The Bromination of Some B-Norandrost-5-enes. X-Ray Molecular Structure of 17β-Acetoxy-4β,6α-dibromo-5β-methyl-7,19-dinorandrost-9(10)-ene

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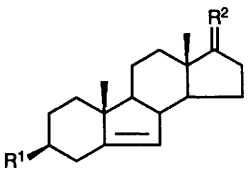
Bromination of 17β-acetoxy-7-norandrost-5-ene gave 17β-acetoxy-6-bromo-7-norandrost-5-ene and a rearrangement product, 17β-acetoxy-4β,6α-dibromo-5β-methyl-7,19-dinorandrost-9(10)-ene, the structure of which was established by X-ray crystallography. Bromination of 3β-hydroxy-7-norandrost-5-en-17-one gave 6-bromo-7-norandrosta-3,5-dien-17-one and 6-bromo-3β-hydroxy-7-norandrost-5-en-17-one.

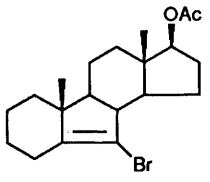
The stereochemical analysis of many reactions of steroidal alkenes is based on the results obtained with the 2(3)- and 5(6)-enes. However, a number of the reported reactions of the cyclopentenoid B-norsteroidal 5(6)-enes do not appear to follow the pattern shown in the six-membered series. For example, in the normal series the *trans*-diaxial addition of bromine to a Δ^5-steroid, which leads to the formation of a relatively stable 5α,6β-dibromide, is well documented.[1] Although this dibromide subsequently undergoes epimerization to the 5β,6α-dibromide, it is sufficiently stable to be used to protect the Δ^5-double bond whilst vigorous oxidation occurs elsewhere in the molecule. However, the sparse reports[2] of the addition of bromine to the corresponding B-norsteroids mention the formation of products that rapidly decompose at room temperature. This remarkable contrast led us to re-examine the products of the addition of bromine to the Δ^5-7-norsteroids.

Treatment of 17β-acetoxy-7-norandrost-5-ene† (**1**)[3] with bromine in chloroform at −60 °C gave a mono- (**4**) and a dibromo compound (**5**). The former, $C_{20}H_{27}BrO_2$, did not show CH(Br) or alkene CH resonances in the ^{1}H NMR spectrum, whilst its ^{13}C NMR spectrum possessed signals at δ_C 116.2 and 147.9 which were assigned to a bromo alkene. Consequently the compound was formulated as having structure (**4**). The second compound contained two CH(Br) as well as the C*H*(OAc) signals in the ^{1}H NMR spectrum, whilst its ^{13}C NMR spectrum revealed the presence of a fully substituted alkene moiety (δ_C 130.82 and 135.17). Although one CH(Br) signal (δ_H 4.46) was a doublet (*J* 5.1 Hz) establishing the presence of a bromine atom at C-6, the other CH(Br) signal was partially obscured by the 17-H resonance and hence it was difficult to locate the second bromine atom. The structure and stereochemistry of the compound, which is shown in Figure 1, was therefore established by X-ray crystallography.

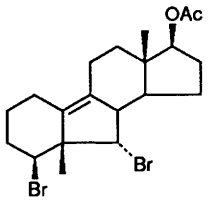
Treatment of 3β-hydroxy-7-norandrost-5-en-17-one (**2**) with bromine in chloroform at −60 °C gave a mixture from which it was possible to isolate a bromo diene (**6**) and the bromo alcohol (**7**) by careful chromatography. The bromo diene (**6**) showed alkene ^{13}C NMR signals at δ_C 120.83 (CH), 132.15 (CH), 122.78 (C), and 116.45 (C). The ^{1}H NMR spectrum had alkene CH signals at δ_H 6.23 (1 H, d, *J* 10 Hz) and 5.95 (1 H, m) but no signals for a CH(Br). The compound retained the two aliphatic tertiary *C*-methyl signals, at δ_H 0.88 and 0.95. The UV spectrum had an absorption at λ_{max} 240 nm, corresponding to the chromophore CH=CH–C=C(Br). Hence the compound was assigned the structure (**6**). On occasions this compound was contaminated by the aromatic compound (**9**). The second product to be isolated from the bromination reaction was the bromo alkene (**7**). This compound showed the alkene ^{13}C signals at δ_C 117.2 and 146.6 (both fully substituted), indicative



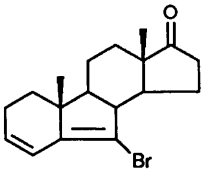
(**1**) R^1 = H, R^2 = α-H, β-OAc
(**2**) R^1 = OH, R^2 = O
(**3**) R^1 = OAc, R^2 = O



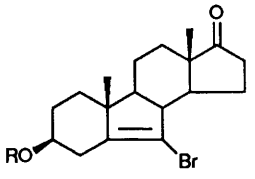
(**4**)



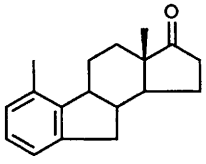
(**5**)



(**6**)



(**7**) R = H
(**8**) R = Ac



(**9**)

of the C=C(Br) system, whilst it retained the C*H*(OH) proton resonance at δ_H 3.58. On acetylation it gave an acetate (**8**). Treatment of the 3β-acetate (**3**)[4] with bromine in chloroform at −60 °C gave an unstable oil from which, after extensive chromatography, it was only possible to isolate the bromo diene (**6**) contaminated with the aromatic compound (**9**) as decomposition products.

† 7-Norandrost-5-en-17β-yl acetate.

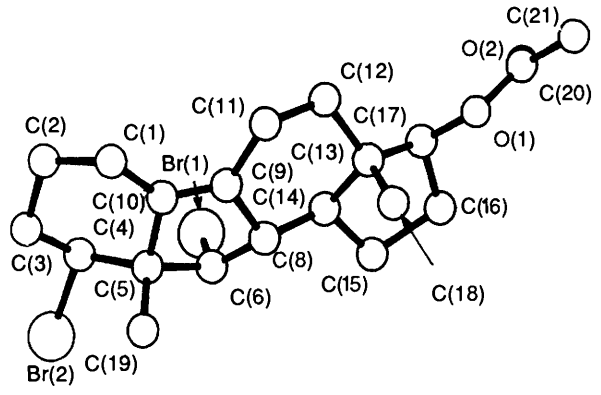
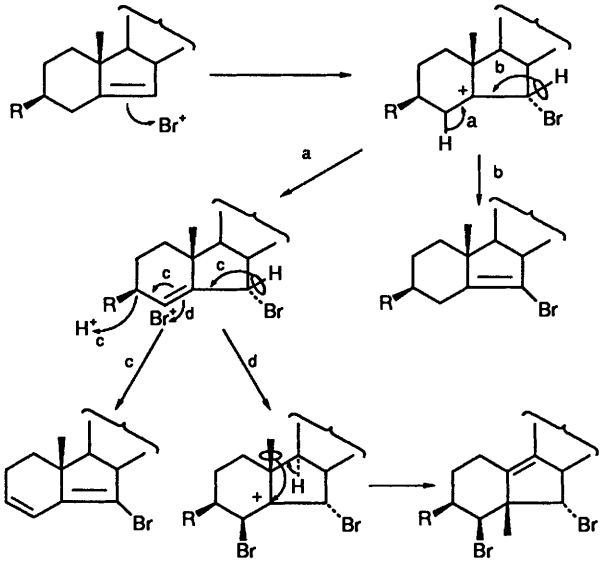


Figure 1. X-Ray structure of 17β-acetoxy-4β,6α-dibromo-5β-methyl-7,19-dinorandrost-9(10)-ene (**5**).

There is a marked contrast between these results and those obtained with normal androst-5-enes. In the normal series the predilection for diaxial addition leads to the 5α,6β-diaxial dibromide. However, such a 5α,6β-diaxial geometry is not possible in the B-nor series, and attack of the bromonium ion occurs from the α-face to form a 6α-bromo steroid.[2] The C-5β position is hindered by the adjacent methyl group and the formation of the various products may be rationalized in terms of the collapse of a C-5 carbocation. Thus loss of a proton leads to Δ^4- and Δ^5-compounds. Further bromination at C-4 may regenerate the C-5 carbocation and initiate the rearrangement of the methyl group. Alternatively loss of a 3-substituent may lead to the bromo diene. This probable mechanism is summarized in the Scheme.



Scheme.

Experimental

Silica for chromatography was Merck 9385. Light petroleum refers to the fraction boiling in the range 60–80 °C. Extracts were dried over sodium sulphate. IR spectra were determined for Nujol mulls, and ^{1}H NMR spectra were determined in deuteriochloroform solution at 360 MHz on a Bruker WM 360 spectrometer. The B-norsteroids were prepared by the method of Knof.[5,6]

Bromination of 17β-*Acetoxy*-7-*norandrost*-5-*ene* (**1**).—A solution of 17β-acetoxy-7-norandrost-5-ene[3] (**1**) (500 mg) in chloroform (10 ml) was treated with bromine (0.1 ml) whilst being cooled in an acetone–solid carbon dioxide-bath until the colour of bromine was discharged. The cold solution was diluted with chloroform, washed with aq. sodium hydrogen carbonate, and dried. The solvent was evaporated off at 30 °C to give a gum, which was chromatographed on silica. Elution with light petroleum gave 17β-*acetoxy*-6-*bromo*-7-*norandrost*-5-*ene** (**4**) (150 mg), which was crystallized from acetone as needles, m.p. 108–110 °C (Found: C, 60.0; H, 7.2. $C_{20}H_{29}BrO_2 \cdot H_2O$ requires C, 60.1; H, 7.8%); ν_{max} 1 746 and 1 633 cm^{-1}; δ 0.84, 0.88, and 2.04 (each 3 H, s) and 4.63 (1 H, t, *J* 7.6 Hz). Further elution, with 2% ethyl acetate–light petroleum gave 17β-*acetoxy*-4β,6α-*dibromo*-5β-*methyl*-7,19-*dinorandrost*-9(10)-*ene*† (**5**) (50 mg), which was crystallized from ethyl acetate–light petroleum as cubes, m.p. 148–149 °C (Found: C, 51.9; H, 6.2. $C_{20}H_{28}Br_2O_2$ requires C, 52.2; H, 6.1%); ν_{max} 1 735 cm^{-1}; δ 0.86, 1.28, and 2.05 (each 3 H, s), 4.46 (1 H, d, *J* 5.1 Hz), and 4.67 (2 H, overlapping multiplets).

Bromination of 3β-*Hydroxy*-7-*norandrost*-5-*en*-17-*one* (**2**).—A solution of 3β-hydroxy-7-norandrost-5-en-17-one[4] (**2**) (1 g) in chloroform (20 ml) was treated with bromine (0.2 ml) while being cooled in an acetone–solid carbon dioxide-bath until the bromine colour was discharged. The solution was diluted with chloroform, washed successively with aq. sodium hydrogen carbonate and water, and dried. The solvent was evaporated off and the residue was chromatographed on silica. Elution with 20% ethyl acetate–light petroleum gave 6-*bromo*-7-*norandrosta*-3,5-*dien*-17-*one* (**6**) (200 mg), which was crystallized from ethyl acetate–light petroleum as needles, m.p. 170–173 °C (Found: C, 63.6; H, 6.95. $C_{18}H_{23}BrO$ requires C, 64.4; H, 6.9%); ν_{max} 1 734 cm^{-1}; λ_{max}(EtOH) 240 nm; δ 0.88 and 0.95 (each 3 H, s), 5.95 (1 H, br m), and 6.23 (1 H, d, *J* 10 Hz). Further elution, with 30% ethyl acetate–light petroleum, gave 6-*bromo*-3β-*hydroxy*-7-*norandrost*-5-*en*-17-*one* (**7**) (400 mg), which was crystallized from ethyl acetate–light petroleum as needles, m.p. 213–217 °C (Found: C, 61.1; H, 7.2. $C_{18}H_{25}BrO_2$ requires C, 61.1; H, 7.1%); ν_{max} 3 468, 1 725, and 1 634 cm^{-1}; δ 0.95 (6 H, s), 3.58 (1 H, t, *J* 11 Hz of t, *J* 4.5 Hz).

On acetylation with acetic anhydride in pyridine, compound (**7**) gave 3β-*acetoxy*-6-*bromo*-7-*norandrost*-5-*en*-17-*one*‡ (**8**), m.p. 140–142 °C (Found: C, 58.2; H, 7.0. $C_{20}H_{27}BrO_3 \cdot H_2O$ requires C, 58.2; H, 7.1%); δ 0.93, 0.95, and 2.05 (each 3 H, s), 4.65 (1 H, t, *J* 11.5 Hz of t, *J* 4.5 Hz). A small quantity of 1-methyl-7-noroestra-1,3,5(10)-trien-17-one (**9**) was detected by its ^{1}H NMR spectrum: δ (90 MHz) 0.91 (3 H, s), 2.38 (3 H, s), and 7.05 (3 H, m), but was not further purified.

Bromination of 3β-*Acetoxy*-7-*norandrost*-5-*en*-17-*one* (**3**).—A solution of 3β-acetoxy-7-norandrost-5-en-17-one (**3**)[4] (1 g) in chloroform (20 ml) was treated with bromine (0.2 ml) whilst being cooled in an acetone–solid carbon dioxide-bath until the colour was discharged. The products were recovered in chloroform, washed with aq. sodium hydrogen carbonate, and dried, and the solvent was evaporated off to give a gum, which was chromatographed on silica. Elution with 10% ethyl acetate–light petroleum gave an oil, ν_{max} 1 746 and 1 730 cm^{-1}; δ (90 MHz) 0.90, 1.25, 2.02, 4.95 (d, *J* 9 Hz), and 5.1 (m) (3β-acetoxy-5β,6α-dibromo-7-norandrostan-17-one?), which did not crystallize. After the product had been left for 3 days, further chromatography gave 6-bromo-7-norandrosta-3,5-dien-17-one (**6**) (100 mg) (identified by its ^{1}H NMR spectrum) as the only product

* 6-Bromo-7-norandrost-5-en-17β-yl acetate.
† 4β,6α-Dibromo-5β-methyl-7,19-dinorandrost-9(10)-en-17β-yl acetate.
‡ 6-Bromo-17-oxo-7-norandrost-5-en-3β-yl acetate.

Table. Fractional atomic co-ordinates (× 10^4) for compound (**5**).

Atom	*x*	*y*	*z*
Br(1)	4 210.6(31)	2 177.5(23)	2 775.9(11)
Br(2)	6 268.5(30)	3 230.4(32)	4 067.6(12)
O(1)	966(17)	4 389(13)	895(6)
O(2)	−1 054(22)	2 654(17)	346(7)
C(1)	552(27)	4 514(22)	4 034(10)
C(2)	1 240(29)	3 574(22)	4 479(9)
C(3)	3 086(25)	3 623(20)	4 530(9)
C(4)	3 895(24)	3 405(20)	3 983(8)
C(5)	3 413(23)	4 424(20)	3 522(8)
C(6)	3 804(25)	4 100(20)	2 905(8)
C(8)	2 442(24)	4 599(19)	2 579(8)
C(9)	1 021(25)	4 560(19)	2 982(7)
C(10)	1 556(24)	4 432(21)	3 508(8)
C(11)	−713(27)	4 683(19)	2 780(10)
C(12)	−990(29)	4 134(22)	2 207(10)
C(13)	332(25)	4 479(21)	1 789(9)
C(14)	2 033(24)	4 028(21)	2 011(8)
C(15)	3 113(30)	4 189(26)	1 519(10)
C(16)	2 034(32)	3 988(27)	988(12)
C(17)	316(26)	3 801(21)	1 241(9)
C(18)	287(26)	6 034(21)	1 715(9)
C(19)	4 059(33)	5 777(24)	3 662(9)
C(20)	−1 678(34)	3 729(26)	488(11)
C(21)	−3 053(35)	4 390(29)	195(11)

that could be obtained pure. Some further fractions contained 1-methyl-7-noroestra-1,3,5(10)-trien-17-one (**9**) (^{1}H NMR). TLC showed that these were not present in the initial product of bromination.

Crystal Structure Determination of Compound (**5**).—$C_{20}H_{28}Br_2O_2$, M = 460.3, orthorhombic, space group $P2_12_12_1$, a = 8.160(3), b = 10.069(10), c = 23.895(5) Å, V = 1 963.3 Å^3, Z = 4, D_c = 1.56 g cm^{-3}, $F(000)$ = 936, monochromated Mo-K_α radiation λ = 0.710 69 Å, μ = 41.0 cm^{-1}. Data were collected using a crystal *ca.* 0.2 × 0.2 × 0.05 mm on an Enraf-Nonius CAD 4 diffractometer in the θ–2θ mode with $\Delta\theta$ = (0.8 + 0.35 tan θ)° and a maximum scan time of 1 min. A total of 2 020 unique reflections were measured for $2 < \theta < 25°$ but diffraction was weak and only 660 reflections with $|F^2| > 3\sigma(F^2)$ where $\sigma(F^2) = \{\sigma^2(I) + (0.04\ I)^2\}^{\frac{1}{2}}/L_p$ were used in the refinement. A correction (max 1.24, min 0.54) for absorption was applied using DIFABS after isotropic refinement.[7]

The structure was solved by routine heavy-atom methods and refined by full-matrix least-squares with Br atoms anisotropic and C and O atoms isotropic. Hydrogen atoms, except those for C(21), were held fixed at calculated positions with $U_{iso} = 1.3\ U_{eq}$ for the atom to which they are bonded. The absolute structure, corresponding to that known on chemical grounds, was confirmed by refinement of the η-parameter.[8] The weighting scheme was $w = 1/\sigma 2(F)$ and the final residuals were R = 0.048, R' = 0.054. Programs were from the Enraf-Nonius SDP-Plus package and were run on a microVax II computer. Fractional atomic co-ordinates are given in the Table.*

* *Supplementary data* (see section 5.6.3 of Instructions for Authors, in the January issue). H-Atom co-ordinates, thermal parameters, bond lengths and angles, and torsion angles have been deposited at the Cambridge Crystallographic Data Centre.

Acknowledgements

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