A Rearrangement in the Nitration of 3β,17β-Diacetoxy-7-norandrost-5-ene

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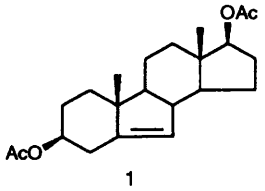
The nitration of 3β,17β-diacetoxy-7-norandrost-5-ene by fuming nitric acid leads to 3β,17β-diacetoxy-5β-nitroxy-6α-nitro-7-norandrostane and to the rearrangement product **2**. A number of minor products were also identified. The formation of these can be rationalized in terms of a Markownikoff directed diaxial (5β,6α) addition to the Δ⁵-double bond of the B-norsteroid which contrasts with the 5α,6β-diaxial addition found in the normal steroids.

In the course of studies on the bromination of B-norsteroids,[1,2] it became apparent that the stereochemistry of addition to 7-norandrost-5-ene differed from that found in the normal Δ⁵-steroid series. Consequently we undertook an investigation of the nitration of 3β,17β-diacetoxy-7-norandrost-5-ene **1**. The results, which form the subject of this paper, reveal not only a different stereochemistry of addition but also a rearrangement which is not found in the normal series.[3-5]



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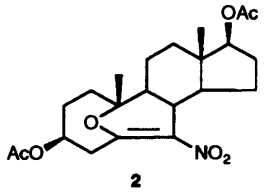

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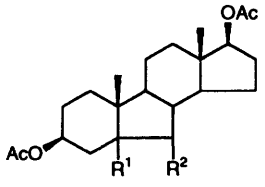
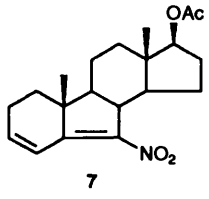


3 R^1 = β-ONO_2, R^2 = α-NO_2
4 R^1 = α-ONO_2, R^2 = α-NO_2
5 R^1 = α-NO_2, R^2 = β-ONO_2
6 R^1 = β-NO_2, R^2 = α-ONO_2



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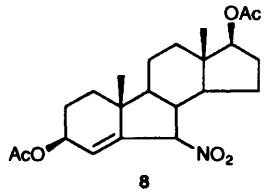

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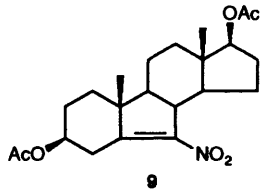

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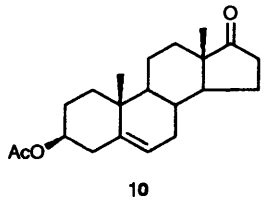

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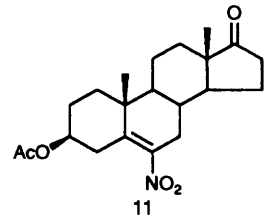

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Treatment of 3β,17β-diacetoxy-7-norandrost-5-ene **1**[6] in diethyl ether at −5 °C with fuming nitric acid gave a complex mixture of products. In a parallel experiment conducted with the same batch of nitric acid, the nitration of 3β-acetoxyandrost-5-en-17-one **10** gave 3β-acetoxy-6-nitroandrost-5-en-17-one **11** in good yield. The complex mixture obtained from the B-norsteroid, was separated into two major components and a number of minor products. The first of the major products, $C_{22}H_{31}O_7N$ **2**, possessed the UV absorption (λ_{max} 271 nm) and ^{13}C NMR signals (δ_C 145.2 and 155.0) of a nitroalkene. There were two acetoxy signals (δ_H 2.05 and 2.07) in the ^1H NMR spectrum. This left one oxygen atom unaccounted for. The quaternary C-10 ^{13}C NMR signal (see Table 1) appeared at δ 86.0 in the region associated with a carbon bearing an oxygen whilst the UV absorption of the nitro-alkene showed a bathochromic shift compared with **11** (λ_{max} 271 *vs.* 260 nm). Thus, an oxygen insertion between C-10 and C-5 had taken place. The unusual structure **2** suggested by the above data, was confirmed by X-ray crystallography (see Fig. 1).

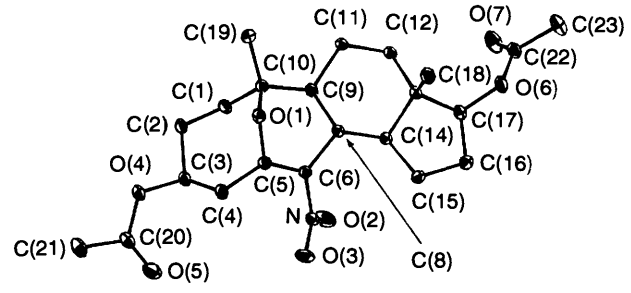


Fig. 1 X-Ray structure of compound **2**

The second major product, $C_{22}H_{32}O_9N_2$ **3** possessed an IR absorption characteristic of a saturated nitro compound (ν_{max}/cm^{-1} 1542) and a doublet resonance in the ^1H NMR spectrum at δ_H 5.36, *J* 9.3 Hz which was assigned to a >C*H*(NO_2) group. The multiplicity of the 3-H ^1H NMR signal suggested the presence of a *cis* A/B ring junction (see Table 2). However, the structure and stereochemistry of this compound were firmly established by X-ray crystallography (see Fig. 2). The NMR data then formed the basis for assigning structures to some of the minor products. In particular compounds with an identical $J_{6,8}$ were assigned the same C-6 stereochemistry.

The structures of the minor isomeric nitro–nitroxy steroids **4–6** followed from their spectroscopic data. Each compound possessed an IR absorption (ν_{max}/cm^{-1} *ca.* 1550) characteristic of a nitro compound. The position of the 6-H resonance (see Table 2) enabled a distinction to be made between those compounds possessing a $CHONO_2$ (δ_H 4.45 and 4.21) and a $CH(NO_2)$ (δ_H 5.36 and 5.85) group. The multiplicity of the 3α-H signal was used to assign the stereochemistry of the A/B ring junction. When the ring junction is *cis* (5β-substituent), the C-3β substituent becomes axial whilst a *trans* ring junction (5α-substituent) leaves the C-3β substituent in the equatorial conformation. Furthermore the electronegative C-5α substit-

Table 1 ^{13}C NMR Data for the nitro steroids, determined in $CDCl_3$

	Compound							
Carbon	**2**	**3**	**4**	**5**	**6**	**8**	**9**	**11**
1	35.4	30.4	27.5	28.2	30.0	35.6	29.7	35.6
2	26.7	23.9	23.6	25.4	24.4	24.6	24.1	26.9
3	70.2	68.1	66.5	70.8	69.4	70.5	71.6	71.7
4	38.5	31.4	32.8	33.7	40.3	123.8	35.7	31.2
5	155.0	95.7	99.1	85.4	80.1	150.5	152.6	137.9
6	145.2	95.0	92.4	96.3	96.4	88.4	147.2	145.9
7								36.1
8	38.5	43.1	42.0	44.5	42.0	43.8	45.8	31.1
9	54.4	44.9	45.4	49.1	49.6	44.9	58.7	49.1
10	86.0	44.7	45.0	45.1	44.5	42.2	45.1	37.4
11	23.4	20.2	20.6	20.8	20.7	20.3	19.9	20.3
12	35.9	35.5	35.6	36.4	36.3	35.7	36.6	31.1
13	43.2	48.9	46.3	45.8	45.1	44.8	45.2	47.4
14	43.1	51.9	48.4	50.5	49.8	53.6	48.3	51.2
15	23.5	22.5	22.4	23.2	23.0	22.9	27.2	21.8
16	27.2	27.3	27.3	27.5	27.5	27.4	27.6	32.3
17	81.6	81.2	81.1	81.8	81.6	81.5	81.6	219.5
18	11.9	12.2	12.2	12.4	12.3	12.3	12.4	13.5
19	23.8	15.3	20.2	15.6	17.0	19.8	15.4	19.8
OAc	170.1	170.2	170.3	170.9	170.0	170.6	170.1	170.0
	171.0	170.9	170.9	171.2	171.1	170.9	171.1	21.2
	21.2	21.1	21.1	21.3	21.3	21.2	21.1	
	21.1	21.0	20.9	21.1	21.1	21.1	21.2	

Table 2 3- and 6-H NMR signals for the nitro–nitrooxy steroids

	Compound			
	3	**4**	**5**	**6**
3-H	5.18	5.04	5.26	5.12
Multiplicity	dd	tt	tt	tt
J/Hz	6.3, 6.6	9.2. 4.6	10.6, 4.9	5.1, 2.8
6-H	5.36	5.85	4.45	4.21
Multiplicity	d	d	d	d
J/Hz	9.3	9.5	7	9.7

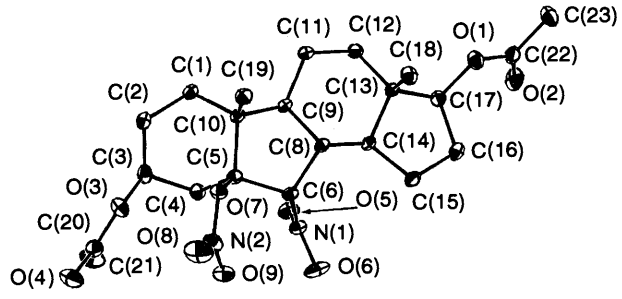
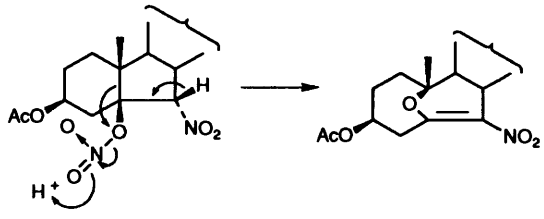


Fig. 2 X-Ray structure of compound **3**

uents deshield the C-3α proton from its normal position for a C*H*(OCOCH$_3$) of δ_H *ca.* 4.7 to 5.1. Some additional evidence for the C-6 stereochemistry of **4** came from an NOE experiment. Irradiation at δ_H 1.03 (19-H) produced an NOE enhancement (2%) at δ_H 5.85 indicating that this compound possessed a β-oriented hydrogen at C-6.

Trace amounts of some unsaturated nitro-steroids were also obtained. The nitro-diene **7** lacked the ^1H NMR signals for the 3-acetate but had signals for a disubstituted alkene at δ_H 6.34 and 6.85. The isomeric nitro mono-alkenes **8** and **9** were distinguished by the presence of a trisubstituted double bond (δ_H 5.68) and CHNO$_2$) resonance (δ_H 5.43) in **8**. The ^{13}C NMR data for **8** and **9** (see Table 1) were consistent with their structures.

The differing stereochemistry of the products of nitration of cholest-5-ene and the B-nor series can be accounted for by a Markownikoff-directed *trans* diaxial addition. This condition is best fulfilled in the B-nor series by the 6α-nitro-5β-nitrooxy system whereas the 6β-nitro-5α-nitrooxy system has a diaxial relationship in the normal series. The origin (see Scheme 1) of



Scheme 1 The formation of compound **2**

the rearrangement product may involve a 1,2-shift with the expulsion of nitrous acid and the relief of interactions between the C-10 methyl and the C-5 substituent which are apparent in Fig. 2. Another interesting difference which is also probably related to the stereochemistry of the initial addition, is the minor amount of the nitro-alkene **9** that was obtained compared to the yield of **11** which was obtained in the normal series.

Experimental

General Experimental Details.—^1H and ^{13}C NMR spectra were determined at 360 and 100.25 MHz respectively on Bruker WM 360 and WH500 spectrometers. *J* values are given in Hz. IR spectra were determined as Nujol mulls. Extracts were dried over sodium sulfate. Silica for chromatography was Merck 9385. Light petroleum refers to the range, b.p. 60–80 °C. Diethyl ether for nitrations was redistilled from P_2O_5 immediately prior to use whilst the fuming nitric acid was from a fresh bottle as supplied by Aldrich. 3β,17β-Diacetoxy-7-norandrost-5-ene **1** was prepared according to the method of Knof.[6]

Nitration of 3β,17β-*Diacetoxy*-7-*norandrost*-5-*ene* **1**.—Fuming nitric acid (6 cm^3) was added dropwise to a stirred solution

Table 3 Crystal data and structure refinement details for compounds **2** and **3**

	2	**3**
Formula	$C_{22}H_{31}NO_7$	$C_{22}H_{31}N_2O_9$
M	421.5	467.5
Crystal system	Triclinic	Orthorhombic
Space group	$P\bar{1}$ (no. 1)	$P2_1P2_1P2_1$ (No. 19)
a, b, c (Å)	7.269(2), 7.353(2), 11.053(3)	9.994(4), 11.413(4), 20.366(5)
α, β, γ, (°)	94.40(2),107.08(2), 102.02(2)	90, 90, 90
V (Å^3)	546.3	2322.9
Z, D_c (g cm^{-3}), $F(000)$	1, 1.28, 226	4, 1.34, 996
μ (cm^{-1})	0.9	1.0
Mo-Kα-radiation	0.710 69	0.710 69
Crystal size (mm)	0.4 × 0.4 × 0.3	0.4 × 0.4 × 0.4
Reflections for calc. cell number, θ_{min}, θ_{max} (°)	25, 7, 10	25, 7, 10
Data reflection ranges	h 0 − 9, k −9 −9, l −14 −14	h 0 − 14, k 0 − 16, l 0 − 28
θ_{min} and θ_{max} (°)	2–28	2–30
Total unique reflections	2631	3810
Significant reflections	2433	2758
R	0.039	0.046
R'	0.049	0.059
($\Delta\rho$) max, min (e Å^{-3})	+0.21, −0.07	+0.18, −0.09

of 3β,17β-diacetoxy-7-norandrost-5-ene (1 g) in diethyl ether (12 cm^3) at −5 °C. After 25 min, at −5 °C, the temperature was raised to 10 °C and stirring was continued until brown fumes appeared (3 h). The mixture was diluted with water and extracted with diethyl ether. The extract was washed thoroughly with aqueous sodium hydrogen carbonate, water and then dried over sodium sulfate. The solvent was evaporated to give a yellow residue which was chromatographed on silica. Elution was started with 10% ethyl acetate–light petroleum and the amount of ethyl acetate in the eluent was increased gradually to afford the following: starting material (42 mg); 17β-acetoxy-6-nitro-7-norandrosta-3,5-diene **7** (10 mg) as a gum, m/z 346 (MH^+) and 330 (M^+ − 15); $\delta_H(CDCl_3)$ 0.94 and 0.96 (each 3 H, s, 18- and 19-H), 2.06 (3 H, s, OAc), 4.65 (1 H, t, J 8.9, 17-H), 6.34 (1 H, dt, J 9.8 and 3) and 6.85 (1 H, dd, J 1.3 and 9.8); ν_{max}/cm^{-1} 1740, 1605, 1547 and 1240. 3β,17β-diacetoxy-6-nitro-7-norandrost-4-ene **8** (24 mg) as a gum, m/z 359 (M − NO_2); $\delta_H(CDCl_3)$ 0.84 (3 H, s, 18-H), 1.03 (3 H, s, 19-H), 2.04 and 2.06 (each 3 H, s, OAc), 4.64 (1 H, t, J 8.8, 17-H), 5.43 (2 H, m, 3- and 6-H) and 5.68 (1 H, d, J 2.5, 4-H); ν_{max}/cm^{-1} 1747, 1636 and 1544. The following fraction gave 3β,17β-diacetoxy-6-nitro-7-norandrost-5-ene **9** (10 mg) as a gum, m/z 429 (M^+), $\delta_H(CDCl_3)$ 0.90 (3 H, s, 18-H), 1.02 (3 H, s, 19-H), 2.06 (6 H, s, OAc), 4.63 (1 H, t, J 8.8, 17-H) and 4.77 (1 H, tt, J 4.5 and 10.1, 3-H); ν_{max}/cm^{-1} 1730, 1628, 1552 and 1510. 3β,17β-diacetoxy-5,10-epoxy-6-nitro-5,10-seco-7-norandrost-5-ene **2** (114 mg) crystallized from ethyl acetate–light petroleum as cubes, m.p. 202–204 °C (Found: C, 62.7; H, 6.9; N, 3.2. $C_{22}H_{31}O_7N$ requires C, 62.7; H, 7.4; N, 3.3%); $\delta_H(CDCl_3)$ 0.87 (3 H, s, 18-H), 1.36 (3 H, s, 19-H), 2.05 and 2.07 (each 3 H, s, OAc), 3.12 (1 H, dd, J 14.5, 6.9, 8-H), 4.70 (1 H, t, J 8.8, 17-H), 4.85 [1 H, d (J 7) of t (J 8) of d (J 2), 3-H]; ν_{max}/cm^{-1} 1733, 1641, 1509 and 1236. 3β,17β-diacetoxy-6α-nitro-5β-nitrooxy-7-norandrostane **3** (242 mg) which crystallized from ethyl acetate light petroleum as cubes, m.p. 176–178 °C (Found: C, 56.0; H, 6.4; N, 5.2. $C_{22}H_{32}O_9N_2$ requires C, 56.4; H, 6.9; N, 5.9%); $\delta_H(CDCl_3)$ 0.83 (3 H, s, 18-H), 1.05 (3 H, s, 19-H), 1.96 and 2.04 (each 3 H, s, OAc), 4.65 (1 H, t, J 7.6, 17-H), 5.18 (1 H, dd, J 6.6 and 6.3, 3-H) and 5.36 (1 H, d, J 9.3, 6β-H); ν_{max}/cm^{-1} 1736, 1693, 1542, 1255 and 1233. 3β,17β-diacetoxy-6α-nitro-5α-nitrooxy-7-norandrostane **4** (39 mg) as a gum, m/z 359 (M − HNO_3 − NO_2) and 299 (M − HNO_3 − NO_2-HOAc); $\delta_H(CDCl_3)$ 0.83 (3 H, s, 18-H), 1.03 (3 H, s, 19-H), 2.02 and 2.05 (each 3 H, s, OAc), 4.67 (1 H, t, J 7.8, 17-H), 5.04 (1 H, tt, J 9.2, 4.6, 3-H) and 5.85 (1 H, d, J 9.5, 6-H); ν_{max}/cm^{-1} 1733, 1635, 1559 and 1545. 3β,17β-diacetoxy-5α-nitro-6β-nitrooxy-7-norandrostane **5** (51 mg) which crystallized from ethyl acetate–light petroleum as needles, m.p. 220–223 °C (Found: C, 56.6; H, 7.0; N, 5.8. $C_{22}H_{32}O_9N_2$ requires C, 56.4; H, 6.9; N, 5.9%); $\delta_H(CDCl_3)$ 0.88 (3 H, s, 18-H), 1.05 (3 H, s, 19-H), 2.04 and 2.06 (each 3 H, s, OAc), 4.45 (1 H, d, J 7.0, 6-H), 4.65 (1 H, t, J 7.5 Hz, 17-H) and 5.26 (1 H, tt, J 10.6, 4.9, 3-H); ν_{max}/cm^{-1} 1737, 1729, 1543 and 1238. 3β,17β-diacetoxy-5β-nitro-6α-nitrooxy-7-norandrostane **6** (72 mg) as a gum, m/z 406 (M − NO_3); $\delta_H(CDCl_3)$ 0.88 (3 H, s, 18-H), 1.07 (3 H, s, 19-H), 2.05 and 2.06 (each 3 H, s, OAc), 4.21 (1 H, d, J 9.7, 6-H), 4.63 (1 H, t, J 8.9, 17-H) and 5.12 (1 H, tt, J 5.1 and 2.8, 3-H); ν_{max}/cm^{-1} 1713, 1551 and 1245.

Nitration of 3β-*Acetoxyandrost*-5-*en*-17-*one* **10**.—Fuming nitric acid (6 cm^3) was added dropwise over 10 min to a stirred solution of the steroid **10** (1 g) in diethyl ether (12 cm^3) at −5 °C. After 25 min at −5 °C, the temperature was allowed to rise to 10 °C and stirring was continued until brown fumes appeared (2 h). The reaction mixture was diluted with water and the product was extracted with diethyl ether. The extract was washed thoroughly with aqueous sodium hydrogen carbonate and water and then dried. The solvent was evaporated to give 3β-acetoxy-6-nitroandrost-5-en-17-one **11** (650 mg), m.p. 205–208 °C (Found: C, 66.2; H, 7.6; N, 3.7. $C_{21}H_{29}O_5N$ requires C, 65.6; H, 7.9; N, 3.6%); $\delta_H(CDCl_3)$ 0.90 (3 H, s, 18-H), 1.17 (3 H, s, 19-H), 2.04 (3 H, s, OAc) and 4.67 (1 H, tt, J 4.3 and 11.3, 3-H); ν_{max}/cm^{-1} 1735, 1527 and 1246.

Crystal Structure Determinations.—A summary of the crystal data and structure refinement details is given in Table 3. Data were collected using an Enraf-Nonius CAD4 diffractomer operating in the θ–2θ mode. Unique reflections were measured for $2 < \theta < 30°$ and those reflections with $|F^2| > 2\sigma(F^2)$ were used in the refinement where $\sigma(F^2) = [\sigma^2(I) + (0.04I)^2]^{\frac{1}{2}}/L_p$. Structures were solved by direct methods using SHELXS-86. Refinement was by full-matrix least-squares with non-hydrogen atoms anisotropic and a weighting scheme of $w = 1/\sigma^2(F)$. Hydrogen atoms were given fixed isotropic thermal parameters of $U_{iso} = 1.3\ U_{eq}$ for the parent atom. Programs were from the Enraf-Nonius MoLEN package. Fractional atomic coordinates and bond lengths and angles for compounds **2** and **3** have been deposited with the Cambridge Crystallographic Data Centre.*

* For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 1*, 1994, Issue 1.

Acknowledgements

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