Studies in the Steroid Group. Part LXXXV.[1] Convenient Preparations of 3,6- and 6,17-Dioxygenated 5α-Androstanes

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Convenient, efficient sequences involving 3α,5-cyclo-intermediates have been developed for obtaining 3,6- and 6,17-dioxygenated 5α-androstanes from the cheap steroid 3β-hydroxyandrost-5-en-17-one. Useful selective reactions of 5α-androstane derivatives are achieved by acetalising diketones in the presence of an ion-exchange resin and by oxidising dihydric alcohols with the Fetizon (silver carbonate) reagent.

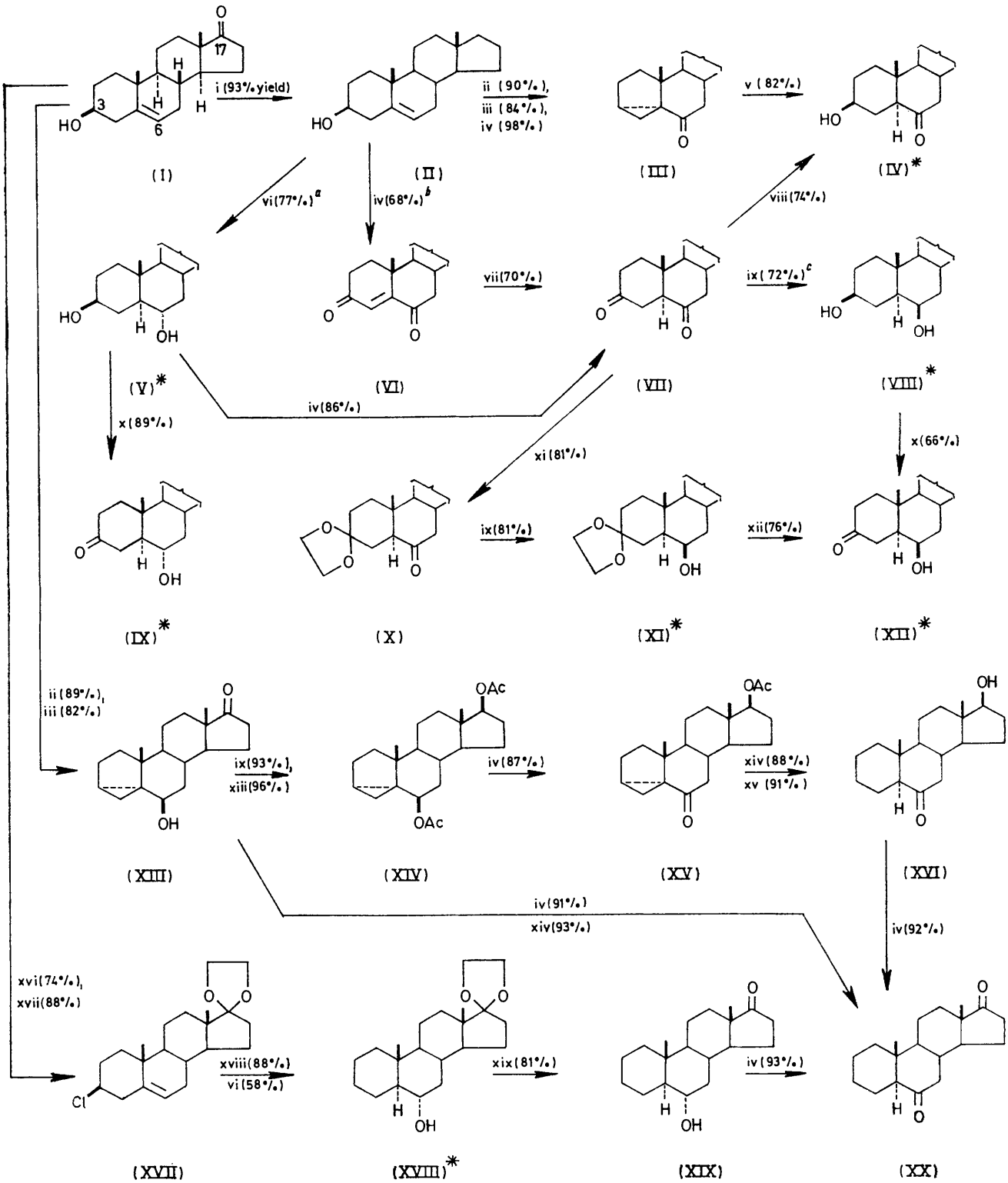
THE microbiological hydroxylation of various diketones and keto-alcohols derived from 5α-androstane has already been described:[2] this paper records the preparation of the 3,6- and 6,17-dioxygenated compounds used there as substrates. Since gram quantities of the disubstituted androstanes were required, it was necessary to develop convenient, efficient sequences based on cheap, commercially available steroids, and suitable for medium-scale work. The main results of the present investigation are portrayed in the Scheme, the detailed nature of which obviates the need for much comment. Although many of the intermediates and products were

[1] Part LXXXIV, I. M. Clark, W. A. Denny, Sir Ewart R. H. Jones, G. D. Meakins, A. Pendlebury, and J. T. Pinhey, *J.C.S. Perkin I*, 1972, 2765.

[2] V. E. M. Chambers, W. A. Denny, J. M. Evans, Sir Ewart R. H. Jones, A. Kasal, G. D. Meakins, and J. Pragnell, *J.C.S. Perkin I*, 1973, 1500.

SCHEME Preparation of 3,6- and 6,17-dioxygenated 5α-androstanes

References to known compounds are given in the Experimental section; new compounds are marked with an asterisk



Reagents: i, Huang-Minlon reduction; ii, *p*-$MeC_6H_4{\cdot}SO_2Cl$–C_5H_5N; iii, KOAc–Me_2CO–H_2O, heat; iv, H_2CrO_4–Me_2CO; v, H_2SO_4–dioxan–H_2O; vi, B_2H_6, then H_2O_2–NaOH; vii, Zn–AcOH, heat; viii, $NaBH_4$–CH_2Cl_2–MeOH, −10 °C; ix, $LiAlH(OBu^t)_3$, 0 °C; x, Ag_2CO_3 on Celite; xi, HO·$[CH_2]_2$·OH–C_6H_6–Amberlite resin, heat; xii, HCl–EtOH–H_2O, 20 °C; xiii, Ac_2O–C_5H_5N; xiv, H_2–Pd–AcOH; xv, KOH–EtOH; xvi, PCl_5–$CHCl_3$, 20 °C; xvii, HO·$[CH_2]_2$·OH–PhMe–*p*-$MeC_6H_4{\cdot}SO_3H$, heat, xviii, Na–Pr^iOH, heat; xix, $HClO_4$–tetrahydrofuran–H_2O, 20 °C.

[a] 5β-Androstane-3β,6β-diol* (10%) was minor product. [b] At 0 °C. [c] 5β-Androstane-3α,6β-diol* (7%) was minor product.

already known, some of them having been obtained by routes other than those shown here, it was difficult at the outset to decide which approaches would best suit our purpose. Stages scattered through the literature had to be pieced together, and attempts made to increase the yields of some stages by modifying the experimental procedures or employing alternative reagents.

The routes finally adopted (see Scheme) start from 3β-hydroxyandrost-5-en-17-one (dehydroepiandrosterone) † (I). Those leading to the 6-ketones (IV), (XVI), and (XX) involve 3α,5-cyclo-intermediates; conjunction of the cyclopropane ring and the 6-oxo-group allows stereoselective ring opening by acid-catalysed hydration and by catalytic reduction. In the alternative route to 3β-hydroxy-5α-androstan-6-one (IV) *via* the 3,6-diketone (VII) the last stage becomes difficult to control as the scale is increased.

Although the 3β,6α-diol (V) is selectively oxidised to the 6α-hydroxy-3-ketone (IX) under the normal conditions of the Fetizon method,[3] the hydroxy-groups of the 3β,6β-diol (VIII) differ only slightly in their rates of reaction. The required oxidation to the 6β-hydroxy-3-ketone (XII) was achieved by a technique (see Experimental section) employing a mixture of solvents whose composition is changed during the oxidation. In the second, preferable route to the 6β-hydroxy-3-ketone, the key stage is selective acetalisation of the 3,6-diketone (VII). Under the usual homogeneous conditions there was insufficient differentiation between the keto-groups, but the use of an insoluble ion-exchange resin [4] as the acidic component led to clean reaction at position 3.

In work related to the present study the Fetizon oxidation of alcohols and the procedure for acetalisation under heterogeneous conditions have been applied to several polyfunctional androstanes. The results, summarised in Tables 1 and 2, illustrate the scope of these methods.

TABLE 1

Fetizon oxidation of 5α-androstane alcohols

Reactants and products are indicated by abbreviated symbols, *e.g.* 3β,7α-(OH)$_2$–17,17(–O–O–) represents 17,17-ethylenedioxy-5α-androstane-3β,7α-diol

Reactant	Product	% Yield
3β-OH–Δ^5	No reaction	
3β,6α-(OH)$_2$	6α-OH–3-CO	94
3β,6β-(OH)$_2$	Mixture [a]	
3β,7α-(OH)$_2$	7α-OH–3-CO	65 [b]
3β,7α-(OH)$_2$–17,17(–O–O–)	7α-OH–3-CO–17,17(–O–O–)	77 [b]
3β,7β-(OH)$_2$	7β-OH–3-CO	77 [b]
3β,7β-(OH)$_2$–17,17(–O–O–)	7β-OH–3-CO–17,17(–O–O–)	97 [b]
3β,7β,11α-(OH)$_3$–17-CO	7β,11α-(OH)$_2$–3,17-(CO)$_2$	76 [b]
3β,11α-(OH)$_2$ [c]	11α-OH–3-CO [c]	92
3β,11β-(OH)$_2$ [d]	11β-OH–3-CO [e]	95
3β,11β,16β-(OH)$_3$ [f]	11β-OH–3,16-(CO)$_2$	85 [h]
3β,12α-(OH)$_2$ [i]	12α-OH–3-CO [g]	80
3β,12β-(OH)$_2$ [i]	12β-OH–3-CO [g]	80
3β,12β,15α-(OH)$_3$ [j]	12β,15α-(OH)$_2$–3-CO [j]	82
3β,15α-(OH)$_2$–11-CO	15α-OH–3,11-(CO)$_2$	60 [k]
11β,17β-(OH)$_2$ [l]	11β-OH–17-CO [l]	98
12β,15α-(OH)$_2$	15α-OH–12-CO	63 [m]
15β,17β-(OH)$_2$	15β-OH–17-CO	85 [m]

[a] See Experimental section. [b] Ref. 5. [c] 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. [d] R. H. Shapiro, D. H. Williams, H. Budzikiewicz, and C. Djerassi, *J. Amer. Chem. Soc.*, 1964, **86**, 2837. [e] A. J. Liston and M. Howarth, *J. Org. Chem.*, 1967, **32**, 1034. [f] Ref. 2. [g] Constants reported in Table 3. [h] 5α-Androstane-3,11,16-trione (no. 85)* (7%) was minor product. [i] Ref. 8. [j] Ref. 6. [k] Ref. 7. [l] W. Klyne and S. Palmer, *J. Chem. Soc.*, 1958, 4545. [m] Ref. 1.

TABLE 2

Acetalisations of 5α-androstanones using Amberlite resin

Reactants and products are indicated by abbreviated symbols as in Table 1

Reactant	Product(s)	% Yield
3,6-(CO)$_2$	3,3(–O–O–)–6-CO	89
3,7-(CO)$_2$ [a]	3,3(–O–O–)–7-CO [b]	94
3,17-(CO)$_2$ [c]	3,3(–O–O–)–17-CO [d]	98
7,17-(CO)$_2$ [a]	7,7(–O–O–)–17-CO [b]	41
	7,7;17,17(–O–O–)$_2$ [b]	49
11,17-(CO)$_2$ [e]	17,17(–O–O–)–11-CO [b]	98
3β-OH–17-CO–Δ^5 [c]	3β-OH–17,17(–O–O–)–Δ^5 [f]	87
3β-OAc–17-CO–Δ^5 [c]	3β-OAc–17,17(–O–O–)–Δ^5 [f]	92
3β,7α-(OH)$_2$–17-CO	3β,7α-(OH)$_2$–17,17(–O–O–)	79 [g]
3β,7β-(OH)$_2$–17-CO	3β,7β-(OH)$_2$–17,17(–O–O–)	76 [g]

[a] Ref. 8. [b] Constants reported in Table 3. [c] G. D. Searle and Co. [d] H. C. Herzog, M. A. Jevnik, M. E. Tully, and E. B. Hershberg, *J. Amer. Chem. Soc.*, 1953, **75**, 4425. [e] 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. [f] L. F. Fieser, *J. Amer. Chem. Soc.*, 1954, **76**, 1945. [g] Ref. 5.

The structures of new compounds were established by their n.m.r. spectra and interconversions with known compounds. In the Experimental section the characterisation of new compounds is recorded (Table 3), and the less well-known procedures are also described. However, since much of the work requires only the careful operation of standard techniques, most of the experimental details are not given here but are available

† Supplied by G. D. Searle and Co.

[3] (*a*) M. Fetizon and M. Golfier, *Compt. rend.*, 1968, **267C**, 900; (*b*) M. Fetizon, M. Golfier, and J. Mourges, *Tetrahedron Letters*, 1972, **43**, 4445.

[4] (*a*) N. B. Lovette, W. L. Howard, and J. H. Brown, *J. Org. Chem.*, 1959, **24**, 1731; (*b*) D. P. Roelofsen, E. R. H. Wils, and H. Van Bekkum, *Rec. Trav. chim.*, 1971, **90**, 1141.

as Supplementary Publication No. SUP 21102.† Arabic numbers 685—700 are given to compounds which are connected with the work on the microbiological hydroxylation of steroids,[5] as explained earlier.[6]

EXPERIMENTAL

For general directions and details of preparative layer chromatography (p.l.c.) see refs. 6 and 7, respectively. Petrol refers to light petroleum (b.p. 60—80°) and THF to tetrahydrofuran. An asterisk indicates that the n.m.r. signals, and possibly also the i.r. absorptions, of a compound have already been reported.[5] N.m.r. signals are described in the form used earlier:[6] the signals and the other characteristics of new compounds, reported in Table 3, are not repeated here, or in the deposited material. The constants (m.p., $[\alpha]_D$) of known compounds are not given if the values found in the present work correspond closely with those in the references cited.

Oxidations with Fetizon's Reagent.—The oxidations in Table 1 were carried out by the procedure described in section (*a*). Oxidation of 5α-androstane-3β,6β-diol (VIII) (no. 220) * in this way gave a mixture of products [section (*b*)]; selective oxidation of the diol was achieved by the modified procedure described in section (*c*).

(*a*) A solution of 5α-androstane-3β,6α-diol (V) (no. 568) * (1 g) in C_6H_6 (300 ml) was refluxed for 4 h with Ag_2CO_3 on Celite[3] (10 g). Work-up gave 6α-*hydroxy*-5α-*androstan*-3-*one* (IX) (no. 551) * (870 mg).

(*b*) Treatment of 5α-androstane-3β,6β-diol (VIII) (100 mg) in C_6H_6 (100 ml) with Ag_2CO_3 on Celite (1·5 g) and separation of the products by p.l.c. [1 small plate, 2 × CH_2Cl_2–Me_2CO–EtOH (16 : 2 : 1)] gave, in order of decreasing R_F value, 5α-androstane-3,6-dione (VII) (no. 35) * (15 mg), m.p. and mixed[8] m.p. 151·5—153°, 6β-*hydroxy*-5α-*androstan*-3-*one* (XII) (no. 553) * (29 mg), and 3β-*hydroxy*-5α-*androstan*-6-*one* (IV) (no. 147) * (43 mg).

Repetition of this experiment using $CHCl_3$ (100 ml) instead of C_6H_6 led to recovery of starting material (94 mg).

(*c*) A solution of the 3β,6β-diol (VIII) (100 mg) in dry $CHCl_3$ (80 ml) was refluxed with Ag_2CO_3 on Celite (2 g) under a Dean–Stark separator containing dry C_6H_6 (15 ml) in the side-arm. After 25 min, and again after 45 min, the liquid in the side-arm was run off and the side-arm was filled with C_6H_6. After a further 15 min (when t.l.c. indicated that about half the starting material had been converted into one product) the solvent was distilled off. More $CHCl_3$ (80 ml) and reagent (2 g) were added and the boiling was continued for 1 h, the solvent in the side-arm being changed twice more. Work-up and p.l.c. gave 5α-androstane-3,6-dione (VII) (15 mg), 6β-hydroxy-5α-androstan-3-one (XII) (68 mg), and 3β-hydroxy-5α-androstan-6-one (IV) (31 mg).

Acetalisations using an Ion-exchange Resin.—In each case a small-scale pilot experiment was carried out to assess the reactivity of the steroidal ketone. The proportions of the reactants, resin, and solvent were adjusted, within the limits given in the following description, to give conditions leading to selective reactions (Table 2).

A stirred solution of the ketone (1—2 g) and $HO{\cdot}[CH_2]_2{\cdot}OH$ (1·5—15 ml) in C_6H_6 (200—500 ml) was refluxed with

TABLE 3

Characterisation of new compounds

	M.p. (°C) (solvent for crystallisation)	$[\alpha]_D$ (°) (concn.)	Analytical figures (%)			N.m.r. signals * (τ values; solvent $CDCl_3$)		
				C	H			
3,3-Ethylenedioxy-5α-androstan-7-one	171—173 (MeOH)	−57 (*c.* 1·0)	Found: $C_{21}H_{32}O_3$ req.:	75·6 75·9	9·3 9·7	H-19 H-18	8·92 9·31	
7,7-Ethylenedioxy-5α-androstan-17-one	174—175 (Me_2CO–petrol)	+67 (*c.* 1·0)	Found: $C_{21}H_{32}O_3$ req.:	75·8 75·9	9·6 9·7	H-19 H-18	9·16 9·13	
7,7;17,17-Bisethylenedioxy-5α-androstane	163—164 (Me_2CO–petrol)	−27 (*c.* 1·0)	Found: $C_{23}H_{36}O_4$ req.:	72·35 73·4	9·4 9·6	H-19 H-18	9·20 9·16	
17,17-Ethylenedioxy-5α-androstan-11-one	112—113 (MeOH)	+20 (*c.* 0·7)	Found: $C_{21}H_{32}O_3$ req.:	75·8 75·9	9·7 9·7	H-19 H-18	9·00 9·22	
3β-Hydroxy-5α-androstan-6-one (IV)	145—147 (Me_2CO)	−35 (*c.* 0·3)	Found: $C_{19}H_{30}O_2$ req.:	78·3 78·6	10·3 10·4	H-19 H-18	9·24 9·28	6·40 (7, *J* 10, 10, 5, and 5, H-3
6α-Hydroxy-5α-androstan-3-one (IX)	183—185 (Me_2CO–petrol)	+35 (*c.* 1·0)	Found: $C_{19}H_{30}O_2$ req.:	78·6 78·6	10·4 10·4	H-19 H-18	8·97 9·27	6·50 (6, *J* 10, 10, and 5, H-6)
17,17-Ethylenedioxy-5α-androstan-6α-ol	147—148 (Me_2CO–petrol)	+2·5 (*c.* 1·0)	Found: $C_{21}H_{34}O_3$ req.:	75·6 75·4	10·5 10·25	H-19 H-18	9·21 9·17	6·62 (6, *J* 10, 10, and 5, H-6
6β-Hydroxy-5α-androstan-3-one (XII)	179—180 (Me_2CO–petrol)	−5 (*c.* 1·0)	Found: $C_{19}H_{30}O_2$ req.:	78·8 78·6	10·25 10·4	H-19 H-18	8·77 9·23	6·24 (q, *J* 3, H-6)
3,3-Ethylenedioxy-5α-androstan-6β-ol (XI)	183—184·5 (MeOH–H_2O)	−12 (*c.* 1·0)	Found: $C_{21}H_{34}O_3$ req.:	75·4 75·4	10·3 10·25	H-19 H-18	8·96 9·27	6·24 (q, *J* 3, H-6)
12α-Hydroxy-5α-androstan-3-one	160—161 (Me_2CO–petrol)	+52 (*c.* 0·85)	Found: $C_{19}H_{30}O_2$ req.:	78·85 78·6	10·4 10·4	H-19 H-18	9·23 9·00	6·17 (t, *J* 3, H-12)
12β-Hydroxy-5α-androstan-3-one	128—130 (Et_2O–petrol)	+31 (*c.* 1·0)	Found: $C_{19}H_{30}O_2$ req.:	78·5 78·6	10·2 10·4	H-19 H-18	9·27 8·98	6·62 (4, *J* 11 and 5, H-12)
11β-Hydroxy-5α-androstane-3,16-dione	198—201 (Me_2CO–petrol)	−133 (*c.* 0·5)	Found: $C_{19}H_{28}O_3$ req.:	75·1 75·0	9·2 9·3	H-19 H-18	8·70 8·85	5·60 (q, *J* 3, H-11)
5β-Androstane-3α,6β-diol	210·5—211 (Me_2CO)	+3·5 (*c.* 0·3)	Found: $C_{19}H_{32}O_2$ req.:	78·3 78·0	10·9 11·0	H-19 H-18	8·88 9·27	6·36 (m, $W_{\frac{1}{2}}$ 24, H-3) 6·23 (m, $W_{\frac{1}{2}}$ 8, H-6)
5α-Androstane-3β,6α-diol (V)	209—211 (Me_2CO–petrol)	+26 (*c.* 1·0)	Found: $C_{19}H_{32}O_2$ req.:	77·9 78·0	11·2 11·0	H-19 H-18	9·17 9·30	6·47 (m, $W_{\frac{1}{2}}$ 26, H-3 and H-6)
5α-Androstane-3β,6β-diol (VIII)	196—197 (Me_2CO–petrol)	−15 (*c.* 0·6)	Found: $C_{19}H_{32}O_2$ req.:	77·8 78·0	10·9 11·0	H-19 H-18	8·95 9·26	6·35 (7, *J* 10, 10, 5, and 5, H-3 6·18 (q, *J* 3, H-6)
5β-Androstane-3β,6β-diol	230—232 (Me_2CO–MeOH)	+1 (*c.* 1·0)	Found: $C_{19}H_{32}O_2$ req.:	78·1 78·0	11·1 11·0	H-19 H-18	8·84 9·27	5·90 (m, $W_{\frac{1}{2}}$ 8, H-3) 6·28 (m, $W_{\frac{1}{2}}$ 8, H-6

* Signals reported in the form used earlier.[6]

† For details of Supplementary Publications see Notice to Authors No. 7 in *J.C.S. Perkin I*, 1973, Index issue.

[5] A. M. Bell, V. E. M. Chambers, Sir Ewart R. H. Jones, G. D. Meakins, W. E. Müller, and J. Pragnell, *J.C.S. Perkin I*, 1974, 312.

[6] 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.

[7] 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.

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

Amberlite resin (IR 120-H) (4—20 g) under a Dean–Stark separator. When t.l.c. indicated that little starting material remained (2—10 h), the mixture was filtered, and the filtrate evaporated to give material which was purified by crystallisation or p.l.c.

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