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STEREOSELECTIVE FORMATION AND BF_3-CATALYSED CLEAVAGE OF STEROIDAL α-EPOXYKETONES

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The base-catalysed epoxidation of α,β-unsaturated ketones often proceeds with a high degree of stereoselectivity (1). Although a variety of steroidal α-epoxyketones has been prepared in this way (2), the reactions of Δ^5-4- and Δ^4-6-ketones with alkaline hydrogen peroxide have not been reported.

Cholest-5-en-4-one (I) in methanol at 20° reacted with a slight excess of aqueous 4*N* potassium hydroxide and 100 vol. hydrogen peroxide to give after 40 hr., a 70% yield of 5,6β-epoxy-5β-cholestan-4-one (II), m.p. 105-108°, $[\alpha]_D$ + 47° (*c* 2.0) (3) [lit. (4), m.p. 102-104°], together with unreacted material (4%). Careful investigation of the reaction product failed to reveal the presence of any 5α,6α-epoxide. Similarly, the reaction with cholest-4-en-6-one (III) after 24 hr. at 20°, afforded only the 4β,5β-epoxy-6-ketone (IV), m.p. 136-137°, $[\alpha]_D$ - 14° (*c* 2.0) [lit. (5), m.p. 139-140°, $[\alpha]_D$ - 8.6°] in 85% yield. The identity of the epoxyketones II and IV was confirmed by comparison with materials prepared using reported methods (4,5). The procedure outlined here provides a convenient stereoselective route to the less accessible epimers in this series.

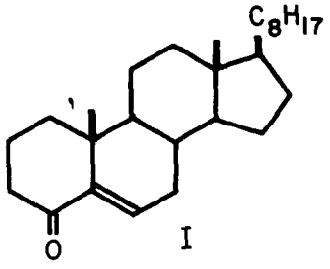
The exclusive formation of products derived from initial β-face attack may be rationalised in terms of favoured anti-parallel approach (6) by the hydroperoxide anion to the terminal position of the conjugated system. Thus in the case of I, the product is formed via a B-ring pre-chair intermediate (V). It must be assumed that the steric demands of the hydroperoxide anion are relatively small and that the reaction course is influenced more by the relative energies of the transition state conformers than by inhibition of prior β-face attack due to the C_{10}-methyl group. In the event of initial

α-face attack on I, the B-ring of the intermediate would assume an energetically unfavourable pre-twist conformation (VI) before collapse to the epimeric epoxyketone.

It was of interest to investigate the effect of boron trifluoride on these epoxyketones since it is evident that the typical Lewis acid-catalysed rearrangements (7) associated with α-epoxyketones possessing an α-bond capable of migration, would be inhibited. Furthermore, the degree of carbonium ion character at C_5 in the co-ordinated complex would be greatly diminished by the adjacent carbonyl group, thereby suppressing the many dramatic rearrangements associated with isolated 4,5- and 5,6-epoxides (8). Accordingly the expectation was that the favoured course of reaction in these systems would involve attack by an external nucleophile at the position β to the carbonyl group rather than intramolecular bond migration (7,9). Preliminary investigations into the action of boron trifluoride on the epoxyketones II and IV tend to support this view.

Treatment of II in dry benzene with freshly distilled boron trifluoride-etherate for periods of 1 min. to 24 hr. at 20° led to 6α-fluoro-5β-cholestan-5-ol-4-one (VII) (10), m.p. 192-194°, $[\alpha]_D$ + 17° (*c* 1.8), $\nu_{max.}^{CHCl_3}$ 3585 (OH) and 1720 cm.$^{-1}$ (CO). The n.m.r. spectrum (3) exhibited at δ 4.64 p.p.m. a multiplet ($J_{H6\beta,F6\alpha}$, 50; $J_{H6\beta,H7\alpha}$, 10 and $J_{H6\beta,H7\beta}$, 7 Hz.) and a sharp signal at δ 2.99 p.p.m. which disappeared on D_2O exchange (C_5-O*H*). When the reaction was followed by t.l.c., starting material was completely consumed after *ca.* 25 min. and the product was obtained in nearly quantitative yields. Similar treatment of IV afforded only 4α-fluoro-5β-cholestan-5-ol-6-one (VIII), m.p. 83-85°, $[\alpha]_D$ - 46° (*c* 1.8), $\nu_{max.}^{CHCl_3}$ 3485 (OH) and 1704 cm.$^{-1}$ (CO), in 80% yield. The n.m.r. signal of the 4β-proton appeared at δ 4.23 p.p.m. as a multiplet ($J_{H4\beta,F4\alpha}$, 50 and $J_{H4\beta,H3\alpha} \sim J_{H4\beta,H3\beta} \sim$ 3 Hz.) while that of the C_5-OH proton was a sharp signal at δ 4.02 p.p.m.

The structural assignments of the products VII and VIII follow from the spectroscopic data and are in accordance with mechanistic expectations.



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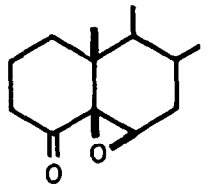

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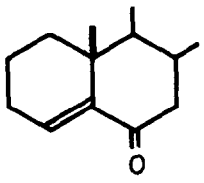

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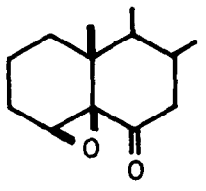

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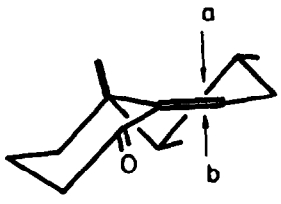

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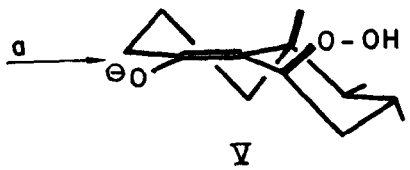
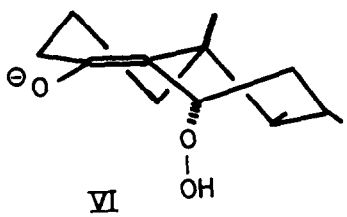


V

II



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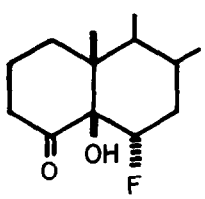

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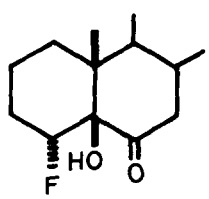

VIII

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3. Rotations were measured in $CHCl_3$ at 20°, and n.m.r. spectra were recorded in $CDCl_3$ on a Varian HA-100 instrument.

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10. The compounds VII and VIII gave satisfactory elemental analyses and mass spectra.