Studies in the Steroid Group. Part LXXXIV.[1] Preparation and Reactions of 15-Oxygenated Androstanes

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Treatment of 15β,16β-epoxy-5α-androstan-17-one with hydrazine and toluene-*p*-sulphonic acid in air gives 5α-androstan-15β-ol; this step markedly improves the chemical route to 5α-androstan-15-one from the 3-ketone. The 15-ketone is also readily obtained from 12β,15α-dihydroxy-5α-androstan-3-one (prepared by microbiological hydroxylation of 5α-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.

5α-ANDROSTAN-15-ONE was not readily available at the time when it was required as a substrate in microbiological hydroxylation studies.[2] The synthesis [3] 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.*

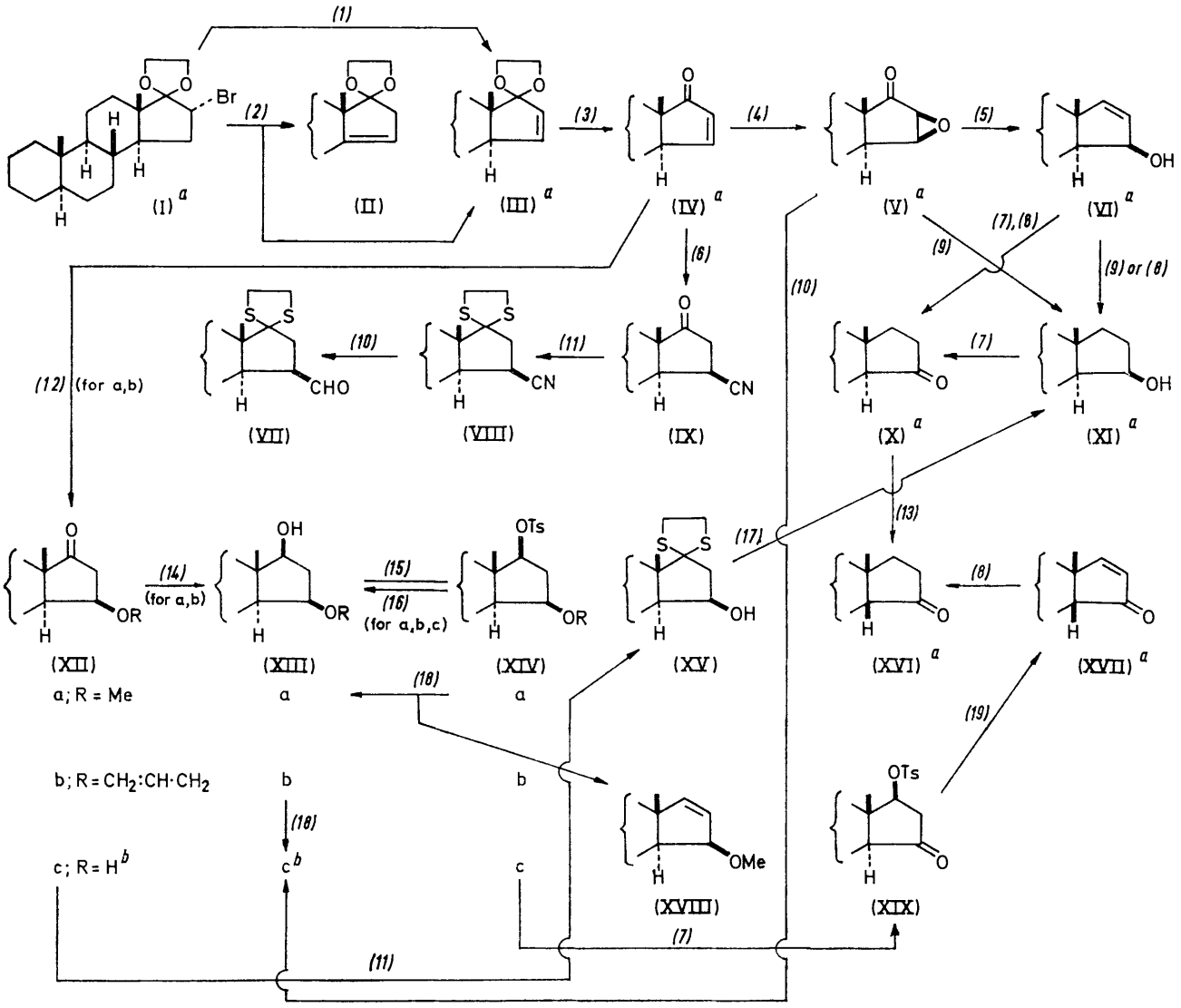
[1] Part LXXXIII, I. M. Clark, A. S. Clegg, W. A. Denny, E. R. H. Jones, G. D. Meakins, and A. Pendlebury, *J.C.S. Perkin I*, 1972, 499.

[2] 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.

[3] 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.

15,*x*-diols and 15-hydroxy-*x*-ketones and their derivatives). There is little systematic information about such compounds in the literature, and since they are being encountered as products of microbiological hydroxylations [4] we hoped to extend knowledge of their chemical behaviour.

Experimental section; new conversions, for example the selective oxidation of 5α-androstane-15β,17β-diol (XIIIc) to the 15β-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



SCHEME 1

Reagents: (*1*), KOBu^t–Me_2SO, 45 °C; (*2*) as (*1*), 55 °C; (*3*) TsOH–Me_2CO–H_2O; (*4*) H_2O_2–NaOH–Bu^{t}OH; (*5*), N_2H_4–H^+, in N_2; (*6*), NaCN–H_2O–THF (tetrahydrofuran); (*7*), H_2CrO_4–Me_2CO; (*8*), H_2,Pd; (*9*), N_2H_4–H^+, in air; (*10*), $LiAlH_4$–THF; (*11*), HS·$[CH_2]_2$·SH–BF_3; (*12*), ROH–NaOH–THF; (*13*), NaOMe–MeOH; (*14*), $LiAlH(OBu^t)_3$–THF; (*15*), TsCl–C_5H_5N; (*16*), $LiAlH_4$–Et_2O; (*17*), Raney Ni; (*18*), as (*1*), 100 °C, then HClaq; (*19*), heat, 90 °C, or $NaHCO_3$–MeOH, reflux; (*20*), Ag_2CO_3 on Celite.

[a] Ref. 6. [b] Ref. 13.

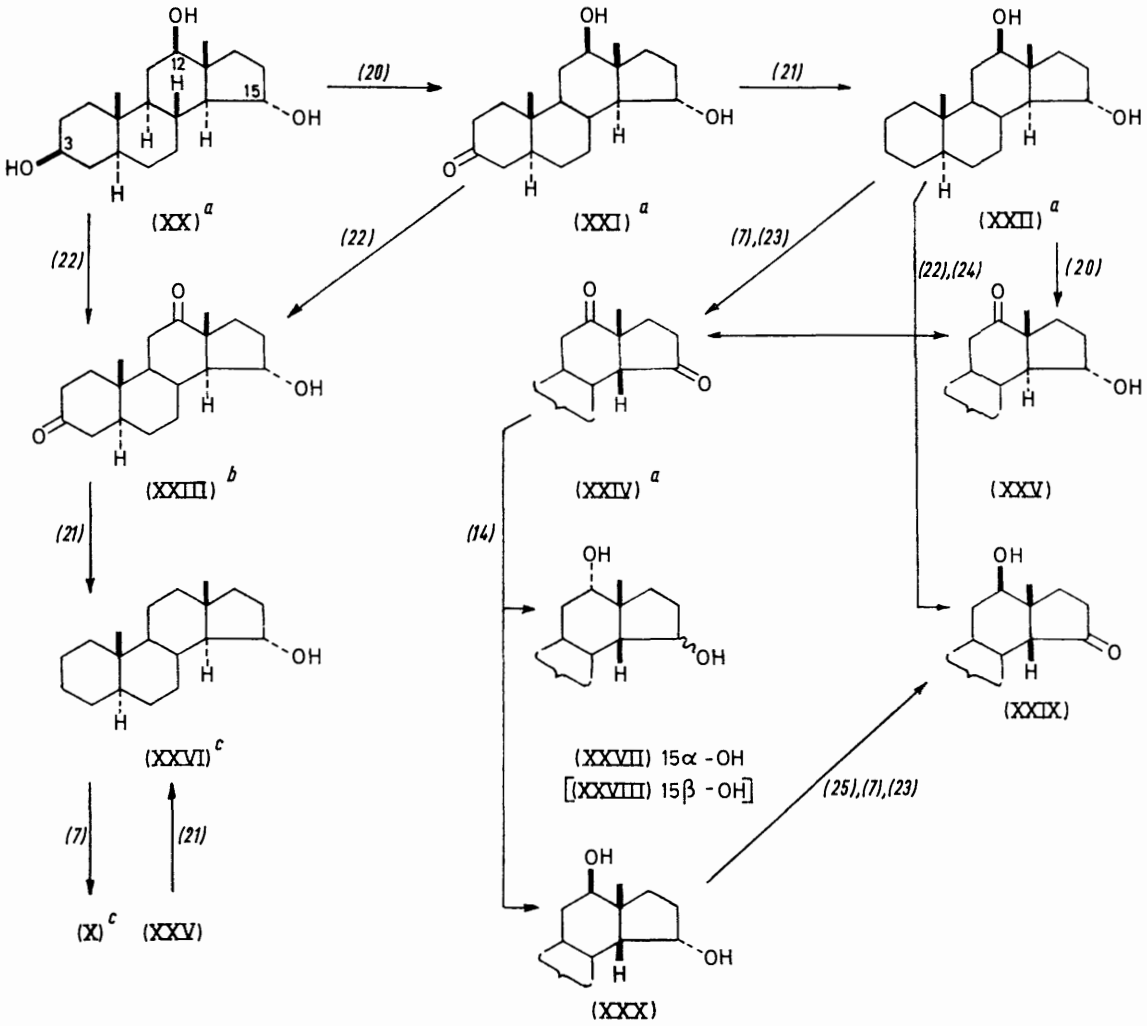
The results are presented in Schemes 1 and 2. References are given after the formulae numbers of known compounds: the rest are new. Interconversions of known compounds carried out without significant modification of the literature procedures are not recorded in the n.m.r. signals (Table) and i.r. absorptions (Experimental section) as explained in our earlier surveys.[4,5]

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

[4] 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.

[5] 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.*,[6] is 5α-androstan-17-one (readily available) ⟶ (I) ⟶ (III) ⟶ (IV) ⟶ (V) ⟶ (VI) ⟶ (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 Δ^{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 on work by Wharton and Bohlen,[7] was reported [6] 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 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 [8] there appears to be no precedent for the present observations. Use of the two efficient steps (V) ⟶ (XI) ⟶ (X) greatly improves the route to the 15-ketone.



SCHEME 2

Reagents as in Scheme 1, and; (*21*), Huang-Minlon reduction; (*22*), AcNHBr–Me_2CO, 20 °C; (*23*), KOH–MeOH; (*24*), Al_2O_3 (chromatography); (*25*), Ac_2O–C_5H_5N.

[a] Ref. 2. [b] Ref. 14. [c] Ref. 6.

Although we could not repeat the reported addition [9] of benzyl alcohol to 5α-androst-15-en-17-one (IV), other Michael reactions gave high yields of products [(IX) and

[6] C. Djerassi, G. von Mutzenbecker, J. Fajkos, D. H. Williams, and H. Budzikiewicz, *J. Amer. Chem. Soc.*, 1965, **87**, 817.

[7] P. S. Wharton and D. H. Bohlen, *J. Org. Chem.*, 1961, **26**, 3615.

[8] J. M. Hoffman and R. H. Schlessinger, *Chem. Comm.*, 1971, 1245.

[9] C. W. Cantrall, R. Littell, and S. Bernstein, *J. Org. Chem.*, 1964, **29**, 64.

(XIIa and b)] with 15β-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. 12β,15α-Dihydroxy-5α-androstan-3-one (XXI), the starting material for this work, is readily obtained by microbiological hydroxylation of 5α-androstan-3-one, and easily reduced to the 3β,12β,15α-triol (XX).[2] The conversions of the triol (XX) into the dihydroxy-ketone (XXI), and of both these compounds into 5α-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

TABLE 1

N.m.r. signals

Signals ($CDCl_3$ solutions; 100 MHz) are described in the form used previously.[a] The n.m.r. and (for the majority) the i.r. absorptions of the following have already been reported: (IV), (X), (XX), (XXI), (XXIII), (XXIV), (XXVI) (ref. 4), (XI), (ref. 5), (XVI) (ref. 2), (XXV) and (XXIX) (ref. 15)

			Other signals		
No.	19-H τ	18-H τ	τ	Form	Assignment
(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] 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 [5α-androstan-3-one ⟶ (XXI) ⟶ (XXIII) ⟶ (XXVI) ⟶ 5α-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 which, *mutatis mutandis*, is similar to that of 'remote oxidation' accomplished by photochemical means:[10] it would be difficult to devise an efficient alternative involving standard chemical processes. The silver carbonate on Celite reagent[11] was more effective than *N*-bromoacetamide for selective oxidation at position 12 of the 12β,15α-diol (XXII). Reduction of the 14β-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 14β-compounds are based on the expectation that the >C*H*·OH proton will be more strongly coupled in 15β-alcohols, the situation resembling that found[4] with the 15α-OH–14α-H system.)

[10] R. Breslow and S. W. Baldwin, *J. Amer. Chem. Soc.*, 1970, **92**, 732.

[11] M. Fetizon and M. Golfier, *Compt. rend.*, 1968, **267***C*, 900.

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 16α-*Bromo*-17,17-*ethylenedioxy*-5α-*androstane* (I) *with Potassium t-Butoxide*.—A solution of the acetal[6] (23 g) and KOBu^t [freshly sublimed; from K (5·6 g)] in Me_2SO (700 ml) was stirred under N_2 at 45 °C for 30 h. Standard manipulation gave the Δ^{15}-acetal (III) (15·1 g), m.p. 120—121·5° (from MeOH) (lit.,[6] 120—121°). A similar experiment carried out at 55 °C afforded material shown by t.l.c. to contain approximately equal amounts of the Δ^{15}-acetal (III) and another compound, which was chromatographed on Al_2O_3 (300 g). Petrol–Et_2O (10 : 1) eluted 17,17-ethylenedioxy-5α-androst-14-ene (II) (3·9 g; m.p. 82—83°, after two crystallisations from MeOH), $[\alpha]_D$ 2° (*c* 1·0) (Found: C, 79·6; H, 10·4. $C_{21}H_{32}O_2$ requires C, 79·8; H, 10·2%), $\nu_{max.}$ 3060 and 1647 cm^{-1}.

A solution of the Δ^{14}-acetal (II) (1·67 g) and TsOH–H_2O (150 mg) in Me_2CO (150 ml)–H_2O (10 ml) was kept at 20 °C for 48 h. Work-up gave 5α-androst-14-en-17-one (1·42 g), m.p. 56—57° (from MeOH–H_2O), $[\alpha]_D$ +142° (*c* 1·0) (lit.,[12] m.p. 56—57°, $[\alpha]_D$ +142°).

Treatment of 15β,16β-*Epoxy*-5α-*androstan*-17-*one* (V) *and of* 5α-*Androst*-16-*en*-15β-*ol* (VI) *with Hydrazine*.—A solution of N_2H_4 (anhydrous; 280 mg) in MeOH (3 ml) was added dropwise to a solution of the epoxy-ketone[6] (500 mg) in dry MeOH (20 ml) which was stirred under N_2 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_2O_3 [20 g; deactivated with H_2O (1 ml)]. Petrol–Et_2O (99 : 1) eluted 5α-androst-16-en-15β-ol (VI) (No. 511) (205 mg; m.p. 75—77°, after crystallisation from C_6H_{14}), $[\alpha]_D$ −70° (*c* 0·4) (lit.,[6] m.p. 76—77°, $[\alpha]_D$ −71°). Hydrogenation of this alcohol (200 mg) in EtOAc (20 ml) over 5% Pd–C (pre-reduced; 130 mg) gave 5α-androstan-15β-ol (XI) (188 mg), m.p. 75·5—77° (from MeOH), $[\alpha]_D$ −33° (*c* 0·5) (lit.,[6] m.p. 75·5—77°, $[\alpha]_D$ −34°).

The results of similar experiments carried out with the epoxy-ketone (500 mg) or the allylic alcohol (VI) (500 mg) and N_2H_4 (280 mg) are shown in Table 2, the result of the

[12] 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 Al_2O_3 [deactivated with H_2O (1%)]. Elution with petrol–Et_2O (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)	Wt (mg) of (XI)
(V)	MeOH		20	N_2	205	
(V)	Bu^tOH	AcOH (200 mg)	20	N_2	163	
(V)	Bu^tOH	AcOH (200 mg)	0	N_2	211	
(V)	Bu^tOH	AcOH (200 mg)	0	Air	40	165
(V)	Bu^tOH	$TsOH,H_2O$ (500 mg)	0	N_2	204	
(V)	Bu^tOH	$TsOH,H_2O$ (500 mg)	0	Air		243
(VI)	MeOH	$TsOH,H_2O$ (500 mg)	0	Air		482

Compounds (VII), (VIII), *and* (IX).—A solution of 5α-androst-15-en-17-one [6] (1 g) and NaCN (2·5 g) in THF (100 ml)–H_2O (2 ml) was refluxed for 2·5 h. Work-up, and crystallisation (MeOH) of the product (1·02 g) gave *17-oxo-5α-androstane-15β-carbonitrile* (IX) (840 mg), m.p. 188—190°, $[\alpha]_D$ +0·5 (*c* 1·1) (Found: C, 80·0; H, 9·5; N, 4·4. $C_{20}H_{29}NO$ requires C, 80·3; H, 9·8; N, 4·5%), $\nu_{max.}$ 2235 and 1750 cm^{-1}, *m/e* 299 (M^+, 100%).

A solution of the preceding ketone (500 mg) and BF_3,Et_2O (0·7 ml) in $HS\cdot[CH_2]_2\cdot SH$ (0·7 ml) was shaken for 5 min at 20 °C, diluted with $CHCl_3$ (12 ml), kept for 12 h at 20 °C, diluted with more $CHCl_3$ (10 ml), and washed with saturated $NaHCO_3$ aq. Work-up gave *17,17-ethylenedithio-5α-androstane-15β-carbonitrile* (VIII) (605 mg), m.p. 191—191·5° (from Me_2CO–C_6H_{14}), $[\alpha]_D$ −82° (*c* 0·9) (Found: C, 70·8; H, 8·8; N, 3·9. $C_{22}H_{33}NS_2$ requires C, 70·5; H, 8·9; N, 3·7%), $\nu_{max.}$ 2240 cm^{-1}, *m/e* 375 (M^+, 15%). A solution of the cyano-thioacetal (370 mg) in THF (10 ml) was added during 15 min to a stirred suspension of $LiAlH_4$ (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 × petrol–Et_2O (9 : 1)] afforded *17,17-ethylenedithio-5α-androstane-15β-carbaldehyde* (VII) (167 mg), m.p. 125—127° (from C_6H_{14}), $[\alpha]_D$ +12° (*c* 1·2) (Found: C, 69·9; H, 8·9. $C_{22}H_{34}OS_2$ requires C, 69·9; H, 9·0%), $\nu_{max.}$ 2705 and 1728 cm^{-1}, *m/e* 378 (M^+, 12%).

Compounds (XIIa and b), (XIIIa and b), *and* (XIVa and b).—Solutions of 5α-androst-15-en-17-one (1 g) in THF (11 ml) and of NaOH (110 mg) in H_2O (2 ml)–MeOH (100 ml) were mixed and kept at 20 °C for 2 h. Work-up gave *15β-methoxy-5α-androstan-17-one* (XIIa) (880 mg; m.p. 109—110°, after crystallisation from MeOH), $[\alpha]_D$ −12° (*c* 1·0) (Found: C, 79·4; H, 10·5. $C_{20}H_{32}O_2$ requires C, 79·0; H, 10·6%), $\nu_{max.}$ 1742 cm^{-1}, *m/e* 304 (M^+, 100%). A similar experiment with $CH_2{:}CH\cdot CH_2\cdot OH$ afforded *15β-allyloxy-5α-androstan-17-one* (XIIb) (950 mg; m.p. 109—110° from MeOH–H_2O), $[\alpha]_D$ −25° (*c* 0·9) (Found: C, 80·0; H, 10·45. $C_{22}H_{34}O_2$ requires C, 80·1; H, 10·4%), $\nu_{max.}$ 1745 cm^{-1}, *m/e* 330 (M^+, 100%).

Solutions of the preceding ketones (1 g) in THF (10 ml) were stirred with $LiAlH(OBu^t)_3$ [from $LiAlH_4$ (200 mg)] in THF (10 ml) at 0 °C for 3 h, and then at 20 °C for 4 h. Work-up gave *15β-methoxy-5α-androstan-17β-ol* (XIIIa) (950 mg; m.p. 124—125°, from Me_2CO–C_6H_{14}), $[\alpha]_D$ −6° (*c* 1·0) (Found: C, 76·8; H, 10·1. $C_{20}H_{34}O_2$ requires C, 76·6; H, 10·1%), $\nu_{max.}$ 3620 cm^{-1}; and *15β-allyloxy-5α-androstan-17β-ol* (XIIIb) (960 mg; m.p. 119—119·5°, from MeOH–H_2O), $[\alpha]_D$ −52° (*c* 1·0) (Found: C, 79·6; H, 11·1. $C_{22}H_{36}O_2$ requires C, 79·6; H, 10·9%). When treated with BzCl–C_5H_5N at 20 °C, the methoxy-alcohol (XIIIa) gave a *benzoate*, m.p. 104—106°, $[\alpha]_D$ −2° (*c* 0·6) (Found: C, 78·9; H, 9·3. $C_{27}H_{38}O_3$ requires C, 79·1; H, 9·3%), $\nu_{max.}$ 1722 cm^{-1}.

Treatment of the preceding hydroxy-ethers with TsCl–C_5H_5N at 0 °C for 1 day and then at 20° for 1 day gave the *methoxy-ester* (XIVa) (85% yield), m.p. 155—156° (from C_6H_{14}), $[\alpha]_D$ −30° (*c* 0·9 (Found: C, 70·5; H, 8·9; S, 7·1. $C_{27}H_{40}O_4S$ requires C, 70·5; H, 8·8; S, 7·1%), and the *allyloxy-ester* (XIVb) (81% yield), m.p. 98—99° (from C_6H_{14}), $[\alpha]_D$ −30° (*c* 0·9) (Found: C, 71·3; H, 8·7. $C_{29}H_{42}O_4S$ requires C, 71·6; H, 8·9%). When solutions of these esters (100 mg) in Et_2O (12 ml) were refluxed with $LiAlH_4$ (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 $KOBu^t$ (freshly sublimed; 68 mg) in dry Me_2SO (7 ml) was kept at 100 °C under 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 × petrol–Et_2O (4 : 1)] gave, in order of decreasing R_F values, (i) *15β-methoxy-5α-androst-16-ene* (XVIII) (46 mg) as an oil (Found: C, 83·1; H, 11·0. $C_{20}H_{32}O$ requires C, 83·4; H, 11·2%), $\nu_{max.}$ 3050 and 1650 cm^{-1}; (ii) starting material (XIVa) (52 mg); and (iii) 15β-methoxy-5α-androstan-17β-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 15β,16β-epoxy-5α-androstan-17-one [6] (V) (400 mg) in THF (20 ml) was refluxed with $LiAlH_4$ (240 mg) for 3 h. Work-up gave 5α-androstane-15β,17β-diol (XIIIc) (No. 516) (347 mg), double m.p. 148—149 and 155—156° (from Me_2CO–C_6H_{14}), $[\alpha]_D$ −21° (*c* 0·8) (lit.,[13] m.p. 148—149°, −21·5°), $\nu_{max.}$ 3625 cm^{-1}.

A solution of 15β-allyloxy-5α-androstan-17β-ol (XIIIb) (1 g) and $KOBu^t$ (freshly sublimed; 560 mg) in dry Me_2SO (20 ml) was kept at 100 °C under N_2 for 1 h, 5N-HCl (5 ml) was added, and the heating continued for 10 min. Chromatography on Al_2O_3 [20 g; deactivated with H_2O (2 ml)] and elution with petrol–Et_2O (9 : 1) gave the 15β,17β-diol (XIIIc) (740 mg), identical with the preceding product.

A solution of the diol (1 g) in dry C_6H_6 (250 ml) was refluxed with Ag_2CO_3 on Celite [11] (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 $MgSO_4$, the insoluble material was washed with $CHCl_3$, and the combined filtrates were evaporated. Chromatography on Al_2O_3 [30 g; deactivated with H_2O (3 g)] and elution with petrol–Et_2O (5 : 1) gave 15β-hydroxy-5α-androstan-17-one (XIIc) (No. 512) (847 mg), m.p. 173—174° (from Me_2CO–C_6H_{14}), $[\alpha]_D$ +52° (*c* 1·0) (lit.,[13] m.p. 172·5—173·5°, $[\alpha]_D$ +60°), $\nu_{max.}$ 3625 and 1745 cm^{-1}. Treatment of the hydroxy-ketone (100 mg) with $HS\cdot[CH_2]_2\cdot SH$ [as for the cyano-ketone (IX)] and p.l.c. [1 small plate, 2 × petrol–Et_2O (9 : 1)] gave *17,17-ethylenedithio-5α-androstan-15β-ol* (XV) (98 mg), m.p. 184—185° (from MeOH–H_2O), $[\alpha]_D$ −47° (*c* 0·9) (Found: C, 68·6; H, 9·3. $C_{21}H_{34}OS_2$ requires C, 68·8; H, 9·3%), $\nu_{max.}$ 3635 cm^{-1}. A solution of this thio-acetal (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 × petrol–Et_2O (9 : 1)] gave starting material (26 mg) and 5α-androstan-15β-ol (XI) (59 mg), m.p. and mixed m.p. 79—81°.

A solution of the diol (XIIIc) (550 mg) and TsCl (325 mg)

[13] A. R. Van Harn and C. Djerassi, *J. Amer. Chem. Soc.*, 1967, **89**, 651.

in C_5H_5N was kept at 0 °C for 12 h. More TsCl (75 mg) was added, and the solution was kept at 0 °C for 12 h, and then at 20 °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 15β-*hydroxy*-5α-*androstan*-17β-*yl toluene*-p-*sulphonate* (XIVc) (559 mg), m.p. 179·5—181° (from Et_2O), $[\alpha]_D$ −1° (*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 °C gave 15-*oxo*-5α-*androstan*-17β-*yl toluene*-p-*sulphonate* (XIX) (185 mg), m.p. 111·5—112·5° (from MeOH), $[\alpha]_D$ +31° (*c* 1·0) (Found: C, 69·6; H, 7·9; S, 7·7. $C_{26}H_{36}O_2S$ requires C, 70·2; H, 8·2; S, 7·2%), $\nu_{max.}$ 1752 cm^{-1}. When heated at 90° for 1 h under N_2, this compound (250 mg) gave 5α,14β-androst-16-en-15-one (XVII) (No. 510) (144 mg; m.p. 80—81·5°, after crystallisation from C_6H_{14}), $[\alpha]_D$ +120° (*c* 1·0) (lit.,[6] m.p. 79—80·5°, $[\alpha]_D$ +120°), $\nu_{max.}$ 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 × 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 5α,14β-androstan-15-one [6] (XVI) (125 mg; m.p. 72—73°, from MeOH–H_2O), $\nu_{max.}$ 1739 cm^{-1}.

Conversion of 5α-*Androstane*-3β,12β,15α-*triol* (XX) *and* 12β,15α-*Dihydroxy*-5α-*androstan*-3-*one* (XXI) *into* 5α-*Androstan*-15-*one* (X).—A stirred solution of the triol [2] (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 × petrol–Me_2CO (1 : 1)] gave the dihydroxy-ketone [2] (XXI) (higher R_F, 360 mg), m.p. and mixed m.p. 172—173°, 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 °C. More Me_2CO (30 ml) was added (to dissolve the precipitate), and the solution was stirred at 20 °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 15α-hydroxy-5α-androstane-3,12-dione [14] (XXIII) (498 mg after crystallisation from Me_2CO–C_6H_{14}), m.p. and mixed m.p. 220—222°, $\nu_{max.}$ (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 5α-androstan-15α-ol [6] (XXVI) (79 mg) (m.p. and mixed m.p. 160—161°; identified by i.r. examination). Oxidation of the 15α-alcohol (100 mg) in Me_2CO at 0 °C with 8N-H_2CrO_4 gave 5α-androstan-15-one [6] (X) (90 mg), m.p. and mixed m.p. 91—92°.

Oxidation of 5α-*Androstane*-12β,15α-*diol* (XXII).—(*a*) A solution of the diol [2] (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 × petrol–Et_2O (1 : 1)] gave 15α-*hydroxy*-5α-*androstan*-12-*one* (XXV) (63 mg; m.p. 181—182°, from Me_2CO–C_6H_{14}), $[\alpha]_D$ +95° (*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 °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) 5α,14β-androstane-12,15-dione [2] (XXIV) (741 mg), m.p. 124—126°, (ii) 15α-hydroxy-5α-androstan-12-one (XXV) (1·7 g), m.p. 180—182°, and (iiii) 12β-*hydroxy*-5α,14β-*androstan*-15-*one* (XXIX) (170 mg; m.p. 151—153°, from MeOH–H_2O), $[\alpha]_D$ −32° (*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 5α,14β-*Androstane*-12,15-*dione* (XXIV).—Treatment of the dione [2] (400 mg) in THF (10 ml) with $LiAlH(OBu^t)_3$, followed by p.l.c. [1 large plate, 5 × petrol–Et_2O (4 : 1)] gave, in order of decreasing R_F values, (i) 5α,14β-*androstane*-12α,15α-*diol* (XXVII) (No. 513) (72 mg; m.p. 220—222°, from Me_2CO–C_6H_{14}), $[\alpha]_D$ +102° (*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) 5α,14β-*androstane*-12β,15α-*diol* (XXX) (No. 515) (148 mg; m.p. 149—150°, from Me_2CO–C_6H_{14}), $[\alpha]_D$ +55° (*c* 1·0) (Found: C, 78·0; H, 11·05%), $\nu_{max.}$ 3635 cm^{-1}, and (iii) 5α,14β-androstane-12α,15β-diol (XXVIII) (No. 514) (122 mg), m.p. 81—89°, unchanged after repeated crystallisation from MeOH–H_2O, $[\alpha]_D$ +42° (*c* 0·8), $\nu_{max.}$ 3633 cm^{-1}.

Treatment of the 12β,15α-diol (XXX) (100 mg) with Ac_2O (5 ml)–C_5H_5N (5 ml) at 20 °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 °C for 24 h. Work-up and p.l.c. [2 small plates, 1 × petrol–Et_2O (1 : 1)] gave the 12β-hydroxy-15-ketone (XXIX) (76 mg), m.p. and mixed m.p. 150—152°.

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[14] A. M. Bell, W. A. Denny, Sir Ewart R. H. Jones, G. D. Meakins, and W. E. Müller, preceding paper.