

Regioselectivity in the Hydroboration of Steroidal Δ^3 -Allylic Alcohols†

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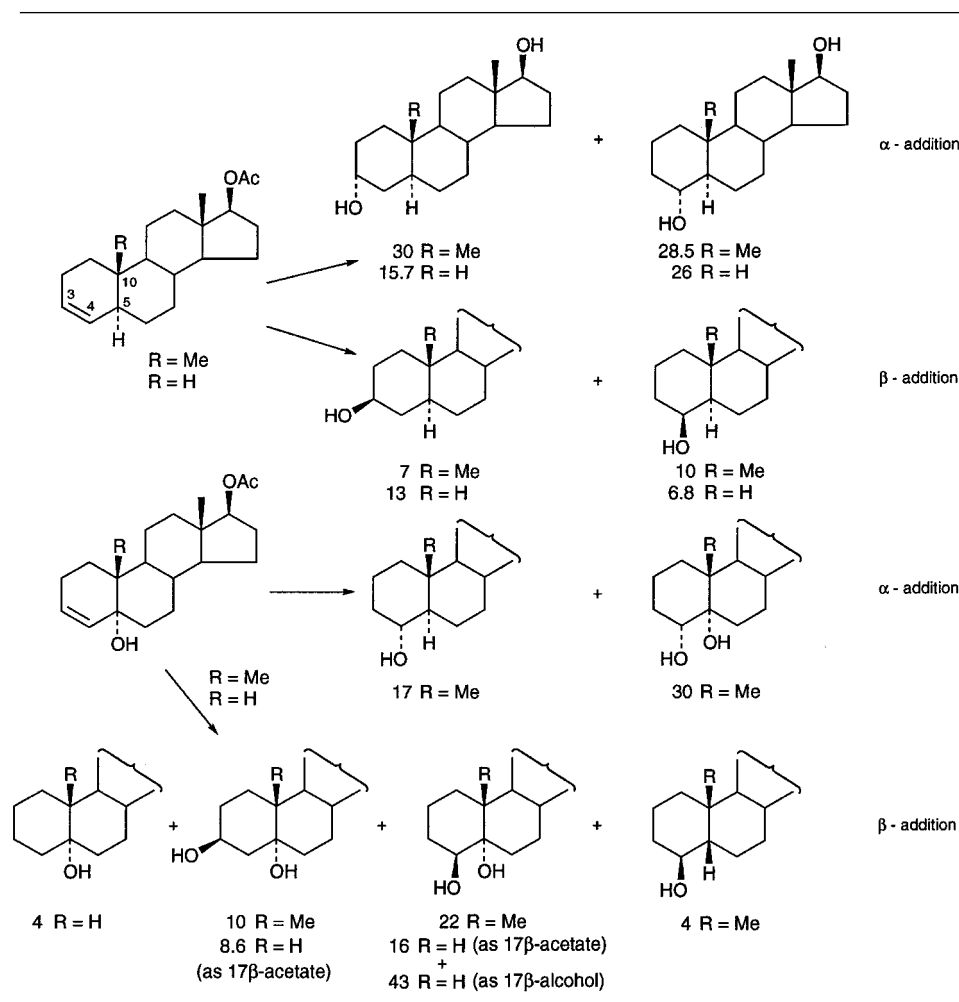
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The presence of an allylic 5 α -hydroxy group in an androst-3-ene increases the proportion of addition of a borane to the adjacent C-4 compared to the unsubstituted steroid and directs the addition to the face of the alkene *anti* to the hydroxy group with stereochemical effects that may oppose those of the C-10 β -methyl group.

Hydroboration proceeds in a *cis*-manner on the less-hindered face of an alkene with anti-Markownikoff regioselectivity.^{1,2} The directing effects of electronegative substituents in allyl derivatives modify the regiospecificity favouring addition of the borane at the 2-position.³ In cyclohex-2-en-1-ols, the hydroxy group also affects the stereospecificity and directs the addition of the borane to the opposite face of the alkene.⁴ Other directing effects in cyclic systems may arise from trans-annular diaxial interactions between the borane and sterically bulky groups. The relative contributions of these effects

The C-10 angular methyl group can also affect the stereochemistry of reactions of the disubstituted androst-3-enes. The absence of a Markownikoff effect can afford greater potential for an adjacent hydroxy group to modify both the regiochemistry and stereochemistry of hydroboration. The hydroboration of 17 β -acetoxy-5 α -hydroxyandrost-3-ene and 17 β -acetoxy-5 α -hydroxy-19-norandrost-3-ene was compared to 17 β -acetoxy-5 α -androst-3-ene and 17 β -acetoxy-19-nor-5 α -androst-3-ene to contrast the directing role of the 10 β -methyl group with that of the pseudo-axial 5 α -hydroxy group.

Table 1 Yields (%) of hydroboration products of androst-3-enes



require evaluation. In the steroid series, the directing effect of an allylic hydroxy group on the hydroboration of the tri-substituted alkene, androst-4-ene, is sufficient to overturn the normal directing effect of the C-10 methyl group.

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The results are shown in Table 1. The structures of the products were readily established from the multiplicity of the $\text{CH}(\text{OH})$ resonances in the ^1H NMR spectra⁶ and by comparison with literature data.⁷

The 5 α -hydroxy group increased the proportion of addition at C-4 in the hydroboration of androst-3-enes despite the fact that this is a more hindered position than C-3. The *trans* directing effect of the 5 α -hydroxy group opposed the steric hindrance of the 10 β -methyl group and increased the amount

of addition to the β -face of the 3-ene. In the case of the 19-nor steroid, lacking this methyl group, only products arising from addition to the β -face were obtained when a 5 α -hydroxy group was present. Comparison of the results of hydroboration of 5 α -hydroxyandrost-3-ene and the corresponding 19-nor steroid suggests that the 10 β -methyl group and the 5 α -hydroxy group have approximately equivalent directing effects.

Experimental

General experimental details have been described previously.⁵ Steroids were crystallized from ethyl acetate or acetone–light petroleum mixtures.

Hydroboration Experiments.—**17 β -Acetoxy-5 α -androst-3-ene.** The steroid (1 g) in dry THF (30 cm³) was treated with borane in THF (30 cm³, 1 M) for 4 h. Water (10 cm³) was added and the solution cooled to 0 °C. Aqueous sodium hydroxide (20 cm³, 10%) was added followed by the dropwise addition of hydrogen peroxide (20 cm³, 30%). The mixture was stirred overnight. Sodium sulfite (2 g) was added followed by acetic acid (1 cm³), water (50 cm³), dil. hydrochloric acid (50 cm³) and ethyl acetate (100 cm³). The organic layer was separated, washed with water, brine and then dried. The solvent was evaporated and the residue chromatographed on silica. Elution with 25% ethyl acetate–light petroleum gave successively (i) 3 β ,17 β -dihydroxy-5 α -androstane (64 mg), needles, mp 167–169 °C (lit.,⁷ 168–169 °C), $\nu_{\max}/\text{cm}^{-1}$ 3450, 3304; δ_{H} (3 H, s, 18-H), 0.79 (3 H, s, 19-H), 3.61 (2 H, m, 3 α - and 17 α -H); (ii) 4 α ,17 β -hydroxy-5 α -androstane (263 mg), prisms, mp 231–233 °C (lit.,⁸ 235–237 °C), $\nu_{\max}/\text{cm}^{-1}$ 3506, 3433; δ_{H} 0.73 (3 H, s, 18-H), 0.81 (3 H, s, 19-H), 3.45 (1 H, dt, J 4.6 and 10.5 Hz, 4 β -H), 3.63 (1 H, t, J 8.6 Hz, 17 α -H); (iii) 4 β ,17 β -dihydroxy-5 α -androstane (92 mg), needles, mp 179–181 °C (lit.,⁸ 176–178 °C), $\nu_{\max}/\text{cm}^{-1}$ 3490, 339; δ_{H} 0.72 (3 H, s, 18-H), 0.99 (3 H, s, 19-H), 3.62 (1 H, t, J 8.6 Hz, 17 α -H), 3.88 (1 H, m, 4 α -H); (iv) 3 α ,17 β -dihydroxy-5 α -androstane (278 mg), prisms, mp 220–223 °C (lit.,⁷ 222–224 °C), $\nu_{\max}/\text{cm}^{-1}$ 3490, 3400; δ_{H} 0.73 (3 H, s, 18-H), 0.79 (3 H, s, 19-H), 3.62 (1 H, t, J 8.6 Hz, 17 α -H), 4.05 (1 H, brs, 3 β -H).

17 β -Acetoxy-19-nor-5 α -androst-3-ene. The 19-nor steroid (1 g) gave (i) 4 β ,17 β -dihydroxy-19-nor-5 α -androstane (63 mg), needles, mp 167–169 °C (Found: C, 77.5; H, 10.8. C₁₈H₃₀O₂ requires C, 77.6; H, 10.9%); $\nu_{\max}/\text{cm}^{-1}$ 3305; δ_{H} 0.74 (3 H, s, 18-H), 3.64 (1 H, t, J 8.2 Hz, 17 α -H), 3.76 (1 H, brs, 4 α -H); (ii) 4 α ,17 β -dihydroxy-19-nor-5 α -androstane (240 mg), plates, mp 200–220 °C (Found: C, 77.5; H, 10.9. C₁₈H₃₀O₂ requires C, 77.5; H, 10.9%); $\nu_{\max}/\text{cm}^{-1}$ 3230; δ_{H} 0.75 (3 H, s, 18-H), 3.21 (1 H, td, J 10.5 and 4.6 Hz, 4 β -H), 3.64 (1 H, t, J 8.2 Hz, 17 α -H); (iii) 3 α ,17 β -dihydroxy-19-nor-5 α -androstane (145 mg), needles, mp 163 °C (Found: C, 77.6; H, 11.0. C₁₈H₃₀O₂ requires C, 77.6; H, 10.9%); $\nu_{\max}/\text{cm}^{-1}$ 3279; δ_{H} 0.72 (3 H, s, 18-H), 3.64 (1 H, t, J 8.2 Hz, 17 α -H), 4.12 (1 H, brs, 3 β -H); (iv) 3 β ,17 β -dihydroxy-19-nor-5 α -androstane (120 mg), needles, mp 141–143 °C (Found: C, 77.5; H, 10.7. C₁₈H₃₀O₂ requires C, 77.6; H, 10.9%); $\nu_{\max}/\text{cm}^{-1}$ 3348; δ_{H} 0.74 (3 H, s, 18-H), 3.57 (1 H, t, J 10.5 and 4.5 Hz, 3 α -H), 3.62 (1 H, t, J 8.1 Hz, 17 α -H).

17 β -Acetoxy-5 α -hydroxyandrost-3-ene. The 5 α -hydroxy steroid (1 g) gave 4 α ,17 β -dihydroxy-5 α -androstane (147 mg) and 4 β ,17 β -dihydroxy-5 α -androstane (30 mg) which were identified by their ¹H NMR spectra. Further chromatography gave 4 α ,5 α ,17 β -trihydroxyandrostane (90 mg), prisms, mp 219–220 °C (Found: C, 71.7; H, 10.3. C₁₉H₃₂O₃·0.5H₂O requires C, 71.9; H,

10.5%); $\nu_{\max}/\text{cm}^{-1}$ 3498, 3409, 3335; δ_{H} 0.73 (3 H, s, 18-H), 0.94 (3 H, s, 19-H), 3.65 (2 H, m, 4 β - and 17 α -H). The 4 α ,17 β -diacetate, prepared with acetic anhydride in pyridine, had mp 170–172 °C (Found: C, 70.7; H, 9.5. C₂₃H₃₆O₅ requires C, 70.4; H, 9.2%); $\nu_{\max}/\text{cm}^{-1}$ 3380, 1720; δ_{H} 0.71 (3 H, s, 18-H), 0.91 (3 H, s, 19-H), 1.96 and 1.99 (each 3 H, s, OAc), 4.51 (1 H, t, J 7.8 Hz, 17 α -H), 4.91 (1 H, dd, J 6.0 and 10.5 Hz, 4 β -H). Further chromatography gave 4 β ,5 α ,17 β -trihydroxyandrostane (281 mg), prisms, 223–225 °C (Found: C, 71.5; H, 10.3. C₁₉H₃₂O₃·0.5H₂O requires C, 71.9; H, 10.5%); $\nu_{\max}/\text{cm}^{-1}$ 3490, 3400, 3367; δ_{H} 0.74 (3 H, s, 18-H), 1.18 (3 H, s, 19-H), 3.54 (1 H, t, J 2.8 Hz, 4 α -H), 3.64 (1 H, t, J 8.4 Hz, 17 α -H). The 4 β ,17 β -diacetate, prepared with acetic anhydride in pyridine, had mp 181–183 °C (Found: C, 70.2; H, 9.0. C₂₃H₃₆O₅ requires C, 70.4; H, 9.2%); $\nu_{\max}/\text{cm}^{-1}$ 3240, 1740, 1720; δ_{H} 0.74 (3 H, s, 18-H), 1.10 (3 H, s, 19-H), 1.96 and 1.99 (each 3 H, s, OAc), 4.54 (1 H, t, J 7.8 Hz, 17 α -H), 4.65 (1 H, t, J 2.6 Hz, 4 α -H). Further elution gave 3 β ,5 α ,17 β -trihydroxyandrostane (201 mg), mp 192–194 °C (lit.,⁹ 193–196 °C).

17 β -Acetoxy-5 α -hydroxy-19-norandrost-3-ene. The 5 α -hydroxy-19-nor steroid (1 g) gave successively (i) 5 α ,17 β -dihydroxy-19-norandrostane (40 mg) as a gum, m/z 292 (M⁺), 274 (M–H₂O) 256 (M–2H₂O); $\nu_{\max}/\text{cm}^{-1}$ 3512; δ_{H} 0.75 (3 H, s, 18-H), 3.65 (1 H, t, J 8.2 Hz, 17 α -H); (ii) 17 β -acetoxy-4 β ,5 α -dihydroxy-19-norandrostane (160 mg), plates, mp 187–189 °C (Found: C, 71.3; H, 9.7. C₂₀H₃₂O₄ requires C, 71.4; H, 9.6%); $\nu_{\max}/\text{cm}^{-1}$ 3320, 1742; δ_{H} 0.78 (3 H, s, 18-H), 2.02 (3 H, s, OAc), 3.47 (1 H, t, J 3.0 Hz, 4 α -H), 4.58 (1 H, t, J 8 Hz, 17 α -H); (iii) 17 β -acetoxy-3 β ,5 α -dihydroxy-19-norandrostane (80 mg), needles, mp 218–220 °C (Found: C, 70.7; H, 9.6. C₂₀H₃₂O₄ requires C, 71.4; H, 9.6%); $\nu_{\max}/\text{cm}^{-1}$ 3358, 1720; δ_{H} 0.75 (3 H, s, 18-H), 2.04 (3 H, s, OAc), 3.98 (1 H, tt, J 9.6 and 4.5 Hz, 3 α -H), 4.62 (1 H, t, J 8.2 Hz, 17 α -H); (iv) 4 β ,5 α -17 β -trihydroxy-19-norandrostane (410 mg), prisms, 203–205 °C (Found: C, 71.5; H, 10.2. C₁₈H₃₀O₃·0.5H₂O requires C, 71.2; H, 10.3%); $\nu_{\max}/\text{cm}^{-1}$ 3450; δ_{H} 0.74 (3 H, s, 18-H), 3.48 (1 H, t, J 2.8 Hz, 4 α -H), 3.65 (1 H, t, J 8 Hz, 17 α -H).

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