Regio- and Stereo-chemical Effects in the Hydroboration of Δ^2-Steroidal Allylic and Homoallylic Alcohols†

J. Chem. Research (S), 1997, 282–283†

James R. Hanson,* Mansur D. Liman and Sivajini Nagaratnam

School of Molecular Sciences, University of Sussex, Brighton, Sussex BN1 9QJ, UK

A comparison between the hydroboration of Δ^2-steroidal 1α-allylic and 5α-homoallylic alcohols reveals that whereas both have a stereochemical directing effect, only the allylic alcohol modifies the regiospecificity of the reaction.

An allylic hydroxy group has a significant effect on the products that are formed from an alkene by hydroboration and oxidation with alkaline hydrogen peroxide.[1–3] In cyclic systems a significant proportion of the addition takes place adjacent and *trans* to the hydroxy group of the allylic alchol.[4] These effects on regioselectivity may compete with the normal stereochemical directing effects of the steroid carbon skeleton.[5,6] In order to evaluate the relative significance of electronic and steric contributions, we compared the results of hydroboration of the α-oriented axial allylic alcohol, 17β-acetoxy-1α-hydroxy-5α-androst-2-ene (**2**) and the α-oriented axial homoallylic alcohol, 5α,17β-dihydroxy-5α-androst-2-ene (**3**). In both cases the axial hydroxy group is *trans* to the sterically directing 10β-methyl group.

The substrates were prepared by literature methods.[7,8,9] The hydroboration and oxidation reactions were carried out using 1 M borane in tetrahydrofuran followed by oxidation with alkaline hydrogen peroxide. The products were separated by chromatography on silica and the results are shown in Fig. 1. The structures of the products were established from the multiplicity of the CH(OH) resonances in the ^{1}H NMR spectrum[10] and by comparison with literature data.[11]

The axial 2β-H of 2α,17β-dihydroxy- and 2α,5α,17β-trihydroxy-5α-androstane appeared as a triplet (*J* 10.9 Hz) of triplets (*J* 4.6 Hz) indicative of two diaxial and two axial:equatorial couplings. In 17β-acetoxy-1α,2α-dihydroxy-5α-androstane and the corresponding triol, the 2β-H (δ_H 3.82 and 3.85 respectively) appeared as a doublet (*J* 10.9 Hz) of double-doublets (*J* 2.9 and 5.2 Hz). The 1β-H of the 17β-acetate was a doublet (δ_H 3.66, *J* 2.9 Hz). The smaller 1β:2α-coupling constant is probably indicative of a slightly different conformation of ring A brought about by hydrogen bonding in the

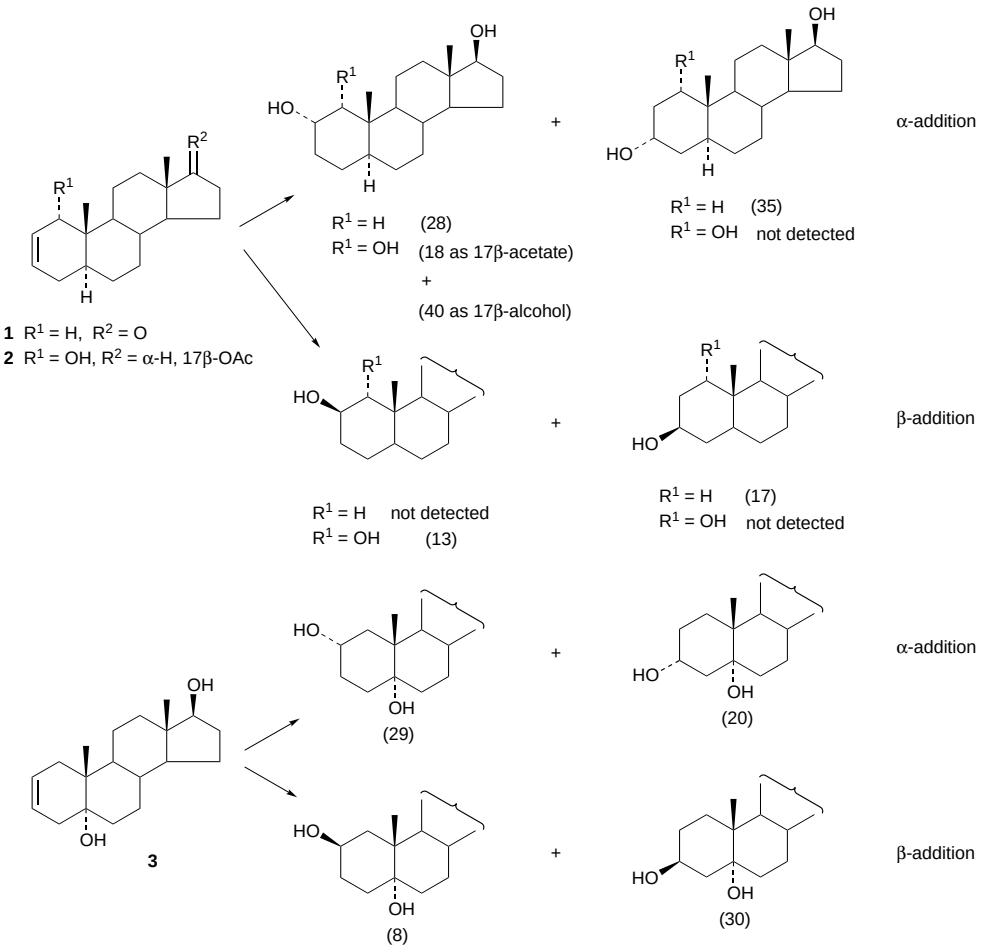

Fig. 1 Yields (%) of hydroboration products of androst-2-enes

*To receive any correspondence.

†This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1997, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.

1:2 glycol. The equatorial 2α-H signals were broad singlets. The 3α,17β- and 3β,17β-dihydroxy- and 3α,5α,17β- and 3β,5α,17β-trihydroxy-5α-androstanes were known compounds.[11–13]

The influence of the allylic hydroxy group on the regiochemistry of the reaction can be seen in the increased proportion of hydroboration of 17β-acetoxy-1α-hydroxy-5α-androst-2-ene at C-2 compared to the unsubstituted case. However the potential 1:3-diaxial interaction with the 10β-methyl group reduces the *trans* directing effect of the hydroxy group. On the other hand the homoallylic 5α-hydroxy group had relatively little effect on the position of the hydroboration but increased the proportion of β-face addition possibly through the formation of bulky borate esters on the α-face of the molecule.

Experimental

General experimental details have been described previously.[5] The steroids were crystallized from ethyl acetate or acetone:light petroleum mixtures. 5α-Androst-2-en-17-one (**1**) had mp 107–108 °C (lit.,[7] 108–109 °C). 17β-Acetoxy-1α-hydroxyandrost-2-ene, prepared by the treatment of 17β-acetoxy-1α,2α-epoxyandrostan-3-one with hydrazine hydrate,[8] had mp 131–133 °C (Found: C, 75.4; H, 9.8. $C_{21}H_{32}O_3$ requires C, 75.9; H, 9.7%), ν_{max}/cm^{-1} 3510, 1734; δ_H ($CDCl_3$) 0.72 (3 H, s, 18-H), 0.81 (3 H, s, 19-H), 2.04 (3 H, s, OAc), 3.71 (1 H, brs, 1β-H), 4.59 (1 H, t, *J* 8 Hz, 17α-H), 5.87 (2 H, s, 2- and 3-H). 5α,17β-Dihydroxyandrost-2-ene had mp 171–173 °C (lit.,[9] 171–172 °C).

Hydroboration Experiments.—(*a*) 5α-Androst-2-en-17-one (**1**) (1 g) in dry THF (30 cm^3) was treated with 1 M borane in THF (20 cm^3) under nitrogen at 0 °C for 4 h. Water (10 cm^3) was added and the solution was cooled. Aqueous 10% sodium hydroxide (20 cm^3) was added followed by the dropwise addition of 30% hydrogen peroxide (30 cm^3). The mixture was stirred overnight. Sodium sulfite (2 g) was added followed by acetic acid (1 cm^3), water (50 cm^3), dil. hydrochloric acid (100 cm^3) and ethyl acetate (100 cm^3). The mixture was stirred for a further 15 min. The organic phase was separated, washed with water, brine and dried. The solvent was evaporated to give a residue which was chromatographed on silica. Elution with 25% ethyl acetate:light petroleum gave 3α,17β-dihydroxy-5α-androstane (370 mg), prisms, mp 221–223 °C (lit.,[11] 222–224 °C). Elution with 28% ethyl acetate:light petroleum gave 3β,17β-dihydroxy-5α-androstane (180 mg), needles, mp 167–169 °C) (lit.,[11] 168 °C). Further elution with 30% ethyl acetate:light petroleum gave 2α,17β-dihydroxy-5α-androstane (302 mg), needles, mp 172–174 °C (Found: C, 77.7; H, 11.0. $C_{19}H_{32}O_2$ requires C, 78.0; H, 11.0%), ν_{max}/cm^{-1} 3490, 3382; δ_H ($CDCl_3$) 0.73 (3 H, s, 18-H), 0.80 (3 H, s, 19-H), 3.63 (1 H, t, *J* 8.6 Hz, 17α-H), 3.77 (1 H, tt, *J* 4.6 and 10.9 Hz, 2β-H).

(*b*) 17β-Acetoxy-1α-hydroxy-5α-androst-2-ene (**2**) (600 mg) in dry THF (20 cm^3) was treated with 1 M borane in THF (14 cm^3) and oxidized with aqueous sodium hydroxide and hydrogen peroxide as above. The product was chromatographed on silica. Elution with 20% ethyl acetate:light petroleum gave 17β-acetoxy-1α,2α-dihydroxy-5α-androstane (110 mg), needles, mp 113–114 °C (Found: C, 68.7; H, 9.5. $C_{21}H_{34}O_4$ requires C, 68.7; H, 9.8%), ν_{max}/cm^{-1} 3512, 1732; δ_H ($CDCl_3$) 0.77 and 0.78 (each 3 H, s, 18- and 19-H), 2.03 (3 H, s, OAc), 3.66 (1 H, d, *J* 2.9 Hz, 1β-H), 3.82 (1 H, ddd, *J* 2.9, 5.2 and 10.9 Hz, 2β-H), 4.56 (1 H, t, *J* 8.2 Hz, 17α-H). Irradiation of the signals at δ_H 0.77 and 0.78 caused an nOe enhancement of the resonances at δ_H 3.66 (3.1%) and 3.82 (6.5%). Further elution gave 1α,2β,17β-trihydroxy-5α-androstane (80 mg), needles, mp 152–155 °C (Found: C, 71.5; H, 10.6. $C_{19}H_{32}O_3\cdot 0\cdot 5H_2O$ requires C, 71.8; H, 10.5%), ν_{max}/cm^{-1} 3340; δ_H ($CDCl_3$) 0.74 (3 H, s, 18-H), 0.77 (3 H, s, 19-H), 3.65 (1 H, t, *J* 8.2 Hz, 17α-H), 3.74 (3 H, s, 1β-H), 4.11 (1 H, brs, 2α-H). Irradiation of the signal at δ_H 0.77 produced an nOe enhancement of the signal at δ_H 3.74 (1.9%). Further elution gave 1α,2α,17β-trihydroxy-5α-androstane (240 mg), needles, mp 140–142 °C (Found: C, 71.4; H, 10.3. $C_{19}H_{32}O_3\cdot 0\cdot 5H_2O$ requires C, 71.8; H, 10.5%), ν_{max}/cm^{-1} 3210; δ_H ($CDCl_3$) 0.74 (3 H, s, 18-H), 0.79 (3 H, s, 19-H), 3.64 (2 H, m, 1β- and 17α-H), 3.85 (1 H, ddd, *J* 2.9, 5.2 and 10.9 Hz, 2β-H).

(*c*) 5α,17β-Dihydroxyandrost-2-ene (1.2 g) was treated with 1 M borane in THF (20 cm^3) and oxidized with aqueous sodium hydroxide and hydrogen peroxide as above. The products were separated by chromatography on silica. Elution with 30% ethyl acetate:light petroleum gave 3α,5α,17β-trihydroxyandrostane (251 mg), plates, mp 193–195 °C (lit.,[12] 194–196 °C). Further elution gave 2β,5α,17β-trihydroxyandrostane (105 mg), needles, mp 207–209 °C (Found: C, 70.0; H, 11.0. $C_{19}H_{32}O_3\cdot H_2O$ requires C, 69.9; H, 10.5%), ν_{max}/cm^{-1} 3499, 3391, 3320; δ_H ($CDCl_3$) 0.74 (3 H, s, 18-H), 1.21 (3 H, s, 19-H), 3.65 (1 H, t, *J* 8.5 Hz, 17α-H), 4.18 (1 H, brs, 2α-H). Elution with 32% ethyl acetate:light petroleum gave 2α,5α,17β-trihydroxyandrostane (368 mg), prisms mp 201–202 °C (Found: C, 72.3; H, 10.8. $C_{19}H_{32}O_3\cdot 0\cdot 5H_2$) requires C, 71.9; 10.5%), ν_{max}/cm^{-1} 3501, 3405, 3310; δ_H ($CDCl_3$) 0.74 (3 H, s, 18-H), 1.00 (3 H, s, 19-H), 3.64 (1 H, t, *J* 8.4 Hz, 17α-H), 4.10 (1 H, tt, *J* 4.5 and 11 Hz, 2β-H). Finally elution with 35% ethyl acetate:light petroleum gave 3β,5α,17β-trihydroxy-androstane (386 mg), plates, mp 193–195 °C (lit.,[13] 194–105 °C).

S. N. thanks the Eastern University, Sri Lanka, for study leave and the British Council for financial assistance.

Received, 24th March 1997; Accepted, 22nd April 1997
Paper E/7/02014G

References

1 H. C. Brown and K. A. Keblys, *J. Am. Chem. Soc*., 1964, **86**, 1791.
2 H. C. Brown and O. J. Cope, *J. Am. Chem. Soc*., 1964, **86**, 1801.
3 H. C. Brown and R. M. Gallivan, *J. Am. Chem. Soc*., 1968, **90**, 2906.
4 E. Dunkelblum, R. Levene and J. Klein, *Tetrahedron*, 1972, **28**, 1009.
5 J. R. Hanson, P. B. Hitchcock, M. Liman and S. Nagaratnam, *J. Chem. Soc*., *Perkin Trans. 1*, 1995, 2183.
6 M. Alam, J. R. Hanson, M. Liman and S. Nagaratnam, *J. Chem. Res. (S)*, 1997, 56.
7 G. C. Wolf and R. T. Blikenstaff, *J. Org. Chem*., 1976, **41**, 1254.
8 P. S. Wharton and D. H. Bohlen, *J. Org. Chem*., 1961, **26**, 3616.
9 H. L. Holland, J. A. Roas and P. C. Chenchaiah, *J. Chem. Soc*., *Perkin Trans. 1*, 1988, 2027.
10 J. E. Bridgeman, P. C. Cherry, A. S. Clegg, J. M. Evans, Sir Ewart Jones, A. Kasal, V. Kumar, G. D. Meakins, Y. Morisawa, E. E. Richards and P. D. Woodgate, *J. Chem. Soc. (C)*, 1970, 250.
11 *Dictionary of Steroids*, ed. R. A. Hill, D. N. Kirk, H. L. Makin and G. M. Murphy, Chapman and Hall, London, 1992.
12 K. I. H. Williams, *Steroids*, 1963, **1**, 377.
13 S. Julia, P. A. Plattner and H. Heusser, *Helv. Chim. Acta*, 1952, **35**, 665.