Neighbouring-group Participation in the Chromium Trioxide Oxidation of Steroidal 4,5-Epoxides. X-Ray Molecular Structure of 4β,6β,17β-Triacetoxy-3β,5α-dihydroxyandrostane

Nazar Flaih, James R. Hanson* and Peter B. Hitchcock
School of Molecular Sciences, University of Sussex, Brighton, Sussex BN1 9QJ, UK

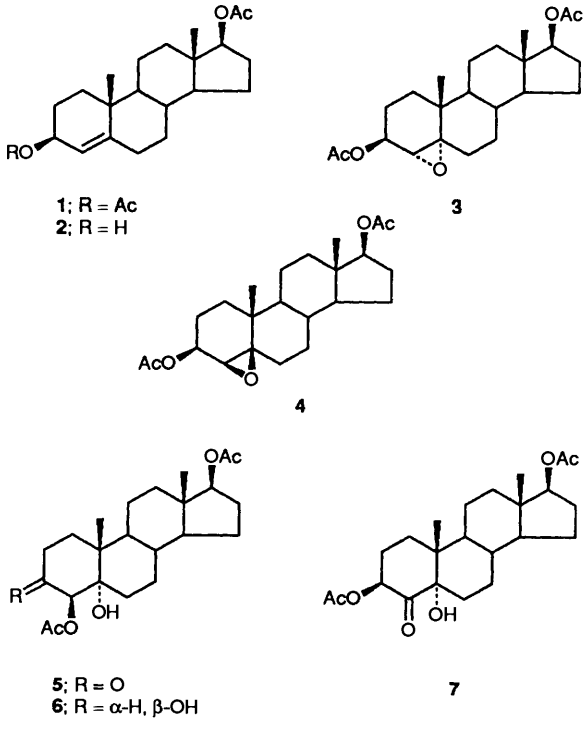
Chromium trioxide oxidation of steroidal 3β-acetoxy-4α,5α-epoxides affords products in which the acetoxy group has migrated to the 4β-position whilst oxidation of the isomeric 4β,5β-epoxides affords 5α-hydroxy-4-ketones without rearrangement. The effect of 3-chloro and 6β-acetoxy substituents is explored.

The oxidation of secondary:tertiary epoxides by chromium trioxide to form α-ketols is a useful transformation. Hence, both steroidal 5α,6α-[1] and 5β,6β-epoxides[2] afford 5α-hydroxy-6-ketones. There is considerable evidence for neighbouring-group participation in the hydrolysis of the steroidal secondary:tertiary 4,5-epoxides.[3–6] This is exemplified by the migration of an acetoxy group from C-3 to C-4 or by the diequatorial opening of the 4α,5α-epoxide in the presence of a 6β-acetate. We have therefore examined the oxidation of some 3β-acetoxy- and 3β,6β-diacetoxy-4,5-epoxides by chromium trioxide in the light of these observations. The results form the subject of this paper.

3β,17β-Diacetoxy-4α,5α-epoxyandrostane **3**[3] was obtained by epoxidation of 3β,17β-diacetoxyandrost-4-ene **1** with *m*-chloroperbenzoic acid (MCPBA). The isomeric 3β,17β-diacetoxy-4β,5β-epoxyandrostane **7**[7] was obtained by epoxidation of 17β-acetoxy-3β-hydroxyandrost-4-ene **2** followed by acetylation.

Oxidation of the 4α,5α-epoxide **3** with chromium trioxide in ethyl methyl ketone at 40 °C[1] gave the 3-keto-4β-acetate **5** in which the 4α-H ^{1}H NMR signal appeared as a singlet at δ 4.91. Hydrolysis of 3β-acetoxy-4α,5α-epoxides is known[3] to give 4β-acetoxy-3β,5α-diols. Oxidation of 4β,17β-diacetoxy-3β,5α-dihydroxyandrostane **6** with chromium trioxide in pyridine gave 4β,17β-diacetoxy-5α-hydroxyandrostan-3-one **5** identical with the sample obtained above. On the other hand oxidation of the isomeric 3β,17β-diacetoxy-4β,5β-epoxyandrostane **4** gave the 4-ketone in which the 3α-H NMR signal appeared as a double-doublet, δ 5.93, *J* 7.9 and 12.2 Hz. The 5-hydroxy signal at δ 2.86 was identified by a ^2H_2O wash which led to its disappearance. Irradiation of the 3α-proton signal gave a nuclear Overhauser enhancement (NOE) (7%) of this signal thus establishing the 5α-hydroxy group's stereochemistry. Hence, rearrangement occurred with the 4α,5α-epoxide but not with the 4β,5β-isomer.

The possibility of neighbouring-group participation was then explored in the light of the possible intervention of a 6β-acetoxy group.[6] 3β,6β-Diacetoxy-4α,5α-epoxyandrostan-17-one **10** and 3β,6β,17β-triacetoxy-4α,5α-epoxyandrostane **11** were prepared as follows. Hydrolysis of 3β-acetoxy-5α,6α-epoxyandrostan-17-one **8** with periodic acid, acetylation of the resulting 6β-hydroxy group and dehydration of the 5α-hydroxy group with thionyl chloride[8] gave the 4-ene **9**, which was in turn epoxidized to afford 3β,6β-diacetoxy-4α,5α-epoxyandrostan-17-one **10**. Alternatively, reduction of the 17-ketone **9**, epoxidation and acetylation afforded 3β,6β,17β-triacetoxy-4α,5α-epoxyandrostane **11**. Oxidation of both substrates with chromium trioxide gave separable mixtures of the 4β-acetoxy-3-ketones **12** and **13** and the 4β-acetoxy-3β,5α-diols **14** and **15** in which migration of the 3β-acetate to C-4 had taken place. This was established by the multiplicity and chemical shift of the 4-H NMR signals [δ 5.59 and 5.57, singlet, in compounds **12** and **13**; 5.03 and 4.94 (broad singlet) in compounds **14** and **15**]. The full stereochemistry of the product **15** was established by X-ray crystallography. Hence, oxidation has given the 5α-hydroxy steroid.



The presence of a 3α-chlorine has been shown[2] to provide steric hindrance to the oxidation of 5β,6β-epoxides and hence its effect was examined here. 17β-Acetoxy-3α-chloro-4β,5β-epoxyandrostane **16** was prepared by treatment of the corresponding 3β-alcohol **17**[9] with triphenylphosphine–carbon tetrachloride. The corresponding 17β-acetoxy-3β-chloro-4β,5β-epoxyandrostane **18** was prepared by similar treatment of the 3α-alcohol **19**. The 3α-chloro compound **16** was resistant to oxidation and was recovered unchanged after reaction treatment for 5 h. On the other hand oxidation of the 3β-chloro compound **18** gave an inseparable mixture of the 3β-chloro-4β,5α-diol **20** and the corresponding 4-ketone **21**. This was eventually resolved by hydrogenolysis of the chloride with tributyltin hydride to afford the 4β,5α-diol and the 4-ketone, compounds **22** and **23**.

Therefore the oxidative opening of steroidal 4α,5α-epoxides

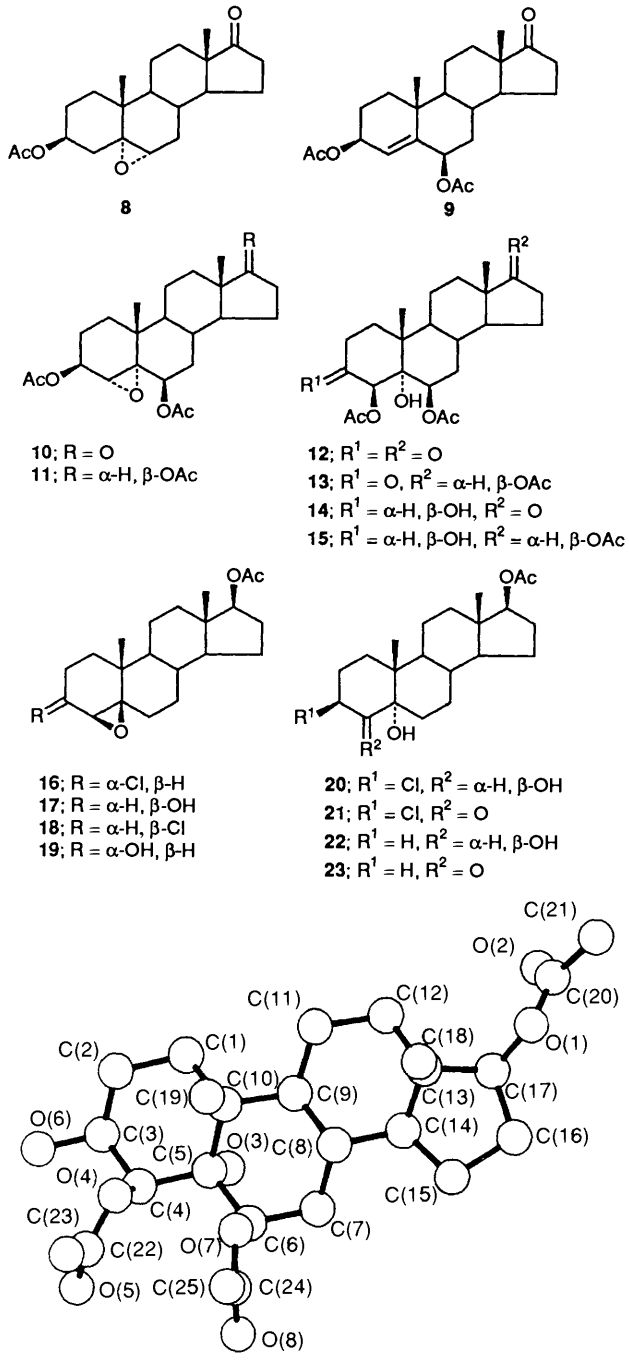


Fig. 1 X-Ray molecular structure of 4β,6β,17β-triacetoxy-3β,5α-dihydroxyandrostane **15**

is accompanied by neighbouring-group participation from C-3 and there is steric hindrance from a 3α-chlorine atom.

Experimental

IR spectra were determined as Nujol mulls and ^{1}H NMR spectra were obtained for solutions in deuteriochloroform on a Bruker WM 360 spectrometer. *J*-Values are given in Hz. Extracts were dried over sodium sulphate. Silica for chromatography was Merck 9385. Light petroleum refers to the fraction boiling in the range 60–80 °C.

Oxidation of 3β,17β-*Diacetoxy*-4α,5α-*epoxyandrostane*.—Aq. chromium trioxide (75%) (1 cm^3) was added dropwise to a stirred solution of 3β,17β-diacetoxy-4α,5α-epoxyandrostane **3**[3] (500 mg) in ethylmethyl ketone (6 cm^3) at 35–40 °C. The solution was left for 20 min and then poured into water. The product was recovered in ethyl acetate. The combined extracts were washed thoroughly with water and dried. The solvent was evaporated off under reduced pressure to afford 4β,17β-*diacetoxy*-5α-*hydroxyandrostan*-3-*one* **5** (450 mg), which crystallized from ethyl acetate–light petroleum as needles, m.p. 162–165 °C (Found: 68.2; H, 8.5. $C_{23}H_{34}O_6$ requires C, 68.0; H, 8.4%); ν_{max}/cm^{-1} 3411 and 1734; δ 0.79 (3 H, s, 18-H$_3$), 1.10 (3 H, s, 19-H$_3$), 4.59 (1 H, t, *J* 8.5, 17-H) and 4.91 (1 H, s, 4-H).

Oxidation of 4β,17β-*Diacetoxy*-3β,5α-*dihydroxyandrostane*.—A solution of the steroid **6**[3] (300 mg) in pyridine (8 cm^3) was added to a stirred solution of chromium trioxide (1 g) in pyridine (15 cm^3). The mixture was stirred for 5 h at room temperature and then poured into diethyl ether (70 cm^3). Insoluble inorganic salts were removed by filtration through Celite. The Celite was washed with diethyl ether. The combined filtrates were washed successively with dil. hydrochloric acid, aq. sodium hydrogen carbonate and water, and were dried. Evaporation of the solvent afforded 4β,17β-diacetoxy-5α-hydroxyandrostan-3-one **5** (270 mg), identified by its IR and NMR spectra.

Oxidation of 3β,17β-*Diacetoxy*-4β,5β-*epoxyandrostane*.—Aq. chromium trioxide (75%) (2 cm^3) was added dropwise to a stirred solution of 3β,17β-diacetoxy-4β,5β-epoxyandrostane **7**[7] (750 mg) in ethyl methyl ketone (10 cm^3) at 35–40 °C. The solution was left for 15 min and then poured into water. The product was recovered in ethyl acetate. The combined extracts were washed thoroughly with water and dried. The solvent was evaporated off under reduced pressure to afford 3β,17β-*diacetoxy*-5α-*hydroxyandrostan*-4-*one* **7** (610 mg), which was crystallized from diethyl ether–light petroleum as needles, m.p. 196–198 °C (Found: C, 68.0; H, 8.4. $C_{23}H_{34}O_6$ requires C, 68.0; H, 8.4%); ν_{max}/cm^{-1} 3515, 1739 and 1717; δ 0.77 (3 H, s, 18-H$_3$), 0.79 (3 H, s, 19-H$_3$), 2.03 and 2.14 (each 3 H, s, OAc), 2.86 (1 H, s, removed by washing with D_2O, 5-OH), 4.59 (1 H, dd, *J* 7.8 and 9, 17-H) and 5.93 (1 H, dd, *J* 7.9 and 12.2, 3-H).

Epoxidation of 3β,6β-*Diacetoxyandrost*-4-*en*-17-*one*.—A solution of 3β,6β-diacetoxyandrost-4-en-17-one **9**[10] (4 g) in chloroform (150 cm^3) was treated with MCPBA (5 g) at 0 °C. The mixture was allowed to attain room temperature and was stirred for 48 h. The solution was washed successively with aq. sodium sulphite, aq. sodium hydrogen carbonate and water, and was dried. The solvent was evaporated off to afford 3β,6β-*diacetoxy*-4α,5α-*epoxyandrostan*-17-*one* **10** (4 g), which was crystallized from ethyl acetate–light petroleum as needles, m.p. 168–170 °C (Found: C, 68.5; H, 8.1. $C_{23}H_{32}O_6$ requires C, 68.3; H, 8.0%); ν_{max}/cm^{-1} 1741; δ 0.88 (3 H, s, 18-H$_3$), 1.19 (3 H, s, 19-H$_3$), 2.03 and 2.07 (each 3 H, s, OAC), 3.15 (1 H, s, 4-H), 4.29 (1 H, t, *J* 3, 6-H) and 4.89 (1 H, t, *J* 8, 3-H).

Oxidation of 3β,6β-*Diacetoxy*-4α,5α-*epoxyandrostan*-17-*one*.—Aq. chromium trioxide (75%) (1 cm^3) was added dropwise to a stirred solution of 3β,6β-diacetoxy-4α,5α-epoxyandrostan-17-one **10** (450 mg) in ethyl methyl ketone (5 cm^3) at 35–40 °C. The mixture was left for 35 min and was then poured into water. The product was recovered in ethyl acetate. The extracts were washed thoroughly with water and dried. The solvent was evaporated off under reduced pressure and the residue was chromatographed on silica. Elution with 25% ethyl acetate–light petroleum gave 4β,6β-*diacetoxy*-5α-*hydroxyandrostane*-3,17-*dione* **12** (100 mg), which was crystallized from ethyl acetate–light petroleum as needles, m.p. 227–229 °C (Found: C, 64.5; H, 7.95. $C_{23}H_{32}O_7 \cdot 0.5H_2O$ requires C, 64.3; H, 7.7%); ν_{max}/cm^{-1} 3397, 1741, 1738 and 1735; δ 0.92 (3 H,

Table 1 Fractional atomic co-ordinates (× 10^4)

	Molecule a			Molecule b		
	x	*y*	*z*	*x*	*y*	*z*
O(1)	4 675(4)	−600(0)	−2 203(3)	13 111(3)	6 118(10)	5 884(3)
O(2)	3 733(6)	226(15)	−3 205(3)	14 116(5)	5 574(17)	6 896(3)
O(3)	1 016(3)	958(7)	−680(2)	9 878(3)	4 670(7)	7 774(2)
O(4)	1 946(3)	2 646(7)	1 063(2)	7 972(3)	2 060(7)	6 801(2)
O(5)	1 199(4)	1 258(10)	1 589(3)	6 809(4)	3 614(10)	6 755(3)
O(6)	453(3)	4 608(9)	554(2)	8 391(4)	910(8)	8 160(3)
O(7)	2 984(3)	35(7)	826(2)	8 244(3)	4 946(8)	6 049(2)
O(8)	2 687(6)	−2 209(11)	1 340(4)	7 594(6)	7 461(11)	6 024(4)
C(1)	1 708(4)	4 207(10)	−670(3)	10 236(5)	1 300(11)	7 487(4)
C(2)	1 315(5)	5 038(12)	−169(4)	9 545(5)	464(11)	7 710(4)
C(3)	782(4)	3 847(12)	79(4)	9 028(5)	1 733(11)	7 938(3)
C(4)	1 309(4)	2 245(11)	406(3)	8 583(5)	2 989(11)	7 369(4)
C(5)	1 745(4)	1 430(10)	−72(3)	9 289(5)	3 908(11)	7 157(4)
C(6)	2 218(5)	−248(10)	208(3)	8 934(5)	5 440(11)	6 668(3)
C(7)	2 537(5)	−1 091(10)	−309(4)	9 669(5)	6 324(11)	6 521(4)
C(8)	3 088(5)	67(10)	−573(3)	10 304(5)	5 161(12)	6 313(4)
C(9)	2 596(4)	1 716(10)	−862(3)	10 646(5)	3 688(11)	6 841(3)
C(10)	2 316(4)	2 680(10)	−323(3)	9 867(4)	2 654(11)	6 912(3)
C(11)	3 100(5)	2 834(11)	−1 196(4)	11 330(5)	2 648(14)	6 677(4)
C(12)	3 374(5)	1 867(12)	−1 742(4)	12 108(5)	3 681(13)	6 655(4)
C(13)	3 896(5)	253(12)	−1 421(4)	11 791(5)	5 108(13)	6 129(3)
C(14)	3 314(5)	−807(10)	−1 150(4)	11 089(5)	6 121(12)	6 291(4)
C(15)	3 804(6)	−2 514(13)	−979(4)	10 960(5)	7 707(13)	5 823(4)
C(16)	4 202(7)	−2 703(14)	−1 568(4)	11 867(6)	8 001(13)	5 793(5)
C(17)	3 998(5)	−993(13)	−1 948(4)	12 464(5)	6 486(14)	6 178(4)
C(18)	4 792(5)	709(15)	−892(4)	11 451(6)	4 367(15)	5 412(4)
C(19)	3 138(5)	3 361(10)	266(3)	9 355(5)	1 765(11)	6 246(4)
C(20)	4 462(7)	−45(14)	−2 844(4)	13 891(6)	5 659(16)	6 276(5)
C(21)	5 286(7)	235(21)	−3 016(6)	14 520(6)	5 249(24)	5 923(5)
C(22)	1 828(5)	2 035(11)	1 614(4)	7 139(5)	2 459(13)	6 552(4)
C(23)	2 592(7)	2 479(15)	2 271(4)	6 636(6)	1 298(16)	5 977(5)
C(24)	3 176(6)	−1 055(13)	1 350(4)	7 580(6)	6 063(14)	5 759(5)
C(25)	4 020(6)	−696(16)	1 897(4)	6 873(6)	5 461(18)	5 126(5)

s, 18-H_3), 1.45 (3 H, s, 19-H_3), 2.05 and 2.16 (each 3 H, s, OAc), 5.01 (1 H, t, *J* 2.9, 6-H) and 5.59 (1 H, s, 4-H).

Elution with 40% ethyl acetate–light petroleum gave 4β,6β-*diacetoxy*-3β,5α-*dihydroxyandrostan*-17-*one* **14** (220 mg), which was crystallized from acetone as needles, m.p. 217–220 °C (Found: C, 65.3; H, 7.9. $C_{23}H_{34}O_7$ requires C, 65.4; H, 8.1%); ν_{max}/cm^{-1} 3460br and 1737; δ 0.89 (3 H, s, 18-H_3), 1.33 (3 H, s, 19-H_3), 2.04 and 2.13 (each 3 H, s, OAC), 3.35 (1 H, s, OH), 4.33 (1 H, m, 3-H), 5.02 (1 H, t, *J* 2, 6-H) and 5.16 (1 H, d, *J* 3.5, 4-H).

Preparation of 3β,6β,17β-*Triacetoxy*-4α,5α-*epoxyandrostane*.—A solution of 3β,6β,diacetoxyandrost-4-en-17-one **9** (2 g) in methanol (200 cm^3) was treated with sodium borohydride (1 g) at 0 °C for 3 h. The excess of reagent was destroyed with acetic acid (0.5 cm^3) and the solution was poured into water. The product was recovered in ethyl acetate and washed with water, and the solvent was evaporated off to give a gum. This was dissolved in chloroform (100 cm^3) and treated with MCPBA (2.5 g) at 0 °C. The mixture was allowed to attain room temperature and was stirred for 48 h before being washed successively with aq. sodium sulphite, aq. sodium hydrogen carbonate and water. The organic phase was dried and the solvent was evaporated off to give 3β,6β-diacetoxy-4α,5α-epoxyandrostan-17β-ol (1.95 g) as a gum, *m*/*z* 406 (M^+), 347 (M − 59), 330 (M − 76) and 294 (M − 112); δ 0.78 (3 H, s, 18-H_3), 1.19 (3 H, s, 19-H_3), 2.05 and 2.07 (each 3 H, s, OAC), 3.16 (1 H, s, 4-H), 3.67 (1 H, t, *J* 8, 17-H), 4.27 (1 H, t, *J* 3, 6-H) and 4.91 (1 H, t, *J* 8.5, 3-H).

A solution of the alcohol (1.8 g) in dry pyridine (10 cm^3) was treated with acetic anhydride (4 cm^3) at room temperature for 20 h and was then poured into dil. hydrochloric acid. The product was recovered in ethyl acetate, washed successively with aq. sodium hydrogen carbonate and water, and dried. The solvent was evaporated off under reduced pressure to give 3β,6β,17β-*triacetoxy*-4α,5α-*epoxyandrostane* **11** (1.8 g), which was crystallized from ethyl acetate–light petroleum as needles, m.p. 134–135 °C (Found: C, 67.0; H, 8.1. $C_{25}H_{36}O_7$ requires C, 66.9; H, 8.1%); ν_{max}/cm^{-1} 1742; δ 0.85 (3 H, s, 18-H_3), 1.22 (3 H, s, 19-H_3), 2.04, 2.08 and 2.10 (each 3 H, s, OAC), 3.19 (1 H, s, 4-H), 4.31 (1 H, t, *J* 3, 6-H), 4.61 (1 H, dd, *J* 7.9 and 9.1, 17-H) and 4.94 (1 H, dd, *J* 8.1 and 8.9, 3-H).

Oxidation of 3β,6β,17β-*Triacetoxy*-4α,5α-*epoxyandrostane*.—Aq. chromium trioxide (75%) (1 cm^3) was added dropwise to a stirred solution of 3β,6β,17β-triacetoxy-4α,5α-epoxyandrostane (450 mg) in ethyl methyl ketone (5 cm^3) at 35–40 °C. The mixture was left for 40 min and was then poured into water. The product was recovered in ethyl acetate. The extracts were washed thoroughly with water and dried. The solvent was evaporated off and the residue was chromatographed on silica. Elution with 20% ethyl acetate–light petroleum gave 4β,6β,17β-*triacetoxy*-5α-*hydroxyandrostan*-3-*one* **13** (230 mg), which was crystallized from ethyl acetate–light petroleum as needles, m.p. 232–234 °C (Found: C, 64.6; H, 7.7. $C_{25}H_{36}O_8$ requires C, 64.6; H, 7.8%); ν_{max}/cm^{-1} 3420, 1743, 1735 and 1728; δ 0.84 (3 H, s, 18-H_3), 1.43 (3 H, s, 19-H_3), 2.03, 2.04 and 2.16 (each 3 H, s, OAC), 4.60 (1 H, t, *J* 8, 17-H), 4.96 (1 H, t, *J* 2.8, 6-H) and 5.57 (1 H, s, 4-H).

Elution with 45% ethyl acetate–light petroleum gave 4β,6β,17β-*triacetoxy*-3β,5α-*dihydroxyandrostane* **15** (80 mg), which was crystallized from acetone as needles, m.p. 252–255 °C (Found: C, 64.4; H, 8.1. $C_{25}H_{38}O_8$ requires C, 64.4; H, 8.2%); ν_{max}/cm^{-1} 3467, 3450, 1734 and 1730; δ 0.81 (3 H, s, 18-H_3), 1.32 (3 H, s, 19-H_3), 2.03, 2.11 and 2.17 (each 3 H, s, OAC), 4.31

Table 2 Intramolecular distances (Å) and angles (°), with estimated standard deviations in parentheses, for the two independent molecules

(*a*) Bonds	a	b		a	b
O(1)–C(17)	1.417(11)	1.422(12)	O(1)–C(20)	1.33(10)	1.291(10)
O(2)–C(20)	1.173(12)	1.215(12)	O(3)–C(5)	1.442(7)	1.436(8)
O(4)–C(4)	1.427(7)	1.449(8)	O(4)–C(22)	1.324(10)	1.301(9)
O(5)–C(22)	1.178(11)	1.213(13)	O(6)–C(3)	1.418(11)	1.433(11)
O(7)–C(6)	1.454(7)	1.430(8)	O(7)–C(24)	1.342(10)	1.361(11)
O(8)–C(24)	1.210(14)	1.239(14)	C(1)–C(2)	1.555(12)	1.514(13)
C(1)–C(10)	1.569(10)	1.564(11)	C(2)–C(3)	1.494(13)	1.494(13)
C(3)–C(4)	1.552(12)	1.523(11)	C(4)–C(5)	1.556(12)	1.551(12)
C(5)–C(6)	1.548(11)	1.562(11)	C(5)–C(10)	1.570(11)	1.574(12)
C(6)–C(7)	1.511(12)	1.507(13)	C(7)–C(8)	1.519(12)	1.557(13)
C(8)–C(9)	1.543(10)	1.568(11)	C(8)–C(14)	1.543(12)	1.500(12)
C(9)–C(10)	1.557(11)	1.558(12)	C(9)–C(11)	1.535(12)	1.519(13)
C(10)–C(19)	1.555(9)	1.518(9)	C(11)–C(12)	1.565(12)	1.520(13)
C(12)–C(13)	1.552(12)	1.536(13)	C(13)–C(14)	1.519(13)	1.529(13)
C(13)–C(17)	1.532(13)	1.525(14)	C(13)–C(18)	1.523(10)	1.518(12)
C(14)–C(15)	1.550(13)	1.564(14)	C(15)–C(16)	1.59(2)	1.513(15)
C(16)–C(17)	1.550(14)	1.576(14)	C(20)–C(21)	1.52(2)	1.49(2)
C(22)–C(23)	1.528(10)	1.504(13)	C(24)–C(25)	1.464(11)	1.487(12)
(*b*) Angles					
C(17)–O(1)–C(20)	119.5(7)	119.4(7)	C(4)–O(4)–C(22)	118.2(6)	120.8(7)
C(6)–O(7)–C(24)	119.9(6)	117.5(7)	C(2)–C(1)–C(10)	111.1(6)	114.7(6)
C(1)–C(2)–C(3)	113.0(7)	111.2(7)	O(6)–C(3)–C(2)	112.3(8)	110.1(7)
O(6)–C(3)–C(4)	109.3(6)	110.8(6)	C(2)–C(3)–C(4)	112.2(6)	111.0(7)
O(4)–C(4)–C(3)	109.5(6)	107.5(7)	O(4)–C(4)–C(5)	111.8(5)	111.4(6)
C(3)–C(4)–C(5)	111.5(6)	109.8(6)	O(3)–C(5)–C(4)	104.8(5)	105.4(6)
O(3)–C(5)–C(6)	104.3(6)	103.2(6)	O(3)–C(5)–C(10)	105.6(5)	106.0(5)
C(4)–C(5)–C(6)	113.2(6)	114.7(6)	C(4)–C(5)–C(10)	114.0(6)	112.3(7)
C(6)–C(5)–C(10)	113.7(6)	113.9(7)	O(7)–C(6)–C(5)	110.7(6)	111.3(6)
O(7)–C(6)–C(7)	107.5(6)	111.4(6)	C(5)–C(6)–C(7)	111.3(6)	111.4(6)
C(6)–C(7)–C(8)	112.7(7)	115.4(7)	C(7)–C(8)–C(9)	111.6(6)	110.6(7)
C(7)–C(8)–C(14)	110.1(6)	111.0(7)	C(9)–C(8)–C(14)	108.3(6)	108.2(6)
C(8)–C(9)–C(10)	112.4(6)	111.5(6)	C(8)–C(9)–C(11)	112.6(6)	110.6(7)
C(10)–C(9)–C(11)	112.5(6)	114.6(7)	C(1)–C(10)–C(5)	107.3(5)	107.3(6)
C(1)–C(10)–C(9)	110.2(5)	109.7(5)	C(1)–C(10)–C(19)	108.4(6)	108.4(7)
C(5)–C(10)–C(9)	106.7(6)	107.0(7)	C(5)–C(10)–C(19)	113.5(5)	113.4(6)
C(9)–C(10)–C(19)	110.7(6)	110.9(6)	C(9)–C(11)–C(12)	112.4(7)	113.2(8)
C(11)–C(12)–C(13)	110.3(6)	110.5(6)	C(12)–C(13)–C(14)	107.8(6)	108.6(7)
C(12)–C(13)–C(17)	114.1(6)	115.8(6)	C(12)–C(13)–C(18)	110.4(8)	109.2(8)
C(14)–C(13)–C(17)	98.5(7)	100.2(8)	C(14)–C(13)–C(18)	114.8(7)	112.7(6)
C(17)–C(13)–C(18)	110.8(7)	110.2(8)	C(8)–C(14)–C(13)	113.1(7)	116.4(8)
C(8)–C(14)–C(15)	117.5(6)	120.3(6)	C(13)–C(14)–C(15)	103.7(7)	103.4(7)
C(14)–C(15)–C(16)	102.8(7)	103.6(7)	C(15)–C(16)–C(17)	103.9(8)	106.8(8)
O(1)–C(17)–C(13)	115.1(7)	116.3(8)	O(1)–C(17)–C(16)	109.5(7)	110.5(8)
C(13)–C(17)–C(16)	105.1(7)	102.8(6)	O(1)–C(20)–O(2)	123(1)	123(1)
O(1)–C(20)–C(21)	110.5(8)	115.9(8)	O(2)–C(20)–C(21)	126(1)	121.1(8)
O(4)–C(22)–O(5)	123.1(6)	124.8(7)	O(4)–C(22)–C23)	111.9(7)	111.0(8)
O(5)–C(22)–C(23)	125.0(8)	124.2(7)	O(7)–C(24)–O(8)	121.1(7)	120.2(7)
O(7)–C(24)–C(25)	112.9(9)	115.0(9)	O(8)–C(24)–C(25)	125.9(9)	124.9(9)

(1 H, br s, 3-H), 4.58 (1 H, t, *J* 8, 17-H), 4.94 (1 H, br s, 4-H) and 5.13 (1 H, t, *J* 3.5, 6-H).

Preparation of 17β-*Acetoxy*-3α-*chloro*-4β,5β-*epoxyandrostane*.—17β-Acetoxy-4β,5β-epoxyandrostan-3β-ol **17**[9] (750 mg) was added to a solution of triphenylphosphine (800 mg) in carbon tetrachloride (20 cm^3)–pyridine (2 cm^3) and the mixture was heated under reflux for 8 h, cooled and evaporated, and the residue was dissolved in ethyl acetate, washed successively with dil. hydrochloric acid, aq. sodium hydrogen carbonate and water, and dried. The solvent was evaporated off and the residue was chromatographed on silica. Elution with 5% ethyl acetate–light petroleum gave 17β-*acetoxy*-3α-*chloro*-4β,5β-*epoxyandrostane* **16** (501 mg), which was crystallized from ethyl acetate–light petroleum as needles, m.p. 110–111 °C (Found: C, 68.8; H, 8.4. $C_{21}H_{31}ClO_3$ requires C, 68.9; H, 8.2%); ν_{max}/cm^{-1} 1728; δ 0.80 (3 H, s, 18-H_3), 1.01 (3 H, s, 19-H_3), 2.00 (3 H, s, OAC), 3.07 (1 H, s, 4-H), 4.15 (1 H, t, *J* 7, 3-H) and 4.6 (1 H, t, *J* 8, 17-H).

Elution with 6% ethyl acetate–light petroleum gave 17β-acetoxy-3β-chloro-4β,5β-epoxyandrostane **18** (137 mg), identified by its IR and NMR spectra.

Preparation of 17β-*Acetoxy*-4β,5β-*epoxyandrostan*-3α-*ol*.—A solution of 17β-acetoxy-4β,5β-epoxyandrostan-3-one (500 mg) in methanol (20 cm^3) was treated with sodium borohydride (200 mg) at 0 °C for 30 min. Acetic acid (1 cm^3) was added, the solution was poured into water, and the solid was filtered off to give 17β-*acetoxy*-4β,5β-*epoxyandrostan*-3α-*ol* **19** (250 mg), which was crystallized from light petroleum as needles, m.p. 169–171 °C (Found: C, 72.3; H, 9.1. $C_{21}H_{32}O_4$ requires C, 72.4; H, 9.3%); ν_{max}/cm^{-1} 3560 and 1740; δ 0.80 (3 H, s, 18-H_3), 1.02 (3 H, s, 19-H_3), 2.08 (3 H, s, OAc), 2.86 (1 H, s, 4-H), 4.00 (1 H, t, *J* 7, 3-H) and 4.60 (1 H, t, *J* 8, 17-H).

Preparation of 17β-*Acetoxy*-3β-*chloro*-4β,5β-*epoxyandrostane*.—17β-Acetoxy-4β,5β-epoxyandrostan-3α-ol **19** (600 mg) was added to a solution of triphenylphosphine (650 mg) in carbon tetrachloride (20 cm^3)–pyridine (2 cm^3). The mixture was heated under reflux for 10 h, then cooled and evaporated, and the residue was dissolved in ethyl acetate. This solution was washed successively with dil. hydrochloric acid, aq. sodium hydrogen carbonate and water, and dried. The solvent was evaporated off and the residue was chromatographed on silica.

Elution with 10% ethyl acetate–light petroleum gave 17β-*acetoxy*-3β-*chloro*-4β,5β-*epoxyandrostane* **18** (500 mg), which was crystallized from methyl acetate–light petroleum as needles, m.p. 109–110 °C (Found: C, 68.5; H, 8.2. $C_{21}H_{31}ClO_3$ requires C, 68.7; H, 8.5%); ν_{max}/cm^{-1} 1732; δ 0.84 (3 H, s, 18-H_3), 1.08 (3 H, s, 19-H_3), 2.03 (3 H, s, OAC), 3.14 (1 H, d, *J* 3, 4-H), 4.16 (1 H, t, *J* 3, 3-H) and 4.60 (1 H, t, *J* 8, 17-H).

Oxidation of 17β-*Acetoxy*-3β-*chloro*-4β,5β-*epoxyandrostane*.—Aq. chromium trioxide (75%) (2 cm^3) was added dropwise to a stirred solution of 17β-acetoxy-3β-chloro-4β,5β-epoxyandrostane **18** (500 mg) in ethyl methyl ketone (15 cm^3) at 35–40 °C. The solution was left for 1 h and was then poured into water. The product was recovered in ethyl acetate. The extract was washed thoroughly with water and dried. The solvent was evaporated off and the residue was chromatographed on silica. Elution with 7% ethyl acetate–light petroleum gave the starting material (252 mg recovery). Further elution with 9% ethyl acetate–light petroleum gave a mixture (169 mg) of 17β-acetoxy-3β-chloro-5α-hydroxyandrostan-4-one **21** and 17β-acetoxy-3β-chloro-4β,5α-dihydroxyandrostane **20** (NMR), which could not be further separated.

A solution of the mixture (150 mg) in dry benzene (10 cm^3) was heated with tributyltin hydride (0.4 cm^3) and azoisobutyronitrile (30 mg) under reflux for 5 h. The solution was cooled, the solvent was evaporated off and the residue was chromatographed on silica. Elution with 9% ethyl acetate–light petroleum gave a mixture (55 mg) from which 17β-*acetoxy*-5α-*hydroxyandrostan*-4-*one* **23** was crystallized as needles, m.p. 194–197 °C (Found: C, 68.6; H, 9.1. $C_{21}H_{32}O_4 \cdot H_2O$ requires C, 68.8; H, 9.35%); ν_{max}/cm^{-1} 3501, 1735 and 1713; δ 0.77 and 0.79 (each 3 H, s, 18- and 19-H_3), 2.02 (3 H, s, OAc) and 4.58 (1 H, t, *J* 8, 17-H).

Elution with 20% ethyl acetate–light petroleum gave 17β-*acetoxy*-4β,5α-*dihydroxyandrostane* **22** (92 mg), which was crystallized from acetone–light petroleum as needles, m.p. 191–192 °C (Found: C, 68.7; H, 9.8. $C_{21}H_{34}O_4 \cdot H_2O$ requires C, 68.4; H, 9.8%); ν_{max}/cm^{-1} 3515 and 1716; δ 0.78 (3 H, s, 18-H_3), 1.18 (3 H, s, 19-H_3), 2.03 (3 H, s, OAc), 3.54 (1 H, d, *J* 2.4, 4-H) and 4.58 (1 H, dd, *J* 7.8 and 9.1, 17-H).

There was no reaction on attempted oxidation of the 3α-chloro-4β,5β-epoxide with chromium trioxide in ethyl methyl ketone at 40 °C for 5 h.

X-Ray Structure Determination of Compound **15**.—*Crystal data*. $C_{25}H_{38}O_8$, M = 466.6, monoclinic, space group $P2_1$, a = 16.221(23), b = 7.960(15), c = 20.878(8) Å, β = 110.90°, V = 2518.4 Å^3, Z = 4, D_c = 1.23 g cm^{-3}, $F(000)$ = 1008, monochromated Mo-$K\alpha$ radiation, λ = 0.710 69 Å, μ = 0.8 cm^{-1}.

Data were collected using a crystal 1.5 × 0.3 × 0.2 mm on an Enraf–Nonius CAD4 diffractometer. Reflections were measured using a θ–2θ scan with $\Delta\theta = (0.8 + 0.35 \tan\theta)°$ and a maximum scan time of 1 min. A total of 4777 unique reflections were measured with $2 < \theta < 25°$ and $+h$, $+k$, $\pm l$ and 2969 reflections with $|F^2| > 3\ \sigma(F^2)$ were used in the refinement where $\sigma(F^2) = \{\sigma^2(I) + (0.04I)^2\}^{\frac{1}{2}}/L_p$. There was no correction for absorption.

The structure was solved by direct methods using SHELXS-86. Non-hydrogen atoms were refined anisotropically by full-matrix least-squares using the Enraf–Nonius SDP-Plus program package. Hydrogen atoms, except for the hydroxy groups and the ester methyl groups, were held fixed at calculated positions with $u_{iso} = 1.3\ u_{eq}$ for the atom to which they are bonded. The absolute structure was assigned from the known chemical synthesis. The weighting scheme was $w = 1/\sigma^2(P)$ and the final residuals were R = 0.077, R' = 0.101. There are two independent molecules with essentially the same geometry. The X-ray molecular structure is shown in Fig. 1. Fractional atomic co-ordinates and intramolecular distances and angles are given in Tables 1 and 2.*

Acknowledgements

We thank the Ministry of Higher Education, Iraq, for financial support for N. F.

* *Supplementary data:* Hydrogen atom co-ordinates, torsional angles and temperature factors have been deposited with the Cambridge Crystallographic Data Centre (see section 5.6.3 of Instructions for Authors, issue 1).

References

1 L. Knof, *Justus Liebigs Ann. Chem.*, 1961, **647**, 53.
2 J. R. Hanson and A. Truneh, *J. Chem. Soc., Perkin Trans. 1*, 1988, 2001.
3 S. Julia and B. Furer, *Bull. Soc. Chim. Fr.*, 1966, 1106.
4 T. H. Campion, G. A. Morrison and J. B. Wilkinson, *J. Chem. Soc., Perkin Trans. 1*, 1976, 2508.
5 M. Ishiguro, H. Saito, Y. Hirano and N. Ikekawa, *J. Chem. Soc., Perkin Trans. 1*, 1980, 2503.
6 G. A. Morrison and J. B. Wilkinson, *J. Chem. Soc., Perkin Trans. 1*, 1989, 2003.
7 S. Julia and B. Furer, *Bull. Soc. Chim. Fr.*, 1966, 1114.
8 J. R. Hanson and P. B. Reese, *J. Chem. Soc., Perkin Trans. 1*, 1988, 331.
9 P. Keller, Frl. Eggart, H. Wehrli, K. Schaffner and O. Jeger, *Helv. Chim. Acta*, 1967, **50**, 2259.
10 M. Davis and V. Petrow, *J. Chem. Soc.*, 1949, 2536.

Paper 0/04911E
Received 31*st October* 1990
Accepted 11*th December* 1990