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The Stereochemistry of an Elimination Reaction accompanying the Hydroboration of a Steroidal Allylic Alcohol†

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Deuterium labelling studies have shown that the facile elimination of the 5β-hydroxy group observed in the course of hydroboration of a 5β-hydroxyandrost-3-ene may involve a *trans* diaxial borane–borinate elimination coupled with a *syn* transfer of hydrogen from the borinate.

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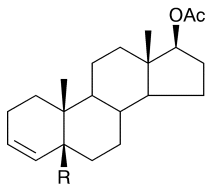
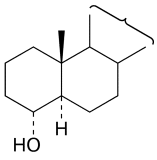
Derivatives of the allylic hydroxy group of crotyl alcohol have been shown[1] to have a significant effect on the regiochemistry of hydroboration in directing the addition of a significant proportion of the borane to the carbon atom adjacent to the hydroxy group. In cyclohex-2-en-1-ols the addition is directed to the face *anti* to the hydroxy group.[2] In the more rigid steroid series we have compared[3,4] the magnitude of these effects with other directing effects of the steroid skeleton such as the axial β-methyl group at C-10. In simpler systems such as the allyl alcohol derivatives,[1,5] the hydroboration may also be accompanied by an elimination reaction in which a mono-ol is formed as a consequence of a borane–borinate elimination reaction and further hydroboration of the resultant alkene. Both *cis* and *trans* mechanisms [see Scheme 1 (a) and (b)] were considered[5] for the elimination but at the time a distinction was not made between them. The 5β-hydroxy group of a 5β-hydroxyandrost-3-ene readily undergoes elimination, for example in the course of attempted methylation with silver oxide and methyl iodide and silylation with trimethylsilyl chloride. Products from an elimination reaction also formed significant components of the hydroboration of 17β-acetoxy-5β-hydroxyandrost-3-ene (**2**). A comparison of these with those obtained from the hydroboration of 17β-acetoxy-5β-androst-3-ene (**1**) has enabled us to examine the stereochemistry of the hydroboration and elimination reaction in this particular situation.



1 R = H
2 R = OH



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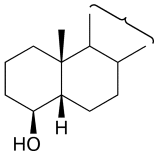
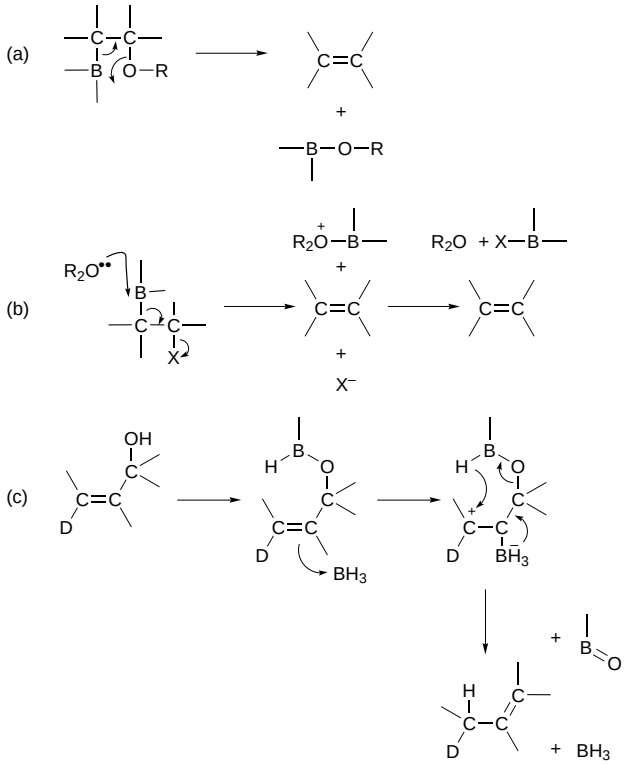


4

17β-Acetoxy-5β-androst-3-ene (**1**) was obtained from testosterone by a Wolff–Kishner reduction followed by acetylation.[6,7] 17β-Acetoxy-5β-hydroxyandrost-3-ene (**2**) was obtained by a Wharton reaction[8,9] with 17β-acetoxy-4β,5β-epoxyandrostan-3-one. The hydroboration–oxidation was carried out with alkaline hydrogen peroxide. The products were separated by chromatography on silica. The results are given in Table 1.



Scheme 1

The structures of the products were readily established from the multiplicity of their CH(OH) resonances in their ^{1}H NMR spectra[10] and by comparison with literature data.[11] In addition the 4α,17β-dihydroxy-5α-androstane (**3**) was readily distinguished from the 4β,17β-dihydroxy-5β-androstane (**4**) by an NOE experiment in which the signal from the 4β-hydrogen (δ_H 3.45) in **3** was enhanced (6.8%) by irradiation of the C-10β methyl group. There was no enhancement of the comparable CH(OH) signal in **4**.

Hydroboration of the 17β-acetoxy-5β-androst-3-ene took place predominantly from the β-face with a small proportion adding from the α-face. The amount of 4β-addition remained essentially the same between the two alkenes. However despite the fact that there is an established propensity[2–4] for an allylic hydroxy group to direct the incoming borane to the *anti* face, no 4α,5β-diols were detected from the hydroboration of 17β-acetoxy-5β-hydroxyandrost-3-ene (**2**). There was in their place a substantial amount of material that had arisen by elimination of the 5β-hydroxy group and rehydroboration of the resultant 4-ene. This would indicate that it is a 4α-borane adduct, which possesses a *trans* diaxial relationship to the

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Table 1 Hydroboration of 5β-androst-3-enes

Substrate	Product	Yield (%)
17β-Acetoxy-5β-androst-3-ene (**1**)	3α,17β-dihydroxy-5β-androstane	11
	3β,17β-dihydroxy-5β-androstane	29
	4α,17β-dihydroxy-5β-androstane	5.5
	4α,17β-dihydroxy-5β-androstane	31.5
17β-Acetoxy-5β-hydroxyandrost-3-ene (**2**)	17β-hydroxy-5α-androstane	3
	4α,17β-dihydroxy-5α-androstane (**3**)	41
	4β,17β-dihydroxy-5β-androstane (**4**)	6
	3α,5β,17β-trihydroxyandrostane	22
	4β,5β,17β-trihydroxyandrostane	27

5β-hydroxy group, that is participating in the elimination reaction.

The stereochemistry of this process was studied further by examining the fate of a deuterium atom at C-3 in the substrate. 3-Deuterio-5β,17β-dihydroxyandrost-3-ene was prepared by carrying out the Wharton reaction with deuteriohydrazine. The ^{1}H NMR spectrum of the product established the presence of deuterium at C-3. The 4-H resonance at δ_H 5.53 now appeared as a singlet whilst there was no signal at δ_H 5.81 corresponding to H-3. The hydroboration and oxidation were repeated. In the ^{1}H NMR spectra of the resultant deuteriated C-4 alcohols **3** and **4**, the 4-H signal in **3** (δ_H 3.42) had collapsed from a triplet (*J* 10.7 Hz) of doublets (*J* 4.5 Hz) to a doublet (*J* 10.7 Hz) of doublets (*J* 4.5 Hz), whilst in **4** the 4-H signal (δ_H 3.87) had changed from a triplet (*J* 10.7 Hz) of doublets (*J* 5.1 Hz) to a triplet (*J* 10.7 Hz). In both cases the C-3 deuterium atom had taken up the C-3α configuration. A plausible explanation for these results is given in Scheme 1(c). A borinate ester is formed from the 5β-hydroxy group. The borane then adds to the *anti* face at C-4 but undergoes a facile *trans* diaxial borane–borinate elimination with the internal transfer of hydride from the borinate group. Thus the hydrogen atom which was introduced at C-3 was on the same side of the molecule as the departing 5β-hydroxy group. Part of the driving force for this particularly facile elimination may be the relief of interactions between the 4α-substituent and the α-face of ring B in a 5β-steriod. The hydration that is observed at C-4 has taken place from the β-face of the molecule where these steric factors do not apply. In this particular situation the steric constraints of the ring system have dominated the *anti*-directing effect of the hydroxy group.

Experimental

General experimental details have been described previously.[3] Steroids were recrystallized from ethyl acetate–petrol mixtures. 17β-Acetoxy-5β-androst-3-ene (**1**), prepared from 17β-hydroxyandrost-4-en-3-one by reduction with hydrazine hydrate and acetylation had mp 139–142 °C (lit.,[6] 138–140 °C) whilst 17β-acetoxy-5β-hydroxyandrost-3-ene (**2**) prepared by reduction of 17β-acetoxy-4β,5β-epoxyandrostan-3-one with hydrazine hydrate had mp 119–121 °C (lit.,[9] 118–119 °C). 3-Deuterio-5β,17β-dihydroxyandrost-3-ene had mp 157–159 °C; δ_H ($CDCl_3$) 0.75 (3 H, s, 18-H), 1.00 (3 H, s, 19-H), 3.63 (1 H, t, *J* 8.5 Hz, 17α-H), 5.53 (1 H, s, 4-H).

Hydroboration Experiments.—(*a*) 17β-Acetoxy-5β-androst-3-ene (2 g) in dry tetrahydrofuran (50 cm^3) was treated with 1 M borane in tetrahydrofuran (40 cm^3) at 0 °C under nitrogen for 4 h. Water (20 cm^3) was added carefully and the solution was then maintained at 0 °C whilst 10% aqueous sodium hydroxide (40 cm^3) was added dropwise followed by 30% hydrogen peroxide (50 cm^3). The mixture was left to stir overnight. Sodium sulfite (2 g), acetic acid (1 cm^3), water (50 cm^3), dilute hydrochloric acid (50 cm^3) and ethyl acetate (100 cm^3) were then added. The stirring was continued for a further 15 min. The organic layer was washed with water and brine and dried over sodium sulfate. The solvent was evaporated to give a gum which was chromatographed on silica. Elution with 25% ethyl acetate–light petroleum gave successively (i) 4α,17β-dihydroxy-5β-androstane (102 mg), prisms, mp 232–234 °C (lit.,[12] 235–237 °C), δ_H ($CDCl_3$) 0.74 (3 H, s, 18-H), 0.81 (3 H, s, 19-H), 3.45 (1 H, dt, *J* 4.6 and 10.6 Hz, 4B-H), 3.63 (1 H, t, *J* 8.6 Hz, 17α-H); (ii) 3β,17β-dihydroxy-5β-androstane (541 mg), needles, mp 162–164 °C (lit.,[11] 165–167 °C), δ_H ($CDCl_3$) 0.71 (3 H, s, 18-H), 0.96 (3 H, s, 19-H), 3.61 (1 H, t, *J* 8.6 Hz, 17α-H), 4.08 (1 H, pent, *J* 4.3 Hz, 3α-H); (iii) 4β,17β-dihydroxy-5β-androstane (**4**) (580 mg), needles, mp 176–178 °C (lit.,[12] 177–178 °C), δ_H ($CDCl_3$) 0.73 (3 H, s, 18-H), 0.99 (3 H, s 19-H), 3.64 (1 H, t, *J* 8.6 Hz, 17α-H), 3.87 (1 H, dt, *J* 5.1 and 10.7 Hz, 4α-H); and (iv) 3α,17β-dihydroxy-5β-androstane (204 mg), prisms, mp 236–238 °C (lit.,[11] 237–238 °C), δ_H ($CDCl_3$) 0.73 (3 H, s, 18-H), 0.94 (3 H, s, 19-H), 3.64 (2 H, m, 3β- and 17α-H).

(*b*) Under similar conditions 17β-acetoxy-5β-hydroxyandrost-3-ene (1 g) gave successively (i) 17β-hydroxy-5α-androstane (31 mg), plates, mp 163–165 °C (lit.,[11] 164–166 °C), δ_H ($CDCl_3$) 0.73 (3 H, s, 18-H), 0.91 (3 H, s, 19-H), 3.64 (1 H, t, *J* 8.6 Hz, 17α-H); (ii) 4α,17β-dihydroxy-5α-androstane (**3**) (364 mg), needles, mp 231–233 °C (lit.,[12] 235–237 °C), δ_H ($CDCl_3$) 0.73 (3 H, s, 18-H), 0.81 (3 H, s, 19-H), 3.42 (1 H, dt, *J* 4.6 and 10.7 Hz), 3.63 (1 H, t, *J* 8.6 Hz); (iii) 4β,17β-dihydroxy-5β-androstane (**4**) (52 mg), mp 178–181 °C, identical with the material described above; (iv) 4β,5β,17β-trihydroxyandrostane (255 mg) prisms, mp 210–212 °C (Found: C, 73.3; H, 10.4. $C_{19}H_{32}O_3$ requires C, 74.0; H, 10.5%), ν_{max}/cm^{-1} 3403, 3375; δ_H ($CDCl_3$) 0.74 (3 H, s, 18-H), 0.97 (3 H, s, 19-H), 3.64 (1 H, t, *J* 8.5 Hz, 17α-H), 4.02 (1 H, dd, *J* 6.5 and 11.2 Hz, 4α-H); (v) 3α,5β,17β-trihydroxyandrostane, (203 mg), prisms, mp 237–239 °C (lit.,[11] 237–238 °C), δ_H ($CDCl_3$) 0.73 (3 H, s, 18-H), 0.96 (3 H, s, 19-H), 3.62 (1 H, t, *J* 8.6 Hz, 17α-H), 4.14 (1 H, broad s, 3β-H).

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