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The Stereochemistry of Reactions of 5β-Androst-3-enes

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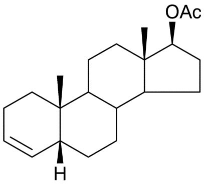
Spectroscopic and crystallographic studies shows that the epoxidation, osmylation and bromination of 17β-acetoxy-5β-androst-3-ene takes place from the β-face of the alkene and that a diequatorial dibromide and bromohydrin accompany the diaxial addition products.

During studies on the stereochemistry of hydroboration of androst-3-enes[1] we observed a marked contrast in the ratio of α to β-face addition between the 5α- and 5β-androstenes. Whilst the stereochemistry of the reactions of the 5α-epimer are dominated by transannular diaxial interactions on the β-face of ring A with the C-10β methyl group, those of the 5β-epimer are more likely to be directed by interactions on the α-face with ring B.[2–5]

The stereochemistry of the epoxide **2**, obtained from 17β-acetoxy-5β-androst-3-ene (**1**)[6] with *m*-chloroperbenzoic acid and of the glycol **4** obtained from 17β-hydroxy-17α-methyl-5β-androst-3-ene by osmylation, were established by X-ray crystallography. Bromination of **1** with bromine in carbon tetrachloride or bromine in glacial acetic acid, gave the same mixture of dibromo compounds **5** and **6** and a smaller amount of a tetrabromide **7**. The stereochemistry of the products were distinguished by the multiplicity of the CHBr resonances whilst that of **6** was confirmed by X-ray crystallography. Treatment of the alkene **1** with *N*-bromosuccinimide and perchloric acid gave the diaxial 3β-bromo-4α-hydroxy bromohydrin **8** as the major product together with a smaller amount of the diequatorial 4β-bromo-3α-hydroxy **9** isomer. Whilst the diaxial bromohydrin **8** possessed the H-3α resonance as a quartet (J 4 Hz) in the diequatorial epimer **9** this proton possessed an axial–equatorial coupling (J 6.3 Hz) and two diaxial couplings (J 9.6 and 11.8 Hz).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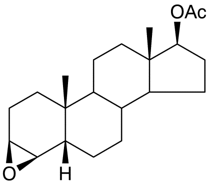
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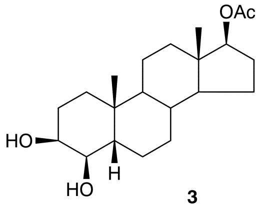
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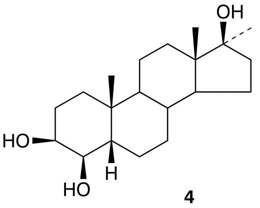
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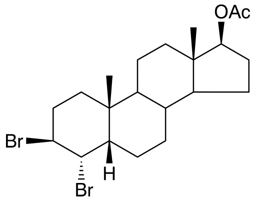
These reactions reveal the propensity of the 5β-androst-3-ene to attack from the β-face of the molecule and for the formation of diequatorial products which relieve the interactions on the α-face of the molecule.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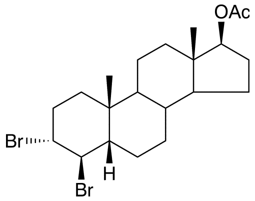
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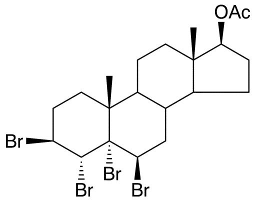
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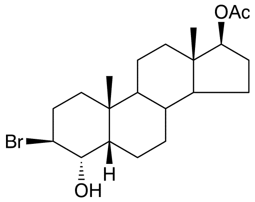
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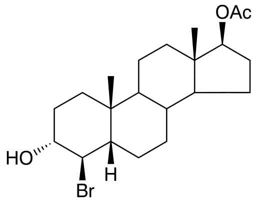
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Crystallographic Data and Structure Determination.—Compound **2**. $C_{21}H_{32}O_3$, $M_r = 332.5$, monoclinic, space group $P2_1$ (No. 4), $a = 7.731(7)$, $b = 10.801(6)$, $c = 11.152(5)$ Å, $\alpha = \gamma = 90°$, $\beta = 104.34(5)°$, $V = 902.2(10)$ Å^3, $Z = 2$, $D_{\text{calc}} = 1.22$ g cm^{-3}, $F(000) = 364$, monochromated Mo$K\alpha$ radiation, $\lambda = 0.71073$ Å, $\mu = 0.08$ mm^{-1}. Data were collected using a crystal size *ca.* $0.4 \times 0.3 \times 0.2$ mm on an Enraf-Nonius CAD4 diffractometer. A total of 1790 reflections were collected for $2 < \theta < 25°$ and $0 < h < 9$, $0 < k < 12$, $-13 < l < 12$, 1279 Reflections with $I > 2\sigma(I)$ were used in the refinement. There was no crystal decay and no absorption correction was applied.

The final R indices were $R_1 = 0.066$, $wR_2 = 0.163$ and R indices (all data) $R_1 = 0.088$, $wR_2 = 0.183$. The goodness of fit on F^2 was 1.07 and the maximum shift/e.s.d. was 0.001.

Compound **4**. $C_{20}H_{34}O_3$, $M_r = 322.5$, orthorhombic, space group $P2_12_12_1$ (No. 19), $a = 6.674(3)$, $b = 12.324(5)$, $c = 21.476(8)$ Å. $\alpha = \beta = \gamma = 90°$, $V = 1766.4(12)$ Å^3, $Z = 4$, $D_{\text{calc.}} = 1.21$ g cm^{-3}, $F(000) = 712$, monochromated Mo$K\alpha$ radiation, $\lambda = 0.71073$ Å, $\mu = 0.08$ mm^{-1}. Data were collected using a crystal size *ca.* $0.4 \times 0.4 \times 0.2$ mm on an Enraf-Nonius CAD4 diffractometer. A total of 1803 reflections were collected for $2 < \theta < 25°$ and $0 < h < 7$, $0 < k < 14$, $0 < l < 25$. 1445 Reflections with $I > 2\sigma(I)$ were used in the refinement. There was no crystal decay and no absorption correction was applied.

The final R indices were $R_1 = 0.045$, $wR_2 = 0.107$ and R indices (all data) $R_1 = 0.063$, $wR_2 = 0.118$. The goodness of fit on F^2 was 1.035 and the maximum shift/e.s.d. was 0.001.

Compound **6**. $C_{21}H_{32}Br_2O_2$, $M_r = 476.3$, orthorhombic, space group $P2_12_12_1$ (No. 19), $a = 7.580(3)$, $b = 9.666(4)$, $c = 28.529(6)$ Å.

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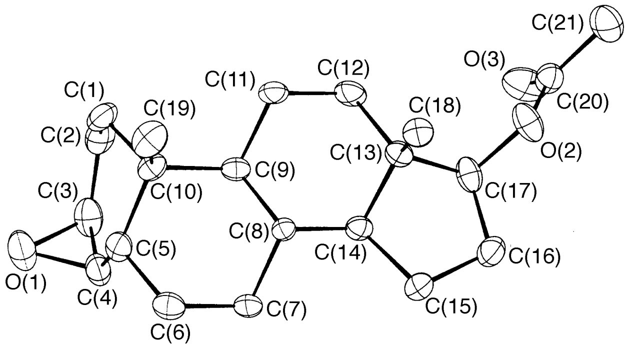

Fig. 1 X-Ray crystal structure of compound **2**

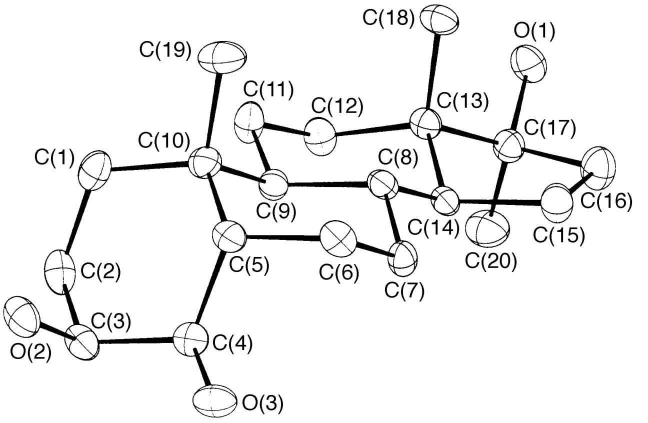

Fig. 2 X-Ray crystal structure of compound **4**

$\alpha = \beta = \gamma = 90°$, $V = 2090.3(13)$ Å^3, $Z = 4$, $D_{calc} = 1.51$ g cm^{-3}, $F(000) = 976$, monochromated MoKα radiation, $\lambda = 0.71073$ Å, $\mu = 0.08$ mm^{-1}. Data were collected using a crystal size *ca.* 0.4 × 0.4 × 0.4 mm on an Enraf-Nonius CAD4 diffractometer. A total of 3450 reflections were collected for $2 < \theta < 25°$ and $0 < h < 10$, $0 < k < 13$, $0 < l < 40$. 1547 Reflections with $I > 2\sigma(I)$ were used in the refinement. There was no crystal decay and no absorption correction was applied.

The final R indices were $R_1 = 0.089$, $wR_2 = 0.207$ and R indices (all data) $R_1 = 0.184$, $wR_2 = 0.278$. The goodness of fit on F^2 was 1.021 and the maximum shift/e.s.d. was 0.006.

The structures **2**, **4** and **6** were solved by direct methods using SHELXS-86[8] and SHELXL-93.[9] The non-hydrogen atoms were refined anisotropically by full matrix least-squares. Hydrogen atoms were included in riding mode with $U_{iso} = 1.2U_{eq}(C)$ or $1.5U_{eq}(C)$ for methyl groups.

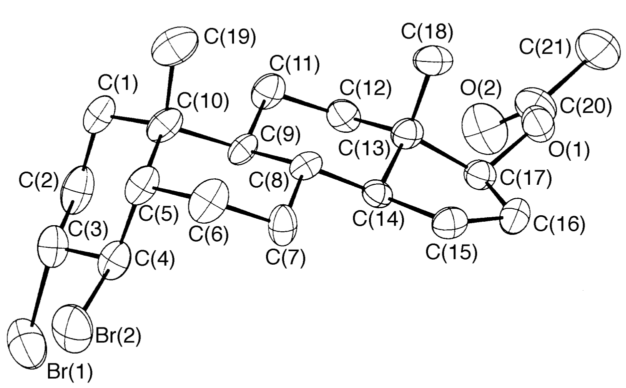

Fig. 3 X-Ray crystal structure of compound **6**

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Techniques used: ^{1}H NMR, IR, X-ray crystallography

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Appendix: Crystal data for **2**, **4** and **6**

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