The Stereochemistry of the Cleavage of Steroidal Epoxides by Ceric Ammonium Nitrate†

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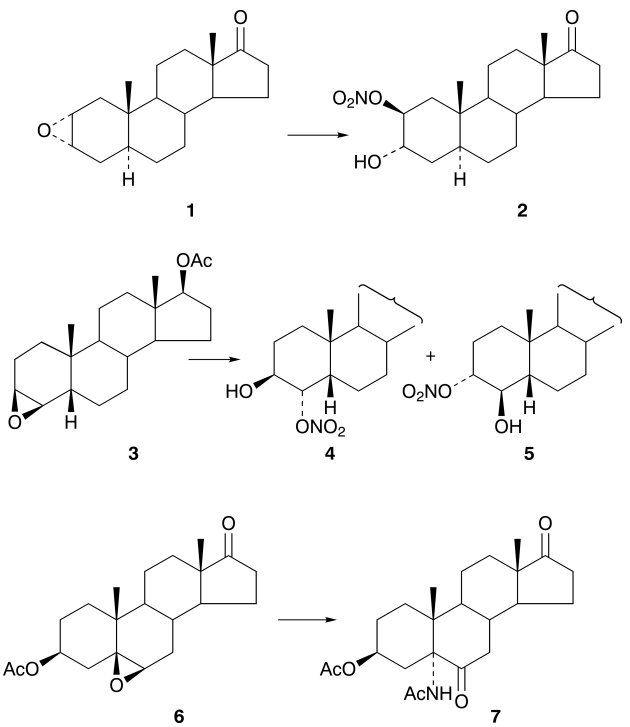
The cleavage of unhindered steroidal epoxides by ceric ammonium nitrate affords the *trans* diaxial β-nitrato alcohols but other products are obtained from more hindered epoxides.

Recently ceric ammonium nitrate has been recommended[1] as a useful reagent for the single-electron cleavage of epoxides affording vicinal nitrato alcohols in good yield under mild conditions. This reagent will also catalyse substitution by other nucleophiles.[2,3] It has been used[3] in this context in the steroid series to catalyse the opening of an unreactive $\Delta^{9(11)}$-5α,10α-epoxide by weakly nucleophilic chloroanilines. It has been suggested[1] that the cleavage of epoxides by ceric ammonium nitrate involves a single-electron transfer opening of the epoxide followed by attack of the nucleophilic component on the resultant radical cation. Such a process does not necessarily have the same stereoelectronic requirement as the conventional acid-catalysed opening of an epoxide. In particular there is the possibility for the transfer of the anionic species, in this case nitrate, from the metal coordination sphere to the developing radical possibly giving rise to a *cis* opening of the epoxide. It was therefore of interest to examine the stereochemical consequences of this reaction in the cleavage of some steroidal epoxides in which the geometry of the normal ionic process is well-defined.[4,5]



A series of di- and tri-substituted ring A and ring B steroidal epoxides were treated with ceric ammonium nitrate in refluxing acetonitrile for 4 h. The results are given in Table 1. The stereochemistry of the products was established from the multiplicity of the CH—O resonances in the ^{1}H NMR spectra.[6] The diaxial products (*e.g.* **2** and **4**) produced typically narrow CH—O resonances whilst the diequatorial product **5** had the H-3 resonance as a triplet (*J* 10.5 Hz) of doublets (*J* 4.7 Hz) and the H-4 resonance as a triplet (*J* 10.5 Hz).

The cleavage of the 2α,3α-, 3α,4α- and 5α,6α-epoxides (*e.g.* **1**) proceeded unexceptionally to provide the diaxial vicinal nitrato alcohols (*e.g.* **2**), paralleling the hydrolysis with mineral acid.[4] However the 3β,4β-epoxide **3** gave the products of both diaxial **4** and diequatorial **5** opening in which the latter predominated. The presence of the 5β-hydroxy group slowed the reaction down considerably and a low yield of the diequatorial product was obtained. Neighbouring group effects on the stereochemistry of the hydrolysis of *cis* 5-hydroxy-3,4-epoxides have been observed previously.[7] The hindered 4α,5α-epoxide underwent rearrangement to form the 4-ketone. Hydrolysis of the 5β,6β-epoxide **6** involved participation of the solvent acetonitrile in a Ritter type of reaction to give the 5α-acetamido derivative **7**. Oxidation of the 6β-alcohol also occurred to give the 6-ketone. The formation of 5α-acetamido-6β-alcohols has been observed[8] in the solvolysis of 5β,6β-epoxides with perchloric acid in acetonitrile.

In conclusion we have shown that relatively unhindered steroidal epoxides are cleaved with ceric ammonium nitrate to form the *trans* diaxial β-nitrato alcohols. However at

Table 1 Cleavage of steroidal epoxides with ceric ammonium nitrate

Substrate	Products	Yield(%)
2α,3α-Epoxy-5α-androstan-17-one	2β,3α-Dinitrato-5α-androstan-17-one	5
	3α-Hydroxy-2β-nitrato-5α-androstan-17-one	38
2α,3α-Epoxy-5α-cholestane	3α-Hydroxy-2β-nitrato-5α-cholestane	60
17β-Acetoxy-3α,4α-epoxy-5α-androstane	17β-Acetoxy-3α-hydroxy-4β-nitrato-5α-androstane	25
17β-Acetoxy-3β,4β-epoxy-5β-androstane	17β-Acetoxy-4β-hydroxy-3α-nitrato-5β-androstane	25
	17β-Acetoxy-3β-hydroxy-4α-nitrato-5β-androstane	12
17β-Acetoxy-3β,4β-epoxy-5β-hydroxyandrostane	17β-Acetoxy-4β,5β-dihydroxy-3α-nitratoandrostane	14
	(recovered starting material)	(51)
17β-Acetoxy-4α,5α-epoxyandrostane	17β-Acetoxy-5α-androstan-4-one	60
3β-Acetoxy-5α,6α-epoxyandrostan-17-one	3β-Acetoxy-5α-hydroxy-6β-nitratoandrostan-17-one	53
3β-Acetoxy-5β,6β-epoxyandrostan-17-one	5α-Acetamido-3β-acetoxyandrostane-6,17-dione	67

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more hindered centres, other reactions such as ketone formation, diequatorial opening and participation of the solvent occur.

Experimental

General experimental details have been described previously.[9]

Reaction of the Epoxides with Ceric Ammonium Nitrate.—The epoxide (500 mg) in acetonitrile (15 cm^3) was treated with ceric ammonium nitrate (1 molar equivalent) and the mixture was heated under reflux for 4 h. The progress of the reaction was monitored by TLC. The solution was poured into water and the products were recovered in ethyl acetate. The extract was washed with water and dried over sodium sulfate. The solvent was evaporated and the residue was chromatographed on silica. The products were eluted with an increasing gradient of ethyl acetate in light petroleum (bp 60–80 °C) and crystallized from ethyl acetate–light petroleum (bp 60–80 °C). The results are given in Table 1.

2*β*,3*α*-*Dinitrato*-5*α*-*androstan*-17-*one*. Mp 150–153 °C, δ_H ($CDCl_3$) 0.86 (3 H, s, 18-H), 0.96 (3 H, s, 19-H), 5.17 and 5.24 (each 1 H, brs, 2*α*- and 3*β*-H), *m*/*z* 396 ($C_{19}H_{28}N_2O_7$, M^+).

3*α*-*Hydroxy*-2*β*-*nitrato*-5*α*-*androstan*-17-*one*. Mp 199–200 °C (Found: C, 64.9; H, 8.4; N, 3.9%. $C_{19}H_{29}NO_5$ requires C, 65.1; H, 8.05; N, 4.0%), δ_H ($CDCl_3$) 0.86 (3 H, s, 18-H), 0.93 (3 H, s, 19-H), 4.03 (1 H, brs, 3*β*-H), 5.07 (1 H, brs, 2*α*-H), *m*/*z* 351 ($C_{19}H_{29}NO_5$, M^+), 288 ($M - 63$, HNO_3).

3*α*-*Hydroxy*-2*β*-*nitrato*-5*α*-*cholestane*. Mp 93–97 °C (Found: C, 72.3; H, 10.7; N, 3.0%. $C_{27}H_{47}NO_4$ requires C, 72.1; H, 10.5; N, 3.1%), δ_H ($CDCl_3$) 0.74 (3 H, s, 18-H), 0.94 (3 H, s, 19-H), 4.01 (1 H, brs, 3*β*-H), 5.07 (1 H, brs, 2*α*-H), *m*/*z* 449 ($C_{27}H_{47}NO_4$, M^+).

17*β*-*Acetoxy*-3*α*-*hydroxy*-4*β*-*nitrato*-5*α*-*androstane*. Mp 174–175 °C (Found: C, 63.9; H, 8.5; N, 3.4%. $C_{21}H_{33}NO_6$ requires C, 63.8; H, 8.4; N. 3.5%), δ_H ($CDCl_3$) 0.77 (3 H, s, 18-H), 0.95 (3 H, s, 19-H), 2.04 (3 H, s, OAc), 4.00 (1 H, brs, 3*β*-H), 4.58 (1 H, t, *J* 8.4 Hz, 17*α*-H), 4.88 (1 H, brs, 4*α*-H).

17*β*-*Acetoxy*-5*α*-*androstan*-4-*one*. Mp 155 °C (lit.,[10] 160 °C), δ_H ($CDCl_3$) 0.73 (3 H, s, 18-H), 0.80 (3 H, s, 19-H), 2.03 (3 H, s, OAc), 4.60 (1 H, t, *J* 8.5 Hz, 17*α*-H) identified by comparison with a sample prepared in the course of hydroboration of 17*β*-acetoxyandrost-4-ene.

17*β*-*Acetoxy*-4*β*-*hydroxy*-3*α*-*nitrato*-5*β*-*androstane*. Mp 209–210 °C (Found: C, 63.7; H, 8.6; N, 3.5%. $C_{21}H_{33}NO_6$ requires C, 63.8; H, 8.4; N, 3.5%), δ_H ($CDCl_3$) 0.78 (3 H, s, 18-H), 1.01 (3 H, s, 19-H), 2.04 (3 H, s, OAc), 3.96 (1 H, t, *J* 10.5 Hz, 4*α*-H), 4.58 (1 H, t, *J* 8.4 Hz, 17*α*-H), 4.84 (1 H, dt, *J* 4.7 and 10.8 Hz, 3*β*-H).

17*β*-*Acetoxy*-3*β*-*hydroxy*-4*α*-*nitrato*-5*β*-*androstane*. Mp 138–140 °C (Found: C, 64.0; H, 8.7; N, 3.4%. $C_{21}H_{33}NO_6$ requires C, 63.8; H, 8.4; N, 3.5%), δ_H ($CDCl_3$) 0.77 (3 H, s, 18-H), 1.00 (3 H, s, 19-H), 2.04 (3 H, s, OAc), 3.91 (1 H, t, *J* 3 Hz, 3*α*-H), 4.61 (1 H, t, *J* 8.5 Hz, 17*α*-H), 5.08 (1 H, brs, 4*β*-H).

17*β*-*Acetoxy*-3*α*-*nitrato*-5*β*-*androstane*-4*β*,5*β*-*diol*. Unstable solid, δ_H ($CDCl_3$) 0.78 (3 H, s, 18-H), 0.99 (3 H, s, 19-H), 4.03 (1 H, d, *J* 10.1 Hz, 4*α*-H), 4.58 (1 H, t, *J* 8.5 Hz, 17*α*-H), 5.20 (1 H, dt, *J* 5.4 and 10.1 Hz, 3*β*-H).

3*β*-*Acetoxy*-5*α*-*hydroxy*-6*β*-*nitratoandrostan*-17-*one*. Mp 189–191 °C (Found: C, 61.6; H, 7.7: N, 3.3%. $C_{21}H_{31}NO_7$ requires C, 61.6; H, 7.6; N, 3.4%), δ_H ($CDCl_3$) 0.88 (3 H, s, 18-H), 1.14 (3 H, s, 19-H), 2.03 (3 H, s, OAc), 4.89 (1 H, brs, 6*α*-H), 5.12 (1 H, tt, *J* 5.5 and 9.8 Hz, 3*α*-H).

5*α*-*Acetamido*-3*β*-*acetoxyandrostane*-6,17-*dione*. Mp 282–283 °C (lit.,[8] 286–288 °C), *m*/*z* 403 ($C_{23}H_{33}NO_5$, M^+), δ_H ($CDCl_3$) 0.85 (3 H, s, 18-H), 0.94 (3 H, s, 19-H), 2.02 and 2.04 (each 3 H, s, Ac), 4.84 (1 H, tt, *J* 5.5 and 10 Hz, 3*α*-H), 6.06 (1 H, brs, NH).

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