Hydroxy-steroids. Part XVIII.¹ Reactions of 17β-Chloro-16α,17α-epoxy- 5α -androstane and the Preparation of 17β -lodo- 16α , 17α -epoxy- 5α androstane

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 17β -Chloro- and 17β -iodo- 16α , 17α -epoxy- 5α -androstane are reactive compounds which undergo ready rearrangement into 16-halogeno-17-ketones. On treatment with aluminium chloride the chloro-epoxide undergoes methyl group migration, to give 17-methyl-18-nor-5α-androst-13(17)-en-16-one in 82% yield. The iodo-epoxide, which is unstable, is best obtained (22% yield) by oxidising 17-iodo- 5α -androst-16-ene with peroxylauric acid in benzene.

Although epoxides of type (A), having an electronattracting substituent at the α -position, have not been studied extensively, interesting reactions have been reported for those in which X = OAc,² OMe,³ NO₂⁴,Cl,⁵⁻⁸ or Br.⁹ For example, the ready rearrangement of α -chloro-epoxides (A; X = Cl) to α -chloro-ketones (B) has been shown to involve migration of chlorine, and the intermediate is considered to be an a-keto-carbonium ion chloride in the form of an ion-pair. Most of the work on steroidal a-halogeno-epoxides is concerned with 17β -chloro- 16α , 17α -epoxy- 5α -androstane ⁸ and 17ßbromo-16 α ,17 α -epoxy-5 α -androstan-3 β -yl acetate.⁹ The former has been reduced with lithium aluminium hydride to 5α -androstan-17 β -ol, and pyrolysed to two products which are discussed later; the latter has been shown to give 16\beta-amino-17-ketones on treatment with a variety of amines.9 These studies, although confined to only a few types of reaction, confirm the expected high reactivity of α -halogeno-epoxides. The present work comprises (i) a more thorough examination of the 17-chloro-epoxide, with particular attention to stereochemical features, and (ii) an investigation of the



epoxidation of 17-iodo-5a-androst-16-ene, a reaction which might lead to an (unstable) α -iodo-epoxide.

Schemes 1 and 2 show the results obtained on topics (i) and (ii), respectively. References are given to known compounds: the rest are new. In view of the detailed nature of the Schemes, which include yields, comment is restricted to a justification of the structural

⁵ M. Mousseron and R. Jacquier, Bull. Soc. chim. France, 1950, 698.

assignments and to points of special interest. As noted previously,1 the flexibility of ring D 10,11 makes it difficult to interpret precisely the spectra of some 16,17-disubstituted steroids; the present uses of spectrometric results (see Table) in structural arguments are simple and free from ambiguity.

The chemical relationships with known compounds establish the positions and configurations of the substituents in new monosubstituted 5a-androstanes, viz. the ethyl ethers (XII), (XIV), and (XVII). With many of the disubstituted compounds the first problem is to differentiate between possible C(17)O-C(16)H(X)-C(15)- H_2 and $C(17)H(X)-C(16)O-C(15)H_2$ isomers. The required distinction follows clearly from the n.m.r. signals due to CH(X), which should be coupled in the former type but not in the latter. The configurations of the substituents X pose more subtle questions. The chloroketone (III), one of a pair of 16-chloro-17-ketones, is reduced under carefully controlled conditions to a chlorohydrin (X) in which the occurrence of strong intramolecular hydrogen bonding is established by i.r. examination. Removal of the chlorine substituent gives the 17β -alcohol (VII). This sequence establishes the 16_β-configuration of the chloro-ketone (III) and, incidentally, confirms the positioning of the chlorine atom at C(16) as indicated by the n.m.r. data. Huang-Minlon reduction of the 16-ethoxy-17-ketone (IX) leads to 16a-ethoxy-5a-androstane (XVII). Although the yield of the reaction is low, the chemical indication of a 16α-configuration for the ethoxy-ketone is supported by comparison of its 16-H signal with those of the epimeric 16-halogeno-17-ketones. [The position is more complicated than the simple representation in Scheme 1 suggests. Treatment of the chloro-epoxide (II) with

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 ⁴ H. Newman and R. B. Angier, Chem. Comm., 1969, 369.

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 ⁸ L. Mamlock and J. Jacques, Bull. Soc. chim. France, 1960,

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¹⁰ F. V. Brutcher and W. Bauer, J. Amer. Chem. Soc., 1962, 84, 2236; F. V. Brutcher and E. J. Leopold, *ibid.*, 1966, 88, 3156.

¹¹ C. Altona, H. J. Geise, and C. Romers, Tetrahedron, 1968, 24, 13.

ethoxide gives a mixture from which only the ethoxyketone (IX) was isolated. The n.m.r. spectrum of the mixture revealed the presence of an isomeric ether, which is presumed to be the 16β -ethoxy-17-ketone. The chemical evidence alone does not exclude the possibility of the isolated product being a 16β -ethoxy-ketone; this could have equilibrated with the 16α -isomer during Treating the chloro-epoxide with aluminium chloride affords the conjugated ketone in high yield, possibly by the illustrated route; structure (VI)⁸ for this compound is supported by the n.m.r. data reported here, and by the product's stability to alkali. (A 14 β -structure would require a boat form for ring c.)

Surprising results were obtained in the catalytic



Hydrogenations (H₂,Pd-C; 20 °C) in the media specified (s.m. indicates recovered starting material).

 $\begin{array}{c} (II) & \frac{(16)}{(17)} & \text{s.m.} (16^{\circ}/_{\circ}) + (III) (40^{\circ}/_{\circ}) + (VIII) (32^{\circ}/_{\circ}) \\ (II) & \frac{(17)}{(17)} & \text{s.m.} (36^{\circ}/_{\circ}) + (III) (40^{\circ}/_{\circ}) + (VIII) (21^{\circ}/_{\circ}) + (XI) (30^{\circ}/_{\circ}) \\ (II) & \frac{(18)}{(19)} & (VIII) & (9^{\circ}/_{\circ}) + (XI) (64^{\circ}/_{\circ}) \\ (II) & \frac{(18)}{(18)} & (VIII) (42^{\circ}/_{\circ}) + (VIII) (29^{\circ}/_{\circ}) + (XII) (64^{\circ}/_{\circ}) \\ (III) & \frac{(18)}{(18)} & \text{s.m.} (9^{\circ}/_{\circ}) + (III) (42^{\circ}/_{\circ}) + (VIII) (29^{\circ}/_{\circ}) + (XII) (13^{\circ}/_{\circ}) \\ (III) & \frac{(18)}{(18)} & (VIII) & (42^{\circ}/_{\circ}) + (VIII) (29^{\circ}/_{\circ}) + (XII) (13^{\circ}/_{\circ}) \\ (III) & \frac{(18)}{(18)} & (VIII) & (20^{\circ}/_{\circ}) + (XII) (13^{\circ}/_{\circ}) \\ (III) & (IIII) & (IIII) & (III) & (IIII) & (IIIII) & (IIIIII) & (IIIIII) & (IIIIII) & (IIIII) & (IIIIII) & (IIIIII) & (IIIIII) & (IIIIII) & (IIIIII) & (IIIIIIII) & (IIIIIII) & (IIIIII) & (IIIIII) & (IIII$

Reagents: $(1), p-O_2N \cdot C_6H_4 \cdot CO_3H - CHCl_3$; $(2), Al_2O_3$; (3), HCl-dioxan, 5 min; (4), MeOH-PhOH; $(5), AlCl_3$; $(6), LiAlH_4 - AlCl_3$; $(7), NaBH_4$; (8), Zn-EtOH; (9), NaOEt-EtOH; $(10), KBH_4$ at pH 7; (11), KOH-MeOH; $(12), LiAlH_4$; $(13), CH_2N_2-HBF_4$; $(14) MeCHN_2-HBF_4$; (15), Huang-Minlon reduction; $(16)--(21), H_2, Pd-C at 20 \,^{\circ}C in (16), EtOAc;$ (17), MeOH, 9h; (18), MeOH, 36h; (19), EtOH; (20), MeOH containing HCl (1 mol. equiv.); (21), EtOH-HCl.

^a Ref. 8. ^b Ref. 20. ^c Elsevier's 'Encyclopaedia of Organic Chemistry,' vol. 14 and supplements. ^d Ref. 23. ^e Ref. 25. ^f Ref. 21.

the reduction, and the product (XVII) and the starting material (IX) might have differed in their 16-configurations.]

Pyrolysis of the chloro-epoxide (II) gave, in low yields a chloro-ketone and a conjugated ketone.⁸ The former, tentatively formulated as 17β -chloro- 5α -androstan-16one, has properties similar to those of the 16α -chloro-17-ketone (IV) (see Experimental section), and the 16-chloro-structure is mechanistically more likely. reduction of the chloro-epoxide (II). Thus, as shown in the lower part of Scheme 1, prolonged hydrogenation with methanol as solvent gave 17β -methoxy- 5α -androstane (XI) in 64% yield. The other reductions were carried out in order to elucidate the course of this transformation. A key observation was that the hydrogenation of 5α -androstan-17-one (VIII) is influenced by the acidity of the medium: in neutral solution the 17β -alcohol (VII) is formed slowly, but in the presence of a little hydrogen chloride the reduction is faster and leads to the 17β -methyl ether (XI). (The literature

azine (XVIII)



(8

Reagents as in Scheme 1, and: (22), N₂H₄-NEt₃; (23), EtOH, heat; (24), I_2 -NEt₃; (25), reagent from NaBH₄-EtOH-Me₂CO; (26), I_2 -AcOH; (27), PhCO₈H-CHCl₃,48h; (28), Peroxylauric acid-C₆H₆,21h; (29), as (28) for 90h; (30), p-ON₂·C₆H₄-CO3H-ČHCl3.

^{c, f} As in Scheme 1. ^g Ref. 9. ^h Ref. 18. ⁱ Ref. 14. ^j Ref. 1

procedures for hydrogenating ketones to methyl ethers employ a platinum catalyst and much larger amounts

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13 J. C. Babcock and L. F. Fieser, J. Amer. Chem. Soc., 1952,

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of hydrogen chloride 12 or hydrogen bromide.13) Consideration of the various results shows that the reduction of the chloro-epoxide (II) proceeds as follows:

(II)
$$\xrightarrow{\text{MeOH}}$$
 (III) $\xrightarrow{\text{H}_{a}-\text{Pd}}$ (VIII) + HCl $\xrightarrow{\text{MeOH}}$ hemi-
acetal

 $-H_{2O}$ 17-methoxy-16,17-olefin $H_{2}-Pd$ (XI)

One of the three iodo-ketones shown in Scheme 2 is the known 16a-iodo-17-ketone (XXIV),9,14 and the new 16-iodo-compound is then the 16^β-isomer (XXV). The structures of the 16-halogeno-17-ketones reported here are supported by their $\Delta M_{\rm D}$ (16 β – 16 α) values: $+70^{\circ}$ for chloro-, $+240^{\circ}$ for bromo-,¹⁵ and $+460^{\circ}$ for iodo-compounds. Formulation of the third iodoketone as a 17-iodo-16-oxoandrostane (XXIII) is confirmed by chemical evidence, but the 17-configuration (shown as β) is not rigidly established. The clearest evidence is provided by comparison of i.r. C=O frequencies. In ring D bromo-ketones the Δv values (increase caused by the bromine substituent) are: 10,16 17α -Br-16-CO, +7 cm⁻¹; 17β -Br-16-CO, +17; 16α -Br-17-CO, +12; 16 β -Br-17-CO, +12. These differences arise from changes in the preferred conformation of ring D as the positions and configurations of the substituents are varied.^{10,11,17} The 16-chloro-17-ketones (III) and (IV), $\Delta v ca$. 17 cm⁻¹, and the 16-iodo-17-ketones (XXIV) and (XXV), Δv ca. 4 cm⁻¹, show the trend expected with variation of the halogen, *i.e.* neither a 16α - nor a 16β -iodine substituent has much effect on the C=O stretching frequency. In contrast, the relatively large Δv value (13 cm⁻¹) for the third iodo-ketone (XXIII) denotes a 17β -iodine substituent; the 17α isomer would be expected to have a shift of less than 4 cm⁻¹.

Preparation of the vinyl iodide (XX)¹⁸ by Barton's method ¹⁹ involves a hydrazone (XIX) (Scheme 2) for which widely different properties have been recorded.9,18 This probably stems from the ease with which an azine is formed during attempted crystallisation of the hydrazone. To obtain even a modest yield of the α -iodo-epoxide (XXI) from the vinyl iodide required the use of a peroxy-acid which gives a weak carboxylic acid. The best procedure was to treat the vinyl iodide

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J. Fishman and W. R. Biggerstaff, J. Org. Chem., 1958, 23, 1190. ¹⁸ J. W. ApSimon, P. V. Demarco, D. W. Mathieson, W. G.

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¹⁹ D. H. R. Barton, R. E. O'Brien, and S. Sternhell, J. Chem. Soc., 1962, 470.



(XX) with peroxylauric acid, and to stop the reaction at the quarter-way stage: beyond this the rate of the product's further reactions exceeded the rate of its formation. With p-nitroperoxybenzoic acid the oxidation gave mainly the 17-oxo-16 β -ester (XXII), despite the low solubility of p-nitrobenzoic acid in chloroform. The iodo-epoxide, which is much less stable than the chloro-epoxide, decomposes in 3 days at 20 °C.

Detailed interpretation of the reactions of the α -halogeno-epoxides is impeded by the lack of quantitative information about the relative stabilities and ease of interconversion of 16α - and 16β -substituted 17-ketones. With halogeno-ketones the 16β-epimers are thought to be the more stable. Although the direct conversion has not been carried out, there is good circumstantial evidence for the base-induced isomerisation of 16ato 16_β-bromo-17-ketones,¹² and under suitably mild conditions (Scheme 2) the 16a-iodo-compound (XXIV) behaves similarly. However, the 16_β-chloro-17-ketone (III) can be partially epimerised to the 16α -isomer (Scheme 1). It seems that while the members of a pair of 16-halogeno-17-ketones are readily interconverted under appropriate conditions, the β -compounds may not be much more stable than the α -epimers. Rearrangement of the chloro-epoxide (II) by brief treatment with acid gives the 16^β-chloro-17-ketone (III), unaccompanied by an appreciable amount of the 16α -epimer (IV). Thus the 16^β-compound is the initial product of the rearrangement; provided that free chloride ion is not involved in the reaction, the chlorine substituent in the starting material must also have a β -configuration. (This supports the 17 β -halogeno-structures proposed for the chloro-,⁸ bromo-,⁹ and iodo-epoxides on the general expectation of α -attack by peroxy-acids in the epoxidation of ring D vinyl halides.)

With different 16-groups the relative stabilities of 16-substituted 17-ketones may be reversed. For example, the 16α -ethoxy-compound (IX) appears to be the predominant epimer under alkaline conditions: the formation of this product by treating the chloro-epoxide (II) with sodium ethoxide illustrates a general mechanistic difficulty. The two most likely paths, involving substitution or rearrangement as the first stage, are as illustrated.



Formation of the 17-oxo-16 β -ester (XXII), probably by nucleophilic attack of the p-nitrobenzoate anion on the

Spectrometric results

N.m.r. signals refer to CDCl_3 solutions examined at 100 MHz. Some signals are described as s (singlet), d (doublet), t (triplet), q (quartet), or m (unresolved multiplet: the letters, d, t, and q are followed, in parentheses, by the coupling constant (J/Hz); m is followed by the half-height width $(W_{\frac{1}{2}}/\text{Hz})$. Where these terms are inappropriate ^a the number of lines is indicated by an italicised number: this is followed, in parentheses, by a set of apparent J values. The C=O vibrations (cm⁻¹) of halogeno-ketones (CCl₄ solutions; 1 cm cells; spectral slit-width 2 cm⁻¹) are given in the 'Other signals ' column

			17-H or 16-H			Other signals		
No.	19-H	18-H	τ	Form	Assignment	τ	Form	Assignment
(I)	9.19	9.14	4.39	4(3, 1.8)	16-H			-
άń	9.21	9.09	6.39	sb	16-H			
(ÌII)	9.19	8.98	6.04	t(8·5)	16-H		$(\nu_{\rm max}, 1759)$	
ÌIVÌ	9.19	9.07	5.56	t(4)	16-H		$(\nu_{\rm max}, 1758)$	
(V)	9.18	9.28	6.23	s	17-H		(
(ÙI)	9.27					7.48	4(17.5, 6)	one 15-H
. ,						8.33	t(1.5)	17-Me
(IX)	9.19	9.06	6.14	4(6.5, 2)	16-H	6.35	m(17)	$O \cdot CH_2 \cdot CH_3$
. ,						8.79	t(7)	$O \cdot CH_2 \cdot CH_3$
(\mathbf{X})	9.21	9.16	5.50	8(16, 8, 2)	16-H			
. ,			6·46 °	t(8)	17-H			
(XI)	9·2 0	9.26	6.77	t(8)	17-H	6.64	s	OMe
(XII)	9.21	9.25	6.68	t(8)	17-H	6.47	q(7)	
						6.50	q(7)	f 0.0112.0113
						8.84	t(7)	$O \cdot CH_2 \cdot CH_3$
(XIV)	9.22	9.10	6.04	m(15)	16-H	6.67	$q(7 \cdot 5)$	$O \cdot CH_2 \cdot CH_3$
						8.82	t(7·5)	$O \cdot CH_2 \cdot CH_3$
(XVII)	9.22	9.31	5.95	8(14, 8, 3)	16-H	6.58	$\mathbf{q}(7)$	$O \cdot CH_2 \cdot CH_3$
						8.82	t(7)	$O \cdot CH_2 \cdot CH_3$
(XX)	9.19	9.28	3.89	4(3, 1.8)	16-H			
(XXI)	9.22	9.25	6.39	S P	16-H			
(XXII)	9.18	8.96	4.76	t(9)	16-H	1.74	m	arom. H
XXIII)	9.18	9.12	5.47	S d	17-H		$(\nu_{\rm max.} \ 1758)$	
$\mathbf{X}\mathbf{X}\mathbf{I}\mathbf{V}$	9.19	9.12	5.11	m(9)	16-H		$(\nu_{\rm max}, 1745)$	
(XXV)	9.19	8.87	5.61	t(9)	16-H		$(\nu_{\rm max.} 1747)$	

^e L. M. Jackman and S. Sternhell, 'Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry,' Pergamon, Oxford, 1969, p. 132. ^b With a shoulder, $W_{\frac{1}{2}}$ of signal ca. 2 Hz. ^c d(8) After exchange with D₂O. ^d $W_{\frac{1}{2}}$ 2.5 Hz.

iodo-epoxide (XXI), appears to provide a precedent for the substitution mechanism. Apart from this and the conversion (II) \longrightarrow (VI) mentioned earlier, all the reactions of the halogeno-epoxides could proceed through halogeno-ketone intermediates; further work on this problem is in progress.

EXPERIMENTAL

For general directions and details of p.l.c. see J. Chem. Soc. (C), 1968, 2674 and 1971, 1136, respectively. The v_{max} values of routine i.r. spectra (CS₂ or CCl₄ solutions, Perkin-Elmer model 257) are accurate to ± 5 cm⁻¹. Petrol refers to light petroleum, b.p. 40—60°, and Al₂O₃ to Camag neutral aluminium oxide, activity 1.

Work in Scheme 1.—17 β -Chloro-16 α ,17 α -epoxy-5 α -androstane (II). A solution of p-nitroperoxybenzoic acid (2·4 g) in CHCl₃ (60 ml) was added to a stirred solution of 16-chloro-5 α -androst-16-ene⁸ (I) in CHCl₃ (24 ml) at 20 °C, and the solution was left in the dark for 20 h. Work-up gave the chloro-epoxide (II), m.p. 200—202° (2 g; from Me₂CO), $[\alpha]_{\rm p}$ +49° (c 1·0) (lit.,⁸ m.p. 201°, $[\alpha]_{\rm p}$ +45°). Reactions of the chloro-epoxide (II). (a) Petrol (80 ml)

Reactions of the chloro-epoxide (II). (a) Petrol (80 ml) was added to a warm solution of the chloro-epoxide (400 mg) in C₆H₆ (20 ml). The cold solution was poured on to Al₂O₃ (40 g) and after 2 h the column was developed in the usual way. Petrol-C₆H₆ (1:1; 500 ml) eluted a mixture of chloro-ketones (340 mg). Et₂O eluted 17β-hydroxy-5α-androstan-16-one (V) (75 mg), m.p. 141—143° (57 mg; from Me₂CO-C₆H₁₄), $[\alpha]_{\rm p}$ -150° (c 0·4; CHCl₃) {lit.,²⁰ m.p. 142°, $[\alpha]_{\rm p}$ -148° (dioxan)}, $v_{\rm max}$ 3532 and 1748 cm⁻¹. The chloro-ketones were separated by p.l.c. [1 large plate, 3 × petrol-ether (49:1)] to give 16β-chloro-5α-androstan-17-one (III) (163 mg; higher $R_{\rm F}$), m.p. 123—125° (112 mg; from Et₂O-C₆H₁₄), $[\alpha]_{\rm p}$ +113° (c 0·5) (Found: C, 74·0; H, 9·7. C₁₉H₂₉CIO requires C, 73·8; H, 9·5%), and 16α-chloro-5α-androstan-17-one (IV) (142 mg; lower $R_{\rm F}$), m.p. 184—186° (97 mg; from Et₂O), $[\alpha]_{\rm p}$ +87° (c 0·4) (Found: C, 74·3; H, 9·8%).

(b) Solutions of the chloro-epoxide (200 mg) in Et₂O (8 ml) and AlCl₃ (100 mg) in Et₂O (8 ml) were mixed, and the resulting solution was refluxed for 2 h. Standard manipulation gave 17-methyl-18-nor-5α-androst-13(17)-en-16-one (VI) (144 mg), m.p. 131-133° (114 mg; from MeOH), $[\alpha]_{\rm D}$ +33° (c 0.5) (lit.,⁸ m.p. 127.5-131°, $[\alpha]_{\rm D}$ +33°) (Found: C, 83.7; H, 10.3. Calc. for C₁₉H₂₈O: C, 83.8; H, 10.4%), $\nu_{\rm max}$ 1703 and 1660 cm⁻¹, $\lambda_{\rm max}$ 241 nm (ε 13,750), m/e 272 (M⁺, 100%), 257 (11), and 244 (25).

(c) LiAlH₄ (14 mg) was added to a stirred solution of AlCl₃ (48 mg) in Et₂O (6 ml). The chloro-epoxide (200 mg) in Et₂O (8 ml) was added, and the solution was refluxed for 2 h. Work-up followed by p.l.c. [2 small plates, $3 \times \text{petrol-Et}_2O$ (9:1)] gave the ketone (VI) (28 mg; higher $R_{\rm F}$), m.p. 131—133°, and 5α -androstan-17 β -ol (VII) (138 mg; lower $R_{\rm F}$), m.p. and mixed m.p. with authentic material 168.5—170°.

(d) A solution of the chloro-epoxide (510 mg) in EtOH (150 ml) was refluxed with Zn powder (AnalaR; 9 g) for 2 days. Filtration, work-up of the filtrate, and p.l.c. [2 large plates, $6 \times \text{petrol-Et}_2O(49:1)$] gave 5α -androstan-17-one (VIII) (168 mg; higher $R_{\rm F}$), m.p. and mixed m.p. with authentic material $117\cdot5-119\cdot5^{\circ}$, and 16α -ethoxy- 5α -androstan-17-one (IX) (191 mg; lower $R_{\rm F}$), m.p. 87–89° (from MeOH-H₂O), $[\alpha]_{\rm D} + 37^{\circ}$ (c 0.4) (Found: C, 83.3;

H, 11.0. $C_{21}H_{34}O_2$ requires C, 83.4; H, 11.3%), ν_{max} 1749, 1122, and 1057 cm⁻¹.

The ethoxy-ketone (80 mg) was reduced by the Huang-Minlon method and the product purified by p.l.c. [1 small plate, $2 \times \text{petrol-Et}_2O$ (49:1)] to give 5 α -androstan-16 α -yl ethyl ether (XVII) (21 mg), m.p. 74—77° (from MeOH), $[\alpha]_D$ —14° (c 0·3) (Found: C, 82·6; H, 11·7. C₂₁H₃₆O requires C, 82·8; H, 11·9%), $\nu_{\text{max.}}$ 1095 and 1060 cm⁻¹.

(e) A solution prepared from Na (400 mg) and EtOH (17.5 ml) and a solution of the chloro-epoxide (175 mg) in EtOH (40 ml) were mixed, and the resulting solution was refluxed for 3 h. Work-up followed by p.l.c. [2 small plates, $5 \times \text{petrol-Et}_2O$ (49:1)] afforded a solid (142 mg) which was shown by n.m.r. to contain *ca*. 75% of the 16 α -ethoxy-17-ketone (IX). [The minor component, probably 16 β -ethoxy-5 α -androstan-17-one, had signals at τ 5.95 (m, 16-H), 9.11 (18-H), and 9.21 (19-H).] Crystallisation from MeOH-H₂O gave impure 16 α -ethoxy-17-ketone (30 mg), m.p. 82-87°.

(f) A solution of the chloro-epoxide (200 mg) in dioxan (10 ml)-N-HCl (2 ml) was kept at 50 °C for 5 min. Work-up followed by p.l.c. [2 small plates, $3 \times \text{petrol-Et}_2O(49:1)$] gave the 16β-chloro-17-ketone (III) (134 mg), m.p. and mixed m.p. 121-124°.

(g) A solution of the chloro-epoxide (50 mg) in Et₂O (10 ml) was stirred with NaBH₄ (25 mg) for 12 h at 20 °C. Work-up gave 5α -androstan-17 β -ol (VII) (39 mg), m.p. and mixed m.p. 167—169°.

Reactions of 16β-chloro-5α-androstan-17-one (III). (a) A solution of the chloro-ketone (100 mg) in MeOH (2 ml) was stirred at 15 °C in a flask fitted with an automatic pHcontrolled titration apparatus, adjusted so that a mixture of AcOH-MeOH (1:10) was added dropwise to the solution whenever the pH fell below a value of 7. KBH₄ (130 mg) was added to the solution. (This resulted in the intermittent discharge of the AcOH-MeOH into the solution as its pH started to fall.) After 20 min more KBH₄ (20 mg) was added, and the stirring was continued for a further 40 min. Work-up gave 16β-chloro-5α-androstan-17β-ol (X) (92 mg), m.p. 120-122.5° (72 mg; from MeOH), [α]_D +1° (c 0.6) (Found: C, 72.9; H, 10.2; Cl, 11.4. C₁₉H₃₁ClO requires C, 73.4; H, 10.1; Cl, 11.4%), ν_{max}. (CCl₄; 1 cm cells) 3640w and 3564s cm⁻¹.

A solution of the chloro-alcohol (16 mg) in Et₂O (5 ml) was stirred with LiAlH₄ (20 mg) at 21 °C for 12 h. P.l.c. [1 small plate, $3 \times \text{petrol-Et}_2O$ (9:1)] afforded starting material (4 mg; higher $R_{\rm F}$) and 5α -androstan-17 β -ol (VII) (8 mg; lower $R_{\rm F}$), m.p. 168—170.5°, identical (mixed m.p., i.r.) with authentic material.

A solution of the chloro-alcohol (20 mg) in MeOH (5 ml)-KOH (300 mg) was refluxed for 4 h. Work-up gave 5α -androstan-17-one (VIII) (11 mg), m.p. 117-119.5°, identical (mixed m.p., i.r.) with authentic material.

(b) A solution of the chloro-ketone (50 mg) and PhOH (60 mg) in MeOH (15 ml) was kept at 20 °C for 36 h. P.l.c. [1 small plate, $2 \times \text{petrol-Et}_2O$ (9:1)] gave the 16β-chloro-17-ketone (III) (24 mg; higher $R_{\rm F}$) and the 16α-chloro-17-ketone (IV) (20 mg; lower $R_{\rm F}$), identified by comparison (i.r., mixed m.p.) with authentic specimens.

Preparation of ethers. The alcohols (VII), (XV),²¹ and (XVI)²¹ (100 mg in each experiment) in CH_2Cl_2

²⁰ D. Varech and J. Jacques, Bull. Soc. chim. France, 1965, 67.
 ²¹ J. Jacques, M. Minssen, and D. Varech, Bull. Soc. chim. France, 1965, 77.

containing 18N-HBF₄ were treated with CH₂N₂ (or MeCHN₂) in Et₂O as described previously ²² to give 5αandrostan-17β-yl methyl ether (XI) (77%), m.p. 85— 86.5° (from Me₂CO), $[\alpha]_{\rm p}$ +4° (c 0.5) (lit.,²³ m.p. 83·5— 85°, $[\alpha]_{\rm p}$ +20°) (Found: C, 82·9; H, 11·9. Calc. for C₂₀H₃₄O: C, 82·7; H, 11·8%), $\nu_{\rm max}$ 1110 and 985 cm⁻¹; 5α-androstan-17β-yl ethyl ether (XII) (44%), m.p. 66—68° (from MeOH-H₂O), $[\alpha]_{\rm p}$ -3° (c 0·4) (Found: C, 82·7; H, 11·6. C₂₁H₃₆O requires C, 82·8; H, 11·9%), $\nu_{\rm max}$ 1125 and 1108 cm⁻¹; 5α-androstan-16β-yl ethyl ether (XIV) (57%), m.p. 83—85° (from MeOH-H₂O), $[\alpha]_{\rm p}$ +34° (c 0·3) (Found: C, 82·5; H, 11·8%), $\nu_{\rm max}$ 1090 cm⁻¹; 5αandrostan-16α-yl ethyl ether (XVII) (53%), m.p. 75—77°, identical (mixed m.p., i.r.) with the material already described.

Hydrogenations. In a typical experiment a solution of the chloro-epoxide (II) (100 mg) in MeOH (30 ml) was hydrogenated at 20 °C over 5% Pd–C for 36 h. Work-up followed by p.l.c. [2 small plates, $2 \times \text{petrol-Et}_2O(19:1)$] afforded 5α -androstan-17 β -yl methyl ether (XI) (higher $R_{\rm F}$), m.p. 85—86.5° (60 mg; from Me₂CO) and 5α -androstan-17-one (VIII) (lower $R_{\rm F}$), m.p. 118—119.5° (8 mg; from MeOH): both products were identical (i.r. comparison) with authentic specimens. The other hydrogenations in Scheme 1 were carried out similarly.²⁴

Work in Scheme 2.—17-Iodo-5 α -androst-16-ene (XX). A solution of 5 α -androstan-17-one (VIII) (3 g), Et₃N (4·5 ml), and aqueous 65% N₂H₄ (14 ml) in EtOH (20 ml) was refluxed for 2 h, cooled, and poured into H₂O (600 ml). The insoluble material was collected and dried to give the crude hydrazone (XIX) (3 g), m.p. 147—156° (lit.,⁹ 154—156°; lit.,¹⁴ 108—109°), whose i.r. spectrum did not show C=O absorption. Attempted crystallisation from EtOH-H₂O gave 5 α -androstan-17-one azine (XVIII), m.p. 217—219·5°, [α]_D +20° (c 0·4) (Found: C, 83·2; H, 11·2; N, 5·2%; M, 544. C₃₈H₆₀N₂ requires C, 83·7; H, 11·1; N, 5·1%; M, 544).

A solution (ca. 12.5 ml) made by dissolving I₂ (4 g) in tetrahydrofuran (16 ml) was added dropwise at 20 °C to a stirred solution of the crude hydrazone (XIX) (2.2 g) and Et₃N (12 ml) in tetrahydrofuran (40 ml) until the I₂ colour persisted. Work-up, which included treatment with aq. Na₂S₂O₃ and crystallisation from Me₂CO, gave the iodo-compound (XX) (1.9 g), m.p. 124—126°, $[\alpha]_{\rm D}$ +18° (c 1.1) (lit.,¹³ m.p. 111—113°, $[\alpha]_{\rm D}$ +22°), m/e 384 (M⁺, 100%), 369 (96), 257 (68), and 242 (49).

Reactions with peroxy-acids. (a) Solutions of peroxylauric acid (98% by titration; 400 mg) in C_6H_6 (5 ml) and the iodo-compound (XX) (400 mg) in C_6H_6 (21 ml) were mixed at 20 °C and the resulting solution was kept in the dark for 21 h. C_6H_6 (40 ml) was added, and the solution was washed (aq. FeSO₄, H₂O, aq. NaHCO₃, H₂O, aq. Na₂S₂O₃, and H₂O), dried, and evaporated. Separation of the product (375 mg) by p.l.c. [1 large plate, $3 \times$ petrol] gave starting material (268 mg; lower R_F) and 17β -iodo-16 α , 17α -epoxy-5 α -androstane (XXI) (92 mg; higher R_F). After crystallisation from Et₂O the iodo-epoxide had m.p. $107-110^{\circ}$ (decomp.), $[\alpha]_D$ +65° (c 1·0) (Found: C, 57·4; H, 7·3. $C_{19}H_{29}$ IO requires C, 57·0; H, 7·3%), m/e 400 (M^+ , 3%), 274 (100), 259 (12), and 254 (92).

The foregoing experiment was repeated with a reaction time of 90 h. P.l.c. [1 large plate, $3 \times \text{petrol-Et}_2O$

(19:1)] of the product (210 mg) gave the iodo-epoxide (37 mg) (lowest $R_{\rm F}$) and more polar material, which was not investigated.

(b) Solutions of peroxybenzoic acid (81%) by titration; 330 mg) in CHCl₃ (20 ml) and the iodo-compound (XX) (400 mg) in CHCl₃ (6 ml) were mixed at 20 °C and the resulting solution was kept in the dark for 48 h. Work-up and p.l.c. as before gave starting material (182 mg) (lowest $R_{\rm F}$) and a complex mixture of more polar products.

(c) A solution of p-nitroperoxybenzoic acid (98% by titration; 0.8 g) in CHCl₃ (21 ml) was added at 22 °C to a stirred solution of the iodo-compound (XX) (1 g) in CHCl₃ (6 ml), and the mixture was stirred in the dark for 21 h. Work-up and p.l.c. [2 large plates, $2 \times \text{petrol}$ followed by $2 \times \text{petrol-Et}_{2}O$ (19:1)] gave the following four compounds (in order of decreasing $R_{\rm F}$): starting material, m.p. 119-123° (205 mg; from Me₂CO); the iodo-epoxide (XXI), m.p. 107-110° (68 mg; from Et₂O); 17β-iodo-5a-androstan-16-one (XXIII), m.p. 165-167° (decomp.) (180 mg, from $\text{Et}_2\text{O}-\text{C}_6\text{H}_{14}$), $[\alpha] - 142^\circ$ (c 1.0) (Found: C, 56.9; H, 7.3; I, 31.0. C₁₉H₂₉IO requires C, 57.0; H 7.3; I, 31.7%), m/e 400 (M^+ , 43%), 263 (100), 248 (12), 244 (25), and 220 (59); 17-oxo-5α-androstan-16β-yl p-nitrobenzoate (XXII) (551 mg), m.p. 199-200° (321 mg; from 3.2%), v_{max} 1759 and 1735 cm⁻¹, λ_{max} 259 nm (ε 14,500), m/e 439 (M^+ , 17%).

Reactions of compounds (XXI), (XXII), (XXIII), and (XXIV). (a) A solution of the keto-ester (XXII) (50 mg) in Et₂O (20 ml) was stirred with LiAlH₄ (50 mg) at 20 °C for 14 h. Work-up gave 5α -androstane-16 β ,17 β -diol (XXVI) (34 mg), m.p. 179—181° (26 mg; from Me₂CO), $[\alpha]_{\rm p}$ +7° (c 0.6), identical (mixed m.p., i.r.) with an authentic specimen.¹

(b) A solution of the iodo-ketone (XXIII) (135 mg) in EtOH (20 ml) was refluxed with Zn powder (AnalaR; 1.3 g) for 3 h. After work-up the product was chromatographed on SiO₂ (5 g). Petrol-Et₂O (9:1) eluted 5α-androstan-16-one (88 mg), m.p. 105.5—108° (from C₆H₁₄), $[\alpha]_{\rm D}$ -178° (c 0.6), identical (mixed m.p., i.r.) with an authentic specimen.²⁵

(c) A solution of the iodo-epoxide (XXI) (40 mg) in MeOH (2 ml) was stirred with NaBH₄ (200 mg) at 22 °C for 16 h. Work-up and p.l.c. [1 small plate, $4 \times \text{petrol-Et}_2O$ (19:1)] gave 5α -androstan-17 β -ol, m.p. 168—170° (16 mg; from MeOH), identical (i.r.) with authentic material.

(d) A solution of the iodo-epoxide (XXI) (100 mg) in C_6H_6 (10 ml) was passed through Al_2O_3 (20 g). Elution with C_6H_6 gave an oil (92 mg) which was separated by p.l.c. [2 small plates, $3 \times \text{petrol}-\text{Et}_2O$ (19:1)] into 16β -iodo- 5α -androstan-17-one (XXV) (44 mg; higher R_F), m.p. 129—131.5° (from C_6H_{14}), $[\alpha]_D + 134°$ (c 0.3) [Found: C, 57.2; H, 7.3%; M, 400.1258 (M^+ ion, base-peak of mass spectrum). $C_{19}H_{29}IO$ requires C, 57.0; H, 7.3%; M, 400.1262], and 16α -iodo- 5α -androstan-17-one (XXIV) (48 mg; lower R_F), m.p. 158—162° (lit., ¹⁴ 163—165°) (Found: C, 57.6; H, 7.4%), identical with an authentic specimen prepared as follows.

²³ U. E. Diner, F. Sweet, and R. K. Brown, *Canad. J. Chem.*, 1966, **44**, 1591.

²⁴ V. Kumar, D.Phil. Thesis, Oxford University, 1970.

²⁵ J. E. Bridgeman, C. E. Butchers, E. R. H. Jones, A. Kasal, G. D. Meakins, and P. D. Woodgate, J. Chem. Soc. (C), 1970, 244

²² I. M. Clark, A. S. Clegg, W. A. Denny, Sir Ewart R. H. Jones, G. D. Meakins, and A. Pendlebury, *J.C.S. Perkins I*, 1972, 499.

A solution of I_2 (145 mg) in AcOH (4.5 ml) was added during 1 h at 22 °C to a stirred solution of 5α -androst-16-en-17-yl acetate (XXVII) (105 mg) in AcOH (4.5 ml), and the stirring was continued for a further 2 h. Dilution with H₂O and extraction with CHCl₃ afforded the 16 α -iodoketone (XXIV) (83 mg), m.p. 161-164°.

(e) A solution of NaBH₄ (10 mg) in EtOH (2 ml) was stirred with Me₂CO (0·1 ml) at 22 °C for h. A solution of the 16 α -iodo-ketone (XXIV) (25 mg) in EtOH (1 ml) was added and the stirring continued for 15 min. Work-up and p.l.c. [1 small plate, 3 × petrol-Et₂O (19:1)] gave the 16 β -iodo-ketone (XXV) (14 mg; higher $R_{\rm F}$), m.p. and mixed m.p. 131—134°, and the 16 α -iodo-ketone (XXIV) (8 mg; lower $R_{\rm F}$), m.p. 159—163°, further identified by its i.r. spectrum.

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