Tetrahedron Letters No.54, pp. 4703-4705, 1970. Pergamon Press. Printed in Great Britain.

A NOVEL REACTION OF NITRIC ACID WITH STEROIDS*

C.R. Narayanan, (Miss) M.S. Parker and
(in part) M.S. Wadia

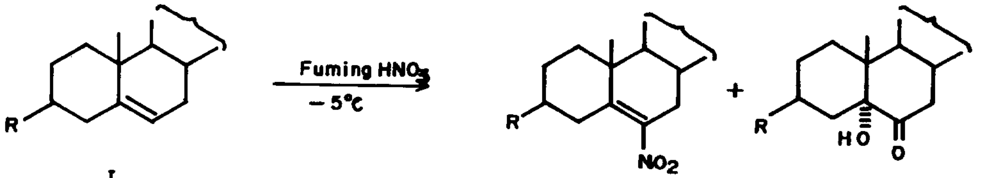
National Chemical Laboratory, Poona 8, India.

(Received in UK 22 September 1970; accepted for publication 21 October 1970)

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[1-3]. 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[4] m.p. 119°, $(\alpha)_D$ 105°, II (R=H), and (2) a ketol $C_{27}H_{46}O_2$ m.p. 151-53°, $(\alpha)_D$ -42°, which was eventually identified as 5α-hydroxy-6-ketocholestane[5], III (R=H), by spectral and chemical data and by comparison with an authentic sample prepared by converting 5-cholestene to 5α, 6β-diol and oxidizing it with NBS to the ketol III[5].

To ascertain whether this was a general reaction, nitration under the same conditions[2] was repeated on a number of other steroid derivatives (Fig.1). In every case the 5α-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_3. In some cases the α-ketol crystallized out first from the solution leaving the nitro compound in the mother liquor.



I

II

III

R=H or Cl or OH or OAc or OCH_3

Fig.1

---

*Communication No.1499 from the National Chemical Laboratory, Poona 8, India.

Besides acting as a strong acid, nitric acid is also known to ionize to a small extent[6] as per the equation $2HNO_3 \rightarrow H_2O + NO_3^- + NO_2^+$. A reaction pathway was therefore envisaged as in Fig.2 to obtain the α-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 α-ketol produced. Finally, when nitration was carried out with the pure 6-nitrosteroid, only the nitrosteroid and no α-ketol was obtained. Hence it was concluded that the nitrosteroid is not an intermediate in the reaction, and the formation of the α-ketol followed an independent pathway.

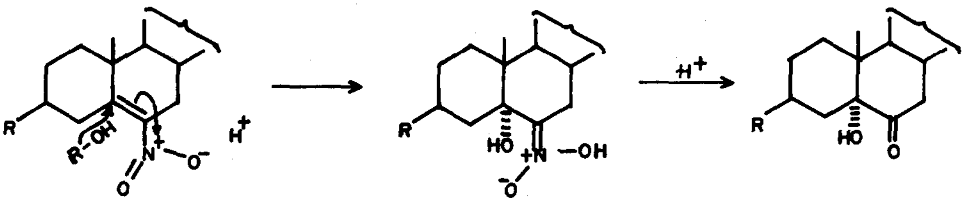


Fig.2

Fuming nitric acid is generally prepared by distilling with sulphuric acid and the former is known to contain oxides of nitrogen[7] including the species 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 to add an anion which may compete for the nucleophillic addition at C_5 to produce a new 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 (R=OAc) and a much reduced amount of the ketol III (R=OAc), a new product $C_{31}H_{50}O_6N_2$, m.p. 168°, $(\alpha)_D$ -39°. Its IR and NMR spectra showed the presence of the C_3-equatorial acetate, (1748 and 1240 cm^{-1}, a broad peak at δ 4.82 (1 H), a singlet at δ 1.96 (3 H), an additional acetate group (1755 cm^{-1}, singlet at δ 2.15, 3 H) and the presence of a nitrite ester (1640, 1580 cm^{-1}). This compound was assigned structure IV, and was found to be identical with the one synthesized as in Fig.4.

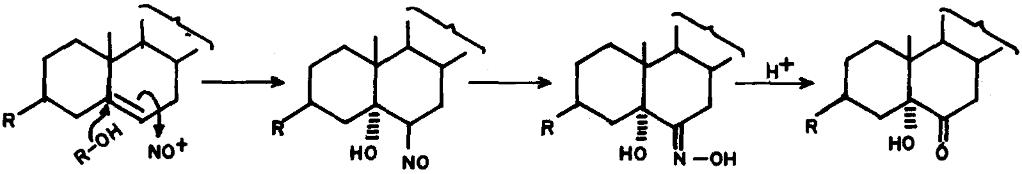
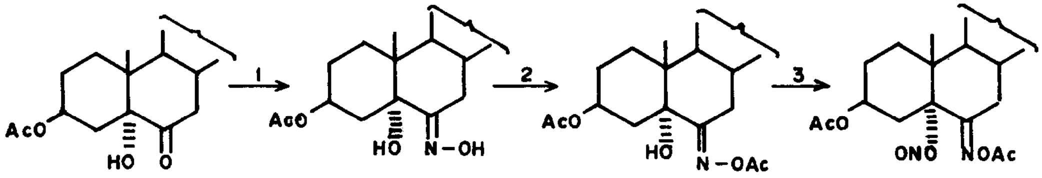


Fig.3



IV

1, NH_2OH; 2, Ac_2O; 3, 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.

REFERENCES

1 See e.g. A. Windaus, Chem. Ber. 36, 3752 (1903); 55, 488 (1920).

2 See e.g. C.E. Aragnostoponlos and L.F. Fieser, J. Amer. Chem. Soc. 76, 532 (1954).

3 See e.g. J.R. Bull, E.R.H. Jones and G.D. Meakins, J. Chem. Soc. 2601 (1965).

4 J. Mauthner and W. Suida, Monatsh. 15, 109 (1894).

5 H. Reich, F.E. Walker and R.W. Collins, J. Org. Chem. 16, 1753 (1951).

6 See e.g. D.H. Millen and W.H. Lee, private communication to C.K. Ingold, Structure and Mechanism in Organic Chemistry, Cornell University Press, 1953, p.277.

7 See e.g. R.J. Gillspie, J. Graham, E.D. Hughes, C.K. Ingold and E.R.A. Peeling, J. Chem. Soc. 2504 (1950).