An unusual hydroboration of 3-hydroxy-3-methyl-Δ^4-steroids

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Hydroboration of 3-hydroxy-3-methyl-Δ^4-steroids, and oxidation of the borane with alkaline hydrogen peroxide, has been shown by X-ray crystallography to give 4β-hydroxy-3α-methyl-5β(H)-steroids irrespective of the stereochemistry at C-3.

Keywords: steroids, hydroboration, X-ray crystallography

The addition of borane to steroidal alkenes takes place predominantly from the α face of the molecule. However, we have shown[1-6] that the stereochemistry of the alcohols that are formed by the hydroboration and oxidation of steroidal allylic alcohols is determined by the stereochemistry of the allylic alcohol. In the case of allylic alcohols on rings A and B of the steroids, this feature over-rides the stereochemical directing effect of the angular C-10 methyl group. Secondary allylic alcohols at C-3 of the steroids direct hydration of a Δ^4-alkene to the face that is *anti* to the alcohol. Thus hydroboration of 17β-acetoxyandrost-4-en-3α-ol and oxidation of the borane with alkaline hydrogen peroxide gave 5β-androstane-3α,4β,17β-triol whilst 17β-acetoxyandrost-4-en-3β-ol gave 5α-androstane-3β,4α,17β-triol.[1] The availability of tertiary methyl carbinols[7] which are epimeric at C-3 provided an opportunity to study the balance between the stereochemical influence of an allylic hydroxyl group and an allylic methyl group on this reaction. In the event the reaction took an unexpected path with results that form the subject of this paper.

3α,17β-Dihydroxy-3β-methylestr-4-ene (**1**), 17β-acetoxy-3β-hydroxy-3α-methylandrost-4-ene (**3**) and 3β,20-dihydroxy-3α,20-dimethylpregn-4-ene (**5**) were prepared[7] by the action of methyl magnesium iodide on 19-nortestosterone, testosterone acetate and progesterone respectively. The hydroboration/oxidation reactions were carried out with borane in tetrahydrofuran followed by oxidation with alkaline hydrogen peroxide. In the ^{1}H NMR spectra of the products which were formed in good yield, the C-3 methyl group signals, singlets in the starting materials, were now doublets (J = 6.2 – 6.5 Hz) whilst the H-4 resonance was a triplet (J = 10 – 11 Hz). Hydrogenolysis of the C-3 alcohols had therefore taken place. Since the ^{1}H NMR spectra would not easily distinguish between the axial:axial couplings arising from a 3α-H : 4β-H : 5α-H and a 3β-H : 4α-H : 5β-H system, the stereochemistry of the three contiguous centres was established by X-ray crystallography (see Figs 1-4). In the case of the estrane **1** and androstane **3** series suitable crystals for X-ray crystallography were obtained from the acetates, compounds **2** and **4**. In the pregnane **5** series one of the products, compound **6**, contained an extra oxygen atom which was located by the X-ray structure in a hydroperoxide at C-20.

A small amount of 17β-hydroxy-3α-methyl-5β-estr-4-one was also obtained from 3α,17β-dihydroxy-3β-methylestra-4-ene. On one occasion the reaction in the pregnane series was worked up by acetylation with acetic anhydride in pyridine. 4β,17β-Diacetoxy-3α-methyl-5β-androstane (**4**) was isolated. The origin of this product may lie in the decomposition of the hydroperoxide **6**. The formation of a C-20 hydroperoxide **6** was unexpected and presumably arises by displacement of a C-20 borate by the hydroperoxide anion.

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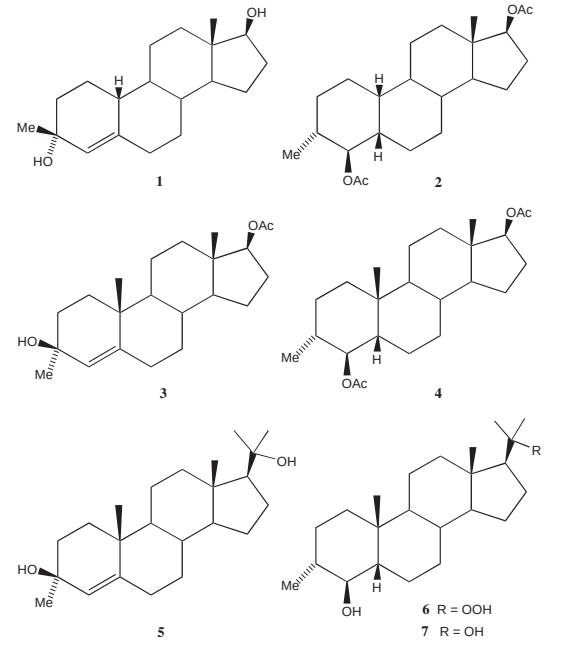

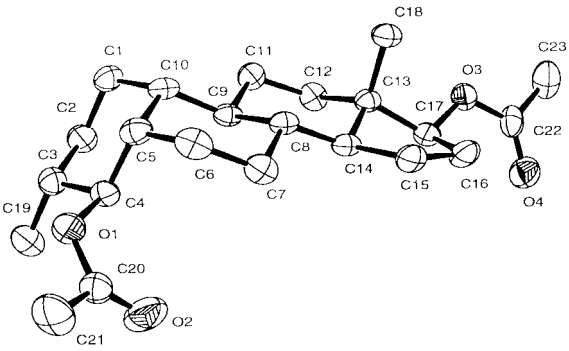

Fig. 1 X-Ray crystal structure of compound **2**.

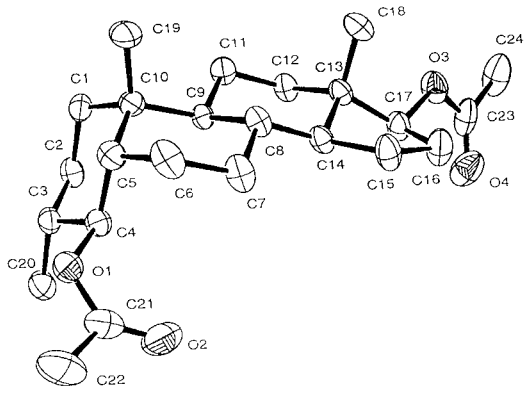

Fig. 2 X-Ray crystal structure of compound **4**.

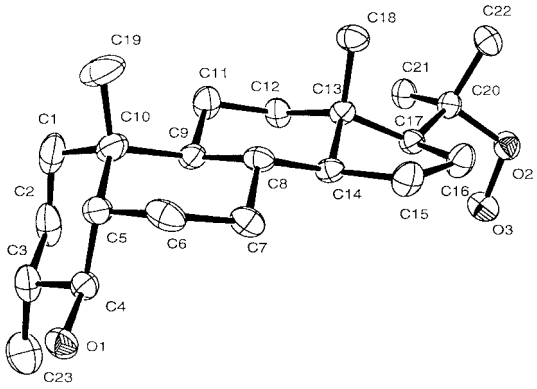

Fig. 3 X-Ray crystal structure of compound **6**.

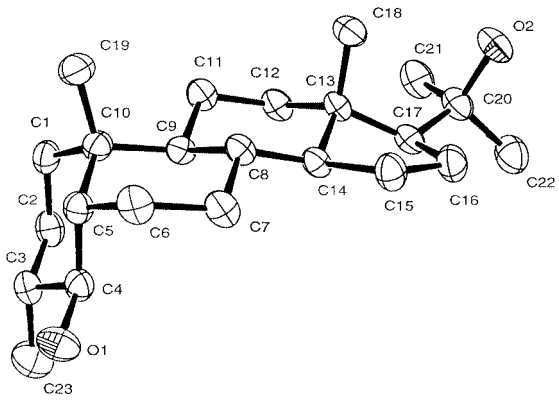

Fig. 4 X-Ray crystal structure of compound **7**.

The X-ray structures showed that in each case the tertiary alcohol at C-3 was replaced by hydrogen and that the stereochemistry at C-3, C-4 and C-5 was the same irrespective of the stereochemistry of the original tertiary alcohol at C-3. A possible explanation of this result is that the borane reacts as a Lewis acid with the tertiary allylic alcohol to generate a planar C-3 carbocation. This then adds hydride from the less-hindered equatorial (β) face. The resultant 3α-axial methyl group then directs the second addition of borane to the β-face of the Δ^4-double bond eventually, after oxidation, generating the 4β-alcohol in the 5β(H) series.

In conclusion, the hydroboration of 3-hydroxy-3-methyl-Δ^4-steroids and oxidation of the borane by alkaline hydrogen peroxide has been shown to lead to hydrogenolysis of the 3-hydroxyl group and the formation of 4β-hydroxy-3α-methyl-5β(H)-steroids irrespective of the stereochemistry of the allylic alcohol at C-3.

Experimental

Light petroleum refers to the fraction bp 60-80 °C. Silica for chromatography was Merck Kieselgel 60 type 9380. IR spectra were determined as nujol mulls. ^{1}H NMR spectra were determined at 300 MHz on a Bruker AMX spectrometer for solutions in deuteriochloroform; mass spectra were measured on a Bruker Daltonics Apex III mass spectrometer. Borane (1M) in tetrahydrofuran was used as supplied by Aldrich Chemicals. Extracts were dried over sodium sulfate.

Hydroboration experiments

The steroid (500 mg) in dry tetrahydrofuran (50 cm^3) was treated with 1M borane in tetrahydrofuran (25 cm^3) at 0 °C and then the mixture was stirred at room temperature for 3 h under nitrogen. Water (25 cm^3) was added, followed by a mixture of hydrogen peroxide (27.5%, 25 cm^3) and sodium hydroxide (10%, 25 cm^3). The mixture was left to stir overnight. Aqueous sodium sulfite (10%, 25 cm^3) was added and the stirring was continued for a further 30 min. The mixture was diluted with water and the products were recovered in ethyl acetate. The extract was washed with aqueous sodium hydrogen carbonate, water and brine, and dried. The solvent was evaporated to give a gum which as chromatographed on silica in ethyl acetate : light petroleum (1 : 4).

Acetylation experiments

The gum from the above experiment, or the separate fractions from the chromatography, were dissolved in pyridine (10 cm^3) and acetic anhydride (3 cm^3) and left at room temperature overnight. The mixture was poured into dil. hydrochloric acid and the products were extracted into ethyl acetate. The extract was washed with water, aqueous copper sulfate and aqueous sodium hydrogen carbonate, and dried. The solvent was evaporated to give a residue which was chromatographed on silica in ethyl acetate : light petroleum (1 : 5).

(a) 3α,17β-Dihydroxy-3β-methylestr-4-ene (1) (500 mg) gave 17β-hydroxy-3α-methyl-5β-estr-4-one (97 mg) and 4β,17β-dihydroxy-3α-methyl-5β-estrane (390 mg). 17β-Hydroxy-3α-methyl-5β-estr-4-one crystallised from light petroleum as needles, m.p. 120–122 °C. IR: ν_{max}/cm^{-1} 3378, 1730; δ_H 0.70 (3H, s, 18-H), 0.97 (3H, d, *J* = 6.5 Hz, 3-Me), 0.9–2.4 (22H, overlapping multiplets), 3.58 (1H, t, *J* = 8.3 Hz, 17-H) [Found: M$^+$ 603.441; $(C_{19}H_{30}O_2)_2Na$ requires 603.438]. 4β,17β-Dihydroxy-3α-methyl-5β-estrane crystallised from ethyl acetate – light petroleum as needles, m.p. 138–139 °C. IR: ν_{max}/cm^{-1} 3412 (br), δ_H 0.71 (3H, s, 18-H), 1.00 (3H, d, *J* = 6.2 Hz, 3-Me), 0.9–2.1 (22H, overlapping multiplets), 3.33 (1H, t, *J* = 10.0 Hz, 4-H), 3.61 (1H, t, *J* = 8.3 Hz, 17-H). [Found: M$^+$ 607.470; $(C_{19}H_{32}O_2)_2Na$ requires 607.470] Acetylation of this alcohol (150 mg) with acetic anhydride in pyridine gave, after chromatography, 4β,17β-diacetoxy-3α-methyl-5β-estrane (**2**) (81 mg), 17β-acetoxy-4β-hydroxy-3α-methyl-5β-estrane (25 mg) and 4β-acetoxy-17β-hydroxy-3α-methyl-5β-estrane (40 mg). 4β,17β-Diacetoxy-3α-methyl-5β-estrane **2** crystallised from light petroleum as needles, m.p. 138–139 °C. IR: ν_{max}/cm^{-1} 1733; NMR: δ_H 0.71 (3H, s, 18-H), 0.80 (3H, d, *J* = 6.2 Hz, 3-Me), 2.01 and 2.05 (each 3H, s, OAc), 0.9–2.1 (22H, overlapping multiplets), 4.52 (1H, t, *J* = 8.5 Hz, 17-H), 4.85 (1H, t, *J* = 11 Hz, 4-H). [Found: M$^+$ 775.514; $(C_{23}H_{36}O_4)_2Na$ requires 775.512] 17β-Acetoxy-4β-hydroxy-3α-methyl-5β-estrane crystallised from light petroleum as needles, m.p. 119–120 °C. IR: ν_{max}/cm^{-1} 3520, 1730; NMR δ_H 0.72 (3H, s, 18-H), 0.97 (3H, d, *J* = 6.2 Hz, 3-Me), 2.00 (3H, s, OAc), 0.9–2.1 (22H, overlapping multiplets), 3.29 (1H, t, *J* = 11 Hz, 4-H), 4.52 (1H, t, *J* = 8.5 Hz, 17-H). [Found: M$^+$ 357.241; $C_{21}H_{34}O_3Na$ requires 357.240]

4β-Acetoxy-17β-hydroxy-3α-methyl-5β-estrane crystallised from light petroleum as needles, m.p. 142–143 °C. IR: ν_{max}/cm^{-1} 3430. 1727. NMR: δ_H 0.73 (3H, s, 18-H), 0.84 (3H, d, *J* = 6.2 Hz, 3-Me), 2.04 (3H, s, OAc), 0.9–2.1 (22H, overlapping multiplets), 3.63 (1H, t, *J* = 8.5 Hz, 17-H), 4.90 (1H, t, *J* = 11 Hz, 4-H). [Found: M$^+$ 691.494; $(C_{21}H_{34}O_3)_2Na$ requires 691.491]

(b) 17β-Acetoxy-3β-hydroxy-3α-methylandrost-4-ene **3** (500 mg) gave, after acetylation and chromatography, 4β,17β-diacetoxy-3α-methyl-5β-androstane (4) (398 mg) which crystallised from light petroleum as needles, m.p. 120–122 °C. IR: ν_{max}/cm^{-1} 1732; NMR: δ_H 0.70 (3H, s, 18-H), 0.82 (3H, d, *J* = 6.2 Hz, 3-Me), 0.92 (3H, s, 19-H), 1.99 and 2.01 (each 3H, s, OAc), 1.0–2.1 (21H, overlapping multiplets), 4.52 (1H, t, *J* = 8.5 Hz, 17-H), 4.94 (1H, t, *J* = 11 Hz, 4-H). Irradiation of the methyl group doublet (δ_H 0.82) produced an nOe enhancement (3.9%) of the triplet at δ_H 4.94. [Found: M$^+$ 413.266; $C_{24}H_{38}O_4Na$ requires 413.266].

(c) 3β,20-Dihydroxy-3α,20-dimethylpregn-4-ene (**5**) (500 mg) gave, after chromatography, 3α,20-dimethyl-20-hydroperoxy-4β-hydroxy-5β-pregnane (**6**) (69 mg) which crystallised from ethyl acetate : light petroleum as needles, m.p.159–162 °C. IR: ν_{max}/cm^{-1} 3422, 3242; NMR: δ_H 0.76 (3H, s, 18-H),0.96 (3H, s, 19-H), 1.04 (3H, d, *J* = 6.7 Hz,3-Me),1.28 and 1.29 (each 3H, s, 20-Me and 21-H), 1.0–2.0 (22H, overlapping multiplets), 3.45 (1H, t, *J* = 10.3 Hz, 4-H). [Found: M$^+$ 387.289; $C_{23}H_{40}O_3Na$ requires 387.287] Further elution gave 4β,20-dihydroxy-3α,20-dimethyl-5β-pregnane (**7**) (296 mg) which crystallised from ethyl acetate:light petroleum as needles, m.p.159–161 °C. IR: ν_{max}/cm^{-1} 3350 (br); NMR: δ_H 0.81 (3H, s, 18-H), 0.97 (3H, s, 19-H), 1.04 (3H, d, *J* = 6.4 Hz, 3-Me), 1.19 and 1.30 (each 3H, s, 20-Me and 21-H), 1.0–2.0 (22H, overlapping multiplets), 3.42 (1H, t, *J* = 10.3 Hz, 4-H). [Found: M$^+$ 371.289; $C_{23}H_{40}O_2Na$ requires 371.292] When the gum was acetylated and the product purified by chromatography, 4β,17β-diacetoxy-3α-methyl-5β-androstane (**4**) (400 mg), identical to the product described above, was isolated.

X-Ray crystallographic data and structure determinations

(a) 4β,17β-Diacetoxy-3α-methyl-5β-estrane (**2**), $C_{23}H_{36}O_4$, M_r 376.52, monoclinic, space group C2 (No.5), *a* = 14.7684(4), *b* = 5.8159(2),

c = 24.9834(8)Å, $\alpha = \gamma = 90°$ β = 95.049(1)°, V = 2137.54(12)Å^3, Z = 4, $D_{calc.}$ 1.17 g cm^{-3}, μ = 0.08 mm^{-1}, F(000) = 824. Data were collected using a crystal of size 0.30 × 0.30 × 0.05 mm^3 on a KappaCCD diffractometer. A total of 8250 reflections were collected for 3.77 < < 25.03 ° and $-17 \le h \le 16$, $-6 \le k \le 6$, $-29 \le l \le 29$. There were 3373 independent reflections and 2739 reflections with $I > 2\sigma(I)$ were used in the refinement. No absorption correction was applied. The structure was solved by direct methods and refined by SHELXL-97. The drawings used ORTEP-3 for Windows. The final R indices were [$I > 2\sigma(I)$] R_1 = 0.046, wR_2 = 0.105 and (all data) R_1 = 0.063, wR_2 = 0.115. The goodness-of-fit on F^2 was 1.024 and the largest difference peak and hole was 0.13 and -0.20e.Å^3.

(b) 4β,17β-Diacetoxy-3α-methyl-5β-androstane (**4**), $C_{24}H_{38}O_4$, M_r 390.54, monoclinic, space group C2 (No.5), a = 22.0608(3), b = 10.1421(2), c = 21.1700(3) Å, $\alpha = \gamma = 90°$, β = 109.859(1)°, V = 4454.95(12) Å^3, Z = 8, $D_{calc.}$ 1.17 g cm^{-3}, μ = 0.08 mm^{-1}, F(000) = 1712. Data were collected using a crystal of size 0.40 × 0.40 × 0.3 mm^3 on a KappaCCD diffractometer. A total of 16662 reflections were collected for 3.71 < θ < 27.47 ° and $-22 \le h \le 28$, $-10 \le k \le 13$, $-24 \le l \le 27$. There were 8175 independent reflections and 7508 reflections with $I > 2\sigma(I)$ were used in the refinement. No absorption correction was applied. The structure was solved by direct methods and refined by SHELXL-97. The drawings used ORTEP-3 for Windows. The final R indices were [$I > 2\sigma(I)$] R_1 = 0.040, wR_2 = 0.098 and (all data) R_1 = 0.046, wR_2 = 0.102. The goodness-of-fit on F^2 was 1.021 and the largest difference peak and hole was 0.20 and -0.16e.Å^3.

(c) 3α,20-Dimethyl-20-hydroperoxy-4β-hydroxy-5β-pregnane (**6**), $C_{23}H_{40}O_3$, M_r 364.55, monoclinic, space group $P2_1$ (No.4), a = 12.6965(2), b = 11.7930(2), c = 14.6564(3) Å, $\alpha = \gamma = 90$ °, β = 109.386(1) °, V = 2070.08(6)Å^3, Z = 4, $D_{calc.}$ 1.17 g cm^{-3}, μ = 0.08 mm^{-1}, F(000) = 808. Data were collected using a crystal of size 0.30 × 0.30 × 0.2 mm^3 on a KappaCCD diffractometer. A total of 22024 reflections were collected for 3.76 < θ < 25.01 ° and $-15 \le h \le 14$, $-14 \le k \le 13$, $-15 \le l \le 17$. There were 7199 independent reflections and 6207 reflections with $I > 2\sigma(I)$ were used in the refinement. No absorption correction was applied. The structure was solved by direct methods and refined by SHELXL-97. The drawings used ORTEP-3 for Windows. The final R indices were [$I > 2\sigma(I)$] R_1 = 0.045, wR_2 = 0.101 and (all data) R_1 = 0.057, wR_2 = 0.107. The goodness-of-fit on F^2 was 1.061 and the largest difference peak and hole was 0.23 and -0.24 e Å^3.

(d) 4β,20-Dihydroxy-3α,20-dimethyl-5β-pregnane (**7**), $C_{23}H_{40}O_2$, M_r 348.55, trigonal, space group $P3_1$ (No.144), a = 13.7556(2), b = 13.7556(2), c = 19.6289(4) Å, $\alpha = \beta = 90°$, $\gamma = 120°$, V = 3216.51(9)Å^3, Z = 6, $D_{calc.}$ 1.08 g cm^{-3}, μ = 0.07 mm^{-1}. F(000) = 1164. Data were collected using a crystal of size 0.4 × 0.3 × 0.3 mm^3 on a KappaCCD diffractometer. A total of 34025 reflections were collected for 4.00 < θ < 25.04 ° and $-16 \le h \le 16$, $-16 \le k \le 16$, $-21 \le l \le 23$. There were 7270 independent reflections and 5954 reflections with $I > 2\sigma(I)$ were used in the refinement. No absorption correction was applied. The structure was solved by direct methods and refined by SHELXL-97. The drawings used ORTEP-3 for Windows. The final R indices were [$I > 2\sigma(I)$] R_1 = 0.047, wR_2 = 0.099 and (all data) R_1= 0.067, wR_2= 0.107. The goodness-of-fit on F^2 was 1.061 and the largest difference peak and hole was 0.15 and -0.13 e Å^3.

The crystallographic data are deposited with the Cambridge Crystallographic Data Centre, as files CCDC 225733-225736 (compounds **2**, **4**, **6** and **7**, respectively).

Received 6 April 2004; accepted 4 June 2004
Paper 04/2443

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