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## The Nitration of $\Delta^5$ -Steroids

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Summary The major product of exothermic nitrations of  $\Delta^{s}$ -steroids is shown to be the 5 $\beta$ -nitro-6-ketone; further reactions of this species are described.

The most common route from  $\Delta^5$  to 6-oxo-steroids involves nitration, followed by reduction and hydrolysis.<sup>1,2</sup> The

nitration came under scrutiny again recently when Narayanan<sup>3</sup> described the isolation of  $5\alpha$ -hydroxy-6-ketones during normal nitration procedures.

The nitration of cholesteryl acetate was first studied from the experimental viewpoint and it was found that the best yields of  $3\beta$ -acetoxy-6-nitrocholest-5-ene (I) were obtained

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when fuming nitric acid (180 ml, 90%) containing sulphuric acid (12 ml, conc.) was added dropwise to cholesteryl acetate (30 g) in ether (420 ml, anhyd.) at 0° during 1 h, followed by stirring for 5 h.

In some cases a strongly exothermic reaction took place. Bowers<sup>2</sup> had described similar occurrences but did not identify the products. Surprisingly, the major product was shown to be  $3\beta$ -acetoxy- $5\beta$ -nitrocholestan-6-one (IIa), m.p. 222°,  $\nu_{max}$  1740, 1725, 1550, 1245, 1020 cm<sup>-1</sup>. The absorption at 1550 cm<sup>-1</sup> is typical of a nitro-group attached to a saturated carbon atom. Significant in the n.m.r. spectrum was a signal, whose width  $(w_{\downarrow} 8 \text{ Hz})$  and field position ( $\delta$  5.08) dictated that it must be assigned to an equatorial hydrogen on carbon carrying an acetate. The AB ring fusion must therefore be cis. The AB portion of an

ABX system at  $\delta$  2.9 ( $J_{AB}$  13,  $J_{AX}$  5,  $J_{BX}$  3 Hz) is consistent with the 4-CH<sub>2</sub>/3 $\alpha$ -H interaction in an AB cis-fused steroid. No other low field signals were present, indicating that the nitro-group must be attached to a tertiary carbon atom. The absence of i.r. absorption between 1610 and 1680 cm<sup>-1</sup> ruled out a 5 $\beta$ -nitrite ester.

To confirm the structure of the nitration product, it was subjected to mild acidic hydrolysis, which afforded (60%) $3\beta$ -hydroxy- $5\beta$ -nitrocholestan-6-one (IIb), m.p. 195°,  $\nu_{max}$ 3400, 1720, 1550, 1070 cm<sup>-1</sup>, n.m.r.  $\delta$  2.8, 3.2 (4-CH<sub>2</sub>). Oxidation of this compound with Jones reagent gave  $5\beta$ nitrocholestane-3,6-dione (III), m.p. 177°, v<sub>max</sub> 1700, 1720, 1550 cm<sup>-1</sup>, n.m.r.  $\delta$  2.92<sup>4</sup> (s, 4-CH<sub>2</sub>). Treatment of this dione with a dilute solution of potassium bicarbonate (4 h, 60°) gave cholest-4-ene-3,6-dione (IV).5

Failure to maintain rapid stirring and 0° temperature when adding potassium hydroxide solution during the work-up of the nitration mixtures from which  $5\beta$ -nitrocompound (IIa) was isolated led to the isolation of  $3\beta$ ,  $5\alpha$ dihydroxycholestan-6-one (Va), m.p. 236-238° (lit.6 m.p. 236-237°). To ascertain if this compound had been formed from the 5 $\beta$ -nitro-6-ketone (IIa) the latter was heated under reflux for 3 h with potassium bicarbonate in aqueous methanol. The major product was indeed  $3\beta$ ,  $5\alpha$ dihydroxycholestan-6-one (Va), whose acetate (Vb) had m.p. 235-236° (lit.<sup>6</sup> m.p. 234-236°).

The isolation of the 5 $\beta$ -nitro-6-ketone makes it possible that the  $5\alpha$ -hydroxy-6-ketones isolated by Narayanan were the products of basic degradation, during the work-up procedure, of the former.

The mechanism of nitration of steroidal olefins by fuming nitric acid and related species has been a subject of much debate.<sup>7</sup> From our results it would appear that competitive processes are involved, the first leading to the 6-nitro-5-ene and the second to the  $5\beta$ -nitro-6-ketone. In cases such as that described, involving violent exothermic reaction, the second process predominates. This may be a radical reaction, proceeding, for example, through an unstable 5 $\beta$ -nitro-6-peroxynitrate,<sup>8</sup> but further work is required to substantiate this.

The replacement of the C-5 tertiary nitro-group by a hydroxy-group with inversion has precedents and proceeds most likely through an intermediate nitrate ester.<sup>9</sup> Alternatively the 5*a*-hydroxy-group might arise by a ring expansion/contraction ketol isomerisation from a 5 $\beta$ hydroxy-6-ketone.<sup>†</sup>

(Received, 2nd February 1972; Com. 154.)

<sup>†</sup> We thank a referee for bringing this to our attention.

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(Y) a; R = OH

b; R = OAc

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