D-Homo-steroids. Part I. Derivatives Monosubstituted in Ring D

By **D. N. Kirk,* W. Klyne, C. M. Peach,** and **M. A. Wilson,** Medical Research Council, Steroid Reference Collection, Chemistry Department, Westfield College, London N.W.3

D-Homo-5α-androstan-17a-one, -17-one, and -16-one, and the corresponding epimeric pairs of alcohols and acetates have been prepared. These are valuable reference compounds quasi-enantiomeric to derivatives monosubstituted in ring A. N.m.r. data are considered; o.r.d. and c.d. curves have been treated elsewhere.

MONOSUBSTITUTED steroids are often particularly suitable for studies of reaction mechanisms [1] and physical properties of alicyclic compounds, since they provide a rigid framework of known stereochemistry and contain no interfering functional groups. Compounds substituted in ring A have been thoroughly explored as examples of cyclohexane derivatives made rigid by *trans*-fusion as the terminal ring of a polycyclic array. Steroids substituted only in ring D have also been used as representatives of the *trans*-hexahydroindane series.

The five-membered nature of ring D detracts from the strictly regular character of the steroid nucleus, *i.e.* as an all-*trans*-fused system of cyclohexane rings, and the strain of the *trans* C/D ring junction greatly affects the chemistry of rings C and D, and possibly that of the rings B and A. In order to provide reference compounds in the strainless tetracyclic series of 'all-*trans*' D-homo-steroids, which are perhydrochrysene derivatives, we have now prepared monofunctional ketones, alcohols, and acetates with substituents at positions 17a, 17 and 16 in the D-homo-series. These represent types enantiomeric in their bicyclic environment with positions 1, 2, and 3 respectively in ring A. We hope to prepare derivatives substituted at C-15 in due course.

The study has included the o.r.d. curves (and some c.d. curves) of the D-homo-ketones and acetates. O.r.d. and c.d. results for the acetates and the saturated ketones have been included in previous papers.[2] O.r.d. results for unsaturated and epoxy-ketones are mentioned briefly here.

Nearly all previous work in the D-homo-steroid series has been concerned with compounds substituted at C-3 and C-11.[3a,b] The synthetic methods used here are essentially the same as those employed by previous workers. (This work was completed before the development of our new, improved route to D-homo-ketones.[3c])

D-Homo-ketones.—D-Homo-5α-androstan-17a-one and -17-one were both prepared in the same synthesis. 'Dehydroepiandrosterone acetate' (3β-acetoxyandrost-5-en-17-one) (I) was converted through the cyanohydrins (II) into a mixture of 17-aminomethyl-17-ols (III), with simultaneous saturation of the 5,6-olefinic bond to give the 5α-configuration. Treatment of the amines with nitrous acid (Tiffeneau ring enlargement) [4] gave the D-homo-17a-ketone (IVa) and a small amount of the 17-ketone (V) (ratio *ca.* 20 : 1).

The oxygen function at C-3 was removed by formation of the toluene-*p*-sulphonate and reduction with lithium

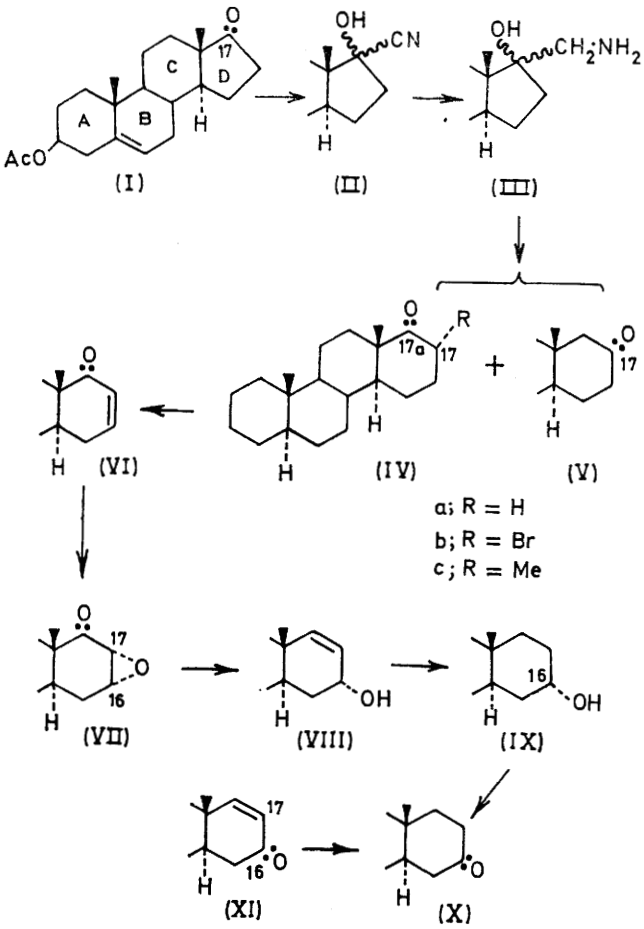
[1] D. N. Kirk and M. P. Hartshorn, 'Steroid Reaction Mechanisms,' Elsevier, Amsterdam, 1968.

[2] (*a*) J. P. Jennings, W. P. Mose, and P. M. Scopes, *J. Chem. Soc.* (*C*), 1967, 1102; (*b*) D. N. Kirk, W. Klyne, and S. R. Wallis, *J. Chem. Soc.* (*C*), 1970, 350.

[3] (*a*) L. F. Fieser and M. Fieser, 'Steroids,' Reinhold, New York, 1959, p. 577; (*b*) N. L. Wendler in 'Molecular Rearrangements,' ed. P. de Mayo, Interscience, New York, vol. 2, 1964, p. 1019; (*c*) D. N. Kirk and M. A. Wilson, *Chem. Comm.*, 1970, 64.

[4] *Cf.* ref. 3*b*, p. 1101.

aluminium hydride. Oxidation of the resulting monofunctional ring D alcohols afforded D-homo-5α-androstan-17a-one in an overall yield of 26%, and a little D-homo-5α-androstan-17-one.

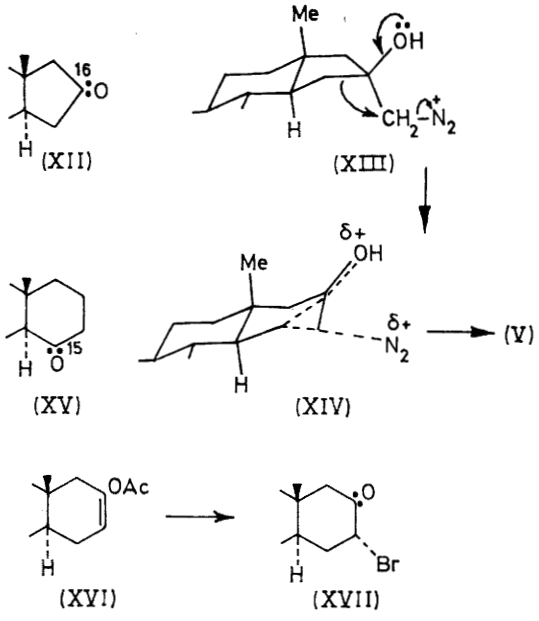


D-Homo-5α-androstan-16-one (X) was prepared in low yield from D-homo-5α-androstan-17a-one (IVa). The 17a-ketone was brominated, preferably with copper(II) bromide in methanol,[5] to give the 17α-bromo-ketone (IVb). Use of bromine (with hydrogen bromide) in acetic acid afforded mainly the 17α-monobromo-compound,[6] but also a little of the 17,17-dibromo-17a-one. The configurations of the bromo-ketones were assigned by analogy with results reported for 5α-cholestan-1-one,[7] and from their o.r.d. curves. The 1-ketone under the same conditions gave mainly 2α-bromo-5α-cholestan-1-one with a little 2,2-dibromo-5α-cholestan-1-one. The rate of bromination of the 17a-ketone (complete in 15 min.) was much greater than that reported [7] for the 1-ketone (16 hr.), which apparently resists enolisation [8] as a consequence of steric interaction with the 11-position.

Dehydrobromination of the 17α-bromo-17a-ketone with lithium carbonate in dimethylacetamide gave D-homo-5α-androst-16-en-17a-one (VI). Inferior yields were obtained by use of either collidine or lithium carbonate and dimethylformamide. Treatment of the unsaturated ketone with alkaline hydrogen peroxide afforded 16α,17α-epoxy-D-homo-5α-androstan-17a-one (VII), the configuration being assigned from the o.r.d. curve.[9] The epoxy-ketone reacted with hydrazine hydrate and hydrazine sulphate [10] (addition of the latter gave a slightly better yield) to give a low yield of D-homo-5α-androst-17-en-16α-ol (VIII) (*cf.* ref. 10*b* for use of this reaction in the preparation of a 2-en-1α-ol from the 1α,2α-epoxy-3-one).

Hydrogenation of the allylic alcohol, followed by oxidation, afforded D-homo-5α-androstan-16-one (X). The saturated 16-ketone (X) was also obtained from the unsaturated alcohol (VIII) by oxidation followed by hydrogenation.

The Tiffeneau ring enlargement was also studied for 3β-hydroxy-5α-androstan-16-one (XII), provided by Professor F. Šorm and Dr. J. Fajkoš. A reaction sequence similar to that already described gave the D-homo-17-ketone (V), with only a trace of the 16-ketone (X). If the cyanohydrins are assumed to consist mainly



of the 16α-cyano-derivative, formed by rear-side attack on the 16-ketone, the most stable conformation of the 16α-aminomethyl-16β-ol and the derived diazonium ion

[5] E. R. Glazier, *J. Org. Chem.*, 1962, **27**, 2937.

[6] D. A. Prins and C. W. Shoppee, *J. Chem. Soc.*, 1946, 494. We are aware of unpublished work by Dr. G. H. R. Summers, Swansea, which extends these studies.

[7] H. P. Sigg and C. Tamm, *Helv. Chim. Acta*, 1960, **43**, 1402; C. W. Shoppee, S. K. Roy, and B. S. Goodrich, *J. Chem. Soc.*, 1961, 1583.

[8] C. Djerassi and T. Nakano, *Chem. Ind.*, 1960, 1385.

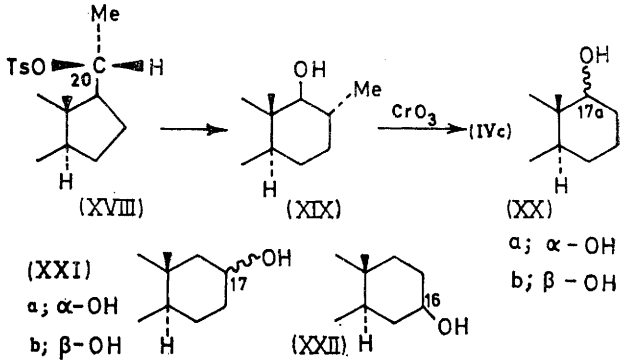
[9] C. Djerassi, W. Klyne, T. Norin, G. Ohloff, and E. Klein, *Tetrahedron*, 1965, **21**, 163; K. Kuriyama, *Tetrahedron Letters*, 1968, 2539.

[10] (*a*) P. S. Wharton and D. H. Bohlen, *J. Org. Chem.*, 1961, **26**, 3615; (*b*) C. Djerassi, D. H. Williams, and B. Berkoz, *ibid.*, 1962, **27**, 2205; (*c*) C. Djerassi, G. von Mutzenbecker, J. Fajkoš, D. H. Williams, and H. Budzikiewicz, *J. Amer. Chem. Soc.*, 1965, **87**, 817.

is likely to be as in (XIII). Migration of the 15,16-bond involves a transition state tending towards the chair form of ring D (XIV), resulting in ready formation of the D-homo-17-ketone (*cf.* ref. 3*b*).

In an unsuccessful attempt to obtain the D-homo-15-ketone (XV), the enolacetate (XVI) of the D-homo-17-ketone (V) was prepared. Bromination gave the 16α-bromo-17-ketone (XVII). The position and configuration of the bromo-substituent were apparent from the o.r.d. curve (*cf.* the 2-ketone, which afforded the 3α-bromo-2-ketone [8,11]). Attempts to dehydrobrominate the 16α-bromo-17-ketone gave a complex mixture (t.l.c. and i.r. spectra) of saturated and αβ-unsaturated ketones, which could not be separated. This approach to the 15-ketone was discontinued in view of the small amount of material available. Alternative routes are under investigation.

The 17α-methyl-D-homo-17a-ketone (IVc) was also prepared. Hirschmann [12] reported recently that a 5α-pregnan-20β-yl tosylate (XVIII) undergoes a D-homo-rearrangement in boiling formic acid. The initial product was the tosylate of the D-homo-17aβ-alcohol (XIX) but prolonged reaction gave the formate of the same alcohol. We have applied this reaction to the monofunctional 20β-tosylate to obtain, after hydrolysis of the formate ester, the monofunctional 17α-methyl-D-homo-5α-androstan-17aβ-ol (XIX). Oxidation gave the corresponding 17a-ketone (IVc), the structure of which was confirmed from its n.m.r. spectrum and o.r.d. curve. The features of the n.m.r. spectrum associated with ring D agreed well with those published by Morrow and his co-workers [13] for 3β-acetoxy-17α-methyl-D-homo-5α-androst-5-en-17a-one. The o.r.d. of the latter compound, provided by Parke-Davis and Co., Detroit, Michigan, was in good agreement with the curve obtained for our 17α-methyl-D-homo-5α-androstan-17a-one.[2b]



D-*Homo-alcohols*.—The results of reducing each of the D-homo-ketones with a variety of reagents are summarised in Table 1. The proportions of epimeric alcohols obtained by reducing the corresponding oxo-groups in ring A are included for comparison. All reducing agents convert the 17a-ketone largely into the equatorial 17aβ-alcohol, as reported for related compounds.[12,14] The contrast with C-1 when lithium aluminium hydride is used [15] is no doubt due to steric interference between C-1 and C-11. The case of C-1 cannot be regarded as typical.

In a separate attempt to make the 17aα-alcohol the tosylate of the 17aβ-alcohol (XXb) was treated with

TABLE 1

Reduction products from D-homo-ketones: comparison with ring A ketones

Ketone position (D-homo)	Reagent	D-Homo-alcohol (%) Axial	D-Homo-alcohol (%) Equatorial	Ketone position (ring A)	Alcohols (%) from reduction of ring A ketones: Axial	Alcohols (%) from reduction of ring A ketones: Equatorial	Ref.
C-17a (IVa)	AlH_3	19	69	C-1	9 (1α)	91 (1β)	*a*
	$Al(OCHMe_2)_3$	14 *	74 *				
	Ni–EtOH	11 * (17aα)	74 * (17aβ)				
	H_2–Pt	8	79		None found	*ca.* 100	*b*
	$LiAlH_4$	4	88		52	28	*c*
C-17a (17α-Me) (IVc)	$Al(OCHMe_2)_3$	Trace (17aα)	90% (17aβ)				
	$LiAlH_4$		*ca.* 100%				
	H_2–Pt		*ca.* 100%				
	Na–EtOH		*ca.* 100%				
C-17 (V)	H_2–Pt	88 (17β)	4 (17α)	C-2	*ca.* 100 (2β)	None found (2α)	*d*
	$LiAlH_4$	84 (17β)	Trace (17α)		52	37	*e*
	Na–PrOH		63		3	97	*a*
C-16 (X)	H_2–Pt	60 (16α)	15 (16β)	C-3	*ca.* 66 (3α)	*ca.* 33 (3β)	*e*
	$LiAlH_4$	Trace (16α)	90 (16β)		6, 10	94, 90	*a*, *e*

* Allowance made for recovered ketone.

[a] D. C. Ayres, D. N. Kirk, and R. Sawdaye, *J. Chem. Soc.* (*B*), 1970, 505; [b] G. von Mutzenbecher and R. D. Cross, *Steroids* 1965, **5**, 429; C. W. Shoppee, R. E. Lack, S. C. Sharma, and L. R. Smith, *J. Chem. Soc.* (*C*), 1967, 1155; P. Striebel and C. Tamm, *Helv. Chim. Acta*, 1954, **37**, 1094; [c] Ref. 15. [d] L. Ruzicka, P. A. Plattner, and M. Furrer, *Helv. Chim. Acta*, 1944, **27**, 524. [e] W. G. Dauben, E. J. Blanz, J. Jiu, and R. A. Michel, *J. Amer. Chem. Soc.*, 1956, **78**, 3752.

[11] C. W. Shoppee and T. E. Bellas, *J. Chem. Soc.*, 1963, 3366.

[12] H. Hirschmann, F. B. Hirschmann, and A. P. Zala, *J. Org. Chem.*, 1966, **31**, 375; *cf.* earlier work on the 'Urane' series of compounds from pregnant mares' urine, W. Klyne and C. W. Shoppee, *Chem. and Ind.*, 1952, 470.

[13] D. F. Morrow, M. E. Brokke, G. W. Moersch, M. E. Butler, C. F. Klein, W. A. Nevklis, and E. C. Y. Huang, *J. Org. Chem.*, 1965, **30**, 212.

[14] R. O. Clinton, R. G. Christiansen, H. C. Neumann, and S. C. Laskewski, *J. Amer. Chem. Soc.*, 1957, **79**, 6475.

[15] H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.*, 1956, 3289; G. von Mutzenbecher and A. D. Cross, *Steroids*, 1965, **5**, 429.

tetra-n-butylammonium acetate in *N*-methyl-2-pyrrolidone,[16] but afforded only a low yield of the 17aα-acetate, together with elimination products. Gas chromatography showed that there were two principal olefins. They could not be separated by column chromatography, and were not studied further.

reported the formation of isopropyl ethers at C-3, so our major product was probably a 16-isopropoxy-derivative. It was not examined further.

All the D-homo-alcohols described were converted into their acetates for o.r.d. studies, reported elsewhere.[2a] O.r.d. data for the saturated D-homo-ketones have also

TABLE 2

O.r.d. data ($n \rightarrow \pi^*$) for D-homo-ketone derivatives (in methanol unless otherwise stated)

	First extremum		Second extremum		
D-Homo-5α-androstane derivative	λ (nm.)	[φ]	λ (nm.)	[φ]	*a*
17α-Bromo-17a-one (IVb)	313	−260pk	270	−2300tr	+26
17,17-Dibromo-17a-one	345	+3650	291	−5240	+89
16α-Bromo-17-one (XVII) [in MeOH–dioxan (4 : 1)]	331	−1200	286	+13,300	−250
17-En-16-one (XI)	358	+1380	301	−3800	+52 *
16-En-17a-one (VI)	347	+605	289	−3140	+37 †
			(Δε +0·85; 326 nm.)		
16α,17α-Epoxy-17a-one (VI)	330	+4350	289	−3650	+80
(VI) (in hexane)	337	+4610	294	−3550	+82

* Curve shape roughly 'enantiomeric' with that for 5α-cholest-1-en-3-one: $[\phi]_{332.5}$ −815°; $[\phi]_{315}$ +4620°; *a* −54 (dioxan) (A. E. Lippmann, E. W. Foltz, and C. Djerassi, *J. Amer. Chem. Soc.*, 1955, **77**, 4364; *cf.* c.d.: $[\theta]_{345}$ −3500 (P. Witz, H. Herrmann, J. M. Lehn, and G. Ourisson, *Bull. Soc. chim. France*, 1963, 1101). † Curve shape roughly 'enantiomeric' with that for 5α-cholest-2-en-1-one: $[\phi]_{366}$ −1525°; $[\phi]_{311}$ +7660°; *a* −92 (C. Djerassi, R. Riniker, and B. Riniker, *J. Amer. Chem. Soc.*, 1956, **78**, 6377).

TABLE 3

N.m.r. data for C(17a)-, C(17)-, and C(16)-substituted D-homo-5α-androstanes

(τ values for solutions in CCl_4; Me_4Si as internal standard). Δτ is the chemical shift increment relative to the same protons in D-homo-5α-androstane. 'Reference values' of Δτ are adapted from Zürcher (ref. 18). Except where otherwise indicated, comparisons are made between increments for 18-Me in the D-homo-compound and for 19-Me in ring A derivatives as follows: (*a*) C(17a)- and C(1)-substituents; (*b*) C(17)- and C(2)-substituents; (*c*) C(16)- and C(3)-substituents. Where no reference value is available from Zürcher's data for ring A, the increment is given for the effect of the appropriate ring C substituent on the 18-Me shift (values marked *)

		Δτ			Δτ	
	18-Me	Found	Reference value	19-Me	Found	Other signals
D-Homo-5α-androstane	9·19			9·23		
Ketones						
17a-one (IVa)	8·934	−0·256	−0·375	9·20	−0·03	
17-one (V)	9·23	+0·04	+0·025	9·23	0·00	
16-one (X)	8·975	−0·215	−0·242	9·21	−0·02	
Alcohols						
17aβ-ol (XXb)	9·225	+0·035	−0·05	9·225	−0·005	
17aα-ol (XXa)	9·175	−0·015	−0·02	9·22	−0·01	
17β-ol (XXIb)	8·96	−0·23	−0·25	9·22	−0·01	17α-H, 5·92 (10 Hz)
17α-ol (XXIa)	9·18	−0·01	−0·025 *	9·23	0·00	
16β-ol (XXII)	9·16	−0·03	−0·033	9·22	−0·01	
16α-ol (IX)	9·20	+0·01	0·00	9·23	0·00	16β, 5·96 (9 Hz)
17-en-16α-ol (VIII)	9·20	+0·01	−0·05	9·20	−0·03	16β-H, 5·92 (8 Hz); 17-H and 17a-H, 4·37 (4 Hz)
Acetates						
17aβ-OAc (XXb; acetate)	9·134	−0·056	0·0 *	9·23	0·0	Ac, 8·0; 17aα-H, 5·48 (12 Hz)
17aα-OAc (XXa; acetate)	9·10	−0·09	−0·083 *	9·22	−0·01	Ac, 7·93; 17aβ-H, 5·38 (5 Hz)
17β-OAc (XXIb; acetate)	8·885	−0·305	−0·150	9·21	−0·02	Ac, 8·02; 17α-H, 4·95 (8 Hz)
17α-OAc (XXIa; acetate)	9·12	−0·07	−0·058 *	9·24	+0·01	Ac, 8·08; 17β-H, *ca.* 5·17 (*ca.* 30 Hz)
16β-OAc (XXII; acetate)	9·15	−0·04	−0·050	9·23	0·00	Ac, 8·03; 16α-H, 5·54 (32 Hz)
16α-OAc (IX; acetate)	9·17	−0·02	−0·025	9·22	−0·01	Ac, 7·97; 16β-H, 5·32 (7 Hz)
17-en-16α-OAc	9·16	−0·03	−0·075	9·20	−0·03	Ac, 8·00; 17-H and 17a-H 4·35 (5 Hz)

The D-homo-17-ketone showed the expected resemblances to the quasi-enantiomeric 5α-2-ketone. The D-homo-16-ketone behaved in a manner analogous to a 5α-3-ketone, except in one respect, not included in Table 1.

3-Ketones have been efficiently reduced to give the axial alcohols by use of propan-2-ol containing chloroiridic acid and trimethyl phosphite;[17] this method was therefore applied to the 16-ketone (X), but the product appeared to be an ether rather than an alcohol. Henbest

been presented and discussed.[2b] Data for the new bromo-, αβ-unsaturated, and αβ-epoxy-ketones are recorded in Table 2.

N.m.r. Spectra.—The main features of the n.m.r. spectra of the monofunctional ketones, alcohols, and acetates are recorded in Table 3. A comparison with

[16] H. B. Henbest and W. R. Jackson, *J. Chem. Soc.*, 1962, 954.
[17] Y. M. Y. Haddad, H. B. Henbest, J. Husbands, and T. R. B. Mitchell, *Proc. Chem. Soc.*, 1964, 361; P. A. Browne and D. N. Kirk, *J. Chem. Soc.* (*C*), 1969, 1653.

data for the analogous monofunctional steroids with the same substituents at C-1, C-2, or C-3 show close similarity between the corresponding increments (*cf.* ref. 18) in chemical shifts for adjacent angular methyl groups. The new data are valuable in complementing those already available. Values for C-17a in particular are free from the uncertainties at the only comparable positions in normal steriods, *viz.* C-1, where there is a high probability of distortion due to the proximity of C-11 or C-12, in which case the five-membered ring D and the side chain usually present at C-17 must affect the chemical shift of the C-18 protons.

EXPERIMENTAL

M.p.s were determined with a Köfler hot-stage apparatus. I.r. spectra, unless otherwise stated, refer to potassium chloride discs. U.v. spectra were determined for solutions in methanol. Alumina used was Spence type H. Light petroleum refers to the fraction of b.p. 40—60°. G.l.c. retention times were determined with the help of P. M. Shaw (see Table 4).

TABLE 4

G.l.c. data for monofunctional D-homo-5α-androstanes; relative retention times with respect to D-homo-5α-androstane (= 1) (5α-androstane = 0·65); column of 5% QFI on Diatoport S at 200°

Substituent position	Ketone	α-OH	β-OH	α-OAc	β-OAc
17a	5·15	2·90	3·25	4·85	5·40
17	6·05	3·65	2·90	5·10	5·60
16	6·85	3·05	3·50	4·80	5·60

D-*Homo*-5α-*androstan*-17a-*one* (IVa) *and* -17-*one* (V).—3β-Acetoxyandrost-5-en-17-one (10 g.) in absolute ethanol (300 ml.) was treated with potassium cyanide (63 g.). The mixture was cooled in ice and stirred during dropwise addition of glacial acetic acid (70 ml.), then for a further 1 hr. at 0° and for 2 hr. at room temperature; it was finally poured into water. The precipitated cyanohydrins (II) were washed with 2% acetic acid and water, then used without further purification.

The crude cyanohydrins (10 g.; m.p. 170—175°) in glacial acetic acid (200 ml.), were hydrogenated over Adams platinum (2 g.) until uptake of hydrogen was complete (4 hr.). The solution was, filtered, concentrated under reduced pressure to *ca.* 40 ml., then diluted with water (150 ml.). Neutral by-products were removed by extraction with ether (2 × 150 ml.) to leave a clear solution of the steroid amines (III).

Tiffeneau ring enlargement. The solution was cooled in ice, and treated with acetic acid (16 ml.) followed by sodium nitrate (4 g.) in the minimum of water. After 20 hr. at 0° the precipitated ketones were collected and washed with water.

Removal of the C-3 *substituent.* The crude 3β-acetoxyketones (8 g.) were heated in methanol (200 ml.) containing potassium hydroxide (4 g.) under reflux for 1 hr. Water was added to precipitate the steroids, and the dried solids (6·8 g.) were dissolved in dry pyridine (40 ml.) containing toluene-*p*-sulphonyl chloride (8 g.) and left overnight at room temperature. The crude tosylates were precipitated with ice–water, washed, and dried (8·8 g.; m.p. 165—166°). This material was heated under reflux for 16 hr. with lithium aluminium hydride (3·6 g.) in dry tetrahydrofuran (90 ml.) and dry ether (450 ml.). After destruction of excess of reagent with ethyl acetate followed by dilute sulphuric acid, the product was isolated with ether. The resulting white solid (5·86 g.) in acetone was treated dropwise with 8N-chromic acid (Jones reagent). Dilution with water gave a mixture (3·3 g.) of D-homo-5α-androstan-17a-one and D-homo-5α-androstan-17-one, which were separated by chromatography on alumina (110 g.). Elution with light petroleum gave first D-*homo*-5α-*androstan*-17a-*one* (IVa) (2·35 g.) as plates from methanol, m.p. 141·5—142·5°, $\nu_{max.}$ 1720 cm.$^{-1}$, $\lambda_{max.}$ 294 nm. (ε 41) (Found: C, 83·2; H, 11·1. $C_{20}H_{32}O$ requires C, 83·3; H, 11·2%). A small amount (160 mg.) of a mixture of the two ketones followed, and further elution with light petroleum afforded D-*homo*-5α-*androstan*-17-*one* (V) as plates from methanol (123 mg.), m.p. 171—172°, $\nu_{max.}$ 1725 cm.$^{-1}$, $\lambda_{max.}$ 294 nm. (ε 22) (Found: C, 83·5; H, 10·9. $C_{20}H_{32}O$ requires C, 83·3; H, 11·2%)

17α-*Bromo*-D-*homo*-5α-*androstan*-17a-*one* (IVb).—(a) *By use of bromine in acetic acid.* The 17a-ketone (IVa) (1·4 g.) in acetic acid was treated with hydrogen bromide in acetic acid (45% w/v; 2 drops), followed by M-bromine in acetic acid (5 ml.). A precipitate formed after 2 min. Water was added after 15 min. to complete precipitation of the product, which was then dissolved in light petroleum and chromatographed on silica gel (50 g.). Elution with light petroleum–benzene (9 : 1) gave a trace of what appeared to be the 17,17-*dibromo-compound*, m.p. 163—164°, $\lambda_{max.}$ 315 nm. (Found: Br, 35·4. $C_{20}H_{30}Br_2O$ requires C, 35·8%). Further elution with the same solvent gave the 17α-*bromo*-17a-*ketone* (IVb) as needles (from methanol) (1·585 g.) m.p. 206—207°, $\lambda_{max.}$ 294 nm. (ε 44) (Found: C, 65·0; H, 8·55; Br, 22·0. $C_{20}H_{31}BrO$ requires C, 65·4; H, 8·45; Br, 21·8%).

(b) *By use of copper*(II) *bromide in methanol.* A solution of 17a-ketone (IVa) (2·35 g.) and dried copper(II) bromide (3·85 g.) in methanol (300 ml.) was heated under reflux for 24 hr., then the methanol was removed under reduced pressure. Water was added to the residue and the steroid was extracted with chloroform. Crystallisation from acetone gave the 17α-bromo-17a-ketone (IVb), identical with the product obtained in (a).

D-*Homo*-5α-*androst*-16-*en*-17a-*one* (VI).—*NN*-Dimethylacetamide (20 ml.), the 17α-bromo-17a-ketone (IVb) (621 mg.), and anhydrous lithium carbonate (370 mg.) were heated under reflux with stirring for 15 min, cooled and poured into water. The precipitated 16-*en*-17a-*one* crystallised as plates from methanol (447 mg.), m.p. 117—118°, $\nu_{max.}$ 1690 cm.$^{-1}$, $\lambda_{max.}$ 225 nm. (ε 5860) (Found: C, 84·0; H, 10·55. $C_{20}H_{30}O$ requires C, 83·9; H, 10·6%).

16α,17α-*Epoxy*-D-*homo*-5α-*androstan*-17a-*one* (VII).—To a solution of the 16-en-17a-one (VI) (447 mg.) in methanol (40 ml.) cooled in ice was added 2N-sodium hydroxide (1·6 ml.), followed immediately by 30% hydrogen peroxide (1·6 ml.), and the mixture was left at 0° for 72 hr. The crystals which separated were recrystallised once from acetone (yield 321 mg.; m.p. 148—151°). This material appeared to be homogeneous (t.l.c.) and the u.v. spectrum showed no maximum between 220 and 300 nm.; $\nu_{max.}$ (Nujol) 1735 cm.$^{-1}$. This sample was used without further purification.

D-*Homo*-5α-*androst*-17-*en*-16α-*ol* (VIII).—A mixture of

[18] R. F. Zürcher, *Helv. Chim. Acta*, 1963, **46**, 2054.

hydrazine hydrate (10 ml.) and the epoxy-ketone (VII) (972 mg.), together with hydrazine sulphate (2·63 g.), was heated under reflux with stirring for 15 min.; nitrogen was evolved and the mixture turned dark brown.

Water was added and the product was extracted into ether, to give a brown gum (711 mg.) which was chromatographed on silica gel (20 g.). Elution with light petroleum gave brown gums. The more polar fractions, eluted by light petroleum–benzene (9 : 1), were rechromatographed to give the crude unsaturated alcohol (VIII) as a white solid, m.p. 148—149°, $\nu_{max.}$ 3600 (OH) and 1650 (C:C) cm.$^{-1}$. This compound did not crystallise readily and so was hydrogenated directly to give the saturated 16α-alcohol (IX).

D-*Homo*-5α-*androstan*-16α-*ol* (IX).—The crude unsaturated alcohol (VIII) (290 mg.) in methanol (30 ml.) was hydrogenated over 5% palladium–charcoal to give the 16α-*alcohol* (IX), m.p. 133—134° (from aqueous methanol) (Found: C, 82·8; H, 12·0. $C_{20}H_{34}O$ requires C, 82·7; H, 11·8%).

D-*Homo*-5α-*androstan*-16-*one* (X).—The 16α-alcohol (IX) in acetone was oxidised with 8N-chromic acid to give the 16-*ketone*, which crystallised from methanol (containing a trace of pyridine) as fine needles, m.p. 132—133°, $\nu_{max.}$ 1710 cm.$^{-1}$, $\lambda_{max.}$ 281 nm. (ε 34) (Found: C, 83·0; H, 10·9. $C_{20}H_{32}O$ requires C, 83·3; H, 11·2%). If pyridine was omitted the ketone was partially transformed into the 16,16-dimethoxy-derivative, $\nu_{max.}$ *ca.* 1100 cm.$^{-1}$.

D-*Homo*-5α-*androst*-16-*en*-17-*one* (XI).—D-Homo-5α-androst-17-en-16α-ol (45 mg.) in acetone (5 ml.) was oxidised with 8N-chromic acid to give the *unsaturated ketone* (40 mg.) as needles from methanol, m.p. 149—149·5°, $\nu_{max.}$ 1670 and 787 cm.$^{-1}$, $\lambda_{max.}$ 228 nm. (ε 13,400) (Found: C, 83·5; H, 10·5. $C_{20}H_{30}O$ requires C, 83·9; H, 10·6%). Hydrogenation of this unsaturated ketone over palladium–charcoal gave the 16-ketone (X), m.p. 132—133°.

D-*Homo*-5α-*androstan*-17-*one* (V) *from* 3β-*Hydroxy*-5α-*androstan*-16-*one* (XII).—3β-Hydroxy-5α-androstan-16-one (500 mg.) was treated as described for ring enlargement of the 17-ketone (I), including the steps for removal of the C-3 substituent. Chromatography of the crude ketonic product (250 mg.) gave a trace of material which appeared (t.l.c.) to be the D-homo-16-ketone (X), followed by the D-homo-17-ketone (V) (136 mg.), identical with material already described.

17-*Acetoxy*-D-*homo*-5α-*androst*-16-*ene* (XVI).—D-Homo-5α-androstan-17-one (130 mg.) and isopropenyl acetate (5 ml.) were heated with toluene-*p*-sulphonic acid (10 mg.) for 1 hr., with very slow distillation. The mixture was poured into aqueous sodium hydrogen carbonate and extracted with ethyl acetate to give the *enol acetate* as fine needles (from methanol), m.p. 126—127°, $\nu_{max.}$ 1760 and 1220 cm.$^{-1}$ (Found: C, 79·8; H, 10·1. $C_{22}H_{34}O_2$ requires C, 79·95; H, 10·4%). The same compound was formed when the 17-ketone (22 mg.) was heated for 3 hr. in acetic anhydride (4 ml.) containing toluene-*p*-sulphonic acid (2 mg.). Thin-layer and gas chromatography indicated that the products from these reactions were homogeneous and identical.

16α-*Bromo*-D-*homo*-5α-*androstan*-17-*one* (XVII).—To the enol acetate (XVI) (115 mg.) in acetic acid (9 ml.) and carbon tetrachloride containing sodium acetate (100 mg.) bromine (1·0 mol.) in acetic acid was added during 30 min., and the mixture was left for a further 15 min. before being poured into water. The *bromo-ketone* was extracted with ether and crystallised from acetone; m.p. 132—135° (90 mg.), $\nu_{max.}$ 1720 cm.$^{-1}$. Attempts to dehydrobrominate this material were unsuccessful.

17α-*Methyl*-D-*homo*-5α-*androstan*-17a-*one* (IVc).—5α-Pregnan-20β-ol (1 g.) and toluene-*p*-sulphonyl chloride (2 g.) were dissolved in pyridine overnight at room temperature. The 20β-tosylate (XVIII) was precipitated into water, and crystallised once from acetone (yield 1·36 g.; m.p. 172°). This material, which was homogeneous on t.l.c., was heated in 90% formic acid (60 ml.) under reflux for 2 hr. Evaporation and extraction of the residue with ether afforded a gummy solid (737 mg.). The i.r. spectrum showed the absence of tosylate. The product was hydrolysed in methanol (100 ml.) with potassium hydroxide (1·5 g. in the minimum of water) under reflux for 1 hr, and the crude 17aβ-alcohol (XIX) was partially purified by chromatography on alumina (30 g.). Elution with light petroleum–benzene (7 : 3) afforded the alcohol, which crystallised from methanol as solvated hexagons, m.p. 42—43°. A sample dried *in vacuo* had m.p. 103—105°; after sublimation at 0·1 mm. pressure it had m.p. 106—108° (lit.,[19] 107°). The 17aβ-alcohol (206 mg.) in acetone was oxidised with Jones reagent (0·2 ml.). The 17a-*ketone* (IVc) crystallised from methanol as needles (180 mg.), m.p. 136—137° (lit.,[20] 138°), $\nu_{max.}$ 1710 cm.$^{-1}$, $\lambda_{max.}$ 294 nm. (ε 48) (Found: C, 83·35; H, 11·2. Calc. for $C_{21}H_{34}O$: C, 83·4; H, 11·3%).

D-*Homo-alcohols* (*see Table* 1 *for yields*).

Reduction of D-*Homo*-5α-*androstan*-17a-*one* (IVa).—(a) *By lithium aluminium hydride.* D-Homo-5α-androstan-17a-one (980 mg.) was reduced in the normal way with lithium aluminium hydride (526 mg.) in dry ether (70 ml.), heated under reflux for 2 hr. The resulting solid (950 mg.), m.p. 172—175° was dissolved in light petroleum and chromatographed on silica gel (30 g.). Elution with light petroleum–benzene (1 : 1) afforded the 17aα-*alcohol* (XXa) (35 mg.) as needles (from hexane), m.p. 153—154° (Found: C, 83·3; H, 11·7. $C_{20}H_{34}O$ requires C, 82·7; H, 11·8%). Further elution with light petroleum–benzene (2 : 3) afforded the 17aβ-*alcohol* (XXb) (856 mg.) as needles (from acetone), m.p. 176—178° (Found: C, 83·1; H, 11·5. $C_{20}H_{34}O$ requires C, 82·7; H, 11·8%).

(b) *Catalytic hydrogenation.* The ketone (155 mg.) in acetic acid (40 ml.) was hydrogenated over Adams catalyst (75 mg).

(c) *Meerwein-Ponndorf reduction.* A mixture of the 17a-ketone (197 mg.) and aluminium isopropoxide (204 mg.) in dry toluene (6 ml.) was heated under reflux with stirring for 3 hr.

(d) *By Raney nickel.* The steroid (99 mg.) in ethanol (15 ml.) was stirred and heated under reflux with Raney Nickel (1 ml.) for 5·5 hr.

(e) *By aluminium hydride.* A solution of D-homo-5α-androstan-17a-one (90 mg.) in dry ether (20 ml.) was added dropwise, with stirring to a solution of aluminium hydride (0·4M; 2 ml.) in dry ether (20 ml.) at −70°. After 2 hr. stirring the temperature was allowed to rise and the excess of reagent destroyed with 4N-sulphuric acid.

17aα-*Acetoxy*-D-*homo*-5α-*androstane from the* 17aβ-*Tosyloxy derivative.*—D-Homo-5α-androstan-17aβ-ol (210 mg.) and toluene-*p*-sulphonyl chloride (400 mg.) were dissolved

[19] M. Leboeuf, A. Cavé, and R. Goutarel, *Bull. Soc. chim. France*, 1969, 1628.

[20] M. Leboeuf, A. Cavé, and R. Goutarel, *Bull. Soc. chim. France*, 1969, 2100.

in dry pyridine (2 ml.) during 16 hr. The mixture was poured into ice–water, and the solid product was washed, dried, and crystallised from acetone to give the 17aβ-tosylate, m.p. 175—177° (266 mg.). The crude tosylate (210 mg.) and tetra-n-butylammonium acetate (815 mg; freshly crystallised from benzene) were heated in *N*-methyl-2-pyrrolidone (4·2 ml.; dried and redistilled) for 4 hr. at 160°. Extraction with ether gave a yellow oil, which was chromatographed on alumina (6 g.). Elution with light petroleum afforded a mixture of olefins (69 mg.), $\nu_{max.}$ 1650 cm.$^{-1}$.

17aα-*Acetoxy*-D-*homo*-5α-*androstane* (38 mg.) was obtained on further elution with light petroleum as plates (from methanol), m.p. 105—107° (Found: C, 79·3; H, 10·6. $C_{22}H_{36}O_2$ requires C, 79·5; H, 10·9%). The 17aα-alcohol was obtained by alkaline hydrolysis of the acetate, and identified by comparison with samples obtained previously.

Reduction of D-*Homo*-5α-*androstan*-17-*one* (V).—(a) *By lithium aluminium hydride.* The 17-ketone (50 mg.) in dry ether (10 ml.) was reduced with lithium aluminium hydride (28 mg.) for 2·5 hr. Chromatography of the product on alumina (3 g.) and elution with light petroleum–benzene (4 : 1) gave the 17β-*alcohol* (40 mg.) (XXIb) as fine needles from hexane, m.p. 167—168° (Found: C, 82·5; H, 11·7. $C_{20}H_{34}O$ requires C, 82·7; H, 11·8%). Later eluates contained traces of the 17α-alcohol (t.l.c. and g.l.c.).

(b) *With Adams catalyst.* The 17-ketone (50 mg.) in acetic acid (20 ml.) was hydrogenated over Adams catalyst (25 mg.).

(c) *With sodium–n-propanol.* The 17-ketone (30 mg.) in n-propanol (15 ml.) was stirred under reflux and treated with sodium metal (1 g.). When the sodium had dissolved, methanol (1 ml.) and water were added, and the steroid was extracted with benzene. Chromatography on alumina (2 g.) and elution with light petroleum–benzene gave the 17α-*alcohol* (19 mg.), m.p. 160—162° (from aqueous methanol) (Found: C, 82·6; H, 11·9. $C_{20}H_{34}O$ requires C, 82·7; H, 11·8%).

Reduction of D-*Homo*-5α-*androstan*-16-*one* (X).—(a) *By lithium aluminium hydride.* A solution of the 16-ketone (40 mg.) in dry ether (16 ml.) was heated under reflux with lithium aluminium hydride (20 mg.) for 2 hr., and the product was isolated in the usual way. Crystallisation from methanol gave the 16β-*alcohol* (XXII) as needles, m.p. 144—145° (Found: C, 82·5; H, 11·8. $C_{20}H_{34}O$ requires C, 82·7; H, 11·8%). T.l.c. of the residues revealed a trace of the 16α-alcohol (IX).

(b) *Catalytic hydrogenation.* The 16-ketone (20 mg.) in acetic acid (15 ml.) was hydrogenated over Adams platinum (20 mg.).

(c) *With propan-2-ol containing chloroiridic acid and trimethyl phosphite.* Chloroiridic acid (2 mg.) and trimethyl phosphite (0·1 ml.) were added to the 16-ketone (31 mg.) in 90% aqueous propan-2-ol (5 ml.) and the solution was heated under reflux. Samples withdrawn at intervals up to 64 hr. showed (t.l.c.) that the axial (16α-) alcohol was formed in greater quantity than the 16β-epimer, but when the total steroid product was isolated after 64 hr. it appeared to be mainly an isopropyl ether, $\nu_{max.}$ *ca.* 1130 cm.$^{-1}$.

Reduction of 17α-*Methyl*-D-*homo*-5α-*androstan*-17a-*one* (IVc).—(a) *With sodium and ethanol.* Sodium (170 mg.) was added to a boiling solution of 17α-methyl-D-homo-5α-androstan-17a-one (10 mg.) in ethanol (5 ml.). T.l.c. of the product showed the presence of only the 17aβ-alcohol (t.l.c.), m.p. 42—43°, (from methanol), identical with material already described.

(b) *With lithium aluminium hydride.* The steroid (10 mg.), lithium aluminium hydride (13 mg.), and dry ether (10 ml.) were heated under reflux for 3 hr.

(c) *Catalytic hydrogenation.* The 17α-methyl-D-homo-17a-one (2 mg.) was hydrogenated in acetic acid (5 ml.) over Adams platinum (1 mg.).

(d) *Meerwein-Ponndorf.* Aluminium isopropoxide (70 mg.) and 17α-methyl-D-homo-17a-one (20 mg.) were heated in toluene (3 ml.) under reflux for 3 hr. T.l.c. of the product indicated the presence of two alcohols, the major component being the known 17aβ-epimer. The 17aα-alcohol was not obtained in sufficient quantity for characterisation.

Acetates of the foregoing alcohols were prepared in the usual way (with acetic anhydride–pyridine); see Table 5 for details.

TABLE 5

Acetates of D-homo-5α-androstanols

Acetate of	M.p. and solvent for crystallisation	Analysis ($C_{22}H_{36}O_2$ requires C, 79·5; H, 10·9%) C (%)	H (%)
17aβ-ol	137—139° (plates; methanol)	79·25	10·9
17aα-ol	105—107 (plates; methanol)	79·3	10·6
17β-ol	126—127 (methanol)	79·2	10·8
17α-ol	137—139 (methanol)	79·3	10·8
16β-ol	102—103 (acetone)	79·3	10·7
16α-ol	128—129 (methanol)	79·5	10·9
17aβ-ol (17α-methyl)	137—138 (methanol)	79·3 *	10·9 *

* $C_{23}H_{38}O_2$ requires C, 79·7; H, 11·05%.

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