The Nitration of Δ^5-Steroids

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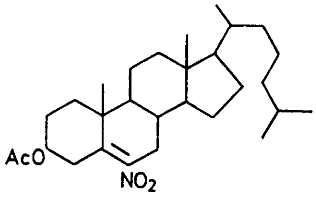
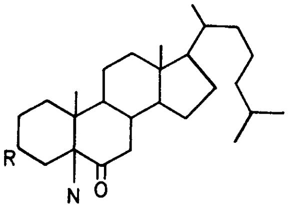
Summary The major product of exothermic nitrations of Δ^5-steroids is shown to be the 5β-nitro-6-ketone; further reactions of this species are described.

THE most common route from Δ^5 to 6-oxo-steroids involves nitration, followed by reduction and hydrolysis.[1,2] The nitration came under scrutiny again recently when Narayanan[3] described the isolation of 5α-hydroxy-6-ketones during normal nitration procedures.

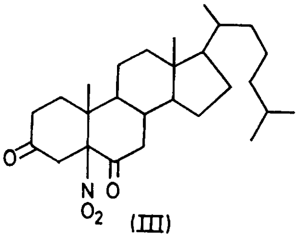
The nitration of cholesteryl acetate was first studied from the experimental viewpoint and it was found that the best yields of 3β-acetoxy-6-nitrocholest-5-ene (I) were obtained when fuming nitric acid (180 ml, 90%) containing sulphuric acid (12 ml, conc.) was added dropwise to cholesteryl acetate (30 g) in ether (420 ml, anhyd.) at 0° during 1 h, followed by stirring for 5 h.



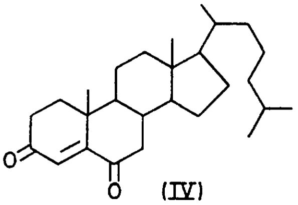
(I)



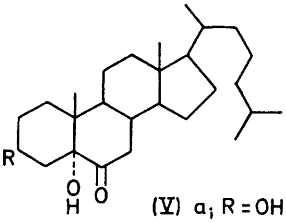
(II) a; R = OAc
b; R = OH



(III)



(IV)



(V) a; R = OH
b; R = OAc

In some cases a strongly exothermic reaction took place. Bowers[2] had described similar occurrences but did not identify the products. Surprisingly, the major product was shown to be 3β-acetoxy-5β-nitrocholestan-6-one (IIa), m.p. 222°, ν_{max} 1740, 1725, 1550, 1245, 1020 cm^{-1}. The absorption at 1550 cm^{-1} is typical of a nitro-group attached to a saturated carbon atom. Significant in the n.m.r. spectrum was a signal, whose width ($w_{\frac{1}{2}}$ 8 Hz) and field position (δ 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 δ 2·9 (J_{AB} 13, J_{AX} 5, J_{BX} 3 Hz) is consistent with the 4-CH_2/3α-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^{-1} ruled out a 5β-nitrite ester.

To confirm the structure of the nitration product, it was subjected to mild acidic hydrolysis, which afforded (60%) 3β-hydroxy-5β-nitrocholestan-6-one (IIb), m.p. 195°, ν_{max} 3400, 1720, 1550, 1070 cm^{-1}, n.m.r. δ 2·8, 3·2 (4-CH_2). Oxidation of this compound with Jones reagent gave 5β-nitrocholestane-3,6-dione (III), m.p. 177°, ν_{max} 1700, 1720, 1550 cm^{-1}, n.m.r. δ 2·92[4] (s, 4-CH_2). 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 5β-nitro-compound (IIa) was isolated led to the isolation of 3β,5α-dihydroxycholestan-6-one (Va), m.p. 236—238° (lit.[6] m.p. 236—237°). To ascertain if this compound had been formed from the 5β-nitro-6-ketone (IIa) the latter was heated under reflux for 3 h with potassium bicarbonate in aqueous methanol. The major product was indeed 3β,5α-dihydroxycholestan-6-one (Va), whose acetate (Vb) had m.p. 235—236° (lit.[6] m.p. 234—236°).

The isolation of the 5β-nitro-6-ketone makes it possible that the 5α-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.[7] 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 5β-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 5β-nitro-6-peroxynitrate,[8] 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.[9] Alternatively the 5α-hydroxy-group might arise by a ring expansion/contraction ketol isomerisation from a 5β-hydroxy-6-ketone.†

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