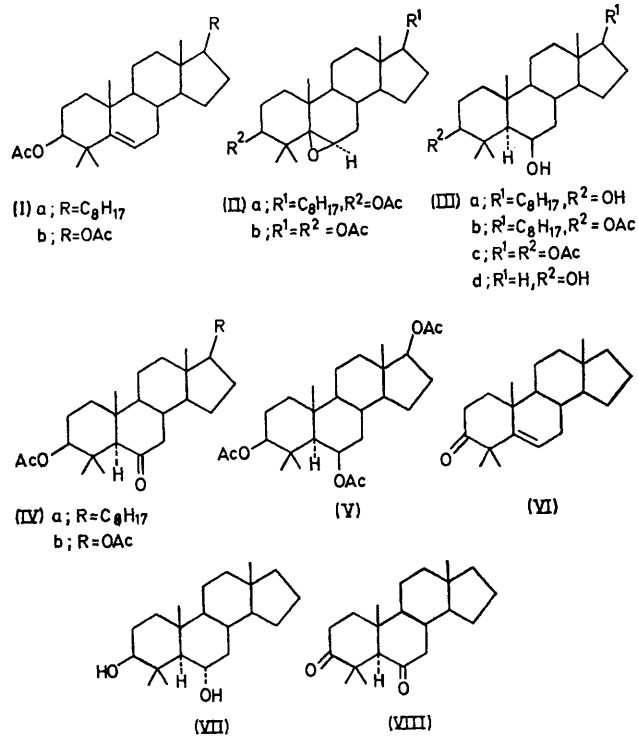
Summary New efficient conversions of certain Δ^5-4,4-dimethylsteroids into the corresponding 5α-6-oxo-derivatives are described.

OF the routes available for converting Δ^5-steroids into their 6-oxo-analogues, the nitration procedure[1] is unsuccessful[2,3] and the *i*-steroid method inapplicable,[4] in the case of 4,4-dimethylsteroids. Those methods which have been used[2,5,6] often give rather low yields.

In a search for more efficient routes to 4,4-dimethyl-Δ^7-6-ketones it was planned to convert a Δ^5-olefin into the bromhydrin, followed by oxidation, rearrangement, and dehydrobromination. Treatment of 3β-acetoxy-4,4-dimethylcholest-5-ene (Ia) with *N*-bromoacetamide in aqueous dioxan–perchloric acid at 0° gave, on addition of ice–water, a non-polar product (90%), whose spectral characteristics indicated it to be the 5β,6β-epoxide (IIa) m.p. 147—148° (lit.[5] m.p. 149—150°), n.m.r. δ 3·26 (6α-H, $w_{\frac{1}{2}}$ 6 Hz). Treatment of 3β,17β-diacetoxy-4,4-dimethylandrost-5-ene (Ib) in the same way gave the corresponding 5β,6β-epoxide (80%) (IIb) m.p. 173—175°. The scope of this spontaneous epoxidation and its stereochemical implications are under investigation.[7]

The preparation of the β-epoxide in excellent yield suggested a route to 4,4-dimethyl-6-oxosteroids by reductive opening of this compound. Treatment of (IIa) with either of Eliel's "mixed hydrides"[8] from lithium aluminium hydride and aluminium chloride resulted in smooth reduction of epoxide and acetate groups to give (79%) 3β,6β-dihydroxy-4,4-dimethyl-5α-cholestane (IIIa), m.p. 157—159°, ν_{max} 3490, 3400, 1030 cm^{-1}, n.m.r. δ 3·12 (3α-H, $w_{\frac{1}{2}}$ 15 Hz), 4·40 (6α-H, $w_{\frac{1}{2}}$ 8 Hz). Comparable yields were obtained upon reduction of the epoxide with lithium in ethylamine.[5] Selective acetylation of the 3β-hydroxy-group was readily achieved to give an almost quantitative yield of 3β-acetoxy-6β-hydroxy-4,4-dimethyl-5α-cholestane (IIIb), m.p. 145—146°, ν_{max} 3550, 1715, 1245, 1030 cm^{-1}, n.m.r. δ 4·40 (6α-H, 3α-H). Jones oxidation of this product gave in quantitative yield 3β-acetoxy-4,4-dimethyl-5α-cholestan-6-one (IVa), m.p. 149—150° (lit.[5] m.p. 151—152°).

In the same way 3β,17β-diacetoxy-5β,6β-epoxy-4,4-dimethylandrostane (IIb) was reduced with lithium aluminium hydride–aluminium chloride or lithium–ethylamine to give, after selective acetylation, 3β,17β-diacetoxy-6β-hydroxy-4,4-dimethyl-5α-androstane (IIIc), m.p. 210—211°. In this series the acetylation was not quite as selective and minor amounts of the triacetate (V) were also isolated. This could be saponified and reacetylated to give further quantities of the 3β,17β-diacetate (IIIc). This compound was convertible by Jones oxidation into 3β,17β-diacetoxy-4,4-dimethyl-5α-androstan-6-one (IVb), m.p. 210—211°.



An efficient sequence leading to 4,4-dimethyl-3,6-dioxo-5α-steroids, involving simultaneous hydroboration of an olefin and reduction of a ketone, was also developed. 4,4-Dimethylandrost-5-en-3-one (VI) was treated for 4 days with a molar solution of diborane in tetrahydrofuran, followed by *in situ* oxidation with alkaline hydrogen peroxide to give (85%) 3β,6α-dihydroxy-4,4-dimethyl-5α-androstane (VII), m.p. 181—182°, ν_{max} 3530, 1040, 1020 cm^{-1}, n.m.r. δ 3·26 (3α-H, $w_{\frac{1}{2}}$ 15 Hz), 4·10 (6β-H, $w_{\frac{1}{2}}$ 15 Hz). Jones oxidation of this diol gave 4,4-dimethyl-5α-androstane-3,6-dione (VIII), m.p. 174—176°, ν_{max} 1720 cm^{-1}. Reduction of the dione with lithium aluminium hydride gave (96%) 3β,6β-dihydroxy-4,4-dimethyl-5α-androstane (IIId), m.p. 157—159°, ν_{max} 3550, 1040, 1020 cm^{-1}, n.m.r. δ 3·20 (3α-H, $w_{\frac{1}{2}}$ 15 Hz), 4·45 (6α-H, $w_{\frac{1}{2}}$ 6 Hz). The route from this compound to the 3β-acetoxy-6-ketone is as already described for the 17-acetoxyandrostane series.

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