Studies in the Steroid Group. Part LXXXII.[1] The Preparation of Nine Mono- and Eight Di-oxoandrostanes, 5α-Estran-17-one, and 5α-Pregnane-2,20-dione

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The following steroids, required as substrates for microbiological studies, have been prepared: 17α-hydroxy-2-oxo-, 7α-hydroxy-3-oxo-, 7β-hydroxy-3-oxo-, 17β-hydroxy-7-oxo-, and 3β-acetyl-5α-androstane. 6β-hydroxyandrost-4-en-3-one, androst-5-en-7-one. 6β-hydroxy-3-oxo- and 6-oxo-5β-androstane. 2,7-, 3,6-, 3,7-, 3,12-, 7,17-, and 11,16-dioxo-5α-androstane, 3β-acetyl-17-oxo-5α-androstane, 5α-estran-17-one, and 5α-pregnane-2,20-dione. This work makes some diketones of the less common types available in reasonable quantity.

As explained previously,[1] oxygenated steroids of the less common types were required for our microbiological hydroxylation work.[2] This paper deals with the preparation of some of the new oxo-androstanes, -estranes, and -pregnanes which have been used as substrates; the following paper is similarly concerned with hydroxyandrostanes and their derivatives For convenience, the hydroxy-steroids which are intermediates in the preparations of ketones are included here. The microbiological study of both types of substrate will be reported later.

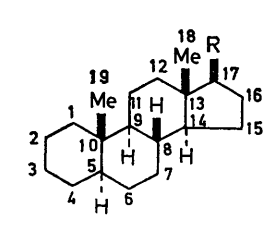
Much of the present work is unexceptional: it is adequately represented in the Schemes and only a few points require comment. With the exception of the 11-ketone (IV) all the starting materials, compounds (I)—(VII) shown at the top of Scheme 1, are commercially available. The names (or abbreviated names) of known compounds are followed by a reference. The structures of the rest, which are new, follow from the methods of preparation and from the results of spectrometric examination. (In this respect, and also because of their relationship to the microbiological work, the ketonic products are the most important. For the majority of the new compounds, n.m.r. and i.r. characteristics have already been published in refs. 3 and 4, respectively: for the remainder, the n.m.r. signals are recorded in the Table at the end of this section, and the i.r. absorptions in the Experimental section.) In the Schemes, arrows not accompanied by reagent numbers

[1] Part LXXXI, J. E. Bridgeman, C. E. Butchers, E. R. H. Jones, A. Ksaal, G. D. Meakins, and P. D. Woodgate, *J. Chem. Soc.* (*C*), 1970, 244. By mistake this paper was given the Part number LXXX.

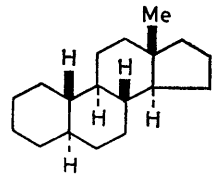
[2] J. W. Blunt, I. M. Clark, J. M. Evans, E. R. H. Jones, G. D. Meakins, and J. T. Pinhey, *J. Chem. Soc.* (*C*), 1971, 1136.

[3] 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.

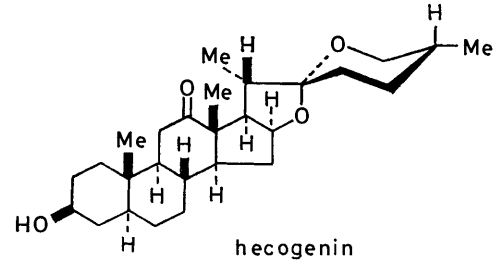
[4] A. D. Boul, J. W. Blunt, J. W. Browne, V. Kumar, G. D. Meakins, J. T. Pinhey, and V. E. M. Thomas, *J. Chem. Soc.* (*C*), 1971, 1130.



R = H 5α-androstane
R = Et 5α-pregnane



5α-estrane



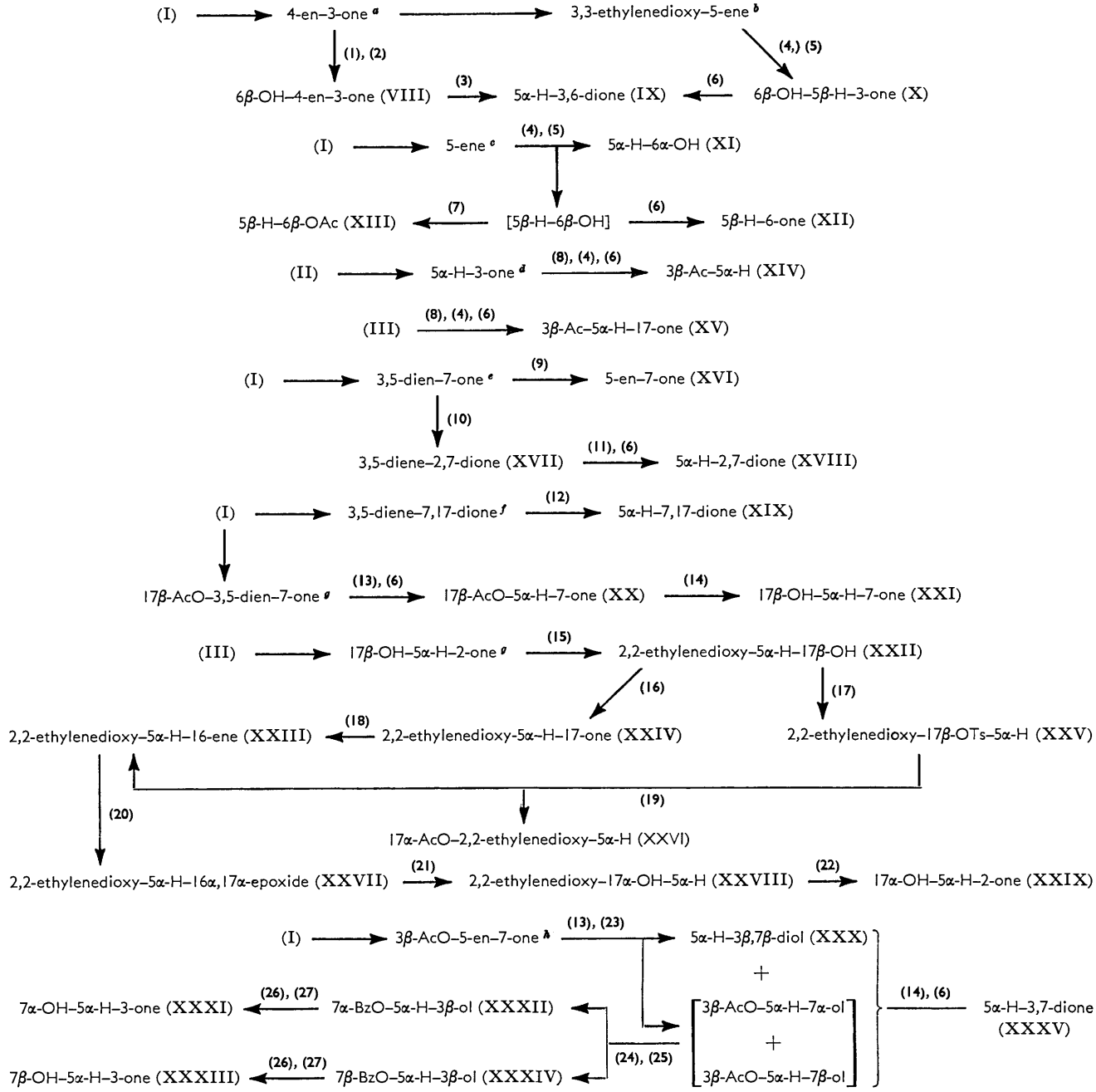
hecogenin
[(25*R*)-3β-hydroxy-5α-spirostan-12-one]

Most of the compounds are derivatives of androstane. For these, abbreviated names are used, *e.g.* the second starting material, described below as 3β-OH-5α-H-17-one, is 3β-hydroxy-5α-androstan-17-one. For other compounds systematic names are given.

SCHEME 1

SCHEME 1 (*Continued*)

Starting materials: 3β-OH-5-en-17-one (I); 3β-OH-5α-H-17-one (II); 17β-OH-5α-H-3-one (III); 3β-OH-5α-H-11,17-dione (IV); hecogenin (V); estrone[3-hydroxyestra-1,3,5(10)-trien-17-one] (VI); 3β-hydroxypregn-5-en-20-ene (VII).



SCHEME 1

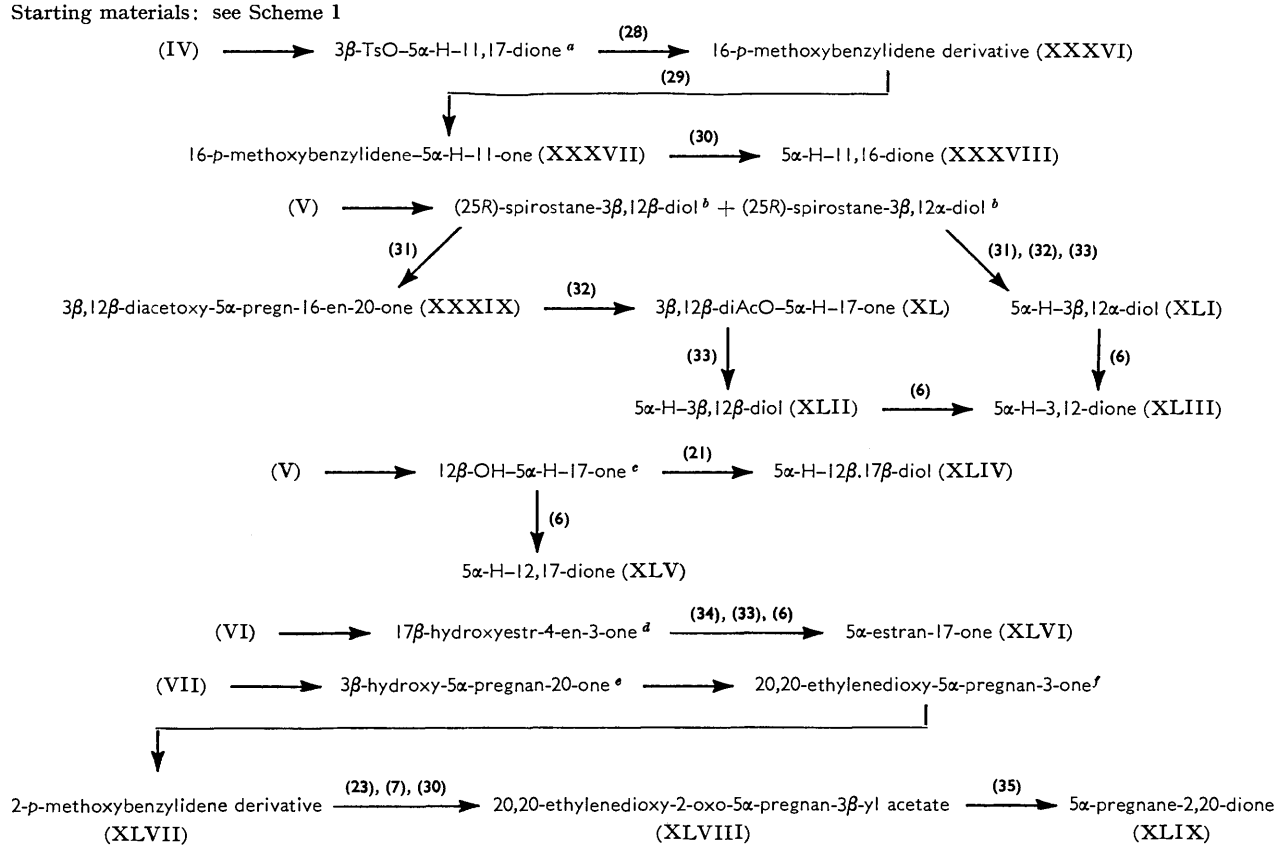
Reagents: (1), $CH_2{:}C(OAc)Me$–TsOH; (2) monoperoxyphthalic acid–Et_2O; (3) HCl–EtOH; (4) B_2H_6; (5) H_2O_2–NaOH; (6) H_2CrO_4–Me_2CO; (7) Ac_2O–C_5H_5N; (8) $MeCH{:}PPh_3$; (9) H_2,Pd–C_6H_6; (10), $(Bu^tO)_2CrO_2$–CCl_4; (11) H_2,Pt–EtOAc; (12), H_2,Pd–EtOH; (13), H_2,Pd–EtOAc; (14), KOH–MeOH; (15) $HO{\cdot}[CH_2]_2{\cdot}OH$–TsOH; (16) CrO_3–C_5H_5N; (17), TsCl–C_5H_5N; (18), *via* hydrazone sequence (D. H. R. Barton, R. E. O'Brien, and S. Sternhell, *J. Chem. Soc.*, 1962, 470); (19) $NMe_4{}^+OAc^-$–*N*-methylpyrrolidone; (20) *m*-$ClC_6H_4{\cdot}CO_3H$–$CHCl_3$; (21), $LiAlH_4$; (22) TsOH–Me_2CO; (23), $NaBH_4$; (24), BzCl–C_5H_5N; (25), HCl–MeOH, 44 °C; (26), H_2CrO_4–MeCOEt; (27) KOH–EtOH.

[a] A. Butenandt, L. Poschmann, G. Failer, U. Schiedt, and E. Biekert, *Annalen*, 1951, **575**, 123. [b] J. A. Marshall and W. S. Johnson, *J. Org. Chem.*, 1963, **28**, 595. [c] C. Djerassi, R. H. Shapiro and M. Vandewalle, *J. Amer. Chem. Soc.*, 1965, **87**, 4892. [d] V. Prelog, L. Ruzicka, P. Meister, and P. Wieland, *Helv. Chim. Acta*, 1945, **28**, 618. [e] R. Beugelmans, R. H. Shapiro, L. J. Durham, D. H. Williams, H. Budzikiewicz, and C. Djerassi, *J. Amer. Chem. Soc.*, 1964, **86**, 2832. [f] J. R. Billeter and K. Miescher, *Helv. Chim. Acta*, 1948, **31**, 629. [g] F. Sondheimer and R. Mechoulam, *J. Amer. Chem. Soc.*, 1958, **80**, 3087. [h] D. H. Williams, N. S. Bhacca, and C. Djerassi, *J. Amer. Chem. Soc.*, 1963, **85**, 2810.

indicate sequences of published reactions which have been used without modification. Details of these sequences can be found by working back from the references accompanying the products. Where the stages leading to known compounds are specified the present route is more convenient, or gives a better yield, than that in the literature.

Our first approach to 5α-androstane-2,7-dione (XVIII) was based on a projected 3 ⟶ 2 keto-transposition [1] of a 7-hydroxy-5α-androstan-3-one. Although an epimeric mixture of the 7-alcohols is obtained easily, preparation of the separate 7-hydroxy-3-ketones, (XXXI) and (XXXIII), was unexpectedly difficult. (A much shorter route to these compounds emerged during the microbiological work and will be described later.) The use of the mixed hydroxy-ketones in a keto-transposition was not pursued because an alternative approach, shown near the top of Scheme 1, led very conveniently to the 2,7-diketone (XVIII).

Conversion of 3β-hydroxy-5α-androstane-11,17-dione (IV) into 5α-androstane-11,16-dione (XXXVIII) required removal of the 3-hydroxy-group and a 17 ⟶ 16 keto-transposition. The observation that the mixed hydride reagent causes reductive elimination of a 3-*p*-tolylsulphonyloxy-group but does not reduce an 11-keto-group is the basis of the four-stage sequence shown in Scheme 2. Adams catalyst was found to be more effective than palladium–charcoal [5] in the hydrogenation of 3β-hydroxypregn-5-en-20-one (VII) to 3β-hydroxy-5α-pregnan-20-one, the starting material in the synthesis of 5α-pregnane-2,10-dione (XLIX). The status of a previously reported 5α-pregnane-2,20-dione [6] is uncertain: a satisfactory elementary analysis was not obtained and the constants of the product differ markedly from those of the diketone described here.



SCHEME 2

Reagents as in Scheme 1, and: (28), *p*-MeO·C_6H_4·CHO–KOH; (29), $LiAlH_4$–$AlCl_3$; (30), O_3; (31), side-chain degradation (as in ref. 8), then oxidation and hydrolysis (as in ref. 8); (32), H_2N·OH, then $POCl_3$; (33) Huang-Minlon reduction; (34), Li–NH_3; (35), Zn–AcOH, heat.

[a] W. Klyne and S. Ridley, *J. Chem. Soc.*, 1956, 4825. [b] R. Hirschmann, C. S. Snoddy, C. F. Hiskey, and N. L. Wendler, *J. Amer. Chem. Soc.*, 1954, **76**, 4013. [c] C. Djerassi and L. Tökes, *J. Amer. Chem. Soc.*, 1966, **88**, 536. [d] A. L. Wilds and N. A. Nelson, *J. Amer. Chem. Soc.*, 1953, **75**, 5366. [e] Ref. 9. [f] W. Schütt and Ch. Tamm, *Helv. Chim. Acta*, 1958, **41**, 1730.

EXPERIMENTAL

For general directions see ref. 2. Petrol refers to light petroleum, b.p. 60—80°. The arabic numbers below 376 in parentheses following formulae numbers are those used

[1] N. Pappas and H. R. Nace, *J. Amer. Chem. Soc.*, 1959, **81**, 4556.

[5] N. Pappas and H. R. Nace, *J. Amer. Chem. Soc.*, 1959, **81**, 4556.

[6] H. R. Nace and A. C. Watterson, *J. Org. Chem.*, 1966, **31**, 2109.

previously in presenting spectrometric results.[2-4] Higher numbers, 376—392, are given to the other compounds described here which have been prepared in connection with microbiological work. For these compounds the n.m.r. signals are listed in the Table, and the i.r. absorptions are given in the following sections. (I.r. values reported here were obtained with a Perkin-Elmer 257 spectrometer and are therefore less accurate than those [4] recorded with a Perkin-Elmer 521 instrument.) The preparations are given in the order used in Schemes 1 and 2, and each section is headed by the systematic name of the end product.

5α-Androstane-3,6-dione (IX) (No. 35).—C_6H_6 (20 ml) was distilled from a solution of androst-4-en-3-one (1 g) in C_6H_6 (50 ml). CH_2:C(OAc)Me (6 ml) and TsOH,H_2O (0·2 g) were added and the solution was distilled slowly for 2 h. More CH_2:C(OAc)Me (2 ml) was added and the distillation was continued for a further 2 h. Isolation with Et_2O gave extracted with Et_2O. The product was dissolved in tetrahydrofuran (30 ml) and cooled to 0 °C. 4N-NaOH (13 ml) and 30% H_2O_2 (13 ml) were added, and the mixture was stirred at 20 °C for 16 h. After work-up, p.l.c. [3 large plates, 1 × petrol–Et_2O (1 : 1)] gave a main fraction (320 mg) which was dissolved in Me_2CO (30 ml)–4N-HCl (5 ml). The solution was heated under reflux for 2 h and then evaporated at 40° and 2 cmHg. Extraction of the residue with Et_2O afforded *6β-hydroxy-5β-androstan-3-one* (262 mg; m.p. 138—140°; from Me_2CO–C_6H_{14}), $[\alpha]_D$ +9° (*c* 0·9) (Found: C, 78·4; H, 10·5. $C_{19}H_{30}O_2$ requires C, 78·6; H, 10·4%), $\nu_{max.}$ 3609 and 1715 cm^{-1}. Oxidation of this compound in Me_2CO with 8N-H_2CrO_4 for 8 min gave 5α-androstane-3,6-dione (82% yield), m.p. and mixed m.p. 150—153°.

5β-Androstan-6-one (XII) (No. 14).—Hydroboration of androst-5-ene (2·5 g) and treatment of the product with

N.m.r. signals

$CDCl_3$ solutions were examined at 100 MHz. Some signals are described as s (singlet), d (doublet), t (triplet), q (quartet), or m (unresolved multiplet): letters d, t, and q are followed, in parentheses, by the coupling constants (*J* Hz); m is followed by the half-height width ($W_{\frac{1}{2}}$ Hz). Where these terms are inappropriate the number of lines is indicated by an italicised number: this is followed by a set of apparent *J* values.

			Other signals						Other signals		
No.	19-H τ	18-H τ	τ	Form	Assignment	No.	19-H τ	18-H τ	τ	Form	Assignment
(X)	8·77	9·24	6·26	q(2)	H-6	(XXVIII)	9·08	9·35	6·28	d(6)	H-17
(XIII)	8·99	9·26	5·26	m(7)	H-6	(XXIX)	9·24	9·34	6·27	d(6)	H-17
(XIV)	9·21	9·31	7·83	s	Ac	(XXX)	9·15	9·28	6·65	*4*(10,10,5)	H-7
			7·58	m(30)	H-3				6·42	*5*(10,10,5,5)	H-3
(XV)	9·19	9·14	7·86	s	Ac	(XXXII)	9·13	9·28	6·39	m(22)	H-3
			7·59	m(30)	H-3				4·78	m(6)	H-7
(XVII)	8·72	9·25	4·00	s	H-6	(XXXIII)	8·95	9·25	6·60	m(18)	H-7
			3·82	d(10)	H-3 and	(XXXIV)	9·09	9·24	6·39	m(21)	H-3
									5·15	m(20)	H-7
			2·99	d(10)	H-4						
(XX)	8·94	9·21	5·35	t(8)	H-17	(XXXVI)	8·94	9·13			
(XXI)	8·93	9·25	6·29	t(8)	H-17	(XXXVII)	8·96	9·27			
(XXII)	9·07	9·26	6·32	t(8)	H-17	(XL)	9·14	9·02	5·29	*5*(10,10,5,5)	H-3
(XXIII)	9·07	9·26	4·33	d *(7)	H-16				5·07	*4*(10,5)	H-12
			4·20	d *(7)	H-17	(XLI)	9·19	9·26	6·39	m(25)	H-3
(XXIV)	9·07	9·13							6·19	t(3)	H-12
(XXV)	9·08	8·95				(XLII)	9·17	9·28	6·38	m(23)	H-3
(XXVI)	9·08	9·25	5·18	d(6)	H-17				6·58	*4*(11,5)	H-12
(XXVII)	9·09	9·28	6·67	d(6)	H-16 and	(XLIII)	8·89	8·95			
			6·93	d(6)	H-17						

* Signals split by further small couplings.

the crude enol acetate. This was dissolved in Et_2O (15 ml) and treated in the dark with an excess of monoperphthalic acid in Et_2O. After 16 h standard work-up gave material which was chromatographed on Al_2O_3 (100 g). Et_2O eluted androst-4-en-3-one (105 mg). Et_2O–MeOH (49 : 1) eluted *6β-hydroxyandrost-4-en-3-one* (VIII) (No. 160) (0·53 g; m.p. 150—152°; from MeOH), $[\alpha]_D$ +15° (*c* 0·4) (Found: C, 79·2; H, 10·0. $C_{19}H_{28}O_2$ requires C, 79·1; H, 9·8%), $\nu_{max.}$ 3610 and 1687 cm^{-1}, $\lambda_{max.}$ 237 nm (ε 18,300). Heating a solution of this compound (170 mg) in EtOH (5 ml)–10N-HCl (0·1 ml) under reflux for 2 h gave *5α-androstane-3,6-dione* (135 mg), m.p. 151·5—153° (from C_6H_{14}), $[\alpha]_D$ −26° (*c* 0·7) (Found: C, 79·2; H, 9·7. $C_{19}H_{28}O_2$ requires C, 79·1; H, 9·8%).

6β-Hydroxy-5β-androstan-3-one (X) (No. 382).—A solution of BF_3,Et_2O (2 ml) in Et_2O (20 ml) was added during 20 min to a stirred solution of 3,3-ethylenedioxyandrost-5-ene (1·25 g) and $NaBH_4$ (0·4 g) in diglyme (13 ml) at 0 °C. The solution was stirred at 20 °C for 1 h, diluted with H_2O and NaOH–H_2O_2 as before gave material (2·5 g) which was separated into three main fractions by p.l.c. [5 large plates, 5 × petrol–Et_2O (9 : 1)]. That of highest R_F was androst-5-ene (610 mg). The central fraction was 5β-androstan-6β-ol (No. 124) (405 mg) (see later). The fraction of lowest R_F was *5α-androstan-6α-ol* (XI) (No. 122) (1·1 g), m.p. 99—100° (from MeOH), $[\alpha]_D$ +23° (*c* 0·4) (Found: C, 82·5; H, 11·4. $C_{19}H_{32}O$ requires C, 82·5; H, 11·7%).

Treatment of 5β-androstan-6β-ol (see before) with Ac_2O–C_5H_5N for 20 h at 20 °C gave 5β-androstan-6β-yl acetate (XIII) (No. 381) (85% yield), m.p. 80—81° (from MeOH), $[\alpha]_D$ −7° (*c* 0·4) (Found: C, 78·8; H, 10·7. $C_{21}H_{34}O_2$ requires C, 79·2; H, 10·8%), $\nu_{max.}$ 1735 cm^{-1}. Oxidation of 5β-androstan-6β-ol in Me_2CO with 8N-H_2CrO_4 for 1 min gave *5β-androstan-6-one* (90% yield), m.p. 107—109° (from MeOH), $[\alpha]_D$ −76° (*c* 0·3) (Found: C, 83·3; H, 11·1. $C_{19}H_{30}O$ requires C, 83·2; H, 11·0%).

3β-Acetyl-5α-androstane (XIV) (No. 376).—A solution of PhLi [from Li (580 mg) and PhBr (6·7 g) in Et_2O (10 ml)]

was added dropwise in N_2 to a stirred solution of $MeCH^{+}PPh_3Br^-$ (13·1 g) in tetrahydrofuran (130 ml). A solution of 5α-androstan-3-one (2·9 g) in Et_2O (20 ml) was added, and the mixture was boiled under reflux for 20 h. After evaporation at 60° and 2 cmHg, the residue was dissolved in Et_2O and washed with 2N-HCl. The product (2·27 g) was dissolved in Et_2O (25 ml)–BF_3,Et_2O (9·5 ml) and the solution was added during 30 min to a stirred solution of $NaBH_4$ (530 mg) in diglyme (47 ml) at 0 °C. After 1·5 h, 8N-H_2CrO_4 (25 ml) was added, and the stirring was continued at 20 °C for a further 1·5 h. The material isolated with Et_2O was chromatographed on Al_2O_3 (200 g). Petrol eluted olefinic material (230 mg). Petrol–Et_2O (19 : 1) eluted 3β-*acetyl*-5α-*androstane* (940 mg; m.p. 89—91°; from EtOH), $[\alpha]_D$ +21° (*c* 1·0) (Found: C, 83·1; H, 11·1. $C_{21}H_{34}O$ requires C, 83·4; H, 11·3%), $\nu_{max.}$ 1718 cm^{-1}. The material obtained by evaporating the EtOH was boiled under reflux for 30 min with MeOH (30 ml)–KOH (0·3 g). Work-up gave more of the ketone (XIV) (630 mg; m.p. and mixed m.p. 89—91°).

3β-*Acetyl*-5α-*androstan*-17-*one* (XV) (No. 380).—17β-Hydroxy-5α-androstan-3-one (3·9 g), treated as in the preceding experiment, gave the *dione* (2·6 g), m.p. 139—142° (from Me_2CO–C_6H_{14}), $[\alpha]_D$ +95° (*c* 0·6) (Found: C, 79·2; H, 10·0. $C_{21}H_{32}O_2$ requires C, 79·7; H, 10·2%), $\nu_{max.}$ 1745 and 1713 cm^{-1}.

Androst-5-*en*-7-*one* (XVI) (No. 346).—A solution of androsta-3,5-dien-7-one (1 g) in C_6H_6 (10 ml) was added to a suspension of freshly reduced 2% Pd–$SrCO_3$ (1 g) in C_6H_6 (25 ml). The mixture was shaken in H_2 at 20° until uptake ceased (5 min). Filtration and evaporation gave *androst*-5-*en*-7-*one* (0·61 g; m.p. 144·5—146°; from EtOH), $[\alpha]_D$ −208° (*c* 0·4) (Found: C, 83·9; H, 10·15. $C_{19}H_{28}O$ requires C, 83·8; H, 10·4%), $\lambda_{max.}$ 237 nm (ε 14,000).

5α-*Androstane*-2,7-*dione* (XVIII) (No. 350).—A mixture of di-t-butyl chromate (38 ml) and AcOH (2·5 ml)–Ac_2O (1 ml) was added during 30 min to a stirred solution of androsta-3,5-dien-7-one (3·14 g) in CCl_4 (250 ml) which was boiling under reflux. The stirring and boiling were continued for 15 h, and the solution was then cooled. A solution of oxalic acid (3 g) in H_2O (36 ml) was added, and the mixture was stirred at 20 °C for 20 h. Work-up of the organic layer gave *androsta*-3,5-*diene*-2,7-*dione* (XVII) (No. 377) (1·51 g of yellow needles, m.p. 207—209°; from MeOH), $[\alpha]_D$ −302° (*c* 0·8) (Found: C, 80·25; H, 8·5. $C_{19}H_{24}O_2$ requires C, 80·0; H, 8·5%), $\nu_{max.}$ 1680 cm^{-1}, $\lambda_{max.}$ 287 nm (ε 19,500).

A solution of this diketone (480 mg) in EtOAc (15 ml) was hydrogenated at 20 °C over PtO_2 (240 mg) for 30 min. After work-up the product was dissolved in Me_2CO and treated with 8N-H_2CrO_4 to give 5α-*androstane*-2,7-*dione* (380 mg; m.p. 187—187·5°; from MeOH), $[\alpha]_D$ −42° (*c* 0·5) (Found: C, 79·2; H, 9·7. $C_{19}H_{28}O_2$ requires C, 79·1; H, 9·8%).

5α-*Androstane*-7,17-*dione* (XIX) (No. 51).—A solution of androsta-3,5-diene-7,17-dione (3·3 g) in EtOH (350 ml) was hydrogenated at 20° over 10% Pd–C (1·55 g) for 55 min. Filtration through Celite and evaporation gave 5α-*androstane*-7,17-*dione* (2·9 g; m.p. 150—152°; from MeOH), $[\alpha]_D$ −11° (*c* 1·0) (Found: C, 78·9; H, 9·6. $C_{19}H_{28}O_2$ requires C, 79·1; H, 9·8%).

17β-*Hydroxy*-5α-*androstan*-7-*one* (XXI) (No. 388).—A solution of 7-oxoandrosta-3,5-dien-17β-yl acetate (2·5 g) in EtOAc (250 ml) was hydrogenated at 20 °C over 10% Pd–C (1·3 g) for 20 min. After work-up the product was dissolved in Me_2CO and treated with 8N-H_2CrO_4 to give 7-*oxo*-5α-*androstan*-17β-*yl acetate* (XX) (No. 389) (1·1 g; m.p. 132—134°, from Et_2O–C_6H_{14}), $[\alpha]_D$ −62° (*c* 0·95) (Found: C, 75·9; H, 9·9. $C_{21}H_{32}O_3$ requires C, 75·9; H, 9·7%), $\nu_{max.}$ 1740 and 1710 cm^{-1}. A solution of this keto-acetate (2 g) in MeOH (50 ml)–KOH (5 g) was boiled under reflux for 15 h to give 17β-*hydroxy*-5α-*androstan*-7-*one* (1·6 g; m.p. 144—146°; from Me_2CO–C_6H_{14}), $[\alpha]_D$ −60° (*c* 1·0) (Found: C, 78·9; H, 10·5. $C_{19}H_{30}O_2$ requires C, 78·4; H, 10·4%), $\nu_{max.}$ 3600 and 1710 cm^{-1}.

17α-*Hydroxy*-5α-*androstan*-2-*one* (XXIX) (No. 384).—A solution of 17β-hydroxy-5α-androstan-2-one (3·5 g) and TsOH,H_2O (100 mg) in C_6H_6 (150 ml)–ethane-1,2-diol (5 ml) was heated under reflux in a Dean–Stark apparatus for 15 h. Work-up gave 2,2-*ethylenedioxy*-5α-*androstan*-17β-*ol* (XXII) (No. 387) (3·81 g), m.p. 154—155° (from Me_2CO–C_6H_{14}), $[\alpha]_D$ +0·6° (*c* 0·9) (Found: C, 75·0; H, 10·05. $C_{21}H_{34}O_3$ requires C, 75·4; H, 10·25%), $\nu_{max.}$ 3600 and 1080 cm^{-1}.

A solution of the hydroxy-acetal (2·65 g) in C_5H_5N (20 ml) was added to a suspension of CrO_3 (2·0 g) in C_5H_5N (40 ml). The mixture was kept at 20 °C for 15 h, diluted with C_6H_6 (150 ml), and filtered successively through Celite and Al_2O_3 [deactivated with H_2O (5%)] to give 2,2-*ethylenedioxy*-5α-*androstan*-17-*one* (XXIV) (No. 378) (2·06 g), m.p. 164—166° (from C_6H_{14}), $[\alpha]_D$ +61° (*c* 1·0) (Found: C, 75·4; H, 9·4. $C_{21}H_{32}O_3$ requires C, 75·85; H, 9·7%), $\nu_{max.}$ 1740 and 1080 cm^{-1}.

A solution of the keto-acetal (1·0 g) in ethane-1,2-diol (40 ml)–N_2H_4,H_2O (2 ml) was heated under reflux for 2 h. The 17-hydrazone (1·03 g), obtained by isolation with C_6H_6, was dissolved in tetrahydrofuran (50 ml), and the stirred solution was treated at 20 °C with a solution of I_2 in tetrahydrofuran (25% v/v; *ca.* 5 ml) until a yellow colour persisted. The mixture was stirred for a further 5 min, diluted with Et_2O (150 ml), and washed successively with H_2O, aq. $Na_2S_2O_5$, and H_2O. Evaporation gave a solid, a solution of which in petrol was filtered through Al_2O_3 [deactivated with H_2O (5%)]. A solution of the product (950 mg) in Pr^iOH (40 ml) was boiled under reflux while Na (1 g) was added in portions during 1 h. When the Na had dissolved the mixture was worked up, and a solution of the product in petrol was filtered through Al_2O_3 [deactivated with H_2O (5%)] to give 2,2-*ethylenedioxy*-5α-*androst*-16-*ene* (XXIII) (610 mg), m.p. 98—99° (from Me_2CO), $[\alpha]_D$ +59° (*c* 1·0) (Found: C, 79·3; H, 9·9. $C_{21}H_{32}O_2$ requires C, 79·7; H, 10·2%), $\nu_{max.}$ 1080 cm^{-1}.

A solution of the unsaturated acetal (167 mg) and *m*-$ClC_6H_4{\cdot}CO_3H$ (140 mg) in $CHCl_3$ (15 ml) was kept at 20 °C for 6 h. The product, isolated with Et_2O, was dissolved in C_6H_6 and filtered through Al_2O_3 to give 2,2-*ethylenedioxy*-16α,17α-*epoxy*-5α-*androstane* (XXVII) (160 mg), m.p. 146—147° (from C_6H_{14}), $[\alpha]_D$ +35° (*c* 1·0) (Found: C, 75·75; H, 9·9. $C_{21}H_{32}O_2$ requires C, 75·85; H, 9·7%), $\nu_{max.}$ 1100 and 945 cm^{-1}.

A solution of the epoxide (130 mg) and $LiAlH_4$ (50 mg) in Et_2O (50 ml) was heated under reflux for 6 h, cooled, and treated with saturated aq. NH_4Cl (0·5 ml). Filtration, and evaporation of the filtrate gave 2,2-*ethylenedioxy*-5α-*androstan*-17α-*ol* (XXVIII) (No. 385) (120 mg), m.p. 194—195° (from Me_2CO–C_6H_{14}), $[\alpha]_D$ +16° (*c* 0·6) (Found: C, 75·3; H, 10·2. $C_{21}H_{34}O_3$ requires C, 75·05; H, 10·25%), $\nu_{max.}$ 3600 cm^{-1}.

A solution of this hydroxy-acetal (70 mg) and TsOH,H_2O (10 mg) in Me_2CO (5 ml)–H_2O (0·05 ml) was kept at 20 °C

for 48 h. Work-up gave 17α-*hydroxy*-5α-*androstan*-2-*one* (XXIX) (No. 384) (65 mg), m.p. 156—159° (from Me_2CO–C_6H_{14}), $[\alpha]_D$ −35° (*c* 0·7) (Found: C, 78·7; H, 10·4. $C_{19}H_{30}O_2$ requires C, 78·6; H, 10·4%).

A solution of 2,2-ethylenedioxy-5α-androstan-17β-ol (XXII) (350 mg) and TsCl (340 mg) in C_5H_5N (10 ml) was kept at 20 °C for 2 days. The solution was poured into ice–H_2O and filtered to give 2,2-*ethylenedioxy*-5α-*androstan*-17β-*yl toluene*-p-*sulphonate* (XXV) (300 mg), m.p. 209—211° (from Me_2CO), $[\alpha]_D$ −190° (*c* 1·0) (Found: C, 68·7; H, 8·0. $C_{28}H_{40}O_5S$ requires C, 68·8; H, 8·25%).

A solution of the tosylate (180 mg) and $NMe_4^+OAc^-$ (1·3 g) in *N*-methylpyrrolidone (7 ml) was kept at 160° for 4 h. Work-up, followed by p.l.c. [1 large plate, 2 × petrol–Me_2CO (4 : 1)] gave 2,2-ethylenedioxy-5α-androst-16-ene (highest R_F) (30 mg), m.p. and mixed m.p. 97—99°, 2,2-*ethylenedioxy*-5α-*androstan*-17α-*yl acetate* (XXVI) (No. 386) (75 mg), m.p. 112—114° (from MeOH), $[\alpha]_D$ −17° (*c* 0·5) (Found: C, 73·3; H, 9·7. $C_{23}H_{36}O_4$ requires C, 73·3; H, 9·6%), $\nu_{max.}$ 1740 cm^{-1}, and 2,2-ethylenedioxy-5α-androstan-17α-ol (lowest R_F) (40 mg), m.p. and mixed m.p. 194—195°.

7α-*Hydroxy*-5α-*androstan*-3-*one* (XXXI) (No. 161) *and* 7β-*Hydroxy*-5α-*androstan*-3-*one* (XXXIII) (No. 383).—A solution of 7-oxoandrost-5-en-3β-yl acetate (7 g) in EtOAc (150 ml) was hydrogenated at 20° over PtO_2 (150 mg) for 1 h. Work-up gave an oil which was dissolved in EtOH (70 ml) and stirred with $NaBH_4$ (0·7 g) at 20 °C for 3 h. AcOH (1 ml) was added and the solution was concentrated to small volume at 50° and 2 cmHg. Extraction with $CHCl_3$ gave a mixture which was separated by p.l.c. [8 large plates, 1 × petrol–EtOAc (9 : 1)]. The fraction of highest R_F was 5α-androstan-3β-yl acetate (622 mg), m.p. 88—89° (from MeOH) (lit.,[7] m.p. 87—88°). The material (4·31 g) of intermediate R_F was a mixture of 7α- and 7β-hydroxy-5α-androstan-3β-yl acetates, $\nu_{max.}$ 3620, 1730, and 1230 cm^{-1}. The fraction of lowest R_F was 5α-*androstane*-3β,7β-*diol* (XXX) (No. 390) (1·6 g), m.p. 149—152° (from Me_2CO–C_6H_{14}), $[\alpha]_D$ +27° (*c* 0·9) (Found: C, 77·8; H, 11·3. $C_{19}H_{32}O_2$ requires C, 78·0; H, 11·0%), $\nu_{max.}$ 3600 and 1025 cm^{-1}.

A solution of the foregoing mixture of 7-hydroxy-3β-acetates (900 mg) in C_5H_5N (10 ml)–BzCl (1 ml) was kept at 20 °C for 10 h. P.l.c. [2 large plates, 1 × petrol–EtOAc (47 : 3)] of the product gave 3β-acetoxy-7α-benzoyloxy-5α-androstane (higher R_F) (380 mg), $\nu_{max.}$ 1733 and 1715 cm^{-1}, and 3β-acetoxy-7β-benzoyloxy-5α-androstane (lower R_F) (560 mg), $\nu_{max.}$ 1735 and 1715 cm^{-1}. Solutions of these products in $CHCl_3$ (2 ml)–MeOH (16 ml)–10N-HCl (0·1 ml) were kept at 43—45° for 16 h. After dilution with brine and extraction with $CHCl_3$, the $CHCl_3$ solutions were washed with 2N-$NaHCO_3$ and H_2O, dried, and evaporated to give 7α-*benzoyloxy*-5α-*androstan*-3β-*ol* (XXXII) (305 mg), m.p. 172—173° (from C_6H_{14}), $[\alpha]_D$ −28° (*c* 1·0) (Found: C, 79·1; H, 9·2. $C_{26}H_{36}O_3$ requires C, 78·75; H, 9·15%), $\nu_{max.}$ 3620 and 1717 cm^{-1}, and 7β-*benzoyloxy*-5α-*androstan*-3β-*ol* (XXXIV) (490 mg), m.p. 211—214° (from Me_2CO–C_6H_{14}), $[\alpha]_D$ +78° (*c* 0·9) (Found: C, 78·7; H, 9·1%), $\nu_{max.}$ 3620 and 1723 cm^{-1}.

Solutions of these hydroxy-benzoates (300 mg) in MeCOEt (15 ml) were treated with 8N-H_2CrO_4 at 20 °C for 10 min. Work-up gave 3-oxo-5α-androstan-7α-yl benzoate (220 mg) as an oil, $\nu_{max.}$ 1720 cm^{-1}, and 3-*oxo*-5α-*androstan*-7β-*yl benzoate* (230 mg), m.p. 213—216° (from Me_2CO–C_6H_{14}), $[\alpha]_D$ +74° (*c* 0·7) (Found: C, 79·3; H, 8·9. $C_{26}H_{34}O_3$ requires C, 79·2; H, 8·7%), $\nu_{max.}$ 1718 cm^{-1}. Solutions of these keto-benzoates (200 mg) in EtOH (15 ml)–KOH (0·75 g) were boiled under reflux for 2 h. Work-up gave 7α-*hydroxy*-5α-*androstan*-3-*one* (130 mg; m.p. 158—160°; from Me_2CO–C_6H_{14}), $[\alpha]_D$ +16° (*c* 1·0) (Found: C, 78·3; H, 10·2. $C_{19}H_{30}O_2$ requires C, 78·6; H, 10·4%), $\nu_{max.}$ 3622 and 1715 cm^{-1}, and 7β-*hydroxy*-5α-*androstan*-3-*one* (115 mg; m.p. 146—149°; from Me_2CO–C_6H_{14}), $[\alpha]_D$ +41° (*c* 0·6) (Found: C, 78·4; H, 10·2%), $\nu_{max.}$ 3645, 3613, and 1715 cm^{-1}.

5α-*Androstane*-3,7-*dione* (XXXV) (No. 36).—7-Oxo-androst-5-en-3β-yl acetate (5·4 g) was hydrogenated as in the preceding experiment. MeOH (100 ml)–KOH (10 g) was added to the product under N_2, and the solution was kept at 20 °C for 15 h. Dilution with H_2O and extraction with CH_2Cl_2 gave material which was dissolved in Me_2CO and treated with 8N-H_2CrO_4. Work-up and crystallisation of the product from Me_2CO–C_6H_{14} gave 5α-*androstane*-3,7-*dione* (3·3 g), m.p. 166—167°, $[\alpha]_D$ −50° (*c* 1·2) (Found: C, 79·3; H, 10·0. $C_{19}H_{28}O_2$ requires C, 79·1; H, 9·8%).

5α-*Androstane*-11,16-*dione* (XXXVIII) (No. 53).—A solution of 11,17-dioxo-5α-androstan-3β-yl toluene-*p*-sulphonate (2 g) and anisaldehyde (6 ml) in MeOH (280 ml)–KOH (14 g) was stirred at 20 °C for 15 h. Collection of the precipitated material gave 16-(p-*methoxybenzylidene*)-11,17-*dioxo*-5α-*androstan*-3β-*yl toluene*-p-*sulphonate* (XXXVI) (2·24 g), m.p. 185—185·5° (from EtOH), $[\alpha]_D$ +51° (*c* 1·02) (Found: C, 70·5; H, 6·8. $C_{34}H_{40}O_6S$ requires C, 70·8; H, 7·0%). A solution of this product (1 g) in diglyme (50 ml) was added during 20 min to a suspension of $LiAlH_4$ (1 g) in Et_2O (100 ml)–$AlCl_3$ (6 g) which was boiling under reflux. The boiling was continued for 48 h. After work-up the product was chromatographed on Al_2O_3 [50 g; deactivated with H_2O (5%)]. Petrol–Et_2O (1 : 1) eluted 16-(p-*methoxybenzylidene*)-5α-*androstan*-11-*one* (XXXVII) (420 mg; m.p. 181—182°; from Et_2O–petrol), $[\alpha]_D$ +38° (*c* 0·9) (Found: C, 82·4; H, 9·0. $C_{27}H_{36}O_2$ requires C, 82·6; H, 9·2%), $\nu_{max.}$ 1710 cm^{-1}. A solution of this ketone (400 mg) in EtOAc (55 ml)–MeOH (85 ml) was ozonised at −70 °C until a blue colour persisted. After the addition of AcOH (1 ml), the solution was warmed to 30 °C, stirred, and kept at 30 °C while Zn dust (4 g) was added during 5 min. The stirring was continued for 1 h, and the mixture was then filtered through Celite. Evaporation at 80° and 2 cmHg gave 5α-*androstane*-11,16-*dione* (304 mg; m.p. 130—131°; from C_6H_{14}), $[\alpha]_D$ −125° (*c* 0·8) (Found: C, 79·0; H, 9·7. $C_{19}H_{28}O_2$ requires C, 79·1; H, 9·8%).

5α-*Androstane*-3,12-*dione* (XLIII) (No. 379).—Side-chain degradation of (25*R*)-5α-spirostane-3β,12β-diol (23 g), followed by oxidation and hydrolysis of the product (conditions described in ref. 8) gave impure material (14·8 g). A solution of this in Ac_2O (100 ml) was boiled under reflux for 12 h. After work-up the mixture of products was chromatographed on Al_2O_3 [400 g; deactivated with H_2O (5%)]. Et_2O–MeOH (49 : 1) eluted 3β,12β-*diacetoxy*-5α-*pregn*-16-*en*-20-*one* (XXXIX) (2·9 g), m.p. 138—140°, $[\alpha]_D$ +25° (*c* 0·4) (Found: C, 72·0; H, 9·1. $C_{25}H_{36}O_5$ requires C, 71·7; H, 9·2%). A solution of this compound (2·9 g) and $H_2N{\cdot}OH{,}HCl$ (0·8 g) in EtOH (16 ml)–C_5H_5N (4 ml) was boiled under reflux for 40 min and worked up to give the 20-oxime (2·2 g). $POCl_3$ (4·0 ml)–C_5H_5N (4·0 ml) was added slowly to a stirred solution of the 20-oxime (2·0 g) in C_5H_5N (10 ml) at 0 °C, and the stirring at 0 °C was

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continued for a further 3 h. After work-up the product was chromatographed on Al_2O_3 (100 g). Et_2O eluted 3β,12β-*diacetoxy*-5α-*androstan*-17-*one* (XL) (No. 393) (1·2 g), m.p. 151—154° (from EtOH–H_2O), $[\alpha]_D$ +30° (*c* 0·2) (Found: C, 70·6; H, 8·8. $C_{23}H_{34}O_5$ requires C, 70·7; H, 8·8%), $\nu_{max.}$ 1743 and 1738 cm^{-1}. Huang–Minlon reduction of the keto-diacetate (1·1 g) gave 5α-*androstane*-3β,12β-*diol* (XLII) (No. 392), m.p. 185—189° (from Me_2CO), $[\alpha]_D$ +11° (*c* 0·9) (Found: C, 78·3; H, 11·3. $C_{19}H_{32}O_2$ requires C, 78·0; H, 11·0%), $\nu_{max.}$ 3620 cm^{-1}.

(25*R*)-Spirostane-3β,12α-diol (9·7 g) was taken through all the stages just described without purification of intermediates, and the material so obtained was chromatographed on Al_2O_3 [400 g; deactivated with H_2O (5%)]. Et_2O–MeOH (49 : 1) eluted a fraction which was purified by p.l.c. [1 large plate, 4 × Et_2O–MeOH (99 : 1)] to give 5α-*androstane*-3β,12α-*diol* (XLI) (No. 391) (140 mg; m.p. 204—206°; from Me_2CO), $[\alpha]_D$ +42° (*c* 0·4) (Found: C, 78·3; H, 11·2%), $\nu_{max.}$ 3614 cm^{-1}.

Oxidation of both the foregoing 3β,12-diols in Me_2CO with 8N-H_2CrO_4 gave 5α-*androstane*-3,12-*dione* (*ca.* 85% yield), m.p. 212—215° (from Me_2CO–C_6H_{14}), $[\alpha]_D$ +71° (*c* 0·9) (Found: C, 78·8; H, 9·9. $C_{19}H_{28}O_2$ requires C, 79·1; H, 9·8%), $\nu_{max.}$ 1715 cm^{-1}.

5α-*Androstane*-12β,17β-*diol* (XLIV) (No. 373) *and* 5α-*Androstane*-12,17-*dione* (XLV) (No. 351).—12β-Hydroxy-5α-androstan-17-one (500 mg) in Et_2O (30 ml) was reduced with $LiAlH_4$ (250 mg), and the product was purified by p.l.c. [1 large plate, 3 × petrol–Et_2O (2 : 1)] to give the 12β,17β-*diol* (410 mg), m.p. 159—160° (from C_6H_{14}), $[\alpha]_D$ +2° (*c* 0·7) (Found: C, 77·7; H, 11·2. $C_{19}H_{32}O_2$ requires C, 78·0; H, 11·0%).

Oxidation of 12β-hydroxy-5α-androstan-17-one (140 mg) in Me_2CO with 8N-H_2CrO_4 gave the 12,17-*diketone* (130 mg), m.p. 182·5—184° (from C_6H_{14}), $[\alpha]_D$ +226° (*c* 0·4) (Found: C, 79·0; H, 9·8. $C_{19}H_{28}O_2$ requires C, 79·1; H, 9·8%).

5α-*Estran*-17-*one* (XLVI) (No. 29).—A solution of 17β-hydroxyestr-4-en-3-one (10 g) in Et_2O (120 ml)–dioxan (120 ml) was added during 15 min to a stirred solution of Li (2 g) in liquid NH_3 (1 l) which was protected from atmospheric moisture by guard-tubes. After 1 h, NH_4Cl (previously dried at 120°) was added in portions until the blue colour disappeared, and the NH_3 was then allowed to evaporate. The material isolated with Et_2O was reduced by the Huang–Minlon method; the product was dissolved in Me_2CO and treated with 8N-H_2CrO_4 to give material which was chromatographed on Al_2O_3 [250 g; deactivated with H_2O (2%)]. C_6H_6 eluted 5α-*estran*-17-*one* (3·6 g; m.p. 121—123°; from C_6H_{14}), $[\alpha]_D$ +119° (*c* 1·0) (Found: C, 83·1; H, 10·6. $C_{18}H_{28}O$ requires C, 83·0; H, 10·8%).

5α-*Pregnane*-2,20-*dione* (XLIX) (No. 353).—A solution of 3β-hydroxypregn-5-en-20-one (10 g) in EtOAc (500 ml) was hydrogenated at 20 °C over PtO_2 (1·0 g) for 1 h, to give 3β-hydroxy-5α-pregnan-20-one (9·4 g), m.p. 193—195° (from Me_2CO–C_6H_{14}), $[\alpha]_D$ +97° (*c* 1·0) (lit.,[9] m.p. 192—194°, $[\alpha]_D$ +82°). This was converted into 20,20-ethylenedioxy-5α-pregnan-3-one (77% yield). A solution of the ethylenedioxy-ketone (3 g) and anisaldehyde (2·7 ml) in EtOH (500 ml)–KOH (25 g) was stirred at 20 °C for 12 h. Work-up gave 20,20-*ethylenedioxy*-2-p-*methoxybenzylidene*-5α-*pregnan*-3-*one* (XLVII) (4·45 g collected by filtration). A small sample crystallised from Me_2CO–C_6H_{14} formed yellow plates, m.p. 190—193°, $[\alpha]_D$ −205° (*c* 0·6) (Found: C, 77·9; H, 8·9. $C_{31}H_{42}O_4$ requires C, 77·8; H, 8·8%), $\nu_{max.}$ 1682 cm^{-1}, $\lambda_{max.}$ 232 (ε 7750) and 323 nm (18,500).

Reduction of this material in tetrahydrofuran (225 ml)–MeOH (25 ml) with $NaBH_4$ (520 mg) at 20 °C for 2 h gave an oil (4·66 g) which was kept in Ac_2O (24 ml)–C_5H_5N (8 ml) at 20 °C for 24 h. A stirred solution of the acetate (5·2 g; $\nu_{max.}$ 1735 cm^{-1}) in EtOAc (500 ml)–MeOH (100 ml) was ozonised at −70 °C until a blue colour persisted, and N_2 was then passed through the solution for 15 min. Me_2S (2 ml) was added during 10 min, the temperature was allowed to rise to −10 °C, and the stirring was continued for 2 h. Concentration of the solution at 50° and 2 cmHg and isolation with Et_2O gave material which was chromatographed on Al_2O_3 [500 g; deactivated with H_2O (10%)]. Petrol–Et_2O (4 : 1) eluted 20,20-*ethylenedioxy*-2-*oxo*-5α-*pregnan*-3β-*yl acetate* (XLVIII) (1·7 g), m.p. 185—187° (from Me_2CO–C_6H_{14}), $[\alpha]_D$ +78° (*c* 0·8) (Found: C, 72·1; H, 9·1. $C_{25}H_{38}O_5$ requires C, 71·7; H, 9·2%), $\nu_{max.}$ 1753, 1734, and 1235 cm^{-1}.

A solution of this keto-acetate (1·7 g) in AcOH (300 ml) was heated under reflux in N_2 for 6 h with activated Zn dust (100 g). Filtration through Celite followed by isolation with Et_2O gave 5α-*pregnane*-2,20-*dione* (0·9 g), m.p. 182—186° (from Me_2CO–C_6H_{14}), $[\alpha]_D$ +133° (*c* 1·0) (Found: C, 79·8; H, 10·05. $C_{21}H_{30}O_2$ requires C, 79·7; H, 10·1%). (A product reported [6] to be 5α-pregnane-2,20-dione had m.p. 135—136°, $[\alpha]_D$ +93°.)

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