Studies in the Steroid Group. Part LXXXIII.[1] 1-, 2-, 3-, 4-, 6-, 12-, 15-, and 16-Monohydroxy-5α-androstanes and their Derivatives

By I. M. Clark, A. S. Clegg, W. A. Denny, Sir Ewart R. H. Jones, G. D. Meakins,* and A. Pendlebury, Dyson Perrins Laboratory, Oxford University, South Parks Road, Oxford OX1 3QY

The following new compounds have been prepared: 2α-, 4α-, 4β-, 6β- and 12α-hydroxy-5α-androstanes; the acetates of these alcohols and of the 1α-, 1β-, 2β-, 6α-, 12β-, 15α- and 15β-hydroxy-5α-androstanes; 3α- and 3β-hydroxy-5α-androst-1-ene and 1β-hydroxy-5α-androst-2-ene; a series of esters and ethers derived from the 3-hydroxy-5α-androstanes. Some methoxy-5α-androstanes were obtained conveniently from the alcohols with diazomethane.

THE present paper records the properties of some monohydroxy-5α-androstanes and their derivatives (esters and ethers) prepared in connection with microbiological hydroxylation studies.[2] These substances were required to serve as substrates, or as reference compounds during the structural elucidation of products obtained microbiologically. Since the work is straightforward it is presented in a form similar to that used previously.[1] The reactions and the products are shown in the Scheme and commentary is unnecessary. The conventions used in the Scheme, the position with regard to new compounds (*i.e.* those whose abbreviated names are not followed by a reference), and the citing of the spectrometric data (in refs. 3 and 4, or here), are fully explained in the preceding paper.[1] Section (*A*) of the Scheme portrays the reduction of 5α-androstane monoketones to alcohols, and acetylation of the latter. These compounds were needed to complete our collection of secondary monohydroxy-5α-androstanes; it is surprising that so few of the alcohols in this section have been described previously. Section (*B*) contains a miscellany of microbiological substrates derived from the 3-hydroxy-5α-androstanes. In section (*C*) the conversion of some hydroxy-compounds into their methyl ethers is shown. Most of the products are known compounds, but they are obtained much more conveniently by the acid-catalysed diazomethane reaction[5] than by the published routes. [3α-Methoxy-5α-androstane (XLI), whose preparation by the present method has already been mentioned[5b] is included in the Scheme for completeness.]

EXPERIMENTAL

For general directions see ref. 2. Arabic numbers are given after the formulae numbers of compounds connected with microbiological work: the n.m.r. signals of these compounds, Nos. 394—411, are listed in the Table. [17β-Hydroxy-5α-androstan-3-one (II) (No. 411) is included, since this compound was inadvertently omitted from the earlier n.m.r. Tables.[3]] Petrol refers to light petroleum, b.p. 60—80°.

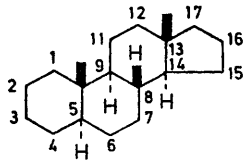
Work in Section (A) *of the Scheme.*—(*a*) A solution of 5α-androst-2-en-1-one (1·6 g) in dry Et_2O (50 ml) was added during 30 min to a stirred suspension of $LiAlH_4$ (0·5 g) in Et_2O (50 ml). The mixture was stirred at 20 °C for 2 h. 2N-NH_4Cl was added and the ethereal layer was separated to give material (1·56 g) which was chromatographed on SiO_2 gel [100 g; deactivated with H_2O (3%)]. Petrol–EtOAc (9 : 1) eluted 5α-*androst*-2-*en*-1β-*ol* (VI) (No. 103) (571 mg), m.p. 99—100° (from hexane), $[\alpha]_D$ +9° (*c* 1·1) (Found: C, 83·1; H, 11·1. $C_{19}H_{30}O$ requires C, 83·15; H, 11·0%), $\nu_{max.}$ 3613 cm^{-1}. Further elution with the same solvent mixture gave 5α-androst-2-en-1α-ol (V) (No. 101) (71 mg), m.p. 102—103° (lit.,[6] 103°), identified by comparison (mixed m.p., i.r. spectra) with authentic material, $\nu_{max.}$ 3615 cm^{-1}.

(*b*) Similar treatment of 5α-androst-1-en-3-one (3·7 g) with $LiAlH_4$ (1·2 g) in Et_2O (200 ml) was followed by chromatography of the product on deactivated SiO_2 gel (200 g). Elution with petrol–Et_2O (93 : 7) gave 5α-*androst*-1-*en*-3α-*ol* (VII) (No. 110) (210 mg), m.p. 127—130° (from hexane) (Found: C, 83·25; H, 11·1%), $\nu_{max.}$ 3615 cm^{-1}, and then 5α-*androst*-1-*en*-3β-*ol* (VIII) (No. 113) (2·33 g), m.p. 121—122° (from hexane) (Found: C, 83·1; H, 11·1%), $\nu_{max.}$ 3608 and 1025 cm^{-1}. Petrol–Et_2O (9 : 1) eluted a mixture (1·06 g) which was separated into three components by p.l.c. [4 large plates, 3 × petrol–Et_2O (3 : 2)]. The band of highest R_F gave 5α-androst-1-en-3α-ol (5 mg); the second band gave 5α-androst-1-en-3β-ol (610 mg); the band of lowest R_F gave 5α-androstan-3β-ol (397 mg), m.p. and mixed m.p. 150—151°.

(*c*) A solution of 5α-androstan-2-one (500 mg) and $NaBH_4$ (100 mg) in tetrahydrofuran (10 ml)–MeOH (1 ml) was stirred at 20 °C for 1 h. The material isolated with Et_2O was separated by p.l.c. [1 large plate, 1 × petrol–Me_2CO (17 : 3)] to give 5α-androstan-2β-ol (XV) (No. 106) (297 mg; higher R_F), m.p. 133—134° (from MeOH), $[\alpha]_D$ +10° (*c* 1·0) (lit.,[7] m.p. 134—135°, $[\alpha]_D$ +12°), and 5α-*androstan*-2α-*ol* (XIII) (No. 105) (139 mg; lower R_F), m.p. 128—129° (from MeOH), $[\alpha]_D$ +5° (*c* 1·0) (Found: C, 82·5; H, 11·7. $C_{19}H_{32}O$ requires C, 82·5; H, 11·7%).

(*d*) Similar reduction of 5α-androstan-4-one (300 mg) with $NaBH_4$ (50 mg) followed by p.l.c. [1 large plate, 1 × petrol–Me_2CO (9 : 1)] gave 5α-*androstan*-4β-*ol* (XIX) (No. 119) (197 mg; higher R_F), m.p. 120—121° (from MeOH), $[\alpha]_D$ +7° (*c* 1·1) (Found: C, 82·6; H, 11·9%), and 3α-*androstan*-4α-*ol* (XVII) (No. 118) (23 mg; lower R_F),

[1] Part LXXXII, A. S. Clegg, W. A. Denny, E. R. H. Jones, V. Kumar, G. D. Meakins, and V. E. M. Thomas, preceding paper.
[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.
[5] (*a*) M. Neeman, M. C. Caserio, J. D. Roberts, and W. S. Johnson, *Tetrahedron*, 1959, **6**, 36; (*b*) J. M. Evans, G. D. Meakins, Y. Morisawa, and P. D. Woodgate, *J. Chem. Soc.* (*C*), 1968, 2841.
[6] H. Powell, D. H. Williams, H. Budzikiewicz, and C. Djerassi, *J. Amer. Chem. Soc.*, 1964, **86**, 2623.
[7] J. E. Gurst and C. Djerassi, *J. Amer. Chem. Soc.*, 1964, **86**, 5542.

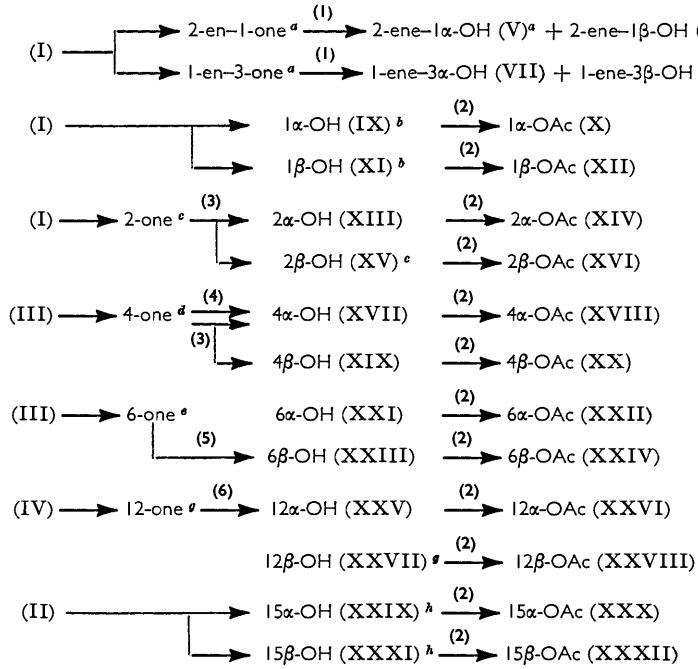


5α-androstane

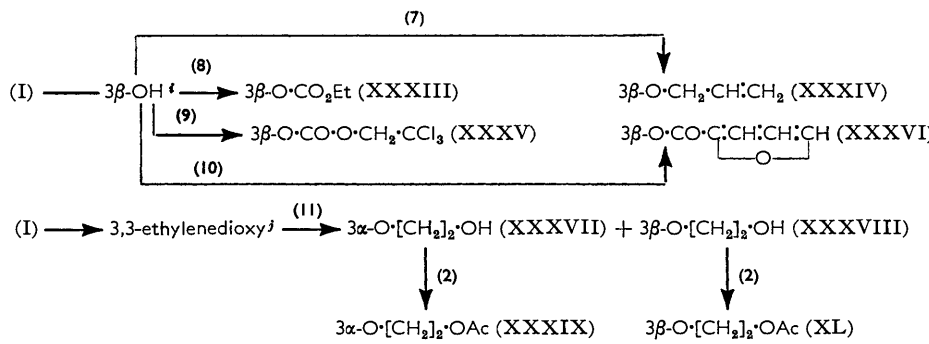
Apart from hecogenin [(25*R*)-3β-hydroxy-5α-spirostan-12-one] all compounds are derived from 5α-androstane and are represented by abbreviated names. Thus the first starting material, described below as 3β-OH–17-one, is 3β-hydroxy-5α-androstan-17-one.

Starting materials: 3β-OH–17-one (I); 17β-OH–3-one (II); 3β-OH–5-en–17-one (III); hecogenin (IV).

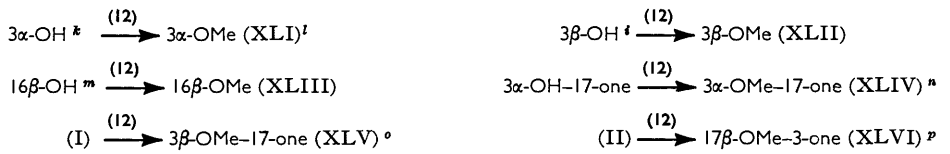
Section (*A*)



Section (*B*)



Section (*C*)



Reagents: (1), $LiAlH_4$; (2), Ac_2O–C_5H_5N; (3), $NaBH_4$; (4), Na–Pr^iOH; (5), $LiAlH(OBu^t)_3$; (6), Ir^{VI} chloride–$(MeO)_3P$–Pr^iOH–H_2O; (7), CH_2:CH·CH_2Cl–KOH; (8), EtO·COCl–C_5H_5N; (9), $CCl_3·CH_2·O·COCl$–C_5H_5N; (10), 2-Furoyl chloride–C_5H_5N; (11), $LiAlH_4$–$AlCl_3$; (12), CH_2N_2–HBF_4.

[a] Ref. 6. [b] G. von Mutzenbecher and A. D. Cross, *Steroids*, 1965, **5**, 429. [c] Ref. 7. [d] J. Gutzwiller and C. Djerassi, *Helv. Chim. Acta*, 1966, **49**, 2108. [e] C. Djerassi, R. H. Shapiro, and M. Vandewalle, *J. Amer. Chem. Soc.*, 1965, **87**, 4892. [f] Ref. 1. [g] C. Djerassi and L. Tökes, *J. Amer. Chem. Soc.*, 1966, **88**, 536. [h] C. Djerassi, G. von Mutzenbecher, J. Fajkos, D. H. Williams, and H. Budzikiewicz, *J. Amer. Chem. Soc.*, 1965, **87**, 817. [i] L. Mamlok and J. Jacques, *Bull. Soc. chim. France*, 1960, 484. [j] A. Marquet, H. B. Kagan, M. Dvolaitzky, L. Mamlok, C. Weidmann, and J. Jacques, *Compt. rend.*, 1959, **248**, 984 [k] A. Butenandt, L. Poschmann, G. Failer, U. Schiedt, and E. Biekert, *Annalen*, 1951, **575**, 123. [l] Ref. 5*b*. [m] D. Varech and J. Jacques, *Bull. Soc. chim. France*, 1965, 67. [n] Ref. 8. [o] Ref. 9. [p] Ref. 10.

SCHEME

N.m.r. signals

$CDCl_3$ solutions were examined at 100 MHz. Signals are described in the form used previously.[1]

No.	19-H τ	18-H τ	Other signals τ	Form	Assignment
(II)	8·98	9·24	6·34	t(8)	H-17
(X)	9·16	9·32	5·17	m(5)	H-1
(XII)	9·05	9·32	5·39	m(17)	H-1
(XXII)	9·16	9·31	5·30	*6*(4,4,2)	H-6
(XXIV)	9·02	9·26	5·01	m(7)	H-6
(XXVI)	9·22	9·22	5·01	t(3)	H-12
(XXVIII)	9·20	9·23	5·34	*4*(11,5)	H-12
(XXXII)	9·05	9·16	5·05	*6*(8,8,3)	H-15
(XXXIII)	9·18	9·31	5·46	m(17)	H-3
(XXXIV)	9·20	9·30	6·73	m(25)	H-3
(XXXV)	9·16	9·30	5·25	m(23)	H-3
(XXXVI)	9·12	9·30	5·08	m(22)	H-3
(XXXVII)	9·21	9·31	6·47	m(10)	H-3
(XXXVIII)	9·19	9·30	6·74	7(11,11,5,5)	H-3
(XXXIX)	9·22	9·31	6·44	m(9)	H-3
(XL)	9·20	9·31	6·76	7(11,11,5,5)	H-3
(XLI)	9·22	9·32	6·58	m(8)	H-3
X(LII)	9·13	9·22	6·16	*10*(7·5,5·5,5·5,2)	H-16

m.p. 166—168° (from MeOH), $[\alpha]_D$ −26° (*c* 0·3) (Found: C, 82·6; H, 11·9%).

(*e*) A solution of 5α-androstan-4-one (100 mg) in Pr^iOH (10 ml) was heated under reflux with Na (1 g) for 1 h. EtOH (1 ml) was added to destroy the excess of Na. Isolation with Et_2O gave 5α-androstan-4α-ol (XVII) (83 mg), m.p. 166·5—168·5° (from C_6H_{14}), $[\alpha]_D$ −29°.

(*f*) A solution of 5α-androstan-6-one (300 mg) in tetrahydrofuran (5 ml) was added to a stirred solution of $LiAlH(OBu^t)_3$ (100 mg) in tetrahydrofuran (5 ml) at 0 °C. Stirring was continued for 3 h at 0 °C and then for 3 h at 20 °C. Work-up followed by p.l.c. [1 large plate, 2 × petrol–Et_2O (9 : 1)] gave 5α-*androstan*-6β-*ol* (XXIII) (No. 366), m.p. 77·5—78·5° (MeOH), $[\alpha]_D$ −13·5° (*c* 1·0) (Found: C, 82·6; H, 11·5. $C_{19}H_{32}O$ requires C, 82·6; H, 11·7%).

(*g*) Ir^{VI} chloride (14 mg) and $(MeO)_3P$ (0·35 ml) were added to a solution of 5α-androstan-12-one (60 mg) in Pr^iOH (3·3 ml)–H_2O (0·6 ml), and the stirred mixture was heated under reflux for 3 days. Work-up gave 5α-*androstan*-12α-*ol* (XXV) (No. 129) (29 mg), m.p. 123·5—126° (from MeOH), $[\alpha]_D$ +41° (*c* 0·6) (Found: C, 82·9; H, 11·9. $C_{19}H_{32}O$ requires C, 82·5; H, 11·7%).

(*h*) The following acetates (all having $\nu_{max.}$ *ca.* 1735 cm^{-1}) were obtained (in over 80% yield) from the corresponding alcohols by treatment with an excess of Ac_2O–C_5H_5N (1 : 1) at 25 °C for 20 h, work-up, and (apart from three compounds) crystallisation from MeOH.

	M.p./°C	$[\alpha]_D$/° (*c* 0·8—1·2)	Analytical figures * C (%)	H (%)
1α-*Acetate* (X) (No. 394)	(Oil)	+34	79·5	10·4
1β-*Acetate* (XII) (No. 395)	(Oil)	+51	79·4	10·6
2α-*Acetate* (XIV) (No. 107)	153—155	−23	79·3	10·6
2β-*Acetate* (XVI) (No. 108)	82·5—83·5	+11	79·0	10·7
4α-*Acetate* (XVIII) (No. 120)	116—118	−5	79·5	10·7
4β-*Acetate* (XX) (No. 121)	117—118	+12	79·2	10·4
6α-*Acetate* (XXII) (No. 397)	112—113	+66	79·2	10·8
6β-*Acetate* (XXIV) (No. 398)	64—66	+36	79·2	10·7
12α-*Acetate* (XXVI) (No. 399)	90—93	+59	79·0	10·6
12β-*Acetate* (XXVIII) (No. 400)	61—64	−15	78·9	10·5
15α-*Acetate* (XXX) (No. 132)	95·5—96·5	+46	79·2	10·8
15β-*Acetate* (XXXII) (No. 401)	(Oil)	−57	78·9	10·6

* $C_{21}H_{34}O_2$ requires C, 79·2; H, 10·75%.

Work in Section (B).—(*a*) EtO·COCl (0·53 ml) was added to a stirred solution of 5α-androstan-3β-ol (1·37 g) in C_6H_6 (6 ml)–C_5H_5N (1·4 ml) at 10 °C, and the solution was kept at 20 °C for 3 h. Work-up gave 5α-*androstan*-3β-*yl ethyl carbonate* (XXXIII) (No. 407) (1·1 g), m.p. 77—78° (from EtOH), $[\alpha]_D$ −7° (*c* 1·1) (Found: C, 75·9; H, 10·3. $C_{22}H_{35}O_3$ requires C, 75·8; H, 10·4%), $\nu_{max.}$ 1748 cm^{-1}.

(*b*) A solution of 5α-androstan-3β-ol (500 mg) and CH_2:$CH{\cdot}CH_2Cl$ (4 ml) in dioxan (10 ml) was boiled under reflux with powdered KOH (4 g) for 6 h. Isolation with Et_2O gave 3β-*allyloxy*-5α-*androstane* (XXXIV) (No. 408) (381 mg), m.p. 42—44° (from EtOH), $[\alpha]_D$ −4·5° (*c* 0·4) (Found: C, 83·3; H, 11·4. $C_{22}H_{36}O$ requires C, 83·5; H, 11·4%), $\nu_{max.}$ 3075, 1645, and 1090 cm^{-1}.

(*c*) $CCl_3{\cdot}CH_2{\cdot}O{\cdot}COCl$ (780 mg) was added to a stirred solution of 5α-androstan-3β-ol (300 mg) in C_6H_6 (6 ml)–C_5H_5N (0·25 ml) at 20 °C. After 12 h, isolation with Et_2O gave 5α-*androstan*-3β-*yl* 2,2,2-*trichloroethyl carbonate* (XXXV) (No. 409) (370 mg), m.p. 111—114° (from EtOH), $[\alpha]_D$ −4° (*c* 1·1) (Found: C, 58·3; H, 7·4; Cl, 23·6. $C_{22}H_{33}Cl_3O_3$ requires C, 58·5; H, 7·3; Cl, 23·6%), $\nu_{max.}$ 1758 cm^{-1}.

(*d*) A solution of 2-furoyl chloride (960 mg) and 5α-androstan-3β-ol (1 g) in C_5H_5N (6 ml) was stirred at 20 °C for 12 h. Isolation with Et_2O gave 5α-*androstan*-3β-*yl* 2-*furoate* (XXXVI) (No. 410) (1·4 g), m.p. 171—172° (from EtOH), $[\alpha]_D$ +3° (*c* 1·0) (Found: C, 77·6; H, 9·2. $C_{24}H_{28}O_3$ requires C, 77·8; H, 9·3%), $\nu_{max.}$ 1728, 1715, and 1297 cm^{-1}.

(*e*) Et_2O (160 ml; distilled from $LiAlH_4$) was added during 15 min, with stirring and cooling, to anhydrous $AlCl_3$ (6·76 g). After a further 15 min a suspension of $LiAlH_4$ (0·484 g) in Et_2O (80 ml) was added during 30 min. A solution of 3,3-ethylenedioxy-5α-androstane (8·06 g) in Et_2O (160 ml) was added with stirring during 30 min, and the mixture was stirred at 20 °C for 15 h. 2N-H_2SO_4 was added, and the material isolated with Et_2O was chromatographed on Al_2O_3 [800 g; deactivated with H_2O (5%)]. Petrol–Et_2O (49 : 1) eluted starting material (393 mg). Petrol–Et_2O (10 : 1) eluted 5α-androstan-3-one (653 mg), m.p. and mixed m.p. 99·5—101·5°. Petrol–Et_2O (2 : 1) eluted 3α-(2-*hydroxyethoxy*)-5α-*androstane* (XXXVII) (No. 403) (2·36 g), m.p. 99—100° (from EtOH–H_2O), $[\alpha]_D$ −2·5° (*c* 1·0) (Found: C, 78·5; H, 11·05. $C_{21}H_{36}O_2$ requires C, 78·7; H, 11·3%), $\nu_{max.}$ 3593 and 1053 cm^{-1}. Petrol–Et_2O (1 : 2) eluted 3β-(2-*hydroxyethoxy*)-5α-*androstane* (XXXVIII) (No. 405) (4·41 g), m.p. 138·5—139·5° (from EtOH), $[\alpha]_D$ −2° (*c* 1·3) (Found: C, 78·5; H, 11·5%), $\nu_{max.}$ 3594 and 1056 cm^{-1}.

Treatment of these alcohols with Ac_2O–C_5H_5N (10 : 1) at 20 °C for 2 days gave, respectively, the 3α-*acetoxy-ether*

(XXXIX) (No. 404) as an oil (Found: C, 76·5; H, 10·4. $C_{23}H_{38}O_3$ requires C, 76·2; H, 10·6%), $\nu_{max.}$ 1745, 1236, and 1116 cm^{-1}, and the 3β-*acetoxy-ether* (XL) (No. 406), m.p. 51·5—52° (from MeOH–H_2O) (Found: C, 76·2; H, 10·6%), $\nu_{max.}$ 1743, 1236, and 1116 cm^{-1}.

Work in Section (C).—A solution of CH_2N_2 in Et_2O was cooled to 0 °C and was added dropwise to a stirred solution of 5α-androstan-3β-ol (2·2 g) and 18N-fluoroboric acid (1·5 ml) in CH_2Cl_2 (20 ml) at 0 °C until the mixture remained yellow. The solution was kept at 0 °C for 1 h, filtered, washed with cold 0·2N-H_2SO_4, $NaHCO_3$ aq., and H_2O, and dried. Evaporation gave 3β-*methoxy-5α-androstane* (XLII) (No. 117) (1·52 g), m.p. 74—75° (from MeOH), $[\alpha]_D$ −7° (*c* 0·4) (Found: C, 82·8; H, 11·9. $C_{20}H_{34}O$ requires C, 82·7; H, 11·8%), $\nu_{max.}$ 1105 cm^{-1}.

Similarly, the following conversions were carried out: 5α-androstan-3α-ol (2·1 g) ⟶ 3α-methoxy-5α-androstane (XLI) (No. 396) (1·75 g), m.p. 55—57° (lit.,[5b] 55—57°); 5α-androstan-16β-ol (73 mg) ⟶ 16β-*methoxy-5α-androstane* (XLIII) (No. 402) (65 mg), m.p. 80—82° (from MeOH), $[\alpha]_D$ −1° (*c* 0·4) (Found: C, 82·3; H, 11·8. $C_{20}H_{34}O$ requires C, 82·7; H, 11·8%), $\nu_{max.}$ 1094 cm^{-1}; 3α-hydroxy-5α-androstan-17-one (3 g) ⟶ 3α-methoxy-5α-androstan-17-one (XLIV) (No. 154) (2·7 g), m.p. 123—125° (from hexane), $[\alpha]_D$ +90° (*c* 0·7) (lit.,[8] m.p. 124·5—126·5°, $[\alpha]_D$ +81°), $\nu_{max.}$ 1745 and 1092 cm^{-1}; 3β-hydroxy-5α-androstan-17-one (1·6 g) ⟶ 3β-methoxy-5α-androstan-17-one (XLV) (No. 155) (0·98 g), m.p. 110—112° (from MeOH), $[\alpha]_D$ +82° (*c* 1·0) (lit.,[9] m.p. 112—114°, $[\alpha]_D$ +78°), $\nu_{max.}$ 1743 and 1110 cm^{-1}; 17β-hydroxy-5α-androstan-3-one (2 g) ⟶ 17β-methoxy-5α-androstan-3-one (XLVI) (No. 183) (1·4 g), m.p. 110—112° (from hexane), $[\alpha]_D$ +33° (*c* 0·7) (lit.,[10] m.p. 89—90·5°), $\nu_{max.}$ 1715 and 1110 cm^{-1}.

We thank the S.R.C. for Studentships (to A. S. C. and A. P.) and a Research Grant, the New Zealand University Grants Committee for a Postdoctoral Fellowship (to W. A. D.), the Rhodes Trust for a Scholarship (to I. M. C.), and Glaxo Laboratories Ltd. for a grant and gifts of chemicals.

[1/1261 *Received, July* 23*rd*, 1971]

[8] R. E. Counsell and P. D. Klimstra, *J. Medicin. Chem.*, 1964, **7**, 119.

[9] J. Hora, *Coll. Czech. Chem. Comm.*, 1966, **31**, 2737.

[10] O. Engelfried and M. Schenk, Ger P., 1,117 572/1962.