

A NOVEL REACTION OF NITRIC ACID WITH STEROIDS\*

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Reaction of nitric acid with unsaturated steroids under mild conditions is known for a very long time and several authors have carried out this reaction to prepare nitrosteroids<sup>1-3</sup>. In our hands this reaction yielded a novel product whose structure and mode of formation is now elucidated.

As a first step to prepare 6-ketocholestane required for some other work, we carried out the long known nitric acid reaction on 5-cholestene I (R=H). TLC of the product showed two major spots and by chromatography on silica gel they were isolated and identified as (1) the expected 6-nitrocholestene<sup>4</sup> m.p. 119°, ( $\alpha$ )<sub>D</sub> 105°, II (R=H), and (2) a ketol C<sub>27</sub>H<sub>46</sub>O<sub>2</sub> m.p. 151-53°, ( $\alpha$ )<sub>D</sub> -42°, which was eventually identified as 5 $\alpha$ -hydroxy-6-ketocholestane<sup>5</sup>, III (R=H), by spectral and chemical data and by comparison with an authentic sample prepared by converting 5-cholestene to 5 $\alpha$ , 6 $\beta$ -diol and oxidizing it with NBS to the ketol III<sup>5</sup>.

To ascertain whether this was a general reaction, nitration under the same conditions<sup>2</sup> was repeated on a number of other steroid derivatives (Fig.1). In every case the 5 $\alpha$ -hydroxy-6-keto-derivative was invariably obtained whose identity was confirmed by independent synthesis. The yield of the ketol III varied from 13 to 130% of the nitro compound, the maximum being when R=H and the minimum when R=OCH<sub>3</sub>. In some cases the  $\alpha$ -ketol crystallized out first from the solution leaving the nitro compound in the mother liquor.

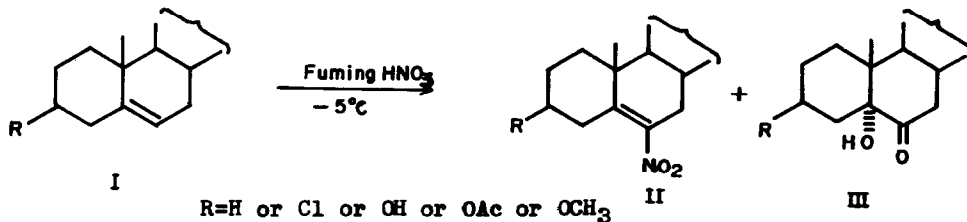


Fig.1

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Besides acting as a strong acid, nitric acid is also known to ionize to a small extent<sup>6</sup> as per the equation  $2\text{HNO}_3 \rightarrow \text{H}_2\text{O} + \text{NO}_3^- + \text{NO}_2^+$ . A reaction pathway was therefore envisaged as in Fig.2 to obtain the  $\alpha$ -ketol from the nitrosteroid. However, repetition of the nitration reaction with extended time or with small amount of added water did not increase the proportion of the  $\alpha$ -ketol produced. Finally, when nitration was carried out with the pure

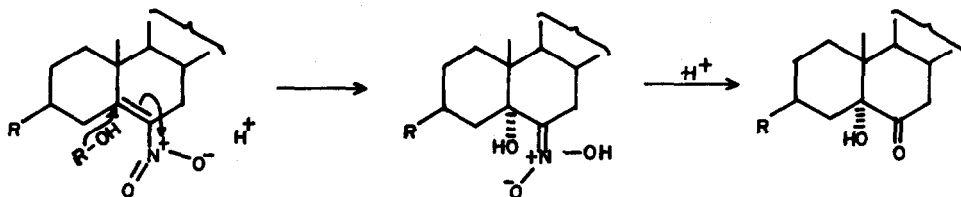


Fig.2

6-nitrosteroid, only the nitrosteroid and no  $\alpha$ -ketol was obtained. Hence it was concluded that the nitrosteroid is not an intermediate in the reaction, and the formation of the  $\alpha$ -ketol followed an independent pathway.

Fuming nitric acid is generally prepared by distilling with sulphuric acid and the former is known to contain oxides of nitrogen<sup>7</sup> including the species  $\text{NO}^+$ . An alternate mechanism was therefore envisaged for the formation of the product as shown in Fig.3. One simple way to test this hypothesis is

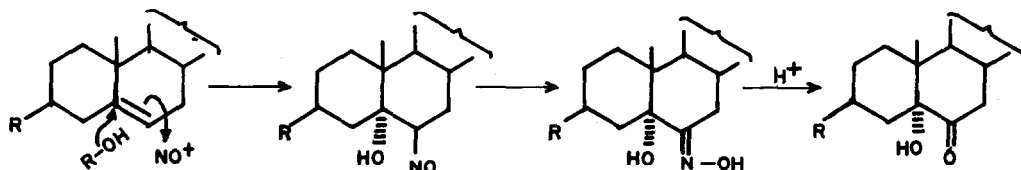
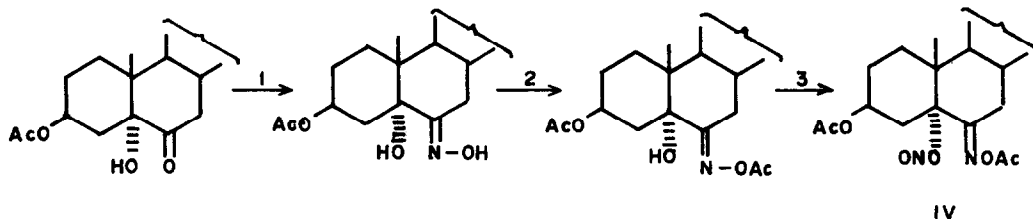


Fig.3

to add an anion which may compete for the nucleophilic addition at  $\text{C}_5$  to produce a new  $\text{C}_5$ -substituted compound. Accordingly nitration of cholesteryl acetate was carried out with fuming nitric acid, with added sodium nitrite and acetic acid. Chromatography of the reaction product gave besides the 6-nitrocholesteryl acetate II ( $\text{R}=\text{OAc}$ ) and a much reduced amount of the ketol III ( $\text{R}=\text{OAc}$ ), a new product  $\text{C}_{31}\text{H}_{50}\text{O}_6\text{N}_2$ , m.p.  $168^\circ$ ,  $(\alpha)_D -39^\circ$ . Its IR and NMR spectra showed the presence of the  $\text{C}_3$ -equatorial acetate, ( $1748$  and  $1240\text{ cm}^{-1}$ ), a broad peak at  $\delta$  4.82 (1 H), a singlet at  $\delta$  1.96 (3 H), an additional acetate group ( $1755\text{ cm}^{-1}$ , singlet at  $\delta$  2.15, 3 H) and the presence of a nitrite ester ( $1640, 1580\text{ cm}^{-1}$ ). This compound was assigned structure IV, and was found to be identical with the one synthesized as in Fig.4.



1,  $\text{NH}_2\text{OH}$ ; 2,  $\text{Ac}_2\text{O}$ ; 3,  $\text{NOCl}$

Fig.4

The mechanism of formation of this product throws some light on one of the several pathways of the reaction of nitric acid, which ultimately result in an oxidation product.

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