

## Studies in the Steroid Group. Part LXXXIV.<sup>1</sup> Preparation and Reactions of 15-Oxygenated Androstanes

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Treatment of 15 $\beta$ ,16 $\beta$ -epoxy-5 $\alpha$ -androstan-17-one with hydrazine and toluene-*p*-sulphonic acid in air gives 5 $\alpha$ -androstan-15 $\beta$ -ol; this step markedly improves the chemical route to 5 $\alpha$ -androstan-15-one from the 3-ketone. The 15-ketone is also readily obtained from 12 $\beta$ ,15 $\alpha$ -dihydroxy-5 $\alpha$ -androstan-3-one (prepared by microbiological hydroxylation of 5 $\alpha$ -androstan-3-one). Two series of substituted (mainly oxygenated) androstanes are described: those substituted at position 15 or at positions 15 and 17, and those substituted at the 12- and 15-, or at the 3-, 12-, and 15-positions.

5 $\alpha$ -ANDROSTAN-15-ONE was not readily available at the time when it was required as a substrate in microbiological hydroxylation studies.<sup>2</sup> The synthesis<sup>3</sup> devised then is convenient, but, with two microbiological stages involved, laborious for the preparation of an appreciable

quantity (*ca.* 10 g) of the 15-ketone. Our first object in the present work was to develop a route suited to large-scale operations. This was intended to be part of a more general investigation of 15-substituted androstanes (*e.g.*

<sup>2</sup> A. M. Bell, P. C. Cherry, I. M. Clark, W. A. Denny, Sir Ewart R. H. Jones, G. D. Meakins, and P. D. Woodgate, *J.C.S. Perkin I*, 1972, 2081.

<sup>3</sup> J. W. Blunt, I. M. Clark, J. M. Evans, E. R. H. Jones, G. D. Meakins, and J. T. Pinhey, *J. Chem. Soc. (C)*, 1971, 1136.

<sup>1</sup> Part LXXXIII, I. M. Clark, A. S. Clegg, W. A. Denny, E. R. H. Jones, G. D. Meakins, and A. Pendlebury, *J.C.S. Perkin I*, 1972, 499.

Experimental section; new conversions, for example the selective oxidation of 5 $\alpha$ -androstane-15 $\beta$ ,17 $\beta$ -diol (XIIIc) to the 15 $\beta$ -hydroxy-17-ketone (XIIc), are described. The structures (in particular the stereochemical features) of the new steroids follow from their relationships to known compounds, and from the interpretation of their



Reagents: (1),  $\text{KOBu}^t\text{-Me}_2\text{SO}$ , 45 °C; (2) as (1), 55 °C; (3)  $\text{TsOH-Me}_2\text{CO-H}_2\text{O}$ ; (4)  $\text{H}_2\text{O}_2\text{-NaOH-Bu}^t\text{OH}$ ; (5),  $\text{N}_2\text{H}_4\text{-H}^+$ , in  $\text{N}_2$ ; (6),  $\text{NaCN-H}_2\text{O-THF}$  (tetrahydrofuran); (7),  $\text{H}_2\text{CrO}_4\text{-Me}_2\text{CO}$ ; (8),  $\text{H}_2\text{, Pd}$ ; (9),  $\text{N}_2\text{H}_4\text{-H}^+$ , in air; (10),  $\text{LiAlH}_4\text{-THF}$ ; (11),  $\text{HS}^-\text{[CH}_2\text{]}_2\text{SH-BF}_3$ ; (12),  $\text{ROH-NaOH-THF}$ ; (13),  $\text{NaOMe-MeOH}$ ; (14),  $\text{LiAlH(OBu}^t\text{)}_3\text{-THF}$ ; (15),  $\text{TsCl-C}_5\text{H}_5\text{N}$ ; (16),  $\text{LiAlH}_4\text{-Et}_2\text{O}$ ; (17), Raney Ni; (18), as (1), 100 °C, then  $\text{HClaq}$ ; (19), heat, 90 °C, or  $\text{NaHCO}_3\text{-MeOH}$ , reflux; (20),  $\text{Ag}_2\text{CO}_3$  on Celite.

<sup>a</sup> Ref. 6.    <sup>b</sup> Ref. 13.

The results are presented in Schemes 1 and 2. References are given after the formulae numbers of known compounds; the rest are new. Interconversions of known compounds carried out without significant modification of the literature procedures are not recorded in the

<sup>4</sup> J. E. Bridgeman, P. C. Cherry, A. S. Clegg, J. M. Evans, E. R. H. Jones, A. Kasal, V. Kumar, G. D. Meakins, Y. Morisawa, E. E. Richards, and P. D. Woodgate, *J. Chem. Soc. (C)*, 1970, 250.

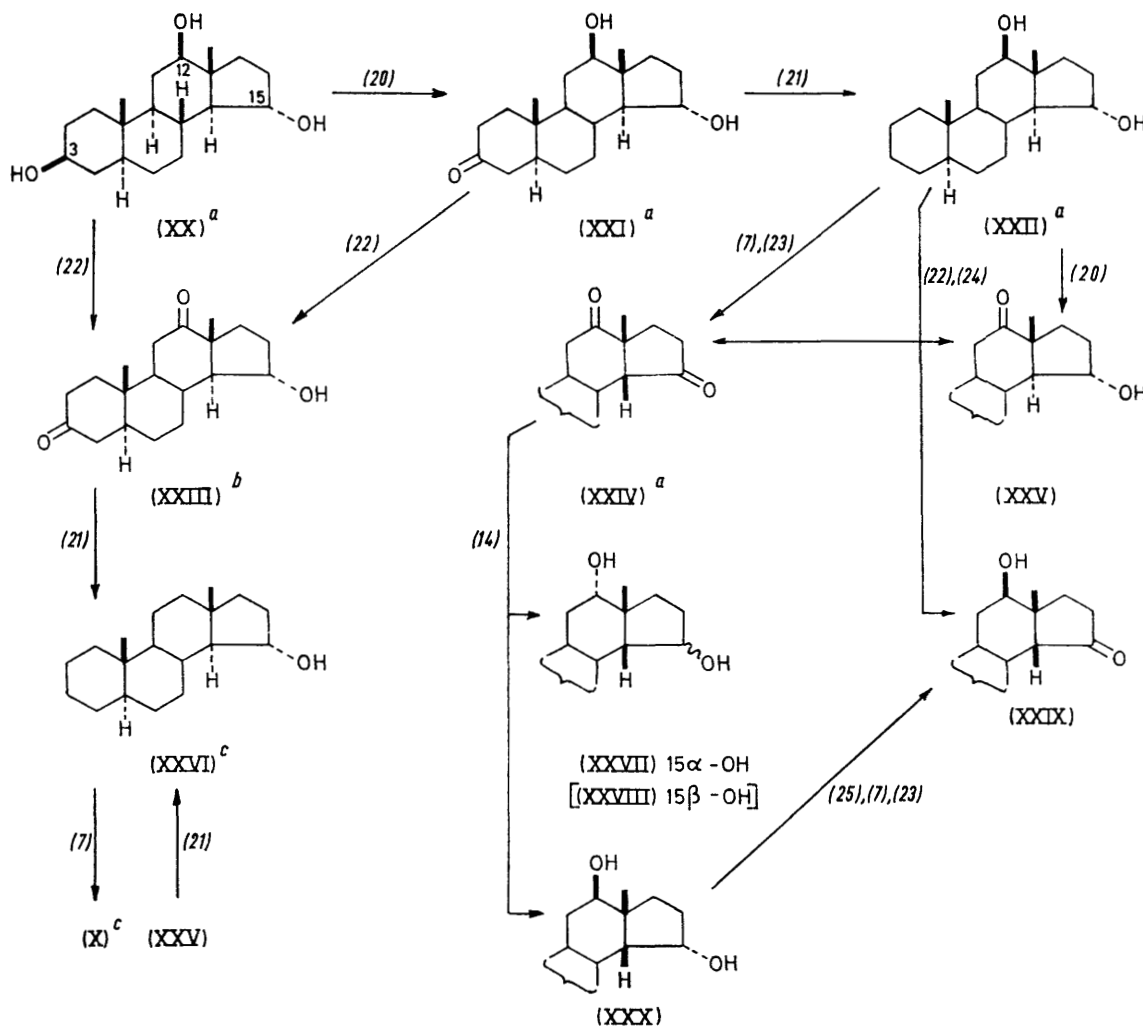
n.m.r. signals (Table) and i.r. absorptions (Experimental section) as explained in our earlier surveys.<sup>4,5</sup>

Scheme 1 portrays androstanes with substituents at position 15 or at positions 15 and 17. The most direct chemical route to 5 $\alpha$ -androstan-15-one (X), that of

<sup>5</sup> A. D. Boul, J. W. Blunt, J. W. Browne, V. Kumar, G. D. Meakins, J. T. Pinhey, and V. E. M. Thomas, *J. Chem. Soc. (C)*, 1971, 1130.

Djerassi *et al.*,<sup>6</sup> is 5 $\alpha$ -androst-17-one (readily available)  $\rightarrow$  (I)  $\rightarrow$  (III)  $\rightarrow$  (IV)  $\rightarrow$  (V)  $\rightarrow$  (VI)  $\rightarrow$  (X), a sequence in which all but two stages had given high yields. In the present work successful dehydrobromination of the bromo-acetal (I) to the  $\Delta^{15}$ -acetal (III) was found to require careful control of temperature. Conversion of the keto-epoxide (V) into the allylic alcohol (VI) with hydrazine and acid, a transformation based

product of higher oxidation level, is formed in nitrogen. Treatment of either the keto-epoxide (V) or the allylic alcohol (VI) with hydrazine and acid in air gives the saturated alcohol (XI). The simplest explanation is that the 16,17-olefinic bond is reduced by di-imide generated from oxygen and the hydrazinium cation: although di-imide may be produced from hydrazine in various ways<sup>8</sup> there appears to be no precedent for the



SCHEME 2

Reagents as in Scheme 1, and; (21), Huang-Minlon reduction; (22), AcNHBr-Me<sub>2</sub>CO, 20 °C; (23), KOH-MeOH; (24), Al<sub>2</sub>O<sub>3</sub> (chromatography); (25), Ac<sub>2</sub>O-C<sub>6</sub>H<sub>5</sub>N.

• Ref. 2. • Ref. 14. • Ref. 6.

on work by Wharton and Bohlen,<sup>7</sup> was reported<sup>6</sup> to give low and variable yields. Investigation (see Experimental section) showed that both the allylic and the saturated alcohols, (VI) and (XI), may be obtained according to the atmosphere (nitrogen or air) in which the reaction is conducted. Surprisingly, the allylic alcohol (VI), the

present observations. Use of the two efficient steps (V)  $\rightarrow$  (XI)  $\rightarrow$  (X) greatly improves the route to the 15-ketone.

Although we could not repeat the reported addition<sup>9</sup> of benzyl alcohol to 5 $\alpha$ -androst-15-en-17-one (IV), other Michael reactions gave high yields of products [(IX) and

<sup>6</sup> C. Djerassi, G. von Mutzenbecker, J. Fajkos, D. H. Williams, and H. Budzikiewicz, *J. Amer. Chem. Soc.*, 1965, **87**, 817.

<sup>7</sup> P. S. Wharton and D. H. Bohlen, *J. Org. Chem.*, 1961, **26**, 3615.

<sup>8</sup> J. M. Hoffman and R. H. Schlessinger, *Chem. Comm.*, 1971, 1245.

<sup>9</sup> C. W. Cantrall, R. Littell, and S. Bernstein, *J. Org. Chem.*, 1964, **29**, 64.

(XIIa and b)] with 15 $\beta$ -substituents which form the basis of the remaining work in Scheme 1.

The compounds in Scheme 2 have hydroxy- or keto-groups at the 12- and 15-, or at the 3-, 12-, and 15-positions. 12 $\beta$ ,15 $\alpha$ -Dihydroxy-5 $\alpha$ -androstan-3-one (XXI), the starting material for this work, is readily obtained by microbiological hydroxylation of 5 $\alpha$ -androstan-3-one, and easily reduced to the 3 $\beta$ ,12 $\beta$ ,15 $\alpha$ -triol (XX).<sup>2</sup> The conversions of the triol (XX) into the dihydroxy-ketone (XXI), and of both these compounds into 5 $\alpha$ -androstan-15-one (X) involve selective oxidations based on the different rates at which the hydroxy-groups (3 > 12 > 15) are attacked. Combination of the microbiological

which, *mutatis mutandis*, is similar to that of 'remote oxidation' accomplished by photochemical means:<sup>10</sup> it would be difficult to devise an efficient alternative involving standard chemical processes. The silver carbonate on Celite reagent<sup>11</sup> was more effective than *N*-bromoacetamide for selective oxidation at position 12 of the 12 $\beta$ ,15 $\alpha$ -diol (XXII). Reduction of the 14 $\beta$ -12,15-dione (XXIV) gave a mixture of stereoisomeric diols, even when a bulky hydride reagent was used. (The configurations of the 15-hydroxy-groups in the 14 $\beta$ -compounds are based on the expectation that the >CH·OH proton will be more strongly coupled in 15 $\beta$ -alcohols, the situation resembling that found<sup>4</sup> with the 15 $\alpha$ -OH-14 $\alpha$ -H system.)

TABLE 1

N.m.r. signals

Signals (CDCl<sub>3</sub> solutions; 100 MHz) are described in the form used previously.\* The n.m.r. and (for the majority) the i.r. absorptions of the following have already been reported: (IV), (X), (XX), (XXI), (XXII), (XXIV), (XXVI) (ref. 4), (XI), (ref. 5), (XVI) (ref. 2), (XXV) and (XXIX) (ref. 15)

No.	19-H $\tau$	18-H $\tau$	Other signals		Assign- ment
			$\tau$	Form	
(I)	9.23	9.14			
(II)	9.19	9.84	4.91	4(4.2, 4)	H-15
(III)	9.19	9.09	4.31	4(5.5, 5)	H-15
			3.81	d(5)	H-16
(V)	9.16	8.85	6.73	d(3.5)	H-15
			6.17	d(3.5)	H-16
(VI)	9.13	8.95	5.50	m(10)	H-15
(VII)	9.19	8.99	0.39	d(4)	CHO
(VIII)	9.16	8.85			
(IX)	9.12	8.82	6.75	7(8, 8, 1.3)	H-15
(XIIa)	9.15	8.90	6.06	t(6)	H-15
(XIIb)	9.13	8.84			
(XIIc)	9.14	8.82	5.89	m(7)	H-15
(XIIIa)	9.18	9.07			
(XIIIb)	9.16	9.01			
(XIIIc)	9.17	8.99	6.42	t(8.5)	H-17
			5.78	7(7, 5, 2.5)	H-15
(XIVa)	9.22	9.02	6.45	m(7)	H-15
(XIVb)	9.21	9.00			
(XIVc)	9.20	8.95	5.76	m(25)	{H-15 H-17}
(XV)	9.17	8.84	5.67	8(7.5, 5.5, 3)	H-15
(XVII)	9.16	9.02	4.12	d(6)	H-16
			2.65	d(6)	H-17
(XVIII)	9.14	8.95	5.99	4(5, 2)	H-15
(XIX)	9.21	9.12	5.37	t(8)	H-17
(XXVII)	9.27	8.90	6.46	m(6)	H-12
			5.75	6(4, 1.5, 1.5)	H-15
(XXVIII) *	9.22	8.95	6.48	m(7)	H-12
			5.55	6(9, 5, 5)	H-15
(XXX)	9.24	8.98	6.06	4(12, 4)	H-12
			5.61	6(4, 1.5, 1.5)	H-15

\* A. S. Clegg, W. A. Denny, E. R. H. Jones, V. Kumar, G. D. Meakins, and V. E. M. Thomas, *J.C.S. Perkin I*, 1972, 492.

\* Not fully characterised.

and chemical results gives a four-step sequence [5 $\alpha$ -androstan-3-one  $\rightarrow$  (XXI)  $\rightarrow$  (XXIII)  $\rightarrow$  (XXVI)  $\rightarrow$  5 $\alpha$ -androstan-15-one] for transposing a keto-group from one end of the steroid molecule to the other. This transposition exemplifies an approach to steroid synthesis

## EXPERIMENTAL

For general directions see ref. 3. Arabic numbers are given after the formulae numbers of compounds connected with microbiological work: the n.m.r. signals of these compounds, Nos. 510—516, are listed in Table 1. Petrol refers to light petroleum, b.p. 40—60°.

*Treatment of 16 $\alpha$ -Bromo-17,17-ethylenedioxy-5 $\alpha$ -androstan-3-one (I) with Potassium *t*-Butoxide.*—A solution of the acetal<sup>6</sup> (23 g) and KOBu<sup>t</sup> [freshly sublimed; from K (5.6 g)] in Me<sub>2</sub>SO (700 ml) was stirred under N<sub>2</sub> at 45 °C for 30 h. Standard manipulation gave the  $\Delta^{15}$ -acetal (III) (15.1 g), m.p. 120—121.5° (from MeOH) (lit.,<sup>6</sup> 120—121°). A similar experiment carried out at 55 °C afforded material shown by t.l.c. to contain approximately equal amounts of the  $\Delta^{15}$ -acetal (III) and another compound, which was chromatographed on Al<sub>2</sub>O<sub>3</sub> (300 g). Petrol-Et<sub>2</sub>O (10:1) eluted 17,17-ethylenedioxy-5 $\alpha$ -androstan-14-ene (II) (3.9 g; m.p. 82—83°, after two crystallisations from MeOH), [ $\alpha$ ]<sub>D</sub> 2° (c 1.0) (Found: C, 79.6; H, 10.4. C<sub>21</sub>H<sub>32</sub>O<sub>2</sub> requires C, 79.8; H, 10.2%),  $\nu_{\max}$  3060 and 1647 cm<sup>-1</sup>.

A solution of the  $\Delta^{14}$ -acetal (II) (1.67 g) and TsOH-H<sub>2</sub>O (150 mg) in Me<sub>2</sub>CO (150 ml)-H<sub>2</sub>O (10 ml) was kept at 20 °C for 48 h. Work-up gave 5 $\alpha$ -androstan-14-en-17-one (1.42 g), m.p. 56—57° (from MeOH-H<sub>2</sub>O), [ $\alpha$ ]<sub>D</sub> +142° (c 1.0) (lit.,<sup>12</sup> m.p. 56—57°, [ $\alpha$ ]<sub>D</sub> +142°).

*Treatment of 15 $\beta$ ,16 $\beta$ -Epoxy-5 $\alpha$ -androstan-17-one (V) and of 5 $\alpha$ -Androst-16-en-15 $\beta$ -ol (VI) with Hydrazine.*—A solution of N<sub>2</sub>H<sub>4</sub> (anhydrous; 280 mg) in MeOH (3 ml) was added dropwise to a solution of the epoxy-ketone<sup>6</sup> (500 mg) in dry MeOH (20 ml) which was stirred under N<sub>2</sub> at 20 °C. After 5 min, AcOH (200 mg) in MeOH (3 ml) was added, and the yellow solution was stirred for 18 h. Evaporation at 2 cmHg and 20 °C to half volume and work-up gave material (493 mg) which was chromatographed on Al<sub>2</sub>O<sub>3</sub> [20 g; deactivated with H<sub>2</sub>O (1 ml)]. Petrol-Et<sub>2</sub>O (99:1) eluted 5 $\alpha$ -androstan-16-en-15 $\beta$ -ol (VI) (No. 511) (205 mg; m.p. 75—77°, after crystallisation from C<sub>6</sub>H<sub>14</sub>), [ $\alpha$ ]<sub>D</sub> -70° (c 0.4) (lit.,<sup>6</sup> m.p. 76—77°, [ $\alpha$ ]<sub>D</sub> -71°). Hydrogenation of this alcohol (200 mg) in EtOAc (20 ml) over 5% Pd-C (pre-reduced; 130 mg) gave 5 $\alpha$ -androstan-15 $\beta$ -ol (XI) (188 mg), m.p. 75.5—77° (from MeOH), [ $\alpha$ ]<sub>D</sub> -33° (c 0.5) (lit.,<sup>6</sup> m.p. 75.5—77°, [ $\alpha$ ]<sub>D</sub> -34°).

The results of similar experiments carried out with the epoxy-ketone (500 mg) or the allylic alcohol (VI) (500 mg) and N<sub>2</sub>H<sub>4</sub> (280 mg) are shown in Table 2, the result of the

<sup>10</sup> R. Breslow and S. W. Baldwin, *J. Amer. Chem. Soc.*, 1970, 92, 732.

<sup>11</sup> M. Fetizon and M. Golfier, *Compt. rend.*, 1968, 267C, 900.

<sup>12</sup> A. C. Campbell, J. McLean, and W. Laurie, *Tetrahedron Letters*, 1969, 483.

experiment already described being included as the first entry. In the fourth experiment the mixture of alcohols produced was separated by chromatography on  $\text{Al}_2\text{O}_3$  [deactivated with  $\text{H}_2\text{O}$  (1%)]. Elution with petrol- $\text{Et}_2\text{O}$  (99 : 1) gave the saturated alcohol (XI) and then the allylic alcohol (VI).

TABLE 2

Compound	Solvent	Acid	T/°C	Atmosphere	Wt (mg) of (VI) (XI)
(V)	MeOH	AcOH (200 mg)	20	N <sub>2</sub>	205
(V)	Bu <sup>t</sup> OH		20	N <sub>2</sub>	163
(V)			0	N <sub>2</sub>	211
(V)			0	Air	40
(V)	MeOH	TsOH, H <sub>2</sub> O (500 mg)	0	N <sub>2</sub>	204
(V)			0	Air	243
(VI)	MeOH		0	Air	482

**Compounds (VII), (VIII), and (IX).**—A solution of 5 $\alpha$ -androst-15-en-17-one<sup>6</sup> (1 g) and NaCN (2.5 g) in THF (100 ml)– $\text{H}_2\text{O}$  (2 ml) was refluxed for 2.5 h. Work-up, and crystallisation (MeOH) of the product (1.02 g) gave 17-oxo-5 $\alpha$ -androstane-15 $\beta$ -carbonitrile (IX) (840 mg), m.p. 188–190°,  $[\alpha]_D^{25} +0.5$  (c 1.1) (Found: C, 80.0; H, 9.5; N, 4.4).  $\text{C}_{20}\text{H}_{32}\text{NO}$  requires C, 80.3; H, 9.8; N, 4.5%,  $\nu_{\text{max}}$  2235 and 1750  $\text{cm}^{-1}$ ,  $m/e$  299 ( $M^+$ , 100%).

A solution of the preceding ketone (500 mg) and  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  (0.7 ml) in  $\text{HS} \cdot [\text{CH}_2]_2 \cdot \text{SH}$  (0.7 ml) was shaken for 5 min at 20 °C, diluted with  $\text{CHCl}_3$  (12 ml), kept for 12 h at 20 °C, diluted with more  $\text{CHCl}_3$  (10 ml), and washed with saturated  $\text{NaHCO}_3$  aq. Work-up gave 17,17-ethylenedithio-5 $\alpha$ -androstane-15 $\beta$ -carbonitrile (VIII) (605 mg), m.p. 191–191.5° (from  $\text{Me}_2\text{CO}-\text{C}_6\text{H}_{14}$ ),  $[\alpha]_D^{25} -82^\circ$  (c 0.9) (Found: C, 70.8; H, 8.8; N, 3.9).  $\text{C}_{22}\text{H}_{33}\text{NS}_2$  requires C, 70.5; H, 8.9; N, 3.7%,  $\nu_{\text{max}}$  2240  $\text{cm}^{-1}$ ,  $m/e$  375 ( $M^+$ , 15%). A solution of the cyanothioacetal (370 mg) in THF (10 ml) was added during 15 min to a stirred suspension of  $\text{LiAlH}_4$  (190 mg) in THF (15 ml) at 20 °C, and the mixture was stirred for 2 h. Work-up and p.l.c. [1 large plate, 3  $\times$  petrol- $\text{Et}_2\text{O}$  (9 : 1)] afforded 17,17-ethylenedithio-5 $\alpha$ -androstane-15 $\beta$ -carbaldehyde (VII) (167 mg), m.p. 125–127° (from  $\text{C}_6\text{H}_{14}$ ),  $[\alpha]_D^{25} +12^\circ$  (c 1.2) (Found: C, 69.9; H, 8.9).  $\text{C}_{22}\text{H}_{34}\text{OS}_2$  requires C, 69.9; H, 9.0%,  $\nu_{\text{max}}$  2705 and 1728  $\text{cm}^{-1}$ ,  $m/e$  378 ( $M^+$ , 12%).

**Compounds (XIIa and b), (XIIIa and b), and (XIVa and b).**—Solutions of 5 $\alpha$ -androst-15-en-17-one (1 g) in THF (11 ml) and of NaOH (110 mg) in  $\text{H}_2\text{O}$  (2 ml)–MeOH (100 ml) were mixed and kept at 20 °C for 2 h. Work-up gave 15 $\beta$ -methoxy-5 $\alpha$ -androstane-17-one (XIIa) (880 mg; m.p. 109–110°, after crystallisation from MeOH),  $[\alpha]_D^{25} -12^\circ$  (c 1.0) (Found: C, 79.4; H, 10.5).  $\text{C}_{20}\text{H}_{32}\text{O}_2$  requires C, 79.0; H, 10.6%,  $\nu_{\text{max}}$  1742  $\text{cm}^{-1}$ ,  $m/e$  304 ( $M^+$ , 100%). A similar experiment with  $\text{CH}_3\text{CH}(\text{CH}_2)_2\text{OH}$  afforded 15 $\beta$ -allyloxy-5 $\alpha$ -androstane-17-one (XIIb) (950 mg; m.p. 109–110° from MeOH– $\text{H}_2\text{O}$ ),  $[\alpha]_D^{25} -25^\circ$  (c 0.9) (Found: C, 80.0; H, 10.45).  $\text{C}_{22}\text{H}_{34}\text{O}_2$  requires C, 80.1; H, 10.4%,  $\nu_{\text{max}}$  1745  $\text{cm}^{-1}$ ,  $m/e$  330 ( $M^+$ , 100%).

Solutions of the preceding ketones (1 g) in THF (10 ml) were stirred with  $\text{LiAlH}(\text{OBu}^t)_3$  [from  $\text{LiAlH}_4$  (200 mg)] in THF (10 ml) at 0 °C for 3 h, and then at 20 °C for 4 h. Work-up gave 15 $\beta$ -methoxy-5 $\alpha$ -androstane-17 $\beta$ -ol (XIIIa) (950 mg; m.p. 124–125°, from  $\text{Me}_2\text{CO}-\text{C}_6\text{H}_{14}$ ),  $[\alpha]_D^{25} -6^\circ$  (c 1.0) (Found: C, 76.8; H, 10.1).  $\text{C}_{20}\text{H}_{34}\text{O}_2$  requires C, 76.6; H, 10.1%,  $\nu_{\text{max}}$  3620  $\text{cm}^{-1}$ ; and 15 $\beta$ -allyloxy-5 $\alpha$ -androstane-17 $\beta$ -ol (XIIIb) (960 mg; m.p. 119–119.5°, from MeOH– $\text{H}_2\text{O}$ ),  $[\alpha]_D^{25} -52^\circ$  (c 1.0) (Found: C, 79.6; H, 11.1).  $\text{C}_{22}\text{H}_{36}\text{O}_2$  requires C, 79.6; H, 10.9%. When treated with

$\text{BzCl}-\text{C}_6\text{H}_5\text{N}$  at 20 °C, the methoxy-alcohol (XIIIa) gave a benzoate, m.p. 104–106°,  $[\alpha]_D^{25} -2^\circ$  (c 0.6) (Found: C, 78.9; H, 9.3).  $\text{C}_{27}\text{H}_{38}\text{O}_3$  requires C, 79.1; H, 9.3%,  $\nu_{\text{max}}$  1722  $\text{cm}^{-1}$ .

Treatment of the preceding hydroxy-ethers with  $\text{TsCl}-\text{C}_6\text{H}_5\text{N}$  at 0 °C for 1 day and then at 20 °C for 1 day gave the methoxy-ester (XIVa) (85% yield), m.p. 155–156° (from  $\text{C}_6\text{H}_{14}$ ),  $[\alpha]_D^{25} -30^\circ$  (c 0.9) (Found: C, 70.5; H, 8.9; S, 7.1).  $\text{C}_{27}\text{H}_{40}\text{O}_4\text{S}$  requires C, 70.5; H, 8.8; S, 7.1%, and the allyloxy-ester (XIVb) (81% yield), m.p. 98–99° (from  $\text{C}_6\text{H}_{14}$ ),  $[\alpha]_D^{25} -30^\circ$  (c 0.9) (Found: C, 71.3; H, 8.7).  $\text{C}_{29}\text{H}_{42}\text{O}_4\text{S}$  requires C, 71.6; H, 8.9%. When solutions of these esters (100 mg) in  $\text{Et}_2\text{O}$  (12 ml) were refluxed with  $\text{LiAlH}_4$  (100 mg) for 1 h, the products were the respective hydroxy-ethers, (XIIIa) (96% yield) and (XIIIb) (95%).

A solution of the methoxy-ester (260 mg) and  $\text{KOBu}^t$  (freshly sublimed; 68 mg) in dry  $\text{Me}_2\text{SO}$  (7 ml) was kept at 100 °C under  $\text{N}_2$  for 1 h. 5N-HCl (1 ml) was added and the heating continued for 5 min. Work-up and p.l.c. [2 small plates, 1  $\times$  petrol- $\text{Et}_2\text{O}$  (4 : 1)] gave, in order of decreasing  $R_F$  values, (i) 15 $\beta$ -methoxy-5 $\alpha$ -androst-16-ene (XVIII) (46 mg) as an oil (Found: C, 83.1; H, 11.0).  $\text{C}_{20}\text{H}_{32}\text{O}$  requires C, 83.4; H, 11.2%,  $\nu_{\text{max}}$  3050 and 1650  $\text{cm}^{-1}$ ; (ii) starting material (XIVa) (52 mg); and (iii) 15 $\beta$ -methoxy-5 $\alpha$ -androstane-17 $\beta$ -ol (XIIIa) (61 mg), m.p. and mixed m.p. 121–124°, identified by i.r. examination.

**Compounds (XIIc), (XIIIc), and (XIVc).**—A solution of 15 $\beta$ ,16 $\beta$ -epoxy-5 $\alpha$ -androstane-17-one<sup>6</sup> (V) (400 mg) in THF (20 ml) was refluxed with  $\text{LiAlH}_4$  (240 mg) for 3 h. Work-up gave 5 $\alpha$ -androstane-15 $\beta$ ,17 $\beta$ -diol (XIIc) (No. 516) (347 mg), double m.p. 148–149 and 155–156° (from  $\text{Me}_2\text{CO}-\text{C}_6\text{H}_{14}$ ),  $[\alpha]_D^{25} -21^\circ$  (c 0.8) (lit.,<sup>13</sup> m.p. 148–149°,  $-21.5^\circ$ ),  $\nu_{\text{max}}$  3625  $\text{cm}^{-1}$ .

A solution of 15 $\beta$ -allyloxy-5 $\alpha$ -androstane-17 $\beta$ -ol (XIIIb) (1 g) and  $\text{KOBu}^t$  (freshly sublimed; 560 mg) in dry  $\text{Me}_2\text{SO}$  (20 ml) was kept at 100 °C under  $\text{N}_2$  for 1 h, 5N-HCl (5 ml) was added, and the heating continued for 10 min. Chromatography on  $\text{Al}_2\text{O}_3$  [20 g; deactivated with  $\text{H}_2\text{O}$  (2 ml)] and elution with petrol- $\text{Et}_2\text{O}$  (9 : 1) gave the 15 $\beta$ ,17 $\beta$ -diol (XIIIc) (740 mg), identical with the preceding product.

A solution of the diol (1 g) in dry  $\text{C}_6\text{H}_6$  (250 ml) was refluxed with  $\text{Ag}_2\text{CO}_3$  on Celite<sup>11</sup> (7 g) for 7 h. More reagent (7 g) was added, and the refluxing was continued for a further 14 h. The mixture was filtered through  $\text{MgSO}_4$ , the insoluble material was washed with  $\text{CHCl}_3$ , and the combined filtrates were evaporated. Chromatography on  $\text{Al}_2\text{O}_3$  [30 g; deactivated with  $\text{H}_2\text{O}$  (3 g)] and elution with petrol- $\text{Et}_2\text{O}$  (5 : 1) gave 15 $\beta$ -hydroxy-5 $\alpha$ -androstane-17-one (XIIc) (No. 512) (847 mg), m.p. 173–174° (from  $\text{Me}_2\text{CO}-\text{C}_6\text{H}_{14}$ ),  $[\alpha]_D^{25} +52^\circ$  (c 1.0) (lit.,<sup>13</sup> m.p. 172.5–173.5°,  $[\alpha]_D^{25} +60^\circ$ ),  $\nu_{\text{max}}$  3625 and 1745  $\text{cm}^{-1}$ . Treatment of the hydroxy-ketone (100 mg) with  $\text{HS} \cdot [\text{CH}_2]_2 \cdot \text{SH}$  [as for the cyanoketone (IX)] and p.l.c. [1 small plate, 2  $\times$  petrol- $\text{Et}_2\text{O}$  (9 : 1)] gave 17,17-ethylenedithio-5 $\alpha$ -androstane-15 $\beta$ -ol (XV) (98 mg), m.p. 184–185° (from MeOH– $\text{H}_2\text{O}$ ),  $[\alpha]_D^{25} -47^\circ$  (c 0.9) (Found: C, 68.6; H, 9.3).  $\text{C}_{22}\text{H}_{34}\text{OS}_2$  requires C, 68.8; H, 9.3%,  $\nu_{\text{max}}$  3635  $\text{cm}^{-1}$ . A solution of this thioacetal (120 mg) in dry EtOH (20 ml) was refluxed with Raney Ni (freshly prepared; 700 mg of a sludge in EtOH) for 20 min. P.l.c. [2 small plates, 1  $\times$  petrol- $\text{Et}_2\text{O}$  (9 : 1)] gave starting material (26 mg) and 5 $\alpha$ -androstane-15 $\beta$ -ol (XI) (59 mg), m.p. and mixed m.p. 79–81°.

A solution of the diol (XIIIc) (550 mg) and  $\text{TsCl}$  (325 mg)

<sup>13</sup> A. R. Van Harn and C. Djerassi, *J. Amer. Chem. Soc.*, 1967, **89**, 651.

in  $C_6H_5N$  was kept at  $0^\circ C$  for 12 h. More  $TsCl$  (75 mg) was added, and the solution was kept at  $0^\circ C$  for 12 h, and then at  $20^\circ C$  for 12 h. Chromatography on  $SiO_2$  [20 g; deactivated with  $H_2O$  (0.25 ml)] and elution with petrol- $Et_2O$  (19:1) gave 15 $\beta$ -hydroxy-5 $\alpha$ -androstan-17 $\beta$ -yl toluene-p-sulphonate (XIVc) (559 mg), m.p.  $179.5-181^\circ$  (from  $Et_2O$ ),  $[\alpha]_D -1^\circ$  ( $c$  0.5) (Found: C, 69.7; H, 8.8; S, 7.2.  $C_{26}H_{36}O_4S$  requires C, 70.0; H, 8.6; S, 7.2%),  $\nu_{max}$  3632  $cm^{-1}$ . Reduction of this compound with  $LiAlH_4$  in boiling  $Et_2O$  gave the diol (XIIIc) (92% yield).

Oxidation of the hydroxy-ester (XIVc) (200 mg) in  $Me_2CO$  with  $8N-H_2CrO_4$  at  $0^\circ C$  gave 15-oxo-5 $\alpha$ -androstan-17 $\beta$ -yl toluene-p-sulphonate (XIX) (185 mg), m.p.  $111.5-112.5^\circ$  (from  $MeOH$ ),  $[\alpha]_D +31^\circ$  ( $c$  1.0) (Found: C, 69.6; H, 7.9; S, 7.7.  $C_{26}H_{36}O_5S$  requires C, 70.2; H, 8.2; S, 7.2%),  $\nu_{max}$  1752  $cm^{-1}$ . When heated at  $90^\circ$  for 1 h under  $N_2$ , this compound (250 mg) gave 5 $\alpha$ ,14 $\beta$ -androst-16-en-15-one (XVII) (No. 510) (144 mg; m.p.  $80-81.5^\circ$ , after crystallisation from  $C_6H_{14}$ ),  $[\alpha]_D +120^\circ$  ( $c$  1.0) (lit.,<sup>6</sup> m.p.  $79-80.5^\circ$ ,  $[\alpha]_D +120^\circ$ ),  $\nu_{max}$  1706  $cm^{-1}$ . The conjugated ketone (XVII) (61 mg) was also obtained by refluxing a solution of the keto-ester (XIX) (150 mg) in  $MeOH$  (50 ml) with  $NaHCO_3$  (30 mg) for 4 h, and purifying the product by p.l.c. [1 small plate, 5  $\times$  petrol- $Et_2O$  (19:1)]. Hydrogenation of the conjugated ketone (XVII) (150 mg) in  $EtOAc$  (40 ml) over 10%  $Pd-C$  (100 mg) for 4 h gave 5 $\alpha$ ,14 $\beta$ -androst-15-one<sup>6</sup> (XVI) (125 mg; m.p.  $72-73^\circ$ , from  $MeOH-H_2O$ ),  $\nu_{max}$  1739  $cm^{-1}$ .

Conversion of 5 $\alpha$ -Androstane-3 $\beta$ ,12 $\beta$ ,15 $\alpha$ -triol (XX) and 12 $\beta$ ,15 $\alpha$ -Dihydroxy-5 $\alpha$ -androstan-3-one (XXI) into 5 $\alpha$ -Androst-15-one (X).—A stirred solution of the triol<sup>2</sup> (XX) (440 mg) in  $PhMe$  (120 ml) was refluxed for 1 h with  $Ag_2CO_3$  on Celite (2.4 g) under a Dean-Stark separator. More reagent (2.4 g) was added, and the heating was continued for 2 h. Work-up and p.l.c. [1 large plate, 1  $\times$  petrol- $Me_2CO$  (1:1)] gave the dihydroxy-ketone<sup>2</sup> (XXI) (higher  $R_F$ , 360 mg), m.p. and mixed m.p.  $172-173^\circ$ , and starting material (lower  $R_F$ , 30 mg).

A solution of  $AcNHBr$  (1.6 g) in  $H_2O$  (20 ml) was added to a stirred solution of the triol (XX) (800 mg) in  $Me_2CO$  (50 ml) at  $20^\circ C$ . More  $Me_2CO$  (30 ml) was added (to dissolve the precipitate), and the solution was stirred at  $20^\circ C$  for 4 h. After work-up, the product was chromatographed on  $Al_2O_3$  [35 g; deactivated with  $H_2O$  (3.5 g)]. Elution with  $CHCl_3-Et_2O$  (1:1) gave 15 $\alpha$ -hydroxy-5 $\alpha$ -androstan-3,12-dione<sup>14</sup> (XXIII) (498 mg after crystallisation from  $Me_2CO-C_6H_{14}$ ), m.p. and mixed m.p.  $220-222^\circ$ ,  $\nu_{max}$  (conditions of ref. 5) 3630, 3613, 1713, and 1707  $cm^{-1}$ .

The hydroxy-diketone (XXIII) (70 mg) was also obtained by oxidising the dihydroxy-ketone (XXI) (200 mg) with  $AcNHBr$  (250 mg).

Huang-Minlon reduction of the hydroxy-diketone (XXIII) (100 mg) afforded 5 $\alpha$ -androstan-15 $\alpha$ -ol<sup>6</sup> (XXVI)

(79 mg) (m.p. and mixed m.p.  $160-161^\circ$ ; identified by i.r. examination). Oxidation of the 15 $\alpha$ -alcohol (100 mg) in  $Me_2CO$  at  $0^\circ C$  with  $8N-H_2CrO_4$  gave 5 $\alpha$ -androstan-15-one<sup>6</sup> (X) (90 mg), m.p. and mixed m.p.  $91-92^\circ$ .

Oxidation of 5 $\alpha$ -Androstane-12 $\beta$ ,15 $\alpha$ -diol (XXII).—(a) A solution of the diol<sup>2</sup> (100 mg) in  $C_6H_6$  (100 ml) was refluxed for 36 h with  $Ag_2CO_3$  on Celite (1 g) under a Dean-Stark separator. The mixture was filtered through  $MgSO_4$ , the insoluble material was washed with  $C_6H_6$  (50 ml), and the combined filtrates were refluxed for 12 h with more reagent (1 g). Work-up and p.l.c. [1 small plate, 1  $\times$  petrol- $Et_2O$  (1:1)] gave 15 $\alpha$ -hydroxy-5 $\alpha$ -androstan-12-one (XXV) (63 mg; m.p.  $181-182^\circ$ , from  $Me_2CO-C_6H_{14}$ ),  $[\alpha]_D +95^\circ$  ( $c$  1.0) (Found: C, 78.5; H, 10.2.  $C_{19}H_{30}O_2$  requires C, 78.6; H, 10.3%),  $\nu_{max}$  (conditions of ref. 5) 3628, 3612, and 1709  $cm^{-1}$ .

(b) The diol (3 g) in  $Me_2CO$  (total volume 180 ml) was oxidised with  $AcNHBr$  (4 g) in  $H_2O$  (50 ml) at  $20^\circ C$  for 4 h. Work-up, chromatography on  $Al_2O_3$  (150 g; deactivated with  $H_2O$  (7.5 ml)), and elution with petrol- $Et_2O$  (4:1) gave, in order of increasing polarity, (i) 5 $\alpha$ ,14 $\beta$ -androstane-12,15-dione<sup>2</sup> (XXIV) (741 mg), m.p.  $124-126^\circ$ , (ii) 15 $\alpha$ -hydroxy-5 $\alpha$ -androstan-12-one (XXV) (1.7 g), m.p.  $180-182^\circ$ , and (iii) 12 $\beta$ -hydroxy-5 $\alpha$ ,14 $\beta$ -androst-15-one (XXIX) (170 mg; m.p.  $151-153^\circ$ , from  $MeOH-H_2O$ ),  $[\alpha]_D -32^\circ$  ( $c$  1.0) (Found: C, 78.3; H, 10.4.  $C_{19}H_{30}O_2$  requires C, 78.6; H, 10.3%),  $\nu_{max}$  3630 and 1740  $cm^{-1}$ .

Reduction of 5 $\alpha$ ,14 $\beta$ -Androstane-12,15-dione (XXIV).—Treatment of the dione<sup>2</sup> (400 mg) in  $THF$  (10 ml) with  $LiAlH(OBu^t)_3$ , followed by p.l.c. [1 large plate, 5  $\times$  petrol- $Et_2O$  (4:1)] gave, in order of decreasing  $R_F$  values, (i) 5 $\alpha$ ,14 $\beta$ -androstane-12 $\alpha$ ,15 $\alpha$ -diol (XXVII) (No. 513) (72 mg; m.p.  $220-222^\circ$ , from  $Me_2CO-C_6H_{14}$ ),  $[\alpha]_D +102^\circ$  ( $c$  0.4) (Found: C, 78.0; H, 11.0.  $C_{19}H_{32}O_2$  requires C, 78.0; H, 11.0%),  $\nu_{max}$  (conditions of ref. 5) 3618, 3440, and 3250  $cm^{-1}$ , (ii) 5 $\alpha$ ,14 $\beta$ -androstane-12 $\beta$ ,15 $\alpha$ -diol (XXX) (No. 515) (148 mg; m.p.  $149-150^\circ$ , from  $Me_2CO-C_6H_{14}$ ),  $[\alpha]_D +55^\circ$  ( $c$  1.0) (Found: C, 78.0; H, 11.05%),  $\nu_{max}$  3635  $cm^{-1}$ , and (iii) 5 $\alpha$ ,14 $\beta$ -androstane-12 $\alpha$ ,15 $\beta$ -diol (XXVIII) (No. 514) (122 mg), m.p.  $81-89^\circ$ , unchanged after repeated crystallisation from  $MeOH-H_2O$ ,  $[\alpha]_D +42^\circ$  ( $c$  0.8),  $\nu_{max}$  3633  $cm^{-1}$ .

Treatment of the 12 $\beta$ ,15 $\alpha$ -diol (XXX) (100 mg) with  $Ac_2O$  (5 ml)- $C_6H_5N$  (5 ml) at  $20^\circ C$  for 12 h gave an oil (106 mg),  $\nu_{max}$  3635 and 1745  $cm^{-1}$ , which was dissolved in  $Me_2CO$  and oxidised with  $8N-H_2CrO_4$ . A solution of the product in  $MeOH$  (20 ml)- $KOH$  (1 g) was kept at  $20^\circ C$  for 24 h. Work-up and p.l.c. [2 small plates, 1  $\times$  petrol- $Et_2O$  (1:1)] gave the 12 $\beta$ -hydroxy-15-ketone (XXIX) (76 mg), m.p. and mixed m.p.  $150-152^\circ$ .

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<sup>14</sup> A. M. Bell, W. A. Denny, Sir Ewart R. H. Jones, G. D. Meakins, and W. E. Müller, preceding paper.