Bromo-, Chloro-, and Amino-derivatives of 5α-Androstane and 5α-Oestrane

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Synthesis of bromo-, chloro-, and amino-5α-androstanes and -5α-oestranes from the corresponding alcohols and oximes is described.

For the purposes of magnetic anisotropy and electric field calculations,[1] certain amino-, chloro-, and bromo-steroids of the 5α-androstane and 5α-oestrane series have been synthesised; their properties are recorded in the present paper. During their preparation certain unusual reactions were observed and brief comments are presented below. Starting materials in all cases were 5α-androstanones synthesised by established routes.[2-10] These reactions proceeded as described previously except in the case of the 7-oxo-isomer where hydrogenation of the precursor, androsta-3,5-dien-7-one [6] in ethanol led to the required ketone in 10% yield only, accompanied by 70% of 7β-ethoxy-5α-androstane. When rigorous measures were taken to remove traces of acid carried over from the penultimate stage, the normal 5α-androstan-7-one resulted. This anomalous reaction probably proceeds by acetalisation followed by elimination of alcohol to give the triunsaturated enol ether 7-ethoxyandrosta-3,5,7-triene. This route is favoured since if androstan-7-one itself is hydrogenated under identical conditions the major product is the corresponding alcohol accompanied by only 2% of the 7-alkoxy-compound.

In general, reduction of the androstanones with lithium aluminium hydride in dry ether gives the axial alcohol, heavily contaminated however, in the case of the 3-, 7-,[11] and 16-ketones, with the equatorial β-isomer. Previous reports [12-14] have shown that β-tosylates may be hydrolysed, with inversion of configuration, by prolonged contact with strongly basic alumina; under such conditions, however, elimination is the predominant reaction and yields of the pure α-isomers are low. We now find that heating the 3-, 7-, and 16β-tosylates with tetra-n-butylammonium hydroxide in dimethyl sulphoxide or *N*-methylpyrrolidone gives the corresponding α-hydroxyandrostanes in *ca.* 90% yield, without significant concomitant elimination.

In general, reactions between the mono-hydroxy-5α-androstanes and thionyl halides or phosphorus pentahalides proceeded as already noted in the cholestane series [15-20] with sulphite formation and elimination forming the major pathway in certain cases: the Scheme summarises the findings.

The preferred route to 3β-bromo-5α-androstane used androst-5-en-3β-ol which with freshly distilled thionyl bromide gave the substitution–bromine addition product 3β,5α,6β-tribromoandrostane, a structure assigned on the basis of the methine proton resonances and the chemical shifts of the C-10 and C-13 methyl signals, and further supported by the i.r. stretching frequencies [21] exhibited by the 5α,6β-vicinal dibromide at 578 and 625 cm^{-1}. Hydrogenation of the tribromide in ethanol over palladium–charcoal gave 3β-bromoandrost-5-ene. Replacement of the poisoned catalyst then allowed hydrogenation to the required 3β-bromo-5α-androstane, accompanied to a large extent, however, by hydrogenolysis to 5α-androstane.

With 5α-androstan-11α-ol, phosphorus pentachloride yielded mainly the 9(11)-ene accompanied in minor amount by the chlorine addition product 9α,11β-dichloro-5α-androstane: thionyl chloride on the other hand gave mostly 11α-chloro-5α-androstane with the elimination product in but minor amount. Our findings differ from a recent publication [7] in one respect: under our present conditions the vicinal 9α,11β-dichloro-compound is the *sole* product of the reaction between phosphorus pentachloride and 5α-androstan-11β-ol or 5α-androst-9(11)-ene.

Difficulty in the synthesis of the axial isomers at C-2, -4, -6, -16, and -17 suggested an exploration of the

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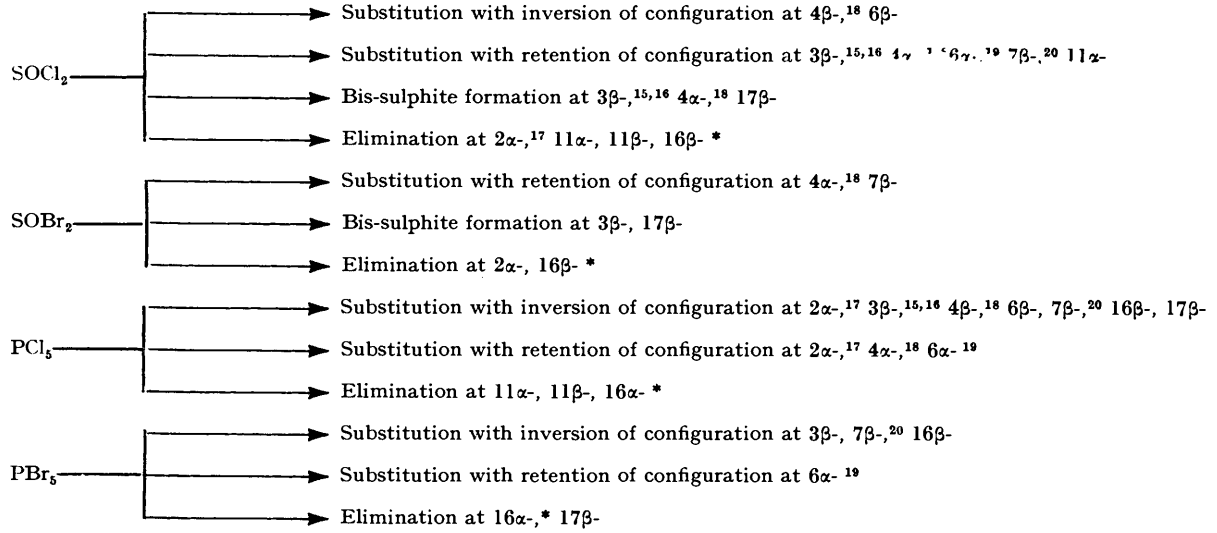
hydrazone route,[22] recently used for the preparation of 17β-chloro-5α-androstan-3-one.[23]

Our observations suggest that this method suffers from two disadvantages which limit its general application. First, only in the case of the 4-, 11-, and 17-oxo-5α-androstanes can the hydrazone be isolated, whilst at all other positions, including C-3 and C-7, the azine is obtained. This subsequently fails to react with *N*-halogenosuccinimide in the following step. Secondly, attempted hydrogenation of the vinyl halides obtained from the 4- and 11-hydrazones with *N*-halogenosuccinimide yielded 5α-androstane itself rather than the halogeno-compound. Only in the case of the 17β-chloro-compounds is the synthesis successful; the corresponding 17β-bromo-steranes, like the 4- and 11-halides, undergo hydrogenolysis to the hydrocarbon.

stereochemistry to the C–halogen bond. In general, the equatorial proton of an axial halogenated isomer resonates at lower field and gives rise to a multiplet ($W_{\frac{1}{2}}$ *ca.* 7 Hz) sharper than the corresponding axial proton of an equatorial halogenated isomer ($W_{\frac{1}{2}}$ *ca.* 25—35 Hz). In every case, the methine proton of a bromo-5α-androstane also resonates at lower field than does that of a corresponding chloro-5α-androstane.

For the synthesis of a series of monoamino-5α-androstanes reduction of the corresponding oximes has been carried out using as reducing agents, sodium in alcohol, lithium aluminium hydride in ether, and hydrogenation over Adams platinum oxide in glacial acetic acid: general details of each technique appear in the Experimental section (*cf.* refs. 28 and 29).

Isolation of individual isomers, either as the free base



SCHEME Substitution reactions of mono-hydroxy-5α-androstanes (superscript references are for the corresponding reactions in the cholestane series)

* For additional minor products at these positions see the Experimental section.

Since 5α-androstan-3-one yields only the azine, the recent claim [24] that a hydrazone is obtained from 17β-acetoxy-5α-androstan-3-one was re-examined. In our hands a product identical in m.p. (215—219°) with that previously described was obtained. Elemental analysis and mass measurement of the molecular ion clearly established this as the azine, however, and not the hydrazone. In our hands recrystallisation of the hydrazones from methanol at 0° was successful and there was no trace of rearrangement to the azine as reported [25] for 5α-androstan-17-one hydrazone.

Spectral data (Tables 1 and 2) allow the assignment of or the acetyl derivative, allowed the assignment of configuration, which was derived on three counts. First, using the methyl resonance of the acetamido-group for which, in a series of acetylated amino-sugars and -cyclanes, it has already been shown [30] that in an axial position, resonance is observed at lower field (τ 7·97—8·04) than in its equatorial counterpart (τ 8·03—8·12). Secondly, for the methine proton of the $>CH\text{–}NH_2$ group the resonance of the equatorial proton is sharper and lies to lower field than the axial isomer [31,32] (Table 3). For substituents in rings A, B, and C these two methods led to the same configurational assign-

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ments. Thirdly, as with the hydroxy-androstanes,[33] clear separation of the corresponding axial and equatorial acetamido-compounds was achieved by g.l.c. (Table 4), the only exception being the C-16α and -16β isomers. retention time of the axial β isomer, probably arises from an intramolecular interaction between the 11α-acetamido-group and the 1β-proton.

Aliquot portions of the crude product from each

Spectroscopic Results.—N.m.r. signals refer to $CDCl_3$ solutions examined at 60 MHz. Some signals are described as s (singlet), d (doublet), t (triplet), or m (unresolved multiplet): the letters d and t are followed, in parentheses, by the coupling constant (J/Hz); m is followed by the half-height width ($W_{\frac{1}{2}}$/Hz). Where these terms are inappropriate,* the number of lines are indicated; this is followed, in parentheses, by a set of apparent J values. A range of resonance is given where a complex signal is observed and analysis impractical. I.r. frequencies unless otherwise indicated refer to 2% CS_2 solutions for halogenated steroids and to 2% CCl_4 solutions for others. Assignments of configuration in the D ring refer to a pseudo-axial or pseudo-equatorial state. I.r. bands are classified as strong (s), medium (m), or weak (w).

TABLE 1

Chloro-steroids

	N.m.r. (τ values)			I.r. ($\nu_{max.}$/cm^{-1})			
	Methyl signals			C–Cl stretch			
Compound	C-19	C-18	Methine	Axial	Equatorial	Other signals	Assignment
3α-Chloro-5α-androstane	9·22	9·30	5·51 m(7)	708 (m)			
3β-Chloro-5α-androstane	9·16	9·31	5·80—6·50		756 (s)		
3β-Chloroandrost-5-ene	8·97	9·28	5·92—6·57		760 (s)	1670	C=C
4α-Chloro-5α-androstane	9·19	9·31	5·76—6·49		747 (s)		
4-Chloroandrost-4-ene	8·96	9·29		766 (s)		1653	C=C
5α-Chloroandrostan-3β-ol	8·91	9·29	5·21—6·10	678 (w)		1045	C–O
						3650	O–H
3β,5α-Dichloroandrostane	8·91	9·31	5·13—5·77	688 (m)	760 (s)		
6α-Chloro-5α-androstane	9·19	9·32	5·79—6·49		760 (s)		
7α-Chloro-5α-androstane	9·20	9·30	5·65 m(6)	588 (s)		703, 622, 565 [a]	
7β-Chloro-5α-androstane	9·17	9·27	6·05—6·60		749 (s)		
9α,11β-Dichloro-5α-androstane [7]	8·68	9·01	5·34—4 (5,2)	660 (s)			
11α-Chloro-5α-androstane [7]	9·07	9·31	5·50—6·15		760 (s)		
16α-Chloro-5α-androstane	9·23	9·31	5·38—5·84		766 (s)		
17-Chloro-5α-androst-16-ene [25,26]	9·19	9·14		807 (s)		1600 [b]	C=C
17α-Chloro-5α-androstane	9·22	9·22	5·96 d(6)	637 (w)			
				675 (w)			
17α-Chloro-5α-oestrane		9·22	5·95 d(6)	637 (w)			
				675 (w)			
17β-Chloro-5α-androstane	9·21	9·21	6·30 t(9)		800 (s)		

* L. M. Jackman and S. Sternhell, ' Applications of N.M.R. Spectroscopy in Organic Chemistry,' Pergamon, Oxford, 1969, p. 13.

[a] This strong band at 703 cm^{-1} is more consistent with an axial C–Cl stretch (*cf.* 3α- at 708 cm^{-1}) than is the previous assignment [21] of 588 cm^{-1}. [b] Band measured in CCl_4 solution.

TABLE 2

Bromo-steroids

	N.m.r. (τ values)				I.r. ($\nu_{max.}$/cm^{-1})			
	Methyl signals				C–Cl stretch		Other	
Compound	C-19	C-18	Methine		Axial	Equatorial	signals	Assignment
2α-Bromo-5α-androstan-3-one	8·91	9·29	5·21 4(13,6)			817 (m)	1735	C=O
3α-Bromo-5α-androstane	9·22	9·31	5·31 m(7)		696 (m)			
3β-Bromo-5α-androstane	9·15	9·31	5·64—6·38			706 (s)		
3β-Bromoandrost-5-ene	8·97	9·30	5·81—6·45			704 (s)	1670	C=C
3β,5α,6β-Tribromoandrostane	8·52	9·25	4·86—5·54	3α-H	578 (w)	709 (s)		
			5·20 4(4,2)	6α-H	625 (s)			
4α-Bromo-5α-androstane	9·18	9·31	5·55—6·22			700 (s)		
5α-Bromoandrostan-3β-yl acetate	8·90	9·31	4·17—4·94		675 (w)		1745	C=O
6α-Bromo-5α-androstane	9·19	9·31	5·67—6·32			704 (s)		
6β-Bromo-5α-androstan-3β-yl acetate	8·90	9·26	5·67 m(7)	6α-H	665 (w)		1740	C=O
			4·94—5·55	3α-H				
7α-Bromo-5α-androstane	9·19	9·29	5·45 m(7)		694 (m)			
7β-Bromo-5α-androstane	9·16	9·28	5·88—6·42			698 (s)		
16α-Bromo-5α-androstane	9·22	9·31	5·26—6·05			736 (s)		
17-Bromo-5α-androst-16-ene [27]	9·19	9·19			804 (s)		1595	C=C
17β-Bromo-5α-androstane	9·18	9·21	6·24 t(9)			776 (s)		

Apart from the C-11 isomer, the equatorial had longer retention times than the axial isomers, an observation consistent with an edge-on interaction between the substituent group and the stationary phase. With the C-11 isomer reversal of this position, *viz.* the longer reduction were acetylated and the proportions of isomers then determined by g.l.c. (Table 4). With one exception (see below), these are in general agreement

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with previous work in the cholestane series.[28,34-43] Preferential formation of the thermodynamically more stable equatorial isomers was observed in the reductions with sodium in alcohol; axial isomers were obtained by using lithium aluminium hydride or catalytic hydrogenation. As steric hindrance increases at C-6 and C-7, the proportion of axial isomers formed with sodium in alcohol also increases, and in the case of C-16 where both α- and β-substituents are subject to approximately the same degree of hindrance, the proportion of isomers was 1 : 1. Hydrogenation over platinum oxide in glacial acetic acid produced the 4β-, 6β-, 11β-, 16β-, and 17β-amino-isomers in high yield indicating an initial α

TABLE 3

Amino-steroids and their acetyl derivatives

Compound	N.m.r. (τ values) * 19-Me	18-Me	Methine	NHCOCH_3
3α-Amino-5α-androstane	9·21	9·29	6·6—6·9	
3α-Acetamido-5α-androstane	9·19	9·31		8·02
3β-Amino-5α-androstane	9·21	9·30	7·2—7·7	
3β-Acetamido-5α-androstane	9·21	9·32		8·07
4α-Amino-5α-androstane	9·19	9·30	7·3—7·8	
4α-Acetamido-5α-androstane	9·13	9·32		8·06
4β-Amino-5α-androstane	8·89	9·31	6·8—7·15	
4β-Acetamido-5α-androstane	9·07	9·32		8·04
4β-Amino-5α-androstane acetate	8·92	9·29		
6α-Amino-5α-androstane	9·20	9·29	7·3—7·8	
6α-Acetamido-5α-androstane	9·13	9·32		8·06
6β-Amino-5α-androstane	8·94	9·26	6·75—7·1	
6β-Acetamido-5α-androstane	9·03	9·26		8·04
6β-Amino-5α-androstane acetate	8·89	9·31		
7α-Amino-5α-androstane	9·20	9·30	6·9—7·1	
7α-Acetamido-5α-androstane	9·19	9·31		7·98
7β-Amino-5α-androstane	9·21	9·27	7·3—7·9	
7β-Acetamido-5α-androstane	9·22	9·32		8·09
11α-Amino-5α-androstane	9·08	9·30	6·8—7·2	
11α-Acetamido-5α-androstane	9·04	9·24		8·12
11β-Amino-5α-androstane	8·97	9·02	6·3—6·6	
11β-Acetamido-5α-androstane	9·10	9·22		8·06
16α/16β-Amino-5α-androstane (mixture)	9·19	9·07 (16β)		
	9·19	9·29 (16α)		
16β-Amino-5α-androstane	9·19	9·07		
16β-Acetamido-5α-androstane	9·18 and (unassignable)	9·22		8·07
17α-Amino-5α-androstane	9·19	9·34		
17α-Acetamido-5α-androstane	9·23	9·23		8·03
17β-Amino-5α-androstane	9·19	9·39		
17β-Acetamido-5α-androstane	9·22	9·33		8·03

* The spectra of the amino-5α-androstanes and their acetate salts were measured in deuteriocyclohexane, and those of the acetamido-5α-androstanes in deuteriochloroform.

TABLE 4

Percentage formation of amino-androstanes from reduction of oximes

Hydroxyimino-androstane	Method of reduction: Sodium metal in alcohol, Amine (%)		$LiAlH_4$ in dry ether, Amine (%)		H_2/PtO_2 in glacial acetic acid, Amine (%)		Relative retention times of acetamido-derivative (Androstane ≡ 1 min)	
	eq	*ax*	*eq*	*ax*	*eq*	*ax*	Axial isomer	Equatorial isomer
3-	89 [a]	11	65	35	40	60	6·19	6·74
4-	86 [b]	14	6	94	5	95	5·66	5·98
6-	77 [a]	23	7	93	3	97	4·63	5·54
7-	68 [a]	32	7	93	49	51	4·02	5·03
11-	81 [c]	19	8	92	0	100	4·64 (α)	4·12 (β)
16- [d]	*ca.* 50 (α) [a]	*ca.* 50 (β)	*ca.* 10 (α)	*ca.* 90 (β)	*ca.* 5 (α)	*ca.* 95 (β)	6·84 (α) [d]	6·82 (β) [d]
17-	95 (β) [b]	5 (α)	100 (β)	0 (α)	100 (β)	0 (α)	6·20 (α)	6·41 (β)

[a] Pentanol. [b] Butanol. [c] Propanol. [d] No separation of the 16α- and 16β-isomers could be achieved: proportions of isomers were obtained by peak height analysis of the 18-H_3 resonances.

[34] C. W. Shoppee and J. C. P. Sly, *J. Chem. Soc.*, 1959, 345.
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attack in all these cases, although with the 3- and 7-positions this reduction was less stereospecific. Lithium aluminium hydride in ether produced over 90% of the axial isomer for all oximes of rings A, B, and C, except that at C-3. Our own findings of 65% equatorial and 35% axial for this position are the reverse of a former claim:[29] we believe that the previous assignment of configuration was incorrect and the present reassessment, based on the considerations outlined above, brings the reduction of 3-hydroxyimino-5α-androstane into line with the reduction of 5α-cholestan-3-one with lithium aluminium hydride where the equatorial hydroxy-isomer predominates.[44]

EXPERIMENTAL

Specimens for analysis were dried at 30° and 0·2 mmHg for at least 6 h and analyses were carried out by Mr. G. Crouch of the School of Pharmacy, London.

I.r. absorption spectra were determined using a Unicam SP 100 or a Perkin-Elmer 547 spectrometer. N.m.r. spectra were measured in deuteriochloroform with internal Me_4Si as standard using a Perkin-Elmer R 12 (60 MHz) instrument. Mass spectra were obtained on an A.E.I. MS 902 instrument. Column chromatography was on aluminium oxide (Spence type H, activity II) or silica gel (Hopkins and Williams, M.F.C.). T.l.c. was on silica gel using light petroleum (b.p. 40—60°), unless otherwise indicated; plates were sprayed with 0·1N-ceric ammonium sulphate then developed (15 min) at 150°. All solvents were dried and distilled before use. Phosphorus pentachloride and pentabromide were freshly sublimed before use and thionyl chloride and bromide were freshly distilled. All hydrogenations were carried out at room temperature and atmospheric pressure.

The chloro-androstanes of general formula $C_{19}H_{31}Cl$ require C, 77·4; H, 10·5; Cl, 12·1% and the bromo-androstanes of formula $C_{19}H_{31}Br$ require C, 67·3; H, 9·14; Br, 23·6%.

7β-Methoxy-5α-androstane.—A solution of uncrystallised androsta-3,5-dien-7-one [6] (1·5 g) in methanol (25 ml) at room temperature was hydrogenated over 10% palladium–charcoal (700 mg). A benzene solution of the resulting oil was chromatographed on alumina (40 g; 3 × 30 cm) when elution (benzene) gave fine needles of *7β-methoxy-5α-androstane* (1 g), m.p. 54° (from methanol) (Found: C, 82·9; H, 11·8. $C_{20}H_{34}O$ requires C, 82·8; H, 11·7%). Further elution with benzene gave 5α-androstan-7-one (500 mg), m.p. 72—73° (from methanol) (lit.,[6] 74—75°).

7β-Ethoxy-5α-androstane.—Hydrogenation of uncrystallised androsta-3,5-dien-7-one [6] (1 g) in ethanol, as above, furnished needles of *7β-ethoxy-5α-androstane* (750 mg), m.p. 73° (from methanol) (Found: C, 82·5; H, 11·3. $C_{21}H_{36}O$ requires C, 82·9; H, 11·9%), τ ($CDCl_3$) 8·84 (3H, t, *J* 7 Hz, OCH_2CH_3) and 6·78 and 6·41 (total 2H, each 8 lines, *J* 8, 7, 7, 7, and 7 Hz, OCH_2CH_3: shown by calculation [45] to be the AB part of an ABX_3 system) (Found: M^+, 304·276304. $C_{21}H_{36}O$ requires *M*, 304·276602), and 5α-androstan-7-one (100 mg).

Further hydrogenation of 5α-androstan-7-one (500 mg) in ethanol containing traces of hydrochloric acid, as above, furnished 7β-ethoxy-5α-androstane (10 mg), m.p. 73°, 5α-androstan-7-one (200 mg), and 5α-androstan-7β-ol (150 mg), m.p. 127—128° (lit.,[11] 124—127°).

Tosylation of Steroid Alcohols.—The steroid alcohols (500 mg) were treated with tosyl chloride (500 mg) in dry pyridine (10 ml) in the usual way to give: 5α-androstan-3β-yl tosylate (500 mg), m.p. 125—126° (from acetone) (lit.,[2] 121—125°); *5α-androstan-7β-yl tosylate* (650 mg), m.p. 89° (from acetone) (Found: C, 72·3; H, 9·0. $C_{16}H_{38}O_3S$ requires C, 72·5; H, 8·9%); 5α-androstan-16β-yl tosylate (600 mg), m.p. 125—126° (from acetone) (lit.,[46] 126°).

Hydrolysis of Tosylates.—A solution of the steroidal tosylate (500 mg) in dimethyl sulphoxide or *N*-methylpyrrolidone (20 ml) was treated with tetra-n-butylammonium hydroxide (5 ml of a 40% w/w solution) on a steam-bath for 1 h after which time t.l.c. (35% ether in petroleum) showed complete absence of starting material. The product was isolated by addition of an excess of water and extraction with ether in the usual manner. In this way, 5α-androstan-3β-yl tosylate gave 5α-androstan-3α-ol (290 mg), m.p. 146—147° (from methanol) (lit.,[47] 144—145°), 5α-androstan-7β-yl tosylate gave 5α-androstan-7α-ol (285 mg), m.p. 110—111° (from methanol) (lit.,[11] 103—106°), and 5α-androstan-16β-yl tosylate gave 5α-androstan-16α-ol (275 mg), m.p. 158—159° (from methanol) (lit.,[46] 160°).

Nucleophilic Substitution in Rings A and B.—Reactions with phosphorus pentahalides. The steroidal alcohol (100 mg) in dry chloroform (10 ml) was added slowly to a suspension of phosphorus pentachloride or pentabromide [48] (200 mg) and dry calcium carbonate (200 mg) in dry chloroform (20 ml). The mixture was allowed to stand at room temperature until t.l.c. showed the absence of starting material, and the crude product was then isolated in the usual manner. Where t.l.c. revealed a large amount of unsaturated material, this was removed by treating a solution in ether with 3% monoperphthalic acid (2 h) and evaporating off the solvent under reduced pressure. A solution of the crude material was then passed through a small column of alumina (5 g; 1 × 15 cm) to give a white amorphous solid or colourless oil. The following halogenosteroids were thus prepared. With phosphorus pentachloride: 5α-androstan-3β-ol furnished *3α-chloro-5α-androstane* (60 mg), m.p. 104—106°, $[\alpha]_D^{20}$ +5·5° (*c* 3·1 in $CHCl_3$) (from methanol) (Found: C, 77·3; H, 10·5%); 5α-androstan-4α-ol furnished *4α-chloro-5α-androstane* (5 mg) as an oil (Found: C, 77·4; H, 10·4; Cl, 11·9%); 5α-androstan-6α-ol furnished *6α-chloro-5α-androstane* (20 mg) as an oil (Found: C, 77·8; H, 10·2; Cl, 12·0%); 5α-androstan-6β-ol furnished *6α-chloro-5α-androstane*, m.p. 105° [from methanol–benzene (5 : 1)] (Found: C, 77·3; H, 10·5%); 5α-androstan-7β-ol furnished *7α-chloro-5α-androstane* (60 mg), m.p. 105° (methanol), $[\alpha]_D^{20}$ −45·6° (*c* 1·9 in $CHCl_3$) (Found: C, 77·3; H, 10·5; Cl, 11·9%); 5α-androstan-2α-ol furnished an inseparable mixture of 2α- and 2β-chloro-5α-androstane (20 mg) as an oil (*cf.* ref. 17).

With phosphorus pentabromide: 5α-androstan-3β-ol furnished *3α-bromo-5α-androstane* (40 mg), m.p. 108—110°, $[\alpha]_D^{20}$ +7·5° (*c* 4·4 in $CHCl_3$) [from methanol–benzene (5 : 1)] (Found: C, 67·3; H, 8·9%); 5α-androstan-6α-ol furnished *6α-bromo-5α-androstane* (23 mg), m.p. 55—56°, $[\alpha]_D^{20}$

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[45] A. A. Bothner-By and J. Castellano, *J. Chem. Phys.*, 1964, **41**, 3863.

[46] J. Jacques, M. Minssen, and D. Varech, *Bull. Soc. chim. France*, 1965, 67.

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[48] C. E. Kaslow and M. M. Marsh, *J. Org. Chem.*, 1947, **12**, 456.

+27·6° (*c* 3·7 in $CHCl_3$) (from methanol) (Found: C, 67·3; H, 9·4; Br, 23·7%); 5α-androstan-7β-ol furnished *7α-bromo-5α-androstane* (12 mg), m.p. 105—106°, $[\alpha]_D^{20}$ −57·8° (*c* 1·3 in $CHCl_3$) (from methanol) (Found: C, 67·4; H, 9·2; Br, 23·6%).

Reactions with thionyl halides. The steroidal alcohol (100 mg) was added slowly to thionyl chloride or bromide [49] (2 ml) with cooling if necessary. When t.l.c. showed complete absence of starting material, water was added cautiously and the product worked up in the usual manner, to yield a crude oil or solid. This material was treated in a manner similar to that employed for the material isolated from reactions with phosphorus pentahalides. Disulphinyl esters were, however, crystallised directly from methanol–benzene (1 : 1). Thus with thionyl chloride: 5α-androstan-3β-ol furnished *3β-chloro-5α-androstane* (60 mg), m.p. 116—117° (from methanol), $[\alpha]_D^{20}$ +10·1° (*c* 2·0 in $CHCl_3$) (Found: C, 77·6; H, 10·6%); androst-5-en-3β-ol [3] furnished *3β-chloroandrost-5-ene* (90 mg), m.p. 118—120° [from methanol–benzene (1 : 1)], $[\alpha]_D^{20}$ −69° (*c* 1·8 in $CHCl_3$) (Found: C, 77·8; H, 9·9. $C_{19}H_{29}Cl$ requires C, 77·9; H, 10·0%); 5α-androstan-4β-ol furnished 4α-chloro-5α-androstane (3 mg) as an oil; 5α-androstan-7β-ol furnished *7β-chloro-5α-androstane* (48 mg), m.p. 80—81° (from methanol), $[\alpha]_D^{20}$ +37° (*c* 1·0 in $CHCl_3$) (Found: C, 77·1; H, 10·6%); 5α-androstan-4β-ol furnished 4α-chloro-5α-androstane (8 mg) as an oil and *bis-(5α-androstan-4α-yl) sulphite* (40 mg), m.p. 189—191° (Found: C, 75·7; H, 10·1; S, 5·10. $C_{38}H_{62}O_3S$ requires C, 76·3; H, 10·4; S, 5·35%).

With thionyl bromide: 5α-androstan-4α-ol furnished *4α-bromo-5α-androstane* (31 mg), m.p. 116—117° (from methanol), $[\alpha]_D^{20}$ −73·5° (*c* 2·9 in $CHCl_3$) (Found: C, 67·4; H, 9·3%); 5α-androstan-7β-ol furnished *7β-bromo-5α-androstane* (45 mg), m.p. 90—91° (from methanol), $[\alpha]_D^{20}$ +75° (*c* 1·3 in $CHCl_3$) (Found: C, 66·9; H, 9·1; Br, 23·4%).

With either thionyl chloride or bromide: 5α-androstan-3β-ol (in the presence of pyridine or ether) furnished *bis-(5α-androstan-3β-yl) sulphite*, m.p. 140° (Found: C, 77·0; H, 10·3; S, 5·30. $C_{38}H_{62}O_3S$ requires C, 76·3; H, 10·4; S, 5·35%).

3β,5α,6β-Tribromoandrostane. Freshly distilled thionyl bromide (2 ml) was added slowly to a solution of androst-5-en-3β-ol [3] (2 g) in dry ether (20 ml) and the mixture allowed to stand until t.l.c. showed the complete absence of starting material. The crude product in benzene–petroleum (1 : 1) was passed through a column of alumina (50 g; 2 × 20 cm) to yield a yellow gum which crystallised from the same solvent after 2 weeks. Further recrystallisation from the same solvent yielded long yellow prisms of pure *3β,5α,6β-tribromoandrostane* (900 mg), m.p. 119—120° (Found: C, 46·6; H, 6·1. $C_{19}H_{29}Br_3$ requires C, 45·9; H, 5·9%).

3β-Bromoandrost-5-ene. 3β,5α,6β-Tribromoandrostane (215 mg) in ether–ethanol (1 : 2) (30 ml) was shaken with hydrogen in the presence of 10% palladium on charcoal (100 mg). When t.l.c. showed conversion of starting material into material of slightly higher R_F, the product was isolated as a crude yellow solid which after two crystallisations from methanol gave colourless needles of *3β-bromoandrost-5-ene* (90 mg), m.p. 99°, $[\alpha]_D^{20}$ −47° (*c* 4 in $CHCl_3$) (Found: C, 67·7; H, 8·8; Br, 23·5. $C_{19}H_{29}Br$ requires C, 67·7; H, 8·7; Br, 23·6%).

3β-Bromo-5α-androstane. Hydrogenation of 3β-bromoandrost-5-ene (3 g) over fresh palladium–charcoal yielded 5α-androstane (500 mg) and *3β-bromo-5α-androstane* (2 g), m.p. 92°, $[\alpha]_D^{20}$ +11·4° (*c* 1·8 in $CHCl_3$) (Found: C, 67·9; H, 9·1; Br, 23·5%).

Reactions in Rings C *and* D.—*Reactions with phosphorus pentahalides.* The steroidal alcohol (100 mg) was treated with phosphorus pentachloride or pentabromide as above. The crude product in light petroleum was chromatographed on alumina (5 g; 1 × 15 cm) and eluates were monitored by t.l.c.; fractions showing single spots were combined and the products crystallised from a suitable solvent. In this way: 5α-androstan-11α-ol furnished 5α-androst-9(11)-ene (50 mg), m.p. 44—45° (from methanol) (lit.,[7] 38—40°) and 9α,11β-dichloro-5α-androstane (20 mg), m.p. 127—128° (from acetone) (lit.,[7] 127—128°) (Found: C, 69·4; H, 9·3; Cl, 21·5. Calc. for $C_{19}H_{30}Cl_2$: C, 69·3; H, 9·1; Cl, 21·6%); 5α-androstan-11β-ol furnished 9α,11β-dichloro-5α-androstane (90 mg) identical with the sample isolated previously; 5α-androst-9(11)-ene furnished 9α,11β-dichloro-5α-androstane (90 mg) identical with the previous samples; 5α-androstan-16β-ol furnished 5α-androst-16-ene (10 mg), m.p. 77—78° (from methanol) (lit.,[50] 78—79°) and *16α-chloro-5α-androstane* (30 mg), m.p. 89—91° (from methanol), $[\alpha]_D^{20}$ +11·5° (*c* 0·9 in $CHCl_3$) (Found: C, 77·8; H, 10·5; Cl, 11·9%); 5α-androstan-16β-ol furnished 5α-androst-16-ene (30 mg) and *16α-bromo-5α-androstane* (15 mg), m.p. 108—110° (from methanol), $[\alpha]_D^{20}$ +16·4° (*c* 0·4 in $CHCl_3$) (Found: C, 67·0; H, 9·0; Br, 23·7); 5α-androstan-16α-ol furnished 5α-androst-16-ene (60 mg) and 16α-chloro-5α-androstane (5 mg), m.p. 89—91°; 5α-androstan-17β-ol furnished 5α-androst-16-ene (5 mg) and *17α-chloro-5α-androstane* (30 mg), m.p. 114—116° (from methanol) (Found: C, 77·1; H, 10·6; Cl, 11·8%); 5α-oestran-17β-ol furnished *17α-chloro-5α-oestrane* (25 ml), as an oil (Found: C, 77·3; H, 10·5; Cl, 12·5. $C_{18}H_{29}Cl$ requires C, 77·0; H, 10·3; Cl, 12·7%); 5α-androstan-17β-ol (with phosphorus pentabromide furnished only 5α-androst-16-ene (80 mg).

Reactions with thionyl halides. The steroidal alcohol (100 mg) was treated with thionyl chloride or bromide as previously described. The crude product, in light petroleum, was chromatographed on alumina (5 g; 1 × 15 cm) and the products crystallised from a suitable solvent. In this way: 5α-androstan-11α-ol furnished 5α-androst-9(11)-ene (20 mg), identical with the sample described previously, and 11α-chloro-5α-androstane (40 mg) as an oil (lit.,[7] oil) (Found: C, 77·3; H, 10·5; Cl, 12·0%); 5α-androstan-11β-ol furnished 5α-androst-9(11)-ene (80 mg) identical with the previous samples; 5α-androstan-16β-ol furnished 5α-androst-16-ene (60 mg), m.p. 77—78° and 16α-chloro-5α-androstane (5 mg), m.p. 88—89°; 5α-androstan-17β-ol (with either thionyl chloride or bromide) furnished *bis-(5α-androstan-17β-yl) sulphite* (40 mg), 212° [from methanol–benzene (1 : 1)] (Found: C, 75·7; H, 10·0; S, 5·3. $C_{38}H_{62}O_3S$ requires C, 76·3; H, 10·4; S, 5·35%).

5α-Androst-16-ene. To a solution of 17-bromo-5α-androst-16-ene (1 g) in refluxing ethanol (150 ml), sodium (9 g) was added in portions and the solution refluxed (2 h). T.l.c. showed complete conversion into material of slightly higher R_F. The crude product in petroleum was then placed on a column of alumina (30 g; 2 × 15 cm) and eluted with the same solvent to give needles of 5α-androst-16-ene (500 mg), m.p. 78—79° (from methanol) (lit.,[50] 78—79°).

Hydrazone or Azine Formation.—A solution of the

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[50] G. M. L. Cragg, C. W. Davey, D. N. Hall, G. D. Meakins, E. E. Richards, and T. L. Whateley, *J. Chem. Soc.* (*C*), 1966, 1266.

steroidal ketone (1 g) in ethanol (50 ml), hydrazine (5 ml), and triethylamine (5 ml) was refluxed (1 h) under nitrogen: t.l.c. then showed the absence of starting material. The crude product was crystallised from methanol. Hydrazones of general formula $C_{19}H_{32}N_2$ require C, 79·2; H, 11·1; N, 9·7%. Azines of general formula $C_{38}H_{60}N_2$ require C, 83·8; H, 11·0; N, 5·2%. In this way were obtained: *5α-androstan-4-one hydrazone* (700 mg), m.p. 150° (decomp.) (Found: C, 79·2; H, 10·7; N, 9·9%); 5α-androstan-17-one hydrazone (820 mg), m.p. 149—150° (lit.,[27] 154—156°); *5α-androstan-2-one azine* (870 mg), m.p. 140—143° (decomp.) (Found: C, 83·6; H, 11·2; N, 5·0%); *5α-androstan-3-one* azine (600 mg), m.p. 210° (Found: C, 83·5; H, 11·2; N, 4·9%); *5α-androstan-6-one azine* (100 mg), m.p. 200° (Found: C, 83·2; H, 11·1; N, 5·2%); *5α-androstan-7-one azine* (400 mg), m.p. 266—268° (Found: C, 83·6; H, 11·1; N, 4·9%); *5α-androstan-16-one azine* (350 mg), m.p. 179—181° (Found: C, 84·1; H, 11·2; N, 5·1%).

5α-Androstan-11-one hydrazone. 5α-Androstan-11-one (1 g) was refluxed (2 days) in digol (50 ml) containing hydrazine hydrate (10 ml). The crude hydrazone was isolated as a solid (900 mg) showing both $\nu_{max.}$ C=O and $\nu_{max.}$ C=N (with associated N–H stretch) in the i.r. spectrum. Since hydrazones undergo rearrangement to azines during purification,[25] no attempt was made to crystallise this material.

Reactions of Hydrazones with N-Halogenosuccinimides.—A slight molar excess of *N*-chloro- or *N*-bromo-succinimide in dry pyridine (5 ml) was added dropwise to a cooled solution of the hydrazone (800 mg) in dry pyridine (5 ml). Nitrogen was evolved briskly. After 10 min, water was added and the product isolated by extraction with ether in the usual manner. A solution of the crude oil in light petroleum was chromatographed on a small column of alumina (1 × 10 cm) to yield a solid which was crystallised from methanol. In this way: 5α-androstan-4-one hydrazone furnished *4-chloroandrost-4-ene* (620 mg), m.p. 85° (Found: C, 77·9; H, 9·7. $C_{19}H_{29}Cl$ requires C, 77·9; H, 10·0%); crude 5α-androstan-11-one hydrazone furnished an inseparable mixture of 11-chloro-5α-androst-9(11)-ene and 11-chloro-5α-androst-11-ene (300 mg), as an oil, $\nu_{max.}$ 830 cm^{-1} (C–Cl), τ 8·90, 9·06, 9·18, and 9·27 (C-19 and C-18 methyls) and 3·80br (m, olefinic H), M^+ 292 (chlorine pattern) and 5α-androstan-11-one (300 mg); 5α-androstan-17-one hydrazone furnished 17-chloro-5α-androst-16-ene (750 mg), m.p. 108—110° (lit.,[51] 111—112°) and 17-bromo-5α-androst-16-ene (800 mg), m.p. 118° (lit.,[27] 122—124°).

Hydrogenation of the Halogenoandrostenes.—The halogenoandrostene (100 mg) was hydrogenated over 10% palladium on charcoal (30 mg), the reaction being followed by t.l.c. The crude product was chromatographed on alumina (5 g; 1 × 15 cm). In this way: 17-chloro-5α-androst-16-ene furnished *17β-chloro-5α-androstane* (30 mg), m.p. 126° (from methanol), $[\alpha]_D^{20}$ +25·4° (*c* 0·8 in $CHCl_3$) (Found: C, 76·8; H, 10·4; Cl, 12·0%) and 5α-androstane (20 mg); 17-bromo-5α-androst-16-ene furnished *17β-bromo-5α-androstane* (10 mg), m.p. 115—116° (from methanol) (Found: C, 66·9; H, 9·1; Br, 23·4%) and 5α-androstane (78 mg); 4-chloroandrost-4-ene furnished only 5α-androstane (80 mg). The inseparable mixture of 11-chloro-5α-androst-9(11)-ene and 11-chloro-5α-androst-11-ene furnished 5α-androstane (100 mg) (m.p. and mixed m.p. 42°) and 5α-androst-9(11)-ene (100 mg) identical with samples previously described.

3β-5α-Dichloroandrostane.—A stream of dry hydrogen chloride was passed through a solution of 3β-chloroandrost-5-ene (2 g) in ether (50 ml) and ethanol (50 ml) until t.l.c. showed total conversion into material of slightly lower R_F (24 h). The product thus obtained slowly crystallised from acetone to yield *3β,5α-dichloroandrostane* (1·9 g), m.p. 131°, $[\alpha]_D^{20}$ −8·4° (*c* 2·0 in $CHCl_3$) (Found: C, 69·6; H, 8·8; Cl, 21·4. $C_{19}H_{30}Cl_2$ requires C, 69·3; H, 9·2; Cl, 21·5%).

5α-Chloroandrostan-3β-ol.—A stream of dry hydrogen chloride gas was passed (24 h) through a solution of androst-5-en-3β-yl acetate [52] (700 mg) in chloroform (20 ml) at room temperature. After this time t.l.c. (30% ether in petroleum) showed partial conversion into material of lower R_F: A crude yellow solid resulted after isolation in the usual manner. Attempts to separate this mixture into its components by chromatography on alumina or silica gel, in benzene, resulted in decomposition to androst-5-en-3β-ol,[3] m.p. 125—126°. Recrystallisation of the crude material from acetone–benzene (1 : 1) gave needles of *5α-chloroandrostan-3β-ol* (150 mg), m.p. 157—158°, $[\alpha]_D^{20}$ −18·4° (*c* 2 in $CHCl_3$) (Found: C, 73·2; H, 10·0; Cl, 11·2. $C_{19}H_{31}ClO$ requires C, 73·4; H, 10·1; Cl, 11·4%). From the mother liquors only androst-5-en-3β-ol (crude yield 300 mg), m.p. 125—126° (lit.,[3] 131°) could be isolated.

5α-Bromoandrostan-3β-yl Acetate.—Androst-5-en-3β-yl acetate [52] (1 g) in dry chloroform (25 ml) was treated, under nitrogen, with a stream of dry hydrogen bromide gas at room temperature for 30 min (*cf.* ref. 53). The usual isolation technique gave a yellow solid which crystallised from acetone–benzene (10 : 1) in colourless plates, *5α-bromoandrostan-3β-yl acetate* (610 mg), which slowly turned pink on standing, m.p. 143—145°, $[\alpha]_D^{20}$ −17·6° (*c* 5 in $CHCl_3$) (Found: C, 64·1; H, 8·5; Br, 20·3. $C_{21}H_{33}BrO_2$ requires C, 63·8; H, 8·3; Br, 20·1%).

6β-Bromo-5α-androstan-3β-yl Acetate.—Androst-5-en-3β-yl acetate [52] (2 g), dried by azeotropic distillation from benzene, was dissolved in dry carbon tetrachloride (40 ml) and streams of dry oxygen and hydrogen bromide were passed through the solution for 1 h (*cf.* ref. 53). T.l.c. showed total conversion into material of slightly lower R_F than either starting material or 5α-bromoandrostan-3β-yl acetate. The resulting dark brown oil in petroleum was chromatographed on silica gel * (30 g; 2 × 20 cm). Elution with 5% ether in petroleum gave a pale yellow solid, *6β-bromo-5α-androstan-3β-yl acetate* (700 mg), m.p. 135—136° (decomp.) (Found: C, 64·1; H, 8·3; Br, 20·3. $C_{21}H_{33}BrO_2$ requires C, 63·8; H, 8·3; Br, 20·1%).

Hydroxyimino-5α-androstenes.—The oxime of 5α-androstan-11-one was prepared by the method of Marples,[54] all other oximes as outlined below.

The 5α-androstanone (1·0 g), hydroxylamine hydrochloride (2·6 g), and sodium acetate trihydrate (4·0 g) in ethanol (50 ml) were refluxed (5 h). Isolation in the usual manner yielded the oxime (1·05 g) which crystallised from acetone–methanol (1 : 1). The following hydroxyimino-5α-androstanes were thus obtained: 3-hydroxyimino-, m.p.

* 6β-Bromo-5α-androstan-3β-yl acetate decomposes rapidly on basic alumina to give a quantitative yield of androst-5-en-3β-ol [3] identical with an authentic sample. This material also decomposes rapidly, in most common solvents, and has a shelf life of *ca.* 1 week.

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[53] C. W. Shoppee and R. Lack, *J. Chem. Soc.*, 1960, 4864.
[54] B. A. Marples, *J. Chem. Soc.* (*C*), 1968, 3015.

185—187° (lit.,[43] 189—189·5°), $\nu_{max.}$ (CCl_4) 3295 (OH) and 1668 cm^{-1} (C=N), τ ($CDCl_3$) 9·08 (19-Me) and 9·29 (18-Me); 4-*hydroxyimino-*, m.p. 157·5—158·5°, $\nu_{max.}$ (CCl_4) 3295 (OH) and 1677 cm^{-1} (C=N) (Found: C, 78·8; H, 10·5; N, 4·55%), τ ($CDCl_3$) 9·20 (19-Me) and 9·29 (18-Me); 6-*hydroxyimino-*, m.p. 219·5—221·5°, $\nu_{max.}$ (CCl_4) 3295 (OH) and 1676 cm^{-1} (C=N) (Found: C, 78·9; H, 10·5; N, 4·9%), τ ($CDCl_3$) 9·24 (19-Me) and 9·30 (18-Me); 7-*hydroxyimino-*, m.p. 129·5—130·5°, $\nu_{max.}$ (CCl_4) 3295 (OH) and 1669 cm^{-1} (C=N) (Found: C, 78·9; H, 10·6; N, 4·6%), τ ($CDCl_3$) 9·04 (19-Me) and 9·28 (18-Me); 11-hydroxyimino-, m.p. 56—58° (lit.,[42] 55—57°; lit.,[54] 88—90°), $\nu_{max.}$ (CCl_4) 3350 (OH) and 1646 cm^{-1} (C=N) (Found: C, 78·5; H, 10·5; N, 4·8%), τ ($CDCl_3$) 8·93 (19-Me) and 9·32 (18-Me); 16-hydroxyimino-, m.p. 196—197° (lit.,[36] 198·5°), $\nu_{max.}$ (CCl_4) 3300 (OH) and 1690 cm^{-1} (C=N), τ ($CDCl_3$) 9·19 (19-Me and 18-Me); 17-hydroxyimino-5α-androstane, m.p. 169—172° (lit.,[34] 173—176°), $\nu_{max.}$ (CCl_4) 3305 (OH) and 1685 cm^{-1} (C=N), τ ($CDCl_3$) 9·19 (19-Me) and 9·10 (18-Me).

All oximes gave a molecular ion of *m/e* 289 ($C_{19}H_{31}NO$ requires C, 78·8; H, 10·8; N, 4·85%).

Methods of Reduction.—All amines were synthesised by reduction of oximes except 17α-amino-5α-androstane which was obtained by the method of Pancrazi.[55]

(a) *Sodium–alcohol reduction.* Small pieces of sodium were added to the hydroxyimino-5α-androstane (300 mg) in a suitable refluxing alcohol (75 ml) (Table 4) until solid alkoxide formed or t.l.c. indicated no starting material was present. Addition of water followed by extraction with ether yielded a yellow oil (310 mg). An aliquot portion was acetylated and submitted to g.l.c.: The bulk of the amino-compounds were isolated as hydrochlorides or acetates from whence the free bases were obtained. Equatorial amines crystallised from methanol in microcrystalline or amorphous form but were homogeneous by g.l.c. analysis.

Variations in the isolation methods applied (i) to the 4α-amino-5α-androstane, where crystallisation of the free base was used, and (ii) to separation of the crude mixture of 7-amino-isomers. This was affected by forming the hydrochlorides in a large volume of dry ether: g.l.c. showed that the 7α-amino-hydrochloride remained in solution whilst the β-isomer was insoluble.

$C_{19}H_{33}N$ (amino-5α-androstanes) requires C, 82·8; H, 12·1; N, 5·1%. $C_{21}H_{35}NO$ (acetamido-5α-androstanes) requires C, 79·4; H, 11·1; N, 4·4%. $C_{19}H_{34}ClN$ (amino-5α-androstane hydrochlorides) requires C, 73·2; H, 11·0; N, 4·5%. $C_{21}H_{37}NO_2$ (amino-5α-androstane acetates) requires C, 75·2; H, 11·1; N, 4·15%.

The following amino-5α-androstanes were thus obtained: 3β-*amino-*,* m.p.† 96—99 and 117—120°, M^+ 275, $[\alpha]_D^{20}$ +1·80° (*c* 0·3 in Pr^nOH), *hydrochloride*, m.p. 270° (decomp.), $\nu_{max.}$ (KBr) 1616 and 1520 cm^{-1} (δNH), acetyl derivative m.p. 235—237° (lit.,[43] 248—248·5°), $\nu_{max.}$ (KBr) 3290 (NH), 1642 (amide I), and 1577 cm^{-1} (amide II), M^+ 317; 4α-*amino-*,* m.p. 123—126°, $[\alpha]_D^{20}$ −21·5° (*c* 0·3 in Pr^nOH), M^+ 275, *acetyl derivative*, m.p. 233—235°, $\nu_{max.}$ (KBr) 3320 (NH), 1650 (amide I), and 1553 cm^{-1} (amide II), M^+ 317 (Found: C, 79·1; H, 10·7; N, 4·35%); 6α-*amino-*,* m.p. 129—132°, $[\alpha]_D^{20}$ +23·2° (*c* 0·14 in Pr^nOH), M^+ 275, *hydrochloride*, sublimes from 260°, $\nu_{max.}$ (KBr) 1610 and 1514 cm^{-1} (δNH) (Found: C, 73·3; H, 10·7; N, 4·75%), *acetyl derivative*, m.p. 195—196°, $\nu_{max.}$ (KBr) 3275 (NH), 1645 (amide I), and 1560 cm^{-1} (amide II), M^+ 317 (Found: C, 79·0; H, 10·9; N, 4·55%); 7β-*amino-*,* m.p. 64—66°, $[\alpha]_D^{20}$ +35·9° (*c* 0·34 in Pr^nOH), M^+ 275, *hydrochloride*, sublimes from 275°, $\nu_{max.}$ (KBr) 1612 and 1580 cm^{-1} (δNH) (Found: C, 72·8; H, 10·8; N, 4·9%), *acetyl derivative*, m.p. 112—114°, $\nu_{max.}$ (KBr) 3288 (NH), 1646 (amide I), and 1570 cm^{-1} (amide II), M^+ 317 (Found: C, 78·9; H, 11·0; N, 4·15%); 11α-amino-, oil (lit.,[54] oil), M^+ 275, *hydrochloride*, sublimes from 205°, $\nu_{max.}$ (KBr) 1615 and 1520 cm^{-1} (δNH) (Found: C, 73·7; H, 10·6; N, 4·6%), *acetyl derivative*, m.p. 203—204°, $\nu_{max.}$ (KBr) 3395 (NH), 1642 (amide I), and 1556 cm^{-1} (amide II), M^+ 317 (Found: C, 79·0; H, 11·2; N, 4·75%); 16α- and 16β-amino-,‡ m.p. 129—138°, M^+ 275, *hydrochloride*, sublimes from 265° (Found: C, 72·9; H, 10·6; N, 4·7%); 17β-amino-, m.p. 106—110° (lit.,[34] 138—141°, lit.,[55] 91°), $[\alpha]_D^{20}$ +7·15° (*c* 0·5 in Pr^nOH), M^+ 275, *acetate*, m.p. 186—188·5°, $\nu_{max.}$ (KBr) 1517 and 1395 cm^{-1} (CO_2^-) (Found: C, 75·0; H, 11·2; N, 4·1%), *hydrochloride*, m.p. 280—285°, $\nu_{max.}$ (KBr) 1612 and 1520 cm^{-1} (NH) (Found: C, 72·8; H, 10·6; N, 4·15%), acetyl derivative, m.p. 202—203° (lit.,[28] 208—209°, lit.,[55] 205°), $\nu_{max.}$ (KBr) 3380 (NH), 1650 (amide I), and 1556 cm^{-1} (amide II), M^+ 317.

All the acetamido-5α-androstanes gave a single peak on g.l.c. analysis (Table 3) which was carried out on a Pye 104 chromatograph fitted with a Kent Chromalog integrator. A 5 ft glass column (diameter ¼ in) packed with 2·5% SE 30 on 100—120 mesh Chromosorb G (acid washed: DMCS treated) was used with nitrogen as the carrier gas (20 ml min^{-1}) at an oven temperature of 225°.

(b) *Catalytic hydrogenation.* The hydroxyimino-5α-androstane (150 mg) in freshly distilled glacial acetic acid (12 ml) was hydrogenated over Adams platinum oxide (50 mg) at normal temperature and pressure. Removal of solvent gave an oil (120 mg) to which dry ether (50 ml) was added. After 24 h the precipitate of amine acetate was collected and converted into the free base as described in (a) above. Column chromatography on alumina (elution with ether–methanol, 4 : 1) yielded the pure axial isomer, which was crystallised from methanol.

Variations from the general procedure were: (i) the acetates of 4β- and 6β-amino-5α-androstanes were soluble in ether and were purified as the acetate salts by column chromatography and recrystallisation from light petroleum (b.p. 40—60°); (ii) with 11-hydroxyimino-5α-androstane the reduction was carried out at 60° and the predominant isomer isolated as its hydrochloride,[54] which was recrystallised from light petroleum (b.p. 40—60°).

(c) *Lithium aluminium hydride reduction.* To the hydroxyimino-5α-androstane (200 mg) in dry refluxing ether (100 ml), lithium aluminium hydride (1 g) was added in portions over 2 days. The crude amino-androstane was isolated in the usual way and purified through its hydrochloride: the free base (axial) was then liberated and crystallised from methanol.

The following substituted 5α-androstanes have thus been isolated from reduction procedure (b); for 7α-amino-,

* Elemental analyses of the free bases thus marked were unsatisfactory (*cf.* ref. 25). All gave a single peak on g.l.c. analysis.

† Double m.p.s for samples of 3β-amino-5α-cholestane have previously been reported.[56]

‡ The mixture of these isomers was inseparable. A pure sample of the 16β-amino-isomer resulted from method (b).

[55] A. Pancrazi, Q. Khuong-Hau, and R. Goutarel, *Bull. Soc. chim. France*, 1970, 4446.

[56] J. L. Pinkus, G. Pinkus, and T. Cohen, *J. Org. Chem.*, 1962, 4356.

procedure (c) was used: 3α-*amino*-,* m.p. 99—104°, $[\alpha]_D^{20}$ −116° (*c* 0·2 in Pr^{n}OH), M^+ 275, acetyl derivative, m.p. 236—238° (lit.,[43] 241—242·5°), $\nu_{max.}$ (KBr) 3275 (NH), 1642 (amide I), and 1560 cm^{-1} (amide II), M^+ 317; 4β-*amino*-, m.p. 71—74°, M^+ 275 (Found: C, 82·3; H, 11·7; N, 4·9%), *acetate*, m.p. 80—83° (Found: C, 74·9; H, 11·0; N, 4·1%), *acetyl derivative*, m.p. 154—156°, $\nu_{max.}$ (KBr) 3335 (NH), 1650 (amide I), and 1552 cm^{-1} (amide II), M^+ 317 (Found: C, 79·2; H, 10·8; N, 4·15%); 6β-*amino*-, m.p. 65—70°, M^+ 275 (Found: C, 82·1; H, 11·8; N, 5·0%), *acetate*, m.p. 75—77 and 95—97° (Found: C, 74·8; H, 10·0; N, 4·0%), *acetyl derivative*, m.p. 145—147°, $\nu_{max.}$ (KBr) 3315 (NH), 1646 (amide I), and 1552 cm^{-1} (amide II), M^+ 317 (Found: C, 79·2; H, 11·0; N, 4·65%); 7α-*amino*-, m.p. 73—75°, $[\alpha]_D^{20}$ −28·7° (*c* 0·5 in Pr^{n}OH), M^+ 275 (Found: C, 82·5; H, 11·6; N, 5·2%), *hydrochloride*, m.p. 254—258° (changes crystalline form at 210—215°), $\nu_{max.}$ (KBr) 1617 and 1520 cm^{-1} (δNH) (Found: C, 72·8; H, 11·0; N, 4·6%), *acetyl derivative*, m.p. 220·5—221·5°, $\nu_{max.}$ (KBr) 3350 (NH), 1625 (amide I), and 1554 cm^{-1} (amide II), M^+ 317 (Found: C, 79·0; H, 10·9; N, 4·2%); 11β-amino-, m.p. 66—67° (lit.,[54] oily solid), M^+ 275 (Found: C, 82·8; H, 12·1; N, 4·95%), hydrochloride, m.p. 242—246° (changes crystalline form at 190—205°) (lit.,[54] 245—248°), *acetyl derivative*, m.p. 211—212°, $\nu_{max.}$ (KBr) 3342 (NH), 1635 (amide I), and 1547 cm^{-1} (amide II), M^+ 317 (Found: C, 79·7; H, 10·7; N, 4·35%); 16β-*amino*-,* m.p. 94—97° (amorphous), $[\alpha]_D^{20}$ −13·5° (*c* 0·5 in Pr^{n}OH), M^+ 275, *acetate*, m.p. 164—167°, $\nu_{max.}$ (KBr) 1550 and 1410 cm^{-1} (CO_2^-) (Found: C, 75·0; H, 10·7; N, 4·45%), *acetyl derivative*, m.p. 143—145°, $\nu_{max.}$ (KBr) 3304 (NH), 1644 (amide I), and 1555 cm^{-1} (amide II), M^+ 317 (Found: C, 79·0; H, 10·8; N, 4·75%); 17α-amino-, m.p. 64—65° (lit.,[55] 66—67°), $[\alpha]_D^{20}$ −16·5 (*c* 0·6 in Pr^{n}OH), M^+ 275, acetyl derivative, m.p. 91—93° (one sample showed a double m.p. 91—93 and 144—146°) (lit.,[55] 148°), $\nu_{max.}$ (KBr) 3300 (NH), 1635 (amide I), and 1564 cm^{-1} (amide II), M^+ 317.

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* Same footnote as on page 1512.