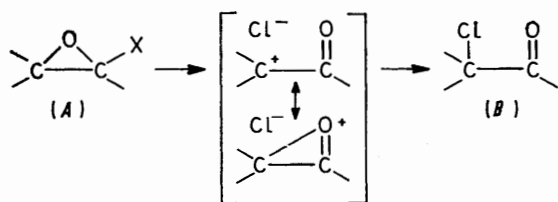


Hydroxy-steroids. Part XVIII.¹ Reactions of 17 β -Chloro-16 α ,17 α -epoxy-5 α -androstane and the Preparation of 17 β -Iodo-16 α ,17 α -epoxy-5 α -androstane

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17 β -Chloro- and 17 β -iodo-16 α ,17 α -epoxy-5 α -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-5 α -androst-13(17)-en-16-one in 82% yield. The iodo-epoxide, which is unstable, is best obtained (22% yield) by oxidising 17-iodo-5 α -androst-16-ene with peroxylic acid in benzene.

ALTHOUGH epoxides of type (A), having an electron-attracting substituent at the α -position, have not been studied extensively, interesting reactions have been reported for those in which X = OAc,² OMe,³ NO₂,⁴ 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 α -keto-carbonium ion chloride in the form of an ion-pair. Most of the work on steroidal α -halogeno-epoxides is concerned with 17 β -chloro-16 α ,17 α -epoxy-5 α -androstane⁸ and 17 β -bromo-16 α ,17 α -epoxy-5 α -androstane-3 β -yl acetate.⁹ The former has been reduced with lithium aluminium hydride to 5 α -androstane-17 β -ol, and pyrolysed to two products which are discussed later; the latter has been shown to give 16 β -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-5 α -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

¹ Part XVII, M. G. Combe, W. A. Denny, G. D. Meakins, Y. Morisawa, and E. E. Richards, *J. Chem. Soc. (C)*, 1971, 2300.

² N. S. Leeds, D. K. Fukushima, and T. F. Gallagher, *J. Amer. Chem. Soc.*, 1954, **76**, 2943; K. L. Williamson, J. I. Coburn, and M. F. Herr, *J. Org. Chem.*, 1967, **32**, 3934.

³ C. L. Stevens, J. J. Beereboom, and K. G. Rutherford, *J. Amer. Chem. Soc.*, 1955, **77**, 4590; C. L. Stevens and C. H. Chang, *J. Org. Chem.*, 1962, **27**, 4392.

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

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 spectroscopic 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 5 α -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)-H₂ and C(17)H(X)-C(16)O-C(15)H₂ 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 chloro-ketone (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 17 β -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 16 α -ethoxy-5 α -androstane (XVII). Although the yield of the reaction is low, the chemical indication of a 16 α -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

⁶ A. Kirmann, P. Duhamel, and M. R. N. Bimorghy, *Bull. Soc. chim. France*, 1964, 3264; *Annalen*, 1966, **691**, 33; G. A. Razuvaev, V. S. Etlis, and N. N. Trofimov, *Zhur. org. Khim.*, 1964, **1**, 2128.

⁷ R. N. McDonald and P. S. Schwab, *J. Amer. Chem. Soc.*, 1963, **85**, 4004; R. N. McDonald and T. E. Tabor, *ibid.*, 1967, **89**, 6573; *J. Org. Chem.*, 1968, 2934; R. N. McDonald and R. N. Steppel, *J. Amer. Chem. Soc.*, 1969, **91**, 782.

⁸ L. Mamlock and J. Jacques, *Bull. Soc. chim. France*, 1960, 484.

⁹ A. Hassner and P. Catsoulacos, *J. Org. Chem.*, 1967, **32**, 549; P. Catsoulacos, *Chimika Chronika*, 1966, **31**, 153.

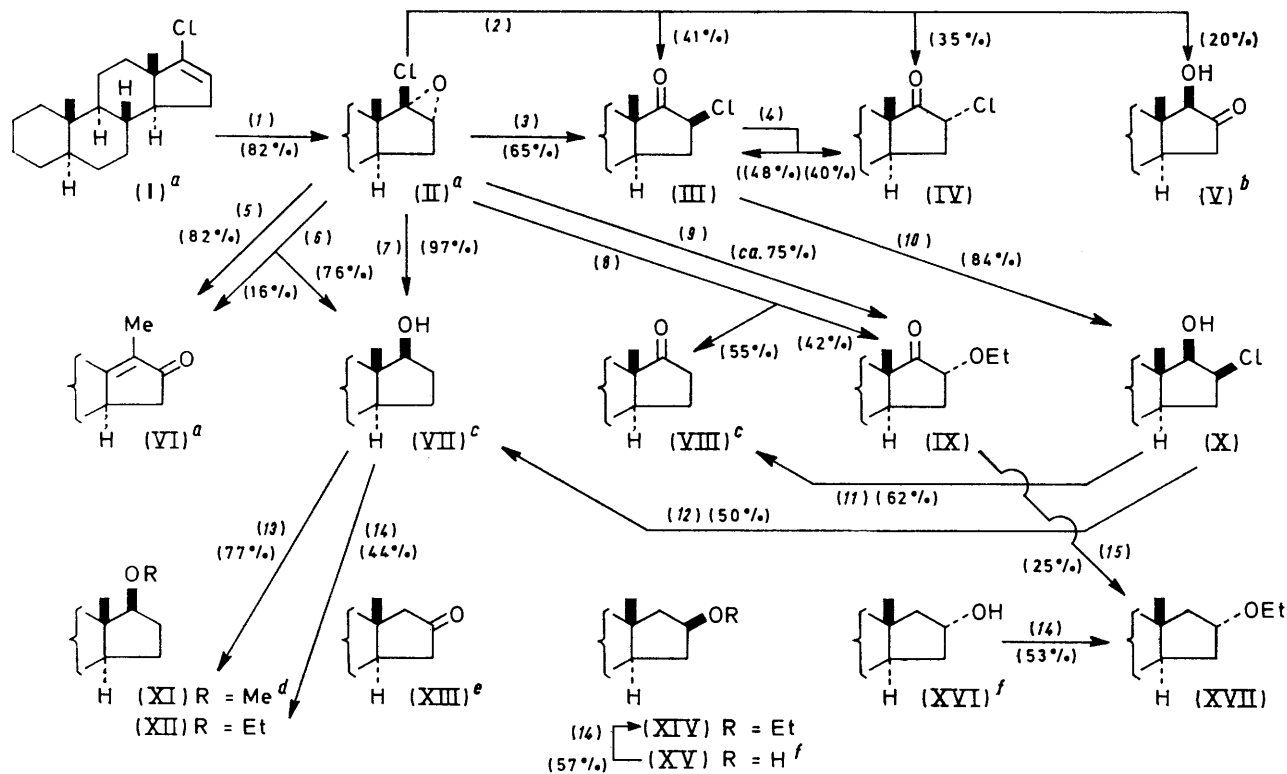
¹⁰ F. V. Brutcher and W. Bauer, *J. Amer. Chem. Soc.*, 1962, **84**, 2236; F. V. Brutcher and E. J. Leopold, *ibid.*, 1966, **88**, 3156.

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 16 β -ethoxy-17-ketone. The chemical evidence alone does not exclude the possibility of the isolated product being a 16 β -ethoxy-ketone; this could have equilibrated with the 16 α -isomer during

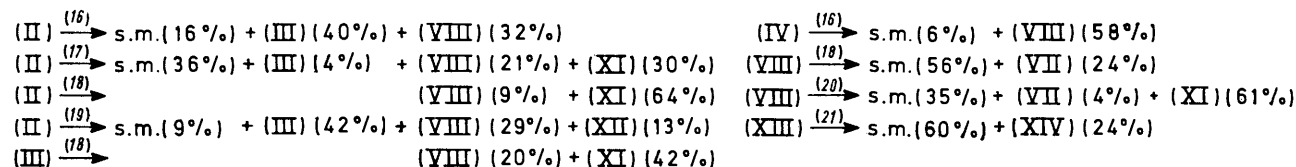
Treating the chloro-epoxide with aluminium chloride affords the conjugated ketone in high yield, possibly by the illustrated route; structure (VI)⁸ for this compound is supported by the n.m.r. data reported here, and by the product's stability to alkali. (A 14 β -structure would require a boat form for ring c.)

Surprising results were obtained in the catalytic



SCHEME 1 Reactions of 17 β -chloro-16 α ,17 α -epoxy-5 α -androstane (II)

Hydrogenations (H_2 , Pd-C; 20 °C) in the media specified (s.m. indicates recovered starting material).



Reagents: (1), p -O₂N-C₆H₄-CO₂H-CHCl₃; (2), Al₂O₃; (3), HCl-dioxan, 5 min; (4), MeOH-PhOH; (5), AlCl₃; (6), LiAlH₄-AlCl₃; (7), NaBH₄; (8), Zn-EtOH; (9), NaOEt-EtOH; (10), KBH₄ at pH 7; (11), KOH-MeOH; (12), LiAlH₄; (13), CH₂N₂-HBF₄; (14) MeCHN₂-HBF₄; (15), Huang-Minlon reduction; (16)-(21), H₂, Pd-C at 20 °C in (16), EtOAc; (17), MeOH, 9 h; (18), MeOH, 36 h; (19), EtOH; (20), MeOH containing HCl (1 mol. equiv.); (21), EtOH-HCl.

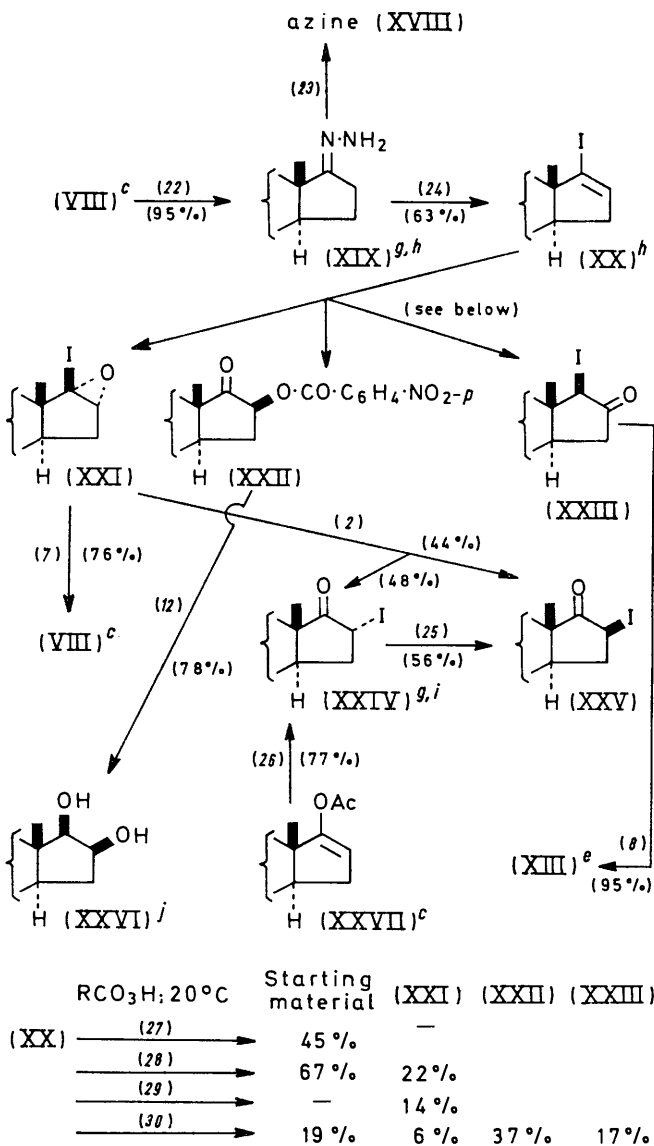
^a Ref. 8. ^b Ref. 20. ^c Elsevier's 'Encyclopaedia of Organic Chemistry,' vol. 14 and supplements. ^d Ref. 23. ^e Ref. 25. ^f Ref. 21.

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 17 β -chloro-5 α -androstan-16-one, has properties similar to those of the 16 α -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 17 β -methoxy-5 α -androstan-17-one (XVI) 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 5 α -androstan-17-one (VIII) is influenced by the acidity of the medium: in neutral solution the 17 β -alcohol (VII) is formed slowly, but in the presence

of a little hydrogen chloride the reduction is faster and leads to the 17 β -methyl ether (XI). (The literature



SCHEME 2 Formation and reactions of 17 β -iodo-16 α ,17 α -epoxy-5 α -androstane (XXI)

Reagents as in Scheme 1, and: (22), N₂H₄-NEt₃; (23), EtOH, heat; (24), I₂-NEt₃; (25), reagent from NaBH₄-EtOH-Me₂CO; (26), I₂-AcOH; (27), PhCO₃H-CHCl₃, 48h; (28), Peroxylauric acid-C₆H₅, 21h; (29), as (28) for 90h; (30), *p*-ON₂C₆H₄-CO₃H-CHCl₃.

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

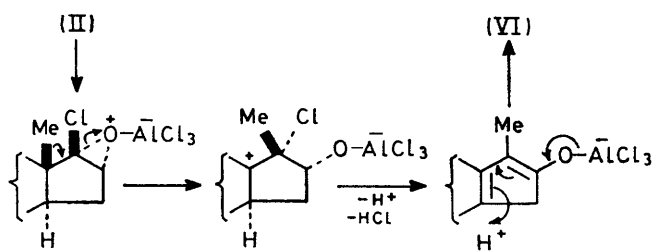
procedures for hydrogenating ketones to methyl ethers employ a platinum catalyst and much larger amounts

¹² M. Venzele, M. Acke, and M. Antennis, *J. Chem. Soc.*, 1963, 5598.

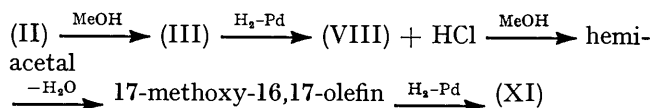
¹³ J. C. Babcock and L. F. Fieser, *J. Amer. Chem. Soc.*, 1952, 74, 5472.

¹⁴ W. F. Johns and G. P. Mueller, U.S.P. 2,910,485 (*Chem. Abs.*, 1960, 54, 2438f).

¹⁵ J. Fajkoš and F. Sorm, *Coll. Czech. Chem. Comm.*, 1959, 24, 766; C. L. Hewett and D. S. Savage, *J. Chem. Soc. (C)*, 1966, 484.



of hydrogen chloride¹² or hydrogen bromide.¹³ Consideration of the various results shows that the reduction of the chloro-epoxide (II) proceeds as follows:



One of the three iodo-ketones shown in Scheme 2 is the known 16 α -iodo-17-ketone (XXIV),^{9,14} and the new 16 β -iodo-compound is then the 16 β -isomer (XXV). The structures of the 16-halogeno-17-ketones reported here are supported by their ΔM_D (16 β - 16 α) values: +70° for chloro-, +240° for bromo-,¹⁵ and +460° for iodo-compounds. Formulation of the third iodo-ketone 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 $\Delta\nu$ values (increase caused by the bromine substituent) are:^{10,16} 17 α -Br-16-CO, +7 cm⁻¹; 17 β -Br-16-CO, +17; 16 α -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), $\Delta\nu$ ca. 17 cm⁻¹, and the 16-iodo-17-ketones (XXIV) and (XXV), $\Delta\nu$ ca. 4 cm⁻¹, show the trend expected with variation of the halogen, *i.e.* neither a 16 α - nor a 16 β -iodine substituent has much effect on the C=O stretching frequency. In contrast, the relatively large $\Delta\nu$ value (13 cm⁻¹) for the third iodo-ketone (XXIII) denotes a 17 β -iodine substituent; the 17 α -isomer would be expected to have a shift of less than 4 cm⁻¹.

Preparation of the vinyl iodide (XX)¹⁸ by Barton's method¹⁹ 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

¹⁶ J. Fajkoš and J. Joska, *Chem. and Ind.*, 1960, 1162; *Coll. Czech. Chem. Comm.*, 1960, 25, 2863.

¹⁷ J. Fishman and C. Djerassi, *Experientia*, 1960, 15, 138; J. Fishman and W. R. Biggerstaff, *J. Org. Chem.*, 1958, 23, 1190.

¹⁸ J. W. ApSimon, P. V. Demarco, D. W. Mathieson, W. G. Craig, A. Karin, L. Saunders, and W. B. Whalley, *Tetrahedron*, 1970, 26, 119.

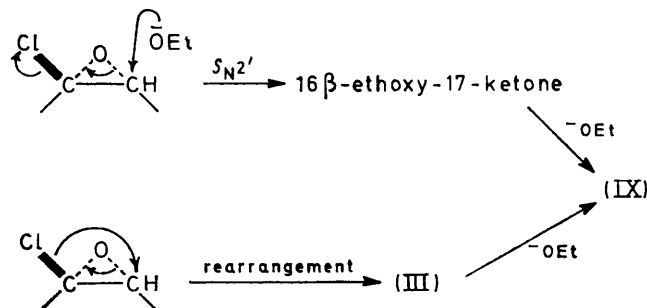
¹⁹ D. H. R. Barton, R. E. O'Brien, and S. Sternhell, *J. Chem. Soc.*, 1962, 470.

(XX) with peroxyauric 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 16 α - and 16 β -substituted 17-ketones. With halogeno-ketones the 16 β -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 16 α - to 16 β -bromo-17-ketones,¹² and under suitably mild conditions (Scheme 2) the 16 α -iodo-compound (XXIV) behaves similarly. However, the 16 β -chloro-17-ketone (III) can be partially epimerised to the 16 α -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 16 α -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 16 α -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 ($W_{1/2}/\text{Hz}$). 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 (CCl_4 solutions; 1 cm cells; spectral slit-width 2 cm^{-1}) are given in the 'Other signals' column

No.	19-H	18-H	τ	17-H or 16-H Form	Assignment	τ	Other signals Form	Assignment
(I)	9.19	9.14	4.39	4(3, 1.8)	16-H			
(II)	9.21	9.09	6.39	s ^b	16-H			
(III)	9.19	8.98	6.04	t(8.5)	16-H		(ν_{max} . 1759)	
(IV)	9.19	9.07	5.56	t(4)	16-H		(ν_{max} . 1758)	
(V)	9.18	9.28	6.23	s	17-H			
(VI)	9.27					7.48	4(17.5, 6)	one 15-H
(IX)	9.19	9.06	6.14	4(6.5, 2)	16-H	8.33	t(1.5)	17-Me
(X)	9.21	9.16	5.50	8(16, 8, 2)	16-H	6.35	m(17)	$\text{O}\cdot\text{CH}_2\cdot\text{CH}_3$
(XI)	9.20	9.26	6.46 ^c	t(8)	17-H	8.79	t(7)	$\text{O}\cdot\text{CH}_2\cdot\text{CH}_3$
(XII)	9.21	9.25	6.77	t(8)	17-H	6.64	s	OMe
(XIII)	9.21	9.25	6.68	t(8)	17-H	6.47	q(7)	} $\text{O}\cdot\text{CH}_2\cdot\text{CH}_3$
(XIV)	9.22	9.10	6.04	m(15)	16-H	6.50	q(7)	
(XV)	9.22	9.10	6.04	m(15)	16-H	8.84	t(7)	
(XVI)	9.22	9.10	6.04	m(15)	16-H	6.67	q(7.5)	
(XVII)	9.22	9.31	5.95	8(14, 8, 3)	16-H	8.82	t(7.5)	$\text{O}\cdot\text{CH}_2\cdot\text{CH}_3$
(XVIII)	9.22	9.31	5.95	8(14, 8, 3)	16-H	6.58	q(7)	$\text{O}\cdot\text{CH}_2\cdot\text{CH}_3$
(XIX)	9.22	9.31	5.95	8(14, 8, 3)	16-H	8.82	t(7)	$\text{O}\cdot\text{CH}_2\cdot\text{CH}_3$
(XX)	9.19	9.28	3.89	4(3, 1.8)	16-H			
(XXI)	9.22	9.25	6.39	s ^b	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		(ν_{max} . 1758)	
(XXIV)	9.19	9.12	5.11	m(9)	16-H		(ν_{max} . 1745)	
(XXV)	9.19	8.87	5.61	t(9)	16-H		(ν_{max} . 1747)	

^a L. M. Jackman and S. Sternhell, 'Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry,' Pergamon, Oxford, 1969, p. 132. ^b With a shoulder, $W_{1/2}$ of signal ca. 2 Hz. ^c d(8) After exchange with D_2O . ^d $W_{1/2}$ 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 ν_{\max} values of routine i.r. spectra (CS_2 or CCl_4 solutions, Perkin-Elmer model 257) are accurate to $\pm 5 \text{ cm}^{-1}$. Petrol refers to light petroleum, b.p. 40–60°, and Al_2O_3 to Camag neutral aluminium oxide, activity 1.

Work in Scheme 1.—17 β -Chloro-16 α ,17 α -epoxy-5 α -androstan-16-ene⁸ (I) in CHCl_3 (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 Me_2CO), $[\alpha]_{\text{D}} + 49^\circ$ (*c* 1.0) (lit.,⁸ m.p. 201°, $[\alpha]_{\text{D}} + 45^\circ$).

Reactions of the chloro-epoxide (II). (a) Petrol (80 ml) was added to a warm solution of the chloro-epoxide (400 mg) in C_6H_6 (20 ml). The cold solution was poured on to Al_2O_3 (40 g) and after 2 h the column was developed in the usual way. Petrol- C_6H_6 (1 : 1; 500 ml) eluted a mixture of chloro-ketones (340 mg). Et_2O eluted 17 β -hydroxy-5 α -androstan-16-one (V) (75 mg), m.p. 141–143° (57 mg; from $\text{Me}_2\text{CO}-\text{C}_6\text{H}_{14}$), $[\alpha]_{\text{D}} - 150^\circ$ (*c* 0.4; CHCl_3) [lit.,²⁰ m.p. 142°, $[\alpha]_{\text{D}} - 148^\circ$ (dioxan)], ν_{\max} 3532 and 1748 cm^{-1} . The chloro-ketones were separated by p.l.c. [1 large plate, 3 \times petrol-ether (49 : 1)] to give 16 β -chloro-5 α -androstan-17-one (III) (163 mg; higher R_{F}), m.p. 123–125° (112 mg; from $\text{Et}_2\text{O}-\text{C}_6\text{H}_{14}$), $[\alpha]_{\text{D}} + 113^\circ$ (*c* 0.5) (Found: C, 74.0; H, 9.7. $\text{C}_{19}\text{H}_{29}\text{ClO}$ requires C, 73.8; H, 9.5%), and 16 α -chloro-5 α -androstan-17-one (IV) (142 mg; lower R_{F}), m.p. 184–186° (97 mg; from Et_2O), $[\alpha]_{\text{D}} + 87^\circ$ (*c* 0.4) (Found: C, 74.3; H, 9.8%).

(b) Solutions of the chloro-epoxide (200 mg) in Et_2O (8 ml) and AlCl_3 (100 mg) in Et_2O (8 ml) were mixed, and the resulting solution was refluxed for 2 h. Standard manipulation gave 17-methyl-18-nor-5 α -androst-13(17)-en-16-one (VI) (144 mg), m.p. 131–133° (114 mg; from MeOH), $[\alpha]_{\text{D}} + 33^\circ$ (*c* 0.5) (lit.,⁸ m.p. 127.5–131°, $[\alpha]_{\text{D}} + 33^\circ$) (Found: C, 83.7; H, 10.3. Calc. for $\text{C}_{19}\text{H}_{28}\text{O}$: C, 83.8; H, 10.4%), ν_{\max} 1703 and 1660 cm^{-1} , λ_{\max} 241 nm (ϵ 13,750), *m/e* 272 (M^+ , 100%), 257 (11), and 244 (25).

(c) LiAlH_4 (14 mg) was added to a stirred solution of AlCl_3 (48 mg) in Et_2O (6 ml). The chloro-epoxide (200 mg) in Et_2O (8 ml) was added, and the solution was refluxed for 2 h. Work-up followed by p.l.c. [2 small plates, 3 \times petrol- Et_2O (9 : 1)] gave the ketone (VI) (28 mg; higher R_{F}), m.p. 131–133°, and 5 α -androstan-17 β -ol (VII) (138 mg; lower R_{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 petrol- Et_2O (49 : 1)] gave 5 α -androstan-17-one (VIII) (168 mg; higher R_{F}), m.p. and mixed m.p. with authentic material 117.5–119.5°, and 16 α -ethoxy-5 α -androstan-17-one (IX) (191 mg; lower R_{F}), m.p. 87–89° (from MeOH- H_2O), $[\alpha]_{\text{D}} + 37^\circ$ (*c* 0.4) (Found: C, 83.3;

H, 11.0. $\text{C}_{21}\text{H}_{34}\text{O}_2$ 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 petrol- Et_2O (49 : 1)] to give 5 α -androstan-16 α -yl ethyl ether (XVII) (21 mg), m.p. 74–77° (from MeOH), $[\alpha]_{\text{D}} - 14^\circ$ (*c* 0.3) (Found: C, 82.6; H, 11.7. $\text{C}_{21}\text{H}_{36}\text{O}$ requires C, 82.8; H, 11.9%), ν_{\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 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- H_2O 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 petrol- Et_2O (49 : 1)] gave the 16 β -chloro-17-ketone (III) (134 mg), m.p. and mixed m.p. 121–124°.

(g) A solution of the chloro-epoxide (50 mg) in Et_2O (10 ml) was stirred with NaBH_4 (25 mg) for 12 h at 20 °C. Work-up gave 5 α -androstan-17 β -ol (VII) (39 mg), m.p. and mixed m.p. 167–169°.

Reactions of 16 β -chloro-5 α -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 pH-controlled 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. KBH_4 (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 KBH_4 (20 mg) was added, and the stirring was continued for a further 40 min. Work-up gave 16 β -chloro-5 α -androstan-17 β -ol (X) (92 mg), m.p. 120–122.5° (72 mg; from MeOH), $[\alpha]_{\text{D}} + 1^\circ$ (*c* 0.6) (Found: C, 72.9; H, 10.2; Cl, 11.4. $\text{C}_{19}\text{H}_{31}\text{ClO}$ requires C, 73.4; H, 10.1; Cl, 11.4%), ν_{\max} (CCl_4 ; 1 cm cells) 3640w and 3564s cm^{-1} .

A solution of the chloro-alcohol (16 mg) in Et_2O (5 ml) was stirred with LiAlH_4 (20 mg) at 21 °C for 12 h. P.l.c. [1 small plate, 3 \times petrol- Et_2O (9 : 1)] afforded starting material (4 mg; higher R_{F}) and 5 α -androstan-17 β -ol (VII) (8 mg; lower R_{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 5 α -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 petrol- Et_2O (9 : 1)] gave the 16 β -chloro-17-ketone (II) (24 mg; higher R_{F}) and the 16 α -chloro-17-ketone (IV) (20 mg; lower R_{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. Varch and J. Jacques, *Bull. Soc. chim. France*, 1965, 67.
²¹ J. Jacques, M. Minssen, and D. Varch, *Bull. Soc. chim. France*, 1965, 77.

containing 18N-HBF₄ were treated with CH₂N₂ (or MeCHN₂) in Et₂O as described previously²² to give 5 α -androstan-17 β -yl methyl ether (XI) (77%), m.p. 85–86.5° (from Me₂CO), [α]_D +4° (c 0.5) (lit.,²³ m.p. 83.5–85°, [α]_D +20°) (Found: C, 82.9; H, 11.9. Calc. for C₂₀H₃₄O: C, 82.7; H, 11.8%), ν_{\max} . 1110 and 985 cm⁻¹; 5 α -androstan-17 β -yl ethyl ether (XII) (44%), m.p. 66–68° (from MeOH–H₂O), [α]_D –3° (c 0.4) (Found: C, 82.7; H, 11.6. C₂₁H₃₆O requires C, 82.8; H, 11.9%), ν_{\max} . 1125 and 1108 cm⁻¹; 5 α -androstan-16 β -yl ethyl ether (XIV) (57%), m.p. 83–85° (from MeOH–H₂O), [α]_D +34° (c 0.3) (Found: C, 82.5; H, 11.8%), ν_{\max} . 1090 cm⁻¹; 5 α -androstan-16 α -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 petrol–Et₂O (19 : 1)] afforded 5 α -androstan-17 β -yl methyl ether (XI) (higher *R_F*), m.p. 85–86.5° (60 mg; from Me₂CO) and 5 α -androstan-17-one (VIII) (lower *R_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 -androstan-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°, [α]_D +18° (c 1.1) (lit.,¹⁸ m.p. 111–113°, [α]_D +22°), *m/e* 384 (*M*⁺, 100%), 369 (96), 257 (68), and 242 (49).

Reactions with peroxy-acids. (a) Solutions of peroxy-lauric acid (98% by titration; 400 mg) in C₆H₆ (5 ml) and the iodo-compound (XX) (400 mg) in C₆H₆ (21 ml) were mixed at 20 °C and the resulting solution was kept in the dark for 21 h. C₆H₆ (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 17 β -iodo-16 α ,17 α -epoxy-5 α -androstan-16-one (XXI) (92 mg; higher *R_F*). After crystallisation from Et₂O the iodo-epoxide had m.p. 107–110° (decomp.), [α]_D +65° (c 1.0) (Found: C, 57.4; H, 7.3. C₁₉H₂₉IO 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 petrol–Et₂O

(19 : 1)] of the product (210 mg) gave the iodo-epoxide (37 mg) (lowest *R_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_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 petrol followed by 2 \times petrol–Et₂O (19 : 1)] gave the following four compounds (in order of decreasing *R_F*): starting material, m.p. 119–123° (205 mg; from Me₂CO); the iodo-epoxide (XXI), m.p. 107–110° (68 mg; from Et₂O); 17 β -iodo-5 α -androstan-16-one (XXIII), m.p. 165–167° (decomp.) (180 mg, from Et₂O–C₆H₁₄), [α] –142° (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-5 α -androstan-16 β -yl *p*-nitrobenzoate (XXII) (551 mg), m.p. 199–200° (321 mg; from Me₂CO–C₆H₁₄), [α]_D +55° (c 1.0) (Found: C, 70.7; H, 7.5; N, 3.3. C₂₆H₃₃NO₅ requires C, 71.1; H, 7.6; N, 3.2%), ν_{\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 5 α -androstan-16 β ,17 β -diol (XXVI) (34 mg), m.p. 179–181° (26 mg; from Me₂CO), [α]_D +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 5 α -androstan-16-one (88 mg), m.p. 105.5–108° (from C₆H₁₄), [α]_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 petrol–Et₂O (19 : 1)] gave 5 α -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 C₆H₆ (10 ml) was passed through Al₂O₃ (20 g). Elution with C₆H₆ gave an oil (92 mg) which was separated by p.l.c. [2 small plates, 3 \times petrol–Et₂O (19 : 1)] into 16 β -iodo-5 α -androstan-17-one (XXV) (44 mg; higher *R_F*), m.p. 129–131.5° (from C₆H₁₄), [α]_D +134° (c 0.3) [Found: C, 57.2; H, 7.3%; *M*, 400.1258 (*M*⁺ ion, base-peak of mass spectrum). C₁₉H₂₉IO requires C, 57.0; H, 7.3%; *M*, 400.1262], and 16 α -iodo-5 α -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 5 α -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 H_2O and extraction with $CHCl_3$ afforded the 16 α -iodo-ketone (XXIV) (83 mg), m.p. 161—164°.

(e) A solution of $NaBH_4$ (10 mg) in EtOH (2 ml) was stirred with Me_2CO (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 \times petrol-Et₂O (19 : 1)] gave the 16 β -iodo-ketone (XXV) (14 mg; higher R_F), m.p. and mixed

m.p. 131—134°, and the 16 α -iodo-ketone (XXIV) (8 mg; lower R_F), m.p. 159—163°, further identified by its i.r. spectrum.

We thank the Salters' Company for a Scholarship (to J. P.), the University of Ceylon and the University of Warsaw for study leave (to V. K. and to J. W., respectively), the New Zealand Grants Committee for a Postdoctoral Fellowship (to W. A. D.), the Science Research Council for a research grant, and Glaxo Research Ltd. for a grant and gifts of chemicals.

[1/1259 Received, July 23rd, 1971]
