Microbiological Hydroxylation of Steroids. Part XI.[1] Convenient Routes to 3,7-, 3,11-, 3,12-, 7,11-, 7,17-, and 11,17-Dioxygenated 5α-Androstanes and to 5α-Androstan-11-one

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Suitable, readily available 3,17-dioxygenated 5α-androstanes are hydroxylated efficiently at position 11 by *Aspergillus ochraceus* and at position 7 by *Rhizopus nigricans*. These reactions, carried out on a reasonable scale, are the basis of convenient routes to derivatives of 5α-androstane (3,7-, 3,11-, 3,12-, 7,11-, 7,17-, and 11,17-dioxygenated compounds, and 5α-androstan-11-one) which are not readily accessible by chemical means.

PREVIOUS work in this series has shown that a range of simple oxygenated androstanes, estranes, and pregnanes are efficiently hydroxylated by various fungi. So far the studies have been concerned with the patterns of hydroxylation, *i.e.* the relationships between the structures of the substrates and those of the products. The knowledge thus gained has now been applied to a separate object of the microbiological studies, the use of fungal cultures for preparing steroids which are relatively inaccessible by purely chemical means.[2]

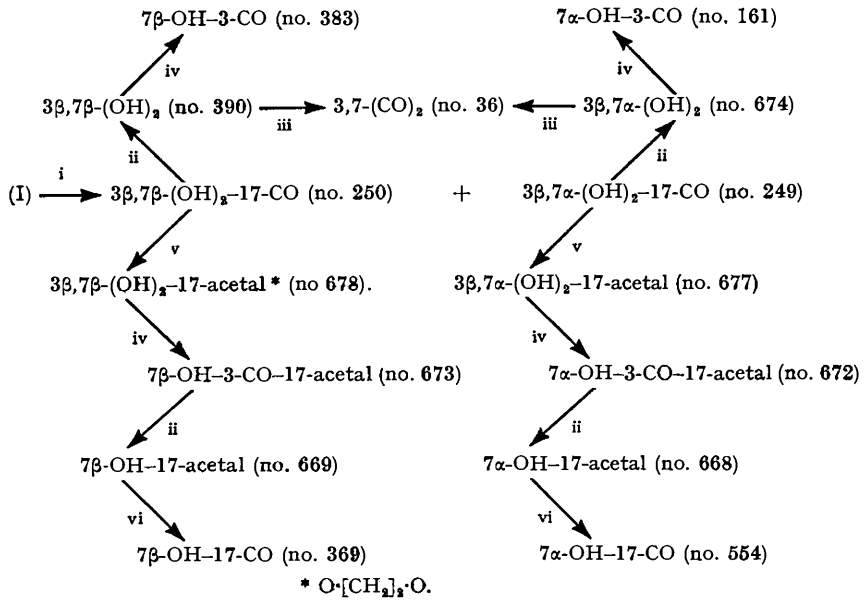
For various purposes, which include the extension of the hydroxylation work to less common steroidal systems, we needed gram quantities of the androstane derivatives enumerated in the Title. Such compounds are reasonably well known, but it is often difficult to

[1] Part X, A. S. Clegg, W. A. Denny, Sir Ewart R. H. Jones, G. D. Meakins, and J. T. Pinhey, *J.C.S. Perkin I*, 1973, 2137.

[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.

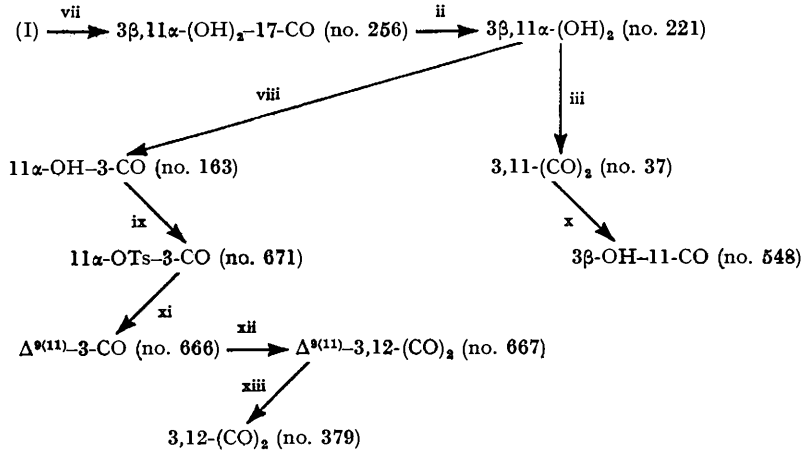
introduce substituents into rings B and C, as shown for example by the tedious preparations of 7α- and 7β-hydroxy-5α-androstan-3-one.[3] In designing microbiological alternatives the important considerations were the structures of the substrates, the nature of the for various selective operations on the products. *Aspergillus ochraceus* and *Rhizopus nigricans* are known [4,5] to be capable of introducing hydroxy-groups at the desired positions when used under appropriate conditions in culture flasks. For preparative work it was essential

SCHEME 1 3,7- and 7,17-Dioxygenated 5α-androstanes



Reagents: i, *A. nigricans*; ii, Huang-Minlon reduction; iii, H_2CrO_4–Me_2CO; iv, Ag_2CO_3 on Celite; v, HO·[CH2]2·OH–Amberlite resin; vi, HCl–H_2O–EtOH

SCHEME 2 3,11- and 3,12-Dioxygenated 5α-androstanes



Reagents as before, and: vii, *A. ochraceus*; viii, AcNHBr; ix, TsCl–C_5H_5N; x, $LiAlH(OBu^t)_3$; xi, Li_2CO_3–LiCl–Me_2N·CHO; xii, Na_2CrO_4–Ac_2O–AcOH; xiii, H_2–Pd.

micro-organisms, and the incubation conditions. It was intended that all the required systems should be obtained from three commercially available, relatively cheap substrates, *viz.* 3β-hydroxy-5α-androstan-17-one (I), 17β-hydroxy-5α-androstan-3-one (II), and 5α-androstane-3,17-dione (III): the use of substrates with substituents at different oxidation levels was expected to open the way that the efficiency of the hydroxylations should not be adversely affected by large-scale batch operation.

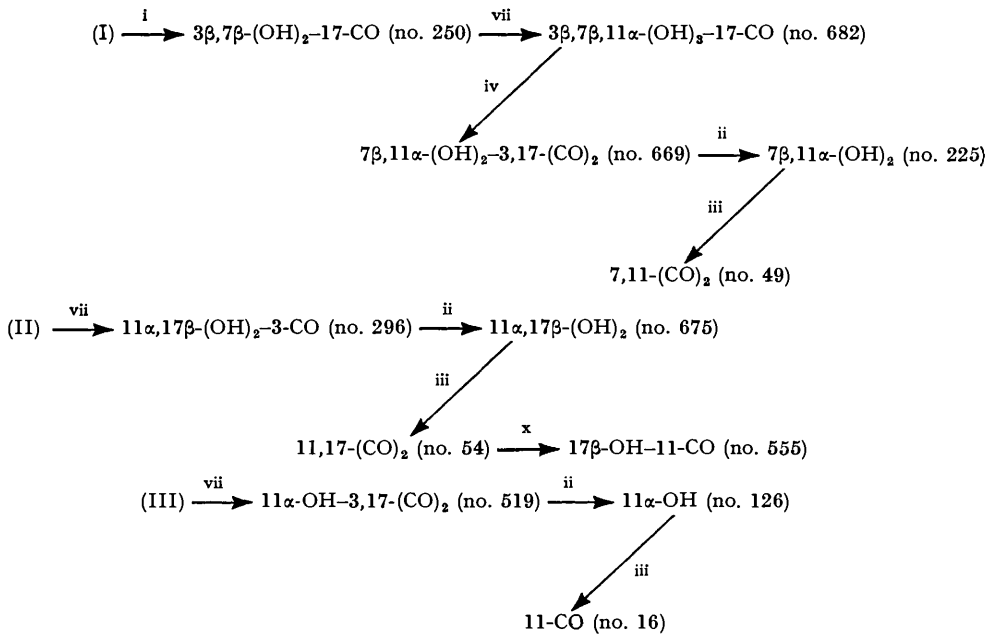
Table 1 and Schemes 1—3 summarise the results obtained. [The use of the (arabic) serial number of steroids throughout this work, and considerations about

[3] A. S. Clegg, W. A. Denny, Sir Ewart R. H. Jones, V. Kumar, G. D. Meakins, and V. E. M. Thomas, *J. Chem. Soc.* (*C*), 1972, 492.

[4] A. M. Bell, J. W. Browne, W. A. Denny, Sir Ewart R. H. Jones, A. Kasal, and G. D. Meakins, *J.C.S. Perkin I*, 1972, 2930.

[5] (*a*) J. W. Browne, W. A. Denny, Sir Ewart R. H. Jones, G. D. Meakins, Y. Morisawa, A. Pendlebury, and J. Pragnell, *J.C.S. Perkin I*, 1973, 1493; (*b*) W. A. Denny, J. M. Evans, Sir Ewart R. H. Jones, A. Kasal, G. D. Meakins, J. Pragnell, and V. E. M. Thomas, *ibid.*, p. 1500.

SCHEME 3 7,11- and 11,17-Dioxygenated 5α-androstanes and 11-oxo-5α-androstane

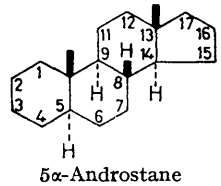


Reagents as before.

TABLE 1

Incubations

The steroids, all derivatives of 5α-androstane, are represented in this Table and the Schemes by abbreviated names, *e.g.*, 7β,11α-(OH)2–3,17-(CO)2 for 7β,11α-dihydroxy-5α-androstane-3,17-dione



5α-Androstane

Substrates:
(I) 3β-hydroxy-5α-androstan-17-one (no. 151),
(II) 17β-hydroxy-5α-androstan-3-one (no. 411),
(III) 5α-androstane-3,17-dione (no. 42)

Fungi:
Rhizopus nigricans (*Rn*),
Aspergillus ochraceus (*Ao*)

(I) —*Rn*→

Starting material	26%
3β,7β-(OH)2–17-CO (no. 250)	40%
3β,7α-(OH)2–17-CO (no. 249)	18%
3β,6α-(OH)2–17-CO (no. 246)	14%
3β-OH–7,17-(CO)2 (no. 558)	1·4%
11α-OH–3,17-(CO)2 (no. 519)	0·5%
Total	98%

(II) —*Ao*→

Starting material	7%
11α,17β-(OH)2–3-CO (no. 296)	79%
6α,11α,17β-(OH)3–3-CO *	2%
3β,11α,17β-(OH)3 * (no. 523)	0·3%

(I) —*Ao*→

Starting material	2%
3β,11α-(OH)2–17-CO(no. 256)	89%
1β,3β-(OH)2–17-CO (no. 676)	1%
11α-OH–3,17-(CO)2 (no. 519)	0·5%
1β,3β,11α-(OH)3–17-CO *	0·3%
3β,17β,11α-(OH)3–17-CO * (no. 682)	0·2%
Total	93%

3β,7β-(OH)2–17-CO —*Ao*→

Starting material	16%
3β,7β,11α-(OH)3–17-CO (no. 682)	78%

(III) —*Ao*→

11α-OH–3,17-(CO)2 (no. 519)	75%

* Isolated as the product formed by acetylation.

the structural elucidation and the reporting of new compounds have been explained earlier.[2] Compounds nos. 666—684 (whose n.m.r. signals are listed in Table 2) are described here.] Of the incubations in Table 1, each involving 20 g of steroid in 5 l of culture fluid, four produced one hydroxylated steroid in greatly predominant amount and one gave a major product accompanied by appreciable quantities of two minor products. Detailed examination of the materials obtained from 3β-hydroxy-5α-androstan-17-one (I) and the 17β-hydroxy-3-ketone (II) revealed steroid balances better than those achieved using culture flasks.[4,5] (While the techniques

give similar results, some of the minor products found here had not been detected previously.) Isolation of all the constituents involves tedious separations: however, the work-up procedures were designed to be suitable for easy harvesting of the main products, and for this restricted purpose the labour is equivalent to that of two or three chemical stages on a comparable scale.

Schemes 1—3 show how the main products were transformed into the required androstane derivatives by standard methods. 3β,7β,11α-Trihydroxy-5α-androstan-17-one, the progenitor of the 7,11-dioxygenated androstanes (first part of Scheme 3) is obtained by successive microbiological stages, the first and the fourth incubations in Table 1: *R. nigricans* introduces a 7β-hydroxy-group into 3β-hydroxy-5α-androstan-17-one, and the product is used as a substrate for 11α-hydroxylation by *A. ochraceus*. Attempts to combine these steps, by adding the second micro-organism to the medium from the first incubation, led to difficulties in isolating the trihydroxy-ketone and the overall yield was lower.

TABLE 2

N.m.r. signals

The results, presented in the form used earlier,[a] were obtained by examining solutions in $CDCl_3$ at 100 MHz.

No.			τ_2	τ_2 (calc.) [a,b]	>C*H*–OR		
666	5α-Androst-9(11)-en-3-one	19	8·84	8·84			
		18	9·31	9·31			
667	5α-Androst-9(11)-ene-3,12-dione	19	8·71	8·71			
		18	9·04	9·04			
668	17,17-Ethylenedioxy-5α-androstan-7α-ol	19	9·21	9·22	H-7	6·1	m(10)
		18	9·16	9·16			
669	17,17-Ethylenedioxy-5α-androstan-7β-ol	19	9·19	9·19	H-7	6·6	m(20)
		18	9·13	9·14			
670	9α,11α-Epoxy-5α-androstan-3-one	19	8·73	8·73	H-11	6·84	d(5)
		18	9·25	9·25			
671	3-Oxo-5α-androstan-11α-yl toluene-*p*-sulphonate	19	8·88		H-11	4·85	*6*(10,10,5)
		18	9·22				
672	17,17-Ethylenedioxy-7α-hydroxy-5α-androstan-3-one	19	8·98	8·98	H-7	6·1	m(10)
		18	9·13	9·12			
673	17,17-Ethylenedioxy-7β-hydroxy-5α-androstan-3-one	19	8·94	8·95	H-7	6·25	m(20)
		18	9·10	9·10			
674	5α-Androstane-3β,7α-diol	19	9·18	9·19	H-3	6·40	m(20)
		18	9·29	9·29	H-7	6·10	m(7)
675	5α-Androstane-11α,17β-diol	19	9·07	9·10	H-11	6·05	m(25)
		18	9·28	9·25	H-17	6·34	t(9)
676	1β,3β-Dihydroxy-5α-androstan-17-one	19	9·14	9·12	H-1	6·57	*4*(11,5)
		18	9·15	9·13	H-3	6·37	*7*(10,10,5,5)
677	17,17-Ethylenedioxy-5α-androstane-3β,7α-diol	19	9·19	9·19	H-3 / H-7	6·42	m(35)
		18	9·15	9·16			
678	17,17-Ethylenedioxy-5α-androstane-3β,7β-diol	19	9·16	9·16	H-3 / H-7	6·42	m(40)
		18	9·13	9·13			
679	7β,11α-Dihydroxy-5α-androstane-3,17-dione	19	8·81	8·81	H-7	6·45	m(20)
		18	9·06	9·04	H-11	5·95	m(20)
680	3β,11α-Diacetoxy-1β-hydroxy-5α-androstan-17-one	19	9·07	9·02	H-1	6·30	m(15)
		18	9·13	9·05	H-3	5·29	m(23)
					H-11	4·88	m(27)
681	3β-Hydroxy-1β,11α-isopropylidenedioxy-5α-androstan-17-one	19	9·10	9·10	H-1	6·40	*4*(11,5)
		18	9·15	9·14	H-3	6·30	m(20)
					H-11	6·00	*6*(11,11,5)
682	3β,7β,11α-Trihydroxy-5α-androstan-17-one	19	9·00	9·02			
		18	9·09	9·07			
683	3β,7β,11α-Triacetoxy-5α-androstan-17-one	19	9·00	9·02	H-3 / H-7	5·50	m(25)
		18	9·05	9·07			
					H-11	4·85	*6*(11,11,5)
684	6α,11α,17β-Triacetoxy-5α-androstan-3-one	19	8·71	8·72	H-6	5·08	m(7)
		18	9·06	9·06	H-11	4·73	*6*(11,11,5)
					H-17	5·32	*4*(9,8)

* Δ^3_1 (19) +0·35, (18) 0·00.

[a] Ref. 2. [b] A. M. Bell, I. M. Clark, W. A. Denny, E. R. H. Jones, G. D.Meakins, W. E. Müller, and E. E. Richards, *J.C.S. Perkin I*, 1973, 2131.

EXPERIMENTAL

For general directions and use of an asterisk to indicate that the n.m.r. signals, and possibly also the i.r. absorptions, of a compound have already been reported, see ref. 2. Where compounds with serial numbers below 666 are stated to have been identified by mixed m.p., the original preparations are contained in, or can be found from, the papers cited. The microbiological procedures and the abbreviations used in reporting the results are given fully in ref. 6. Components of mixtures isolated by p.l.c. are reported in order of decreasing R_F value. Petrol refers to light petroleum, b.p. 60—80°, and s.m. indicates starting material.

Incubations.—A spore suspension of the micro-organism was introduced into medium B (5 l) contained in a Biotech FL 110-01 fermentor. The mixture was stirred for 2 d at 25 °C to produce a healthy growth of the fungus. The steroid (20 g) in EtOH (400 ml) was added at a rate of 20 ml every 1·5 h by means of a peristaltic pump (LKB 12000 Varioperpex); portions (30 ml) of a sterile solution of glucose (9 g) in H_2O (90 ml) were added 13·5, 18, and 22·5 h after the start of the addition of the steroid. After 60 h the mixture was worked up by method II.[6]

(*a*) 3β-Hydroxy-5α-androstan-17-one (I) (no. 151) with *Rhizopus nigricans* ⟶ 20·3 g combined extracts. Chromat. Al_2O_3 (5% deactivated; 600 g). C_6H_6 eluted s.m. (5·2 g). Careful elution with $CHCl_3$, and combination of appropriate fractions based on t.l.c. examination, gave the following materials: (i) a mixture (800 mg), which was separated by p.l.c. [2 large plates, 2 × petrol–Me_2CO (4 : 1)] into 11α-hydroxy-5α-androstane-3,17-dione (no. 519) (109 mg), m.p. (from Me_2CO–petrol) and mixed [5a] m.p. 192—194°, and 3β-hydroxy-5α-androstane-7,17-dione (no. 558) (306 mg), m.p. (from Me_2CO–petrol) and mixed [5b] m.p. 202—204°; (ii) 3β,7β-dihydroxy-5α-androstan-17-one (no. 250) (7·75 g), m.p. (from Me_2CO–hexane) and mixed [4] m.p. 242—244°; (iii) a mixture (2·1 g) (used as described later) shown by n.m.r. to consist of 3β,7β-dihydroxy-5α-androstan-17-one (1 g) and 3β,7α-dihydroxy-5α-androstan-17-one (1·1 g); and (iv) 3β,7α-dihydroxy-5α-androstan-17-one (no. 249) (2·82 g), m.p. (from Me_2CO–hexane) and mixed [5b] m.p. 193—195°. $CHCl_3$–MeOH (9 : 1) eluted 3β,6α-dihydroxy-5α-androstan-17-one (no. 246) (3·05 g), m.p. (from Me_2CO) and mixed [5b] m.p. 222—225°.

(*b*) 3β-Hydroxy-5α-androstan-17-one (I) (no. 151) with *Aspergillus ochraceus* ⟶ 22 g mycelial extract and 4 g broth extract. The mycelial extract crystallised from Me_2CO–hexane to give 3β,11α-dihydroxy-5α-androstan-17-one (no. 256) (14·5 g), m.p. and mixed [5b] m.p. 103—104°. The material from the mother liquor was chromatographed on Al_2O_3 (5% deactivated; 50 g). Petrol–$CHCl_3$ (1 : 1) gave s.m. (430 mg). Petrol–$CHCl_3$ (1 : 2) eluted 11α-hydroxy-5α-androstane-3,17-dione (no. 519) (108 mg), m.p. and mixed [4] m.p. 186—189°. $CHCl_3$ eluted 3β,11α-dihydroxy-5α-androstan-17-one (no. 256) (2·4 g).

Broth extract chromat. Al_2O_3 (5% deactivated; 100 g). $CHCl_3$ eluted more 3β,11α-dihydroxy-5α-androstan-17-one (2·5 g; total 19·4 g). EtOAc eluted 1β,3β-dihydroxy-5α-androstan-17-one (no. 676) (210 mg), m.p. 197—198° (from Me_2CO–hexane), $[\alpha]_D$ +67° (*c* 1·0) (lit.,[7] m.p. 198—199·5°, $[\alpha]_D$ +73°). Elution with EtOAc–MeOH (10 : 1) gave material (200 mg) which was acetylated (Ac_2O–C_5H_5N; 3 : 1, for 2 d) and separated by p.l.c. [1 large plate, 3 × petrol–Me_2CO (4 : 1)] to give 3β,7β,11α-*triacetoxy*-5α-*androstan*-17-*one* (no. 683) (50 mg), m.p. 230—232° (from Me_2CO–petrol), $[\alpha]_D$ −31° (*c* 0·4) (Found: C, 66·85; H, 8·1. $C_{35}H_{36}O_7$ requires C, 66·95; H, 8·1%), and 3β,11α-*diacetoxy*-1β-*hydroxy*-5α-*androstan*-17-*one* (no. 680) (80 mg), m.p.

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

[7] J. J. Schneider, *J. Chromatog.*, 1968, **37**, 89.

184—188° (from Me_2CO–hexane), $[\alpha]_D$ −16° (*c* 0·9) (Found: C, 68·2; H, 8·3. $C_{23}H_{34}O_6$ requires C, 67·95; H, 8·4%), $\nu_{max.}$ 3600 and 1740 cm^{-1}.

(*c*) 17β-Hydroxy-5α-androstan-3-one (II) (no. 411) with *Aspergillus ochraceus* ⟶ 23 g combined extracts. Chromat. Al_2O_3 (5% deactivated; 250 g). Petrol–$CHCl_3$ (1 : 1) eluted s.m. (1·4 g). $CHCl_3$ and EtOAc eluted 11α,17β-dihydroxy-5α-androstan-3-one (no. 296) (17·2 g), m.p. (from acetone) and mixed [4] m.p. 202—204°. EtOAc–MeOH (9 : 1) eluted material which was acetylated (Ac_2O–C_5H_5N; 3 : 1, for 2 d) and separated by p.l.c. (1 large plate, 1 × Et_2O) into 3β,11α,17β-triacetoxy-5α-androstane (no. 619) (92 mg), m.p. (from hexane) and mixed [5b] m.p. 138—140°, and 6α,11α,17β-*triacetoxy*-5α-*androstan*-3-*one* (no. 684) (630 mg), m.p. 186—188° (from Et_2O–hexane), $[\alpha]_D$ −90° (*c* 0·5 in EtOH) (Found: C, 66·6; H, 7·9. $C_{35}H_{36}O_7$ requires C, 66·95; H, 8·1%).

(*d*) 3β,7β-Dihydroxy-5α-androstan-17-one (no. 250) with *Aspergillus ochraceus* ⟶ 22 g combined extract. Chromat. on Al_2O_3 (5% deactivated; 250 g). $CHCl_3$ and then EtOAc eluted s.m. (3·2 g). EtOAc–MeOH (3 : 1) eluted 3β,7β,11α-*trihydroxy*-5α-*androstan*-17-*one* (no. 682) (17·9 g), m.p. 227—229° (from Me_2CO), $[\alpha]_D$ +70° (*c* 1·0) (Found: C, 70·45; H, 9·4. $C_{19}H_{30}O_4$ requires C, 70·8; H, 9·4%), $\nu_{max.}$ (Nujol) 3610 and 1740 cm^{-1}.

(*e*) 5α-Androstane-3,17-dione (III) (no. 42) with *Aspergillus ochraceus* ⟶ 18 g combined extract. Crystallisation (from Me_2CO–hexane) gave 11α-hydroxy-5α-androstane-3,17-dione (no. 519) (15·3 g), m.p. and mixed m.p. 192—194°. P.l.c. [5 large plates, Et_2O–MeOH (49 : 1)] of the material from the mother liquor gave more product (no. 519) (500 mg).

Work in Scheme 1.—Huang-Minlon reduction of the mixture (2·1 g) of 3β,7β- and 3β,7α-dihydroxy-5α-androstan-17-one obtained in incubation (*a*), followed by oxidation with 8N-H_2CrO_4 gave 5α-androstane-3,7-dione (no. 36) (1·8 g), m.p. and mixed [3] m.p. 147—149°.

Huang-Minlon reduction of 3β,7β-dihydroxy-5α-androstan-17-one (no. 250) (2 g) gave 5α-androstane-3β,7β-diol (no. 390) (1·8 g), m.p. and mixed [3] m.p. 149—152°. Oxidation of a portion (100 mg) with 8N-H_2CrO_4 gave 5α-androstane-3,7-dione (80 mg). Oxidation of the remainder with Ag_2CO_3 on Celite under the usual conditions [6] gave 7β-hydroxy-5α-androstan-3-one (no. 383) (1·3 g), m.p. and mixed [3] m.p. 146—149°. Similarly 3β,7α-dihydroxy-5α-androstan-17-one (no. 249) gave 5α-*androstane*-3β,7α-*diol* (no. 674) (91%), m.p. 197—198° (from Me_2CO–hexane), $[\alpha]_D$ −16° (*c* 0·7) (Found: C, 77·7; H, 10·8. $C_{19}H_{32}O_3$ requires C, 78·0; H, 11·0%), $\nu_{max.}$ 3628 cm^{-1}, which was oxidised to 5α-androstane-3,7-dione (81%) and 7α-hydroxy-5α-androstan-3-one (no. 161) (65%), m.p. and mixed [3] m.p. 158—160°.

A solution of 3β,7β-dihydroxy-5α-androstan-17-one (no. 250) (1 g) in HO·$[CH_2]_2$·OH (2·5 ml)–C_6H_6 (300 ml) was heated under reflux for 4 h with Amberlite resin [IR120(H)] (4 g). Work-up gave 17,17-*ethylenedioxy*-5α-*androstane*-3β,7β-*diol* (no. 678) (645 mg), m.p. 170—171° (from Me_2CO–hexane), $[\alpha]_D$ +8° (*c* 0·4) (Found: C, 71·75; H, 9·9. $C_{21}H_{34}O_4$ requires C, 71·95; H, 9·8%), $\nu_{max.}$ 3610 cm^{-1}. Oxidation of the diol (1 g) with Ag_2CO_3 on Celite gave 17,17-*ethylenedioxy*-7β-*hydroxy*-5α-*androstan*-3-*one* (no. 673) (890 mg), m.p. 202—204° (from Et_2O–petrol), $[\alpha]_D$ +22° (*c* 0·7) (Found: C, 72·25; H, 8·95. $C_{21}H_{32}O_4$ requires C, 72·4; H, 9·25%), $\nu_{max.}$ 3615 and 1715 cm^{-1}, converted by Huang-Minlon reduction into 17,17-ethylenedioxy-5α-androstan-7β-ol (no. 669) (785 mg), m.p. 102—105° (from Me_2CO–hexane), $[\alpha]_D$ +10° (*c* 1·0) (lit.,[8] m.p. 98—102°). A solution of the hydroxy-acetal (1 g) in 10N-HCl (1 ml)–H_2O (2 ml)–EtOH (20 ml) was boiled under reflux for 30 min to give 7β-hydroxy-5α-androstan-17-one (no. 369) (750 mg), m.p. 108—110° (slow crystallisation from Me_2CO–hexane), $[\alpha]_D$ +132° (lit.,[8] m.p. 107—109°).

By the same route (similar yields) 3β,7α-dihydroxy-5α-androstan-17-one (no. 249) ⟶ 17,17-*ethylenedioxy*-5α-*androstane*-3β,7α-*diol* (no. 677), m.p. 180—181° (from Me_2CO–hexane), $[\alpha]_D$ −30° (*c* 0·4) (Found: C, 72·25; H, 9·7%) ⟶ 17,17-*ethylenedioxy*-7α-*hydroxy*-5α-*androstan*-3-*one* (no. 670), m.p. 160—161° (from Me_2CO–hexane), $[\alpha]_D$ −9° (*c* 0·9) (Found: C, 72·5; H, 9·3%) ⟶ 17,17-ethylenedioxy-5α-androstan-7α-ol (no. 668), m.p. 141—142° (from Me_2CO–hexane), $[\alpha]_D$ −36° (*c* 0·2) (lit.,[8] m.p. 140—142°) ⟶ 7α-hydroxy-5α-androstan-17-one (no. 554), m.p. 154—155° (from hexane), $[\alpha]_D$ +60° (*c* 0·5) (lit.,[8] m.p. 153—156°), $\nu_{max.}$ (dilute solution in CCl_4; spectral slit-width 1·5—2 cm^{-1}) 3626 and 1745 cm^{-1}.

Work in Scheme 2.—Huang-Minlon reduction of 3β,11α-dihydroxy-5α-androstan-17-one (no. 256) gave 5α-androstane-3β,11α-diol (no. 221) (92%), m.p. (from Me_2CO–hexane) and mixed [4] m.p. 187—189°. A solution of this diol (4·3 g) and AcNHBr (4 g) in Me_2CO (50 ml)–H_2O (2 ml) was kept at 0 °C for 4 h, and the product was chromatographed on Al_2O_3 (5% deactivated; 100 g). Petrol–Et_2O (1 : 1) eluted 11α-hydroxy-5α-androstan-3-one (no. 163) * (3·4 g), m.p. (from Me_2CO–hexane) and mixed [4] m.p. 123—125°. A solution of this hydroxy-ketone (4 g) and TsCl (3·5 g) in C_5H_5N (50 ml) was kept at 0 °C for 12 h and then at 20 °C for 24 h. The product, in petrol–Et_2O (9 : 1), was filtered through Al_2O_3 (10% deactivated; 50 g) to give 3-*oxo*-5α-*androstan*-11α-*yl toluene*-p-*sulphonate* (no. 671) (4·9 g), m.p. 148—149° (from MeOH), $[\alpha]_D$ −5° (*c* 1·4) (Found: C, 69·8; H, 8·15. $C_{26}H_{36}O_4S$ requires C, 70·25; H, 8·15%). A solution of the tosylate (8·6 g), Li_2CO_3 (6 g), and LiCl (4·2 g) in Me_2N·CHO (250 ml) was boiled under reflux for 30 min under N_2 to give 5α-*androst*-9(11)-*en*-3-*one* (no. 666) (4·7 g), m.p. 98—101° (from MeOH), $[\alpha]_D$ +32° (*c* 1·0) (Found: C, 84·0; H, 10·2. $C_{19}H_{28}O$ requires C, 83·8; H, 10·35%), $\nu_{max.}$ 3050 and 1718 cm^{-1}. A solution of this ketone (600 mg) and anhydrous Na_2CrO_4 (675 mg) in AcOH (6 ml)–Ac_2O (3 ml) was stirred at 35 °C for 72 h, and the product was purified by p.l.c. [1 large plate, 1 × petrol–Et_2O (2 : 3)] to give 5α-*androst*-9(11)-*ene*-3,12-*dione* (no. 667) (195 mg), m.p. 195—196° (from Me_2CO–petrol), $[\alpha]_D$ +54° (*c* 1·0) (Found: C, 79·8; H, 9·2. $C_{19}H_{26}O_2$ requires C, 79·7; H, 9·1%), $\nu_{max.}$ 1716 and 1686 cm^{-1}. Hydrogenation of the diketone (500 mg) in EtOAc (10 ml) over 10% Pd–C (100 mg) for 10 h gave 5α-androstane-3,12-dione (no. 379) (405 mg), m.p. (from Me_2CO–petrol) and mixed [3] m.p. 212—213°.

Oxidation of 5α-androstane-3β,11α-diol (no. 221) with 8N-H_2CrO_4 gave 5α-androstane-3,11-dione (no. 37) (85%), m.p. and mixed m.p. 120—122°. Reduction of the dione (no. 37) (4 g) in tetrahydrofuran (40 ml) with a solution prepared by adding Bu^tOH (6·4 g) to $LiAlH_4$ (1 g) in tetrahydrofuran (40 ml) gave 3β-hydroxy-5α-androstan-11-one (no. 548) (3·4 g), m.p. and mixed m.p. 154—155°.

Work in Scheme 3.—A suspension of 3β,7β,11α-trihydroxy-5α-androstan-17-one (no. 682) (1 g) and Ag_2CO_3 on Celite (12 g) in PhMe (200 ml) was heated under reflux for 30 min and then filtered. The filtrate afforded 7β,11α-*dihydroxy*-

[8] M. Mailloux, J. Weinman, and S. Weinman, *Bull. Soc. chim. France*, 1969, 617.

5α-*androstane*-3,17-*dione* (no. 679) (760 mg), m.p. 234—236° (from Me_2CO–hexane), $[\alpha]_D$ +87° (*c* 0·2) (Found: C, 71·2; H, 8·6. $C_{19}H_{28}O_4$ requires C, 71·2; H, 8·8%), $\nu_{max.}$ ($CHCl_3$) 3610, 1740, and 1710 cm^{-1}. Huang-Minlon reduction of this product gave 5α-androstane-7β,11α-diol (no. 225) (86%), m.p. (from EtOAc) and mixed [4] m.p. 203—205°, $[\alpha]_D$ +7° (*c* 0·8), which was oxidised with 8N-H_2CrO_4 to 5α-androstane-7,11-dione (no. 49) (93%), m.p. (from Me_2CO–hexane) and mixed [4] m.p. 147—148°.

Huang-Minlon reduction of 11α,17β-dihydroxy-5α-androstan-3-one (no. 292) (16·5 g) gave 5α-*androstane*-11α,17β-*diol* (no. 673) (13·79 g), m.p. 143—144° (from Me_2CO–hexane), $[\alpha]_D$ −15° (*c* 1·2) (Found: C, 77·7; H, 11·0. $C_{19}H_{32}O_2$ requires C, 78·0; H, 11·0%), $\nu_{max.}$ 3600 cm^{-1}. Oxidation of this diol (no. 673) with 8N-H_2CrO_4 gave 5α-androstane-11,17-dione (no. 54) (10·97 g), m.p. (from hexane) and mixed [4] m.p. 131—133°, which was reduced with $LiAlH_4$ (2·8 g) and Bu^tOH (17·6 g) in tetrahydrofuran (275 ml) to 17β-hydroxy-5α-androstan-11-one (no. 555) (9·9 g), m.p. (from Me_2CO–hexane) and mixed [5b] m.p. 150—153°.

Huang-Minlon reduction of 11α-hydroxy-5α-androstane-3,17-dione (no. 519) (13·5 g) gave 5α-androstan-11α-ol (no. 126) (11·7 g), m.p. (from hexane) and mixed [4] m.p. 107—108°. Oxidation of this alcohol (no. 126) with 8N-H_2CrO_4 gave 5α-androstan-11-one (no. 16) (95%), m.p. (from MeOH) and mixed [2] m.p. 47—51°.

Other Experiments.—A solution of 3β,11α-diacetoxy-1β-hydroxy-5α-androstan-17-one (no. 680) (25 mg) and KOH (10 mg) in MeOH (20 ml) was boiled under reflux for 2 h under N_2. The product was kept in 10N-HCl (0·1 ml)–Me_2CO (10 ml) at 20 °C for 2 h. Chromatography on Al_2O_3 (2% deactivated; 5 g) and elution with $CHCl_3$ gave 3β-*hydroxy*-1β,11α-*isopropylidenedioxy*-5α-*androstan*-17-*one* (no. 681) (15 mg), m.p. 166—168° (from Me_2CO–hexane), $[\alpha]_D$ +54° (*c* 0·4) (Found: C, 72·5; H, 9·6. $C_{22}H_{34}O_4$ requires C, 72·9; H, 9·5%), $\nu_{max.}$ 3610 and 1740 cm^{-1}.

Oxidation of 5α-androst-9(11)-en-3-one (no. 666) (400 mg) in AcOH (25 ml)–H_2O (1 ml) with CrO_3 (700 mg) for 72 h at 20 °C followed by p.l.c. [1 large plate, 1 × petrol–Et_2O (7 : 3)] gave s.m. (50 mg), 5α-androst-9(11)-ene-3,12-dione (no. 667) (40 mg), and 9α,11α-*epoxy*-5α-*androstan*-3-*one* (no. 670) (18 mg), m.p. 130—132° (from Me_2CO–petrol), $[\alpha]_D$ +8° (*c* 0·4) (Found: C, 78·85; H, 9·8. $C_{19}H_{28}O_2$ requires C, 79·1; H, 9·8%), $\nu_{max.}$ 1716 cm^{-1}. The last product was also prepared (85% yield) by treating 5α-androst-9(11)-en-3-one (no. 666) with *m*-$ClC_6H_4 \cdot CO_3H$ in CH_2Cl_2 for 30 min at 20 °C.

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