SHORT PAPER

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The hydroboration of steroidal vinyl halides†

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The hydroboration of 2- and 3-dibromo and dichioromethylene 5α-androstanes has been shown to afford the 2β- and 3α- and 3β-hydroxymethyl-5α-androstanes respectively; a 3-chloro substituent changed both the regio- and stereochemistry of the hydroboration of a 3,5-diene.

Keywords: hydroboration, steroidal vinyl halides

Hydroboration is a widely used method for the anti-Markownikoff hydration of an alkene. The directing effect of the halogen of a vinyl halide has been shown to enhance the extent of addition of the borane to the carbon atom bearing the halogen.[1] Thus in simple situations such as the hydroboration of l-chloro-2-methylpropene, the reaction which proceeded more slowly than with the unsubstituted alkene, gave a C-l borane. The subsequent oxidation with alkaline hydrogen peroxide, led to the aldehyde, 2-methylpropanal.[2] In other systems[3,4] the reaction was accompanied by an α-group transfer involving migration of the halogen to the boron. Thus hydroboration of β-bromostyrene and oxidation with hydrogen peroxide gave 2-phenylethanol. In the light of these results, it was of interest to examine the hydroboration of steroidal exocyclic vinyl dihalides to see if both halogens were displaced from the alkenes and to compare the stereochemistry of the products with those of the hydroboration of the unsubstituted alkenes.[5] In this paper we report the hydroboration of the 2- and 3-bishalomethylene steroids (**1**, and **3**, R = CBr_2 and CCl_2).

The substrates were prepared by treatment of the corresponding 2- and 3-ketones (**1**, R = 0) and (**3**, R = 0) with triphenylphosphine and carbon tetrabromide or carbon tetrachloride in dichloromethane.[6] In the case of 5α-androstane-2,17-dione (**1**,R = 0)[7] only the less-hindered 2-ketone reacted and the products retained the characteristic cyclopentanone absorption at 1742–1745 cm^{-1}. Hydroboration of both 2-dibromomethylene-5α-androstan-l7-one (**1**, R = CBr_2) and 2-dichloromethylene-5α-androstan-l7-one (**1**, R = CCl_2) followed by oxidation of the product with alkaline hydrogen peroxide gave exclusively 17β-hydroxy-2β-hydroxymethyl-5α-androstane **2** (see Table 1). The product was identified by comparison with the sample obtained by hydroboration of 2-methylene-5α-androstan-17-one.[5] Hydroboration and oxidation of both 17β-acetoxy-3-dibromomethylene- and 17β-acetoxy-3-dichloromethylene-5α-androstane (**3**, R = CBr_2 and CCl_2) gave a separable mixture of 17β-hydroxy-3α- and 17β-hydroxy-3β-hydroxymethyl-5α-androstane **4** and **5**. These products were identified by comparison with authentic samples.[5]

These results parallel those obtained by hydroboration of the corresponding unsubstituted 2- and 3-methylene-5α-androstanes.[5] In particular the ratio of 3α:3β-hydroxymethyl compounds was similar suggesting that similar features may determine the stereochemistry of the products. The loss of both halogens may arise through an α-transfer mechanism.[3,4] Since dichloromethylene and dibromomethylene derivatives are readily obtained from the corresponding ketones under mild conditions, this preparation of hydroxymethyl compounds may offer an alternative to the classical Wittig reaction and hydroboration:oxidation sequence. In both cases the yields were better with the dibromomethylene-5α-androstanes.

Table 1 Hydroboration of 2- and 3-dihalomethylene steroids

substrate	product	yield/%
1 R = CBr_2	**2**	58
1 R = CCl_2	**2**	45
3 R = CBr_2	**4**	60
	5	32
3 R = CCl_2	**4**	58
	5	23

Comparison of the results of hydroboration of 17β-acetoxy-3-chloroandrosta-3,5-diene[8] **6** with those of the unsubstituted diene[9] revealed some additional effects of the halogen. The hydroboration of the chlorodiene was slow and a significant amount of the diene was unattacked although the C-17 acetate ester was reduced to the C-17 ethyl ether **7**. Whereas the unsubstituted 3,5-diene gave mainly (41%) 4,6-disubstituted products and a relatively small amount (11%) of a 3β, 6β-dihydroxy-5β-androstane, the major ring A/B diols obtained from the 3-chloro-3,5-diene were 3α,6β-dihydroxy-5β-androstanes (**8** and **9**)(37%). The stereochemistry of this diol was established by X-ray crystallography of the 3α,6β,17β-trihydroxy-5β-androstane (**9**)(Fig. 1). The formation of the 3α,6β-diol may be rationalised by the chlorine directing the addition of the borane to the C-3β position and then inversion of configuration taking place on the α-transfer.

Experimental

Silica for chromatography was Merck 9385. Light petroleum refers to the fraction, b.p.60–80°C. Extracts were dried over sodium sulfate. ^{1}H NMR spectra were determined at 300 MHz for solutions in deuteriochloroform. IR spectra were determined as nujol mulls.

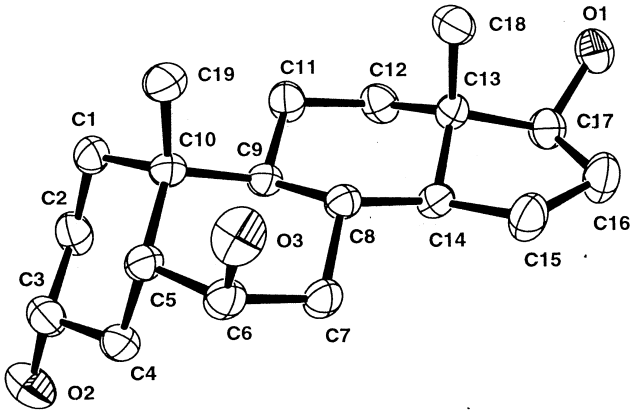

Fig.1 X-Ray crystal structure of compound **9**.

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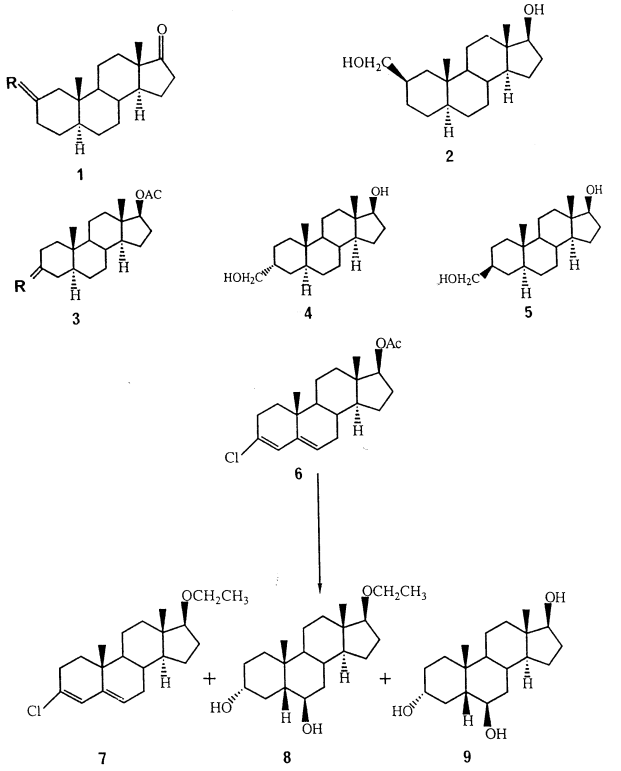
† This is a Short Paper, there is therefore no corresponding material in the *J Chem. Research (M).*



Scheme 1

Preparation of dihalomethylene steroids: (a) Triphenylphosphine (400 mg) was added to a well-stirred solution of carbon tetrabromide (250 mg) in dry dichloromethane (75 cm^3) to give an orange solution. 5α-Androstane-2,17-dione[7](**1**,R = 0) (200 mg) was added and the mixture was stirred for 3 hours. The solution was washed with water and the organic layer was separated and dried. The solvent was evaporated and the residue was chromatographed on silica. Elution with 2% ethyl acetate: light petroleum gave 2-dibromomethylene-5α-androstan-17-one (**1**,R = CBr_2)(180 mg), m.p.94–97°C, [Found: M^+ 442.052 $C_{20}H_{28}Br_2O$ requires M^+ 442.051 (based on ^{79}Br and ^{81}Br)], υ_{max}/cm^{-1} 1745, δ_H 0.79 and 0.80 (each 3H, s, H-18 and H-19), 0.64–2.40 (20H, overlapping multiplets), 2.50 (1H, d, *J* 14.5 Hz), 2.78 (1H, d, *J* 14.2 Hz) (1β and 3β-H).

(b) Under similar conditions 17β-acetoxy-5α-androstan-3-one (**3**, R = 0) (500 mg) gave 17β-acetoxy-3-dibromomethylene-5α-androstane (**3**, R = CBr_2) (410 mg), m.p.125–127°C, (Found: C, 54.6; H, 6.7. $C_{22}H_{32}Br_2O_2$ requires C,54.1; H, 6.6%), υ_{max}/cm^{-1} 1725, δ_H 0.75(3H,s,H-18), 0.82(3H,s,H-19), 1.96(3H,s,OAc), 0.80–2.10(20H, overlapping multiplets), 2.52 (1H,d,*J* 14.3 Hz), 2.77(1H,d, *J* 13.5 Hz),(2α and 4α-H), 4.56(1H,t, *J* 8.4 Hz, H-17).

(c) Triphenylphosphine (400 mg) was added to a well-stirred solution of carbon tetrachloride (20 cm^3) in dichloromethane (75 cm^3) to give an orange solution. 5α-Androstane-2,17-dione (**1**, R = O)(185 mg) was added and the mixture was stirred for 3 hours. The solution was washed with water, dried and the solvent evaporated to give a residue which was chromatographed on silica. Elution with 2% ethyl acetate: light petroleum gave 2-dichloromethylene-5α-androstan-17-one (**1**, R = CCl_2)(150 mg) as an oil, (Found: M^+354.215, $C_{20}H_{28}{}^{35}Cl_20$ requires 354.217) υ_{max}/cm^{-1} 1742, δ_H 0.77 and 0.79 (each 3H, s, H-18 and H-19), 0.66–2.40 (20H, overlapping multiplets), 2.48 (1H, d, *J* 14.4 Hz), 2.76 (1H, d, *J* 15.0 Hz), (1β and 3β-H).

(d) Under similar conditions 17β-acetoxy-5α-androstan-3-one (**3**, R = O) (500 mg) gave 17β-acetoxy-3-dichloromethylene-5α-androstane (**3**, R = CCl_2)(400 mg), m.p.117–120°C, (Found: C, 65.8; H, 7.8.$C_{22}H_{32}Cl_202$ requires C, 66.2; H, 8.l%), υ_{max}/cm^{-1} 1720, δ_H 0.71 (3H, s, H-18), 0.78 (3H, s, H-19), 2.00 (3H, s, OAc), 0.64–2.10 (20H, overlapping multiplets), 2.42 (1H, d, *J* 14.4Hz), 2.68 (1H, d, *J* 15.OHz), (2α and 4α-H), 4.60 (1H, t, *J* 8.4 Hz,H-17).

Hydroboration experiments: (a) 2-Dibromomethylene-5α-androstan-17-one (**1**, R = CBr_2) (150 mg) in dry tetrahydrofuran (15 cm^3) was treated with 1M borane in tetrahydrofuran (10 cm^3) dropwise at 0°C under nitrogen. The solution was left to stir overnight. The excess borane was destroyed by the dropwise addition of water (5 cm^3). The solution was cooled to 0°C and 10% sodium hydroxide (10 cm^3) was added followed by the dropwise addition of 30% hydrogen peroxide (15 cm^3). The mixture was left to stir overnight. Sodium sulfite (1 g) was added followed by acetic acid (0.5 cm^3), water (25 cm^3) and 10% hydrochloric acid (25 cm^3). The mixture was left to stir for 30 min. The solution was extracted with ethyl acetate and the extract was washed with water, brine and dried. The solvent was evaporated to give a residue which was chromatographed on silica to afford 17β-hydroxy-2β-hydroxymethyl-5α-androstane **2** (60 mg) which was identified by comparing its ^1H NMR spectrum with that of an authentic sample.[5]

(b) Under similar conditions (i) 2-dichloromethylene-5α-androstan-17-one (**1**, R = CCl_2)(130 mg) gave 17β-hydroxy-2β-hydroxymethyl-5α-androstane **2** (50 mg). (ii) l7β-acetoxy-3-dibromomethylene-5α-androstane (**3**, R = CBr_2)(400 mg) gave 17β-hydroxy-3α-hydroxymethyl-5α-androstane **4** (150 mg) and 17β-hydroxy-3β-hydroxymethyl-5α-androstane **5** (80 mg), (iii) 17β-acetoxy-3-dichloromethylene-5α-androstane (**3**, R = CCl_2) (380 mg) gave 17β-hydroxy-3α-hydroxymethyl-5α-androstane **4** (170 mg) and 17β-hydroxy-3β-hydroxymethyl-5α-androstane **5** (65 mg).

(c) Under similar conditions 17β-acetoxy-3-chloroandrosta-3,5-diene[8] **6** (500 mg) gave 17β-ethoxy-3-chloroandrosta-3,5-diene **7** (82 mg) as an oil, (Found: M^+ 334.578 $C_{21}H_{31}{}^{35}C10$ requires M^+ 334.575), δ_H 0.77(3H, s, H-18), 0.93(3H, s, H-19), 1.20(3H, t, *J* 7 Hz, OCH_2CH_3), 3.20 (1H, t, *J* 7.9 Hz, H-17), 3.50 (2H, m, OCH_2CH_3), 5.37 (1H, br.s, H-6), 6.03(1H, s, H-4); l7β-ethoxy-5β-androstane-3α,6β-diol 8 (134 mg) as an oil, (Found: M^+ 336.266 $C_{21}H_{36}O_3$ requires M^+ 336.266), υ_{max}/cm^{-1} 3325, δ_H 0.74 (3H, s, H-18), 1.08 (3H, s, H-19), 1.14 (3H, t, *J* 7 Hz. OCH_2CH_3), 3.20 (1H, t, *J* 8.2 Hz, H-17), 3.45 (2H, m, OCH_2CH_3), 3.58 (1H, tt, *J* 11.2 and 4.8 Hz, H-3β), 3.73 (1H, br.s. H-6α); 3α, 6β, 17β-trihydroxy-5β-androstane **9** (40 mg) which crystallized from methanol as needles, m.p. 254–256° (Found: M^+ 308.484 $C_{19}H_{32}O_3$ requires M^+ 308.484), υ_{max}/cm^{-1} 3325, δ_H 0.73 (3H, s, H-18), 1.10 (3H, s, H-19), 3.58 (1H, tt, *J* 11.2 and 4.8 Hz, H-3β), 3.60 (1H, t, *J* 7.9 Hz, H-17), 3.75 (1H, br.s., H-6α).

X-ray crystallographic data and structure determination of 3α, 6β, 17β-trihydroxy-5β-androstane: **9** $C_{19}H_{32}O_3 .H_2O$, M^+ 326.46, orthorhombic, space group $P2_12_12_1$ (no.19), *a* = 7.0703(4), *b* = 12.8414(6), *c* = 19.6485(10) Å, V = 1783.9Å^3, Z = **4**, D_{calc} 1.22 g/cm^{-3}, μ = 0.08 mm^{-1}, F(OOO) 720. The data were collected from a crystal of 0.2 × 0.05 × 0.05 mm. 10316 Reflections were observed for 4.29<θ<27.89° and 9<=*h*<=9, –12<=*k*<=16, –25<=*l*<=20. There were 4155 independent reflections and 3060 reflections with I>2σ(I) were used in the structure determination. The structure was solved by direct methods and refined by full matrix least squares on F^2 using SHELXL-97. The final R values were R_1 = 0.060 ωR_2 = 0.124 and (all data), R_1 = 0.089 and ωR_2 = 0.136. The goodness of fit on F^2 was 1.053 and the largest difference peak and hole was 0.23 and –0.29 eÅ^{-3} The data have been deposited at the Cambridge Crystallographic Data Centre.

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