Nitroamine Radicals as Intermediates in the Functionalization of Non-activated Carbon Atoms

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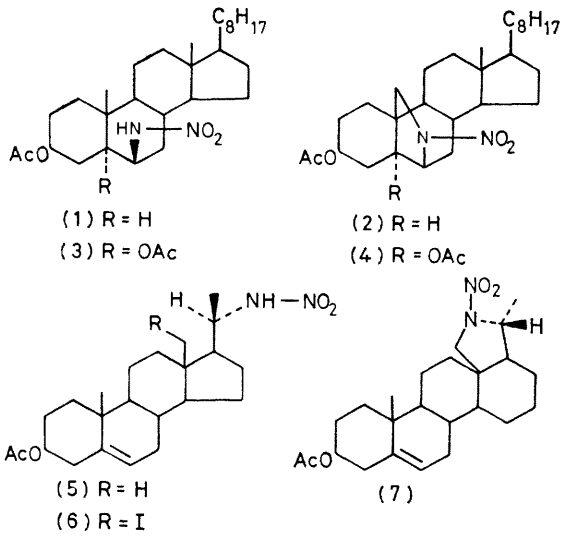
Summary Photolysis of *N*-iodonitroamines generated *in situ* from the steroidal nitroamines 6β-nitroamino-5α-cholestan-3β-ol acetate, 6β-nitroamino-5α-cholestane-3β,5α-diol diacetate, and 20*R*-nitroaminopregn-5-en-3-ol acetate removes hydrogen atoms from the Me-18 and Me-19 groups to give 6β,19-*N*-nitroepimino-5α-cholestan-3β-ol acetate, 6β,19-*N*-nitroepinino-5α-cholestane-3β,5α-diol diacetate, and 18,20*R*-*N*-nitroepiminopregn-5-en-3β-ol acetate

THE free radicals needed to introduce substituents into the C-18 and C-19 steroidal methyl-groups and also into other skeletal positions have been generated by the fragmentation of *N*-halogenoamines (Hofmann-Loffler reaction), *N*-halogenoamides, azides, nitrites (Barton reaction), alcohols, and hypohalites, and also by ketone irradiation [1] Of these, those that give the epimino-compounds are generally the most difficult to apply Hence we are interested in developing a method which enables remote functionalization by the amine radicals R–$\bar{N}$•–X We report here results obtained by the generation of these radicals (X = NO_2) in the steroidal substrates (**1**) [m p 194—196 °C, $[\alpha]_D$ − 42° ($CHCl_3$)], (**3**) [m p 246—247 °C, $[\alpha]_D$ − 84° ($CHCl_3$)], and (**5**) [m p 189—190 °C, $[\alpha]_D$ − 56° ($CHCl_3$)] †

† The nitroamines were prepared by $NaBH_4$ reduction (M J Haire and G A Boswell, Jr , *J Org Chem* , 1977, **42**, 4251) of the corresponding nitroimines The 6-nitroimino-5α-cholestan-3β,5α-diol diacetate has been described previously (A G González, R Freire, M G García-Estrada, J A Salazar, and E Suárez, *An Quim* , 1972, **68**, 1145) The 6-nitroimino-5α-cholestan-3β-ol acetate [amorphous, ν_{max} ($CHCl_3$) 1625, 1560, and 1320 cm^{-1}] and the 20-nitroiminopregn-5-en-3β-ol acetate [m p 175—176 °C, $[\alpha]_D$ −21°, ν_{max} (KBr) 1620, 1580, and 1315 cm^{-1}] have been prepared from the corresponding ketoximes and nitrous acid (G Buchi and H Wuest, *J Org Chem* , 1979, **44**, 4116) Full details will be reported elsewhere



In a typical procedure a solution of the nitroamine in cyclohexane or dichloromethane, treated with I_2 (1 mol. equiv.) and $Pb(OAc)_4$ or HgO (4 mol. equiv.) at 45 °C, was irradiated with two 150 W tungsten filament lamps for 1 h.

The acetate of 6β,19-*N*-nitroepimino-5α-cholestan-3β-ol (**2**), amorphous, was obtained from (**1**)‡ in a yield of 63%§ [chemical ionisation mass spectrum $M^+ + NH_3$, *m/e* 505; mass spectrum $M^+ - NO_2$, $C_{29}H_{48}NO_2$, *m/e* 442·3767; ν_{max} ($CHCl_3$) 1730, 1490, and 1315 cm^{-1}; λ_{max} (EtOH) 241 nm (ε 7400); ^1H n.m.r. *inter alia* δ($CDCl_3$) 4·39 (d, *J* 4 Hz, H-6α) and 3·73br (s, $w_{\frac{1}{2}}$ 4 Hz, 2 × H-19); ^{13}C n.m.r. *inter alia* δ($CDCl_3$) 65·1 (C-6) and 51·2 p.p.m. (C-19)].

Similarly, irradiation of 6β-nitroamino-5α-cholestan-3β,-5α-diol diacetate (**3**) gave (**4**) (60%)§, amorphous, [$M^+ - NO_2$, *m/e* 500; ν_{max} ($CHCl_3$) 1730, 1490, and 1315 cm^{-1}; ^1H n.m.r. δ($CDCl_3$) 5·17 (d, *J* 4 Hz, H-6α) and 3·73br (s, $w_{\frac{1}{2}}$ 4 Hz, 2×H-19; ^{13}C n.m.r. δ($CDCl_3$) 63·8 (C-6) and 49·8 p.p.m. (C-19)].

The same general process was also applied to the functionalization of the 18-methyl-group in (**5**). In this case the 18-iodo-derivative (**6**) was obtained (*ca.* 25%)§ [m.p. 192—194 °C (decomp.), $M^+ - NO_2$, *m/e* 470; ν_{max} 3390, 3250, 1730, 1575, and 1315 cm^{-1}, λ_{max} (EtOH) 224 nm (ε 10,300); ^1H n.m.r. δ($CDCl_3$) 3·05, 3·26 (ABq, J_{AB} 11 Hz, 2 × H-18), and 4·25 (m, H-20); ^{13}C n.m.r. δ($CDCl_3$) 55·75 (C-20) and 7·1 p.p.m. (C-18)]. Treatment of compound (**6**) with silver acetate (4 mol. equiv.) in acetone (18 h at room temperature) gave 18,20*R*-*N*-nitroepiminopregn-5-en-3β-ol acetate (**7**) (100%) [m.p. 190—192 °C, $M^+ - NO_2$, *m/e* 356; ν_{max} 1725, 1490, and 1305 cm^{-1}; λ_{max} (EtOH) 243 nm (ε 9100); ^1H n.m.r. δ($CDCl_3$) 4·38 (q, *J* 6 Hz, H-20) 3·7br (s, $w_{\frac{1}{2}}$ 4 Hz, 2 × H-18); ^{13}C n.m.r. δ($CDCl_3$) 53·7 (C-18) and 65·5 p.p.m. (C-20)].

Since the reduction of nitroamines to amines is a known reaction,[2] this cyclization constitutes a formal synthesis of 1,4-epimino-compounds.

A.R. thanks the Centro Iberoamericano de Cooperación of Spain for a fellowship.

(*Received, 2nd July* 1980; *Com.* 719.)

‡ All new crystalline compounds gave satisfactory analytical data.

§ The yields, which have not been optimized, are of the same order as those described for the photolysis of the corresponding hypoiodites.

[1] K. Heusler and J. Kalvoda in 'Organic Reactions in Steroids Chemistry,' Vol. 2, eds. J. Fried and J. A Edwards, Van Nostrand Reinhold, New York, 1971, p. 237; D. N. Kirk and M. P. Hartshorn, 'Steroid Reaction Mechanisms,' Elsevier Publishing, Amsterdam, 1968, p. 394; J. Kalvoda and K. Heusler, *Synthesis*, 1971, 501; K. Heusler and J. Kalvoda, *Angew. Chem. Int. Ed. Engl.*, 1964, **3**, 525.
[2] P. Bruck and A. H. Lamberton, *J. Chem. Soc.*, 1955, 3997.