Molecular Rearrangement of 3-Substituted 4-Chloro-4,5-epoxide Systems in Ring *A* of Steroids

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Both stereoisomers of the 3-oxo-, 3-hydroxy-, and 3-acetoxy-4-chloro-4,5-epoxy derivatives of 17β-acetoxyandrostanes have been synthesized, and their thermal rearrangement products have been identified. A synthesis of the diosphenols, 17β-acetoxy-4-hydroxyandrost-4-en-3-one and 17β-acetoxy-4-hydroxyandrosta-4,6-dien-3-one, through a novel rearrangement of the 3-hydroxy- and 3-oxo-4-chloro-4,5-epoxides, respectively, is described. In addition to the chloro ketone products from the 3-acetoxy derivatives, rearrangement and elimination products were also formed. Structural determinations are based upon one- and two-dimensional ^{1}H and ^{13}C n.m.r. correlations and analyses.

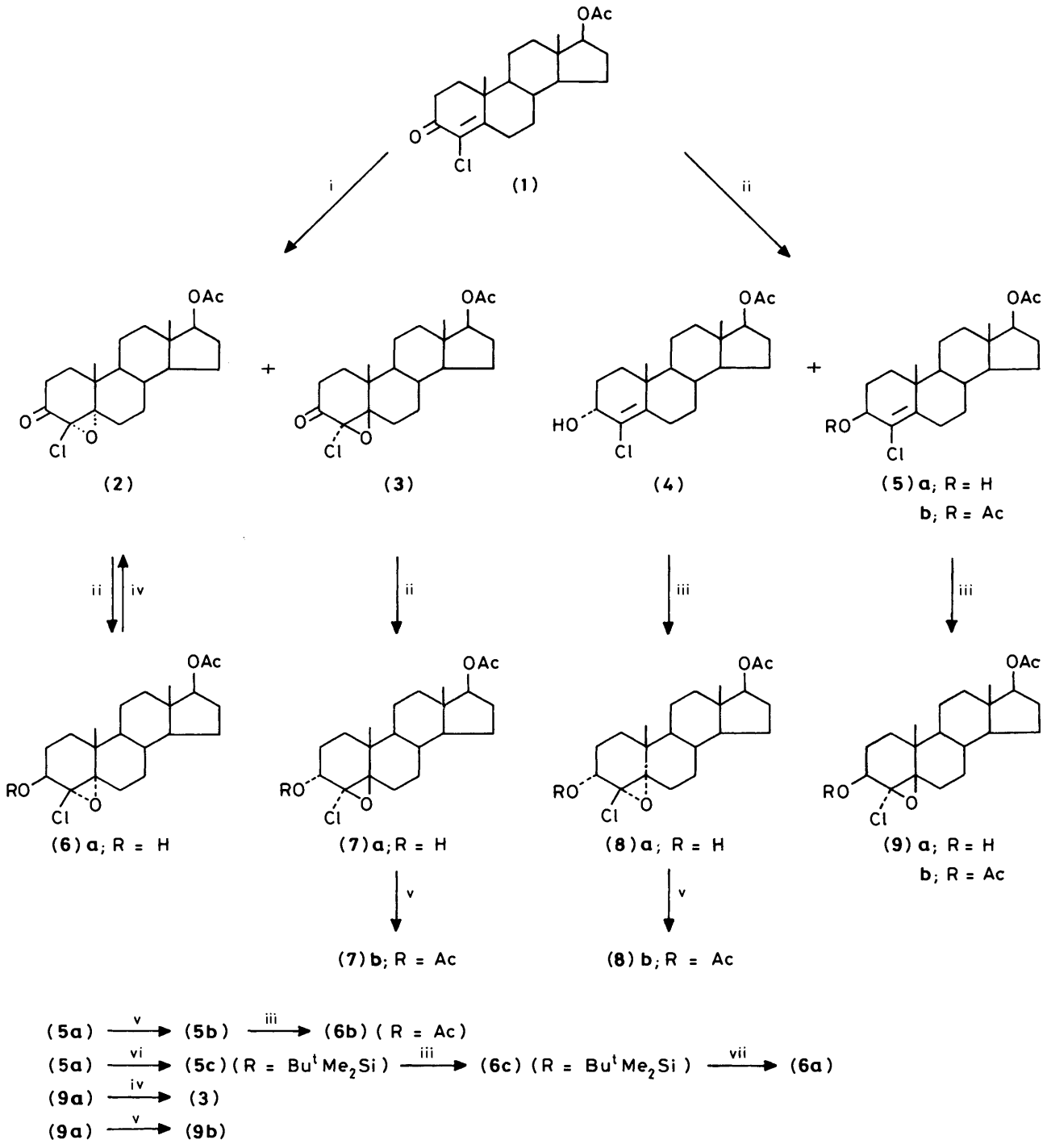
Thermal molecular rearrangement of chloro epoxides and related reactions have been studied,[1,2] and it has been generally accepted[3,4] since the initial postulate of McDonald and Tabor[5] that the rearrangement proceeds through an α-oxocarbenium ion–chloride ion pair. More recently McDonald and Cousins[2] have concluded that the rearrangement proceeds by disrotatory C_β–O bond opening to give an α-oxocarbenium ion–chloride ion pair; this accounts for kinetic data for the stereochemistry of the C–Cl bond formed.

The thermal rearrangements of α-chloro epoxides with a substituent on a carbon atom adjacent to the chlorine have not been studied. We report here the rearrangement of steroid 3-oxo, 3-hydroxy, and 3-acetoxy derivatives of 4-chloro 4,5-epoxides, the syntheses of which are outlined in Scheme 1. 4-Chlorotestosterone acetate (17β-acetoxy-4-chloroandrost-4-en-3-one) (**1**) when treated with hydrogen peroxide and sodium hydroxide slowly reacted to give a mixture of the 5α- (**2**) and 5β- (**3**) epoxy ketones (α:β 2:3 by h.p.l.c.), from which the 5β-epoxy ketone (**3**) was crystallized. The 5α-epoxy ketone (**2**) was separated by h.p.l.c. but was more readily obtained by oxidation of the 5α-epoxy 3β-alcohol (**6a**). Similarly the 5β-epoxy ketone (**3**) was prepared by oxidation of the 5β-epoxy 3β-alcohol (**9a**). The stereochemistry of the 5α- (**2**) and 5β- (**3**) epoxides was thus supported by their preparation from the corresponding epoxy alcohols (**6a**) and (**9a**), respectively (see later).

4-Chlorotestosterone acetate (**1**) was reduced with lithium hydridotri-(t-butoxy)aluminate (LTBA) to give as a minor product the 3α-alcohol (**4**) and as the major product the 3β-alcohol (**5a**), which on acetylation gave the 3β-acetate (**5b**) (Scheme 1). Epoxidation of 3α-alcohol (**4**) and the 3β-alcohol (**5a**) with *m*-chloroperbenzoic acid (*m*CPBA) gave as the main products the 5α-epoxy 3α-alcohol (**8a**) and the 5β-epoxy 3β-alcohol (**9a**), respectively, as expected by analogy with the stereoselective effect of alcohol groups on epoxidation.[6] Acetylation of the epoxy alcohols (**8a**) and (**9a**) gave the corresponding epoxy acetates (**8b**) and (**9b**). Epoxidation of the 3β-acetate (**5b**) with *m*CPBA gave principally the 5α-epoxy 3β-acetate (**6b**), as the alcohol group is not present to direct β-face attack, and furthermore addition to the α-face of the double bond is favoured because of steric hindrance from the 10-Me group. Treatment of the 3β-alcohol (**5a**) with t-butyldimethylsilyl chloride (Bu^tMe_2SiCl) yielded the siloxane (**5c**), which on epoxidation gave mainly the 5α-epoxy siloxane (**6c**); treatment with fluoride ion then gave the 5α-epoxy 3β-alcohol (**6a**). Reduction of the 5α-epoxy ketone (**2**) with LTBA gave a mixture of the 3-epimeric alcohols (3α:3β 1:11 by ^{1}H n.m.r.) with the 5α-epoxy 3β-alcohol (**6a**) as the major product. Reduction of the 5β-epoxide (**3**) with LTBA gave as the major product the 5β-epoxy 3α-alcohol (**7a**) (3α:3β 12:1 by ^{1}H n.m.r.), which on acetylation gave the 5β-epoxy 3α-acetate (**7b**). In both cases reduction of the ketone gave the pseudoequatorial alcohol.

The 5α-epoxy ketone (**2**) on heating to reflux in pyridine stereospecifically rearranged to the 5β-chloro diosphenol (**11a**), further characterized as the acetate (**11b**) (Scheme 2). Heating either the 5α-epoxy ketone (**2**) or the 5β-chloro diosphenol (**11a**) at 240 °C resulted in rearrangement to the dienol (**13**), indicating that the 5β-chloro diosphenol (**11a**) is an intermediate in the rearrangement of the 5α-epoxy ketone (**2**). The 5β-chloro diosphenol (**11a**) when treated with Zn–Cu couple was converted through reduction and rearrangement into the diosphenol (**10a**), and similar treatment of the 5β-chloro diosphenol acetate (**11b**) also gave the rearranged diosphenol acetate (**10b**). An analogous series of reactions occurred with the 5β-epoxy ketone (**3**), which rearranged stereospecifically in pyridine to the 5α-chloro diosphenol (**12a**), further characterized as the acetate (**12b**). Again at 240 °C, both the 5β-epoxy ketone (**3**) and the 5α-chloro diosphenol (**12a**) were converted into the same dienol (**13**) as obtained in the earlier series. The 5α-chloro diosphenol (**12a**) on Zn–Cu couple treatment gave the diosphenol (**10a**); similar treatment of the 5α-chloro diosphenol acetate (**12b**) gave the diosphenol acetate (**10b**). From both (**11b**) and (**12b**) the diosphenol (**10a**) was also obtained. Reduction of the 5β- (**11a** and **b**) and 5α- (**12a** and **b**) chloro derivatives with Zn–Cu couple led to formation of the more highly substituted enolic 4-en-3-one diosphenol system, which for the 5β- and 5α-chloro diosphenol acetates (**11b**) and (**12b**) also requires a shift of the acetyl group from C-3 to C-4; this probably occurs through a cyclic zinc intermediate as shown in Scheme 3. The stereospecificity of the initial rearrangements of the 5α- and 5β-epoxy ketones (**2**) and (**3**) to the 5β- and 5α-chloro derivatives (**11a**) and (**12a**) demonstrates that the rearrangements do not take place through a common intermediate such as the proposed α-oxocarbenium ion–chloride ion pair.[5] A mechanism where C_β–O bond breaking precedes C_α–Cl bond breaking would lead to the observed stereochemistry of the products (**11a**) and (**12a**) and is consistent with the relative stability of the tertiary C-5 carbocation. However, the rearrangement occurs, to retain the stereochemistry at C-5 no significant time interval is possible between loss of the chloride ion from C-4 and addition of chlorine at C-5.

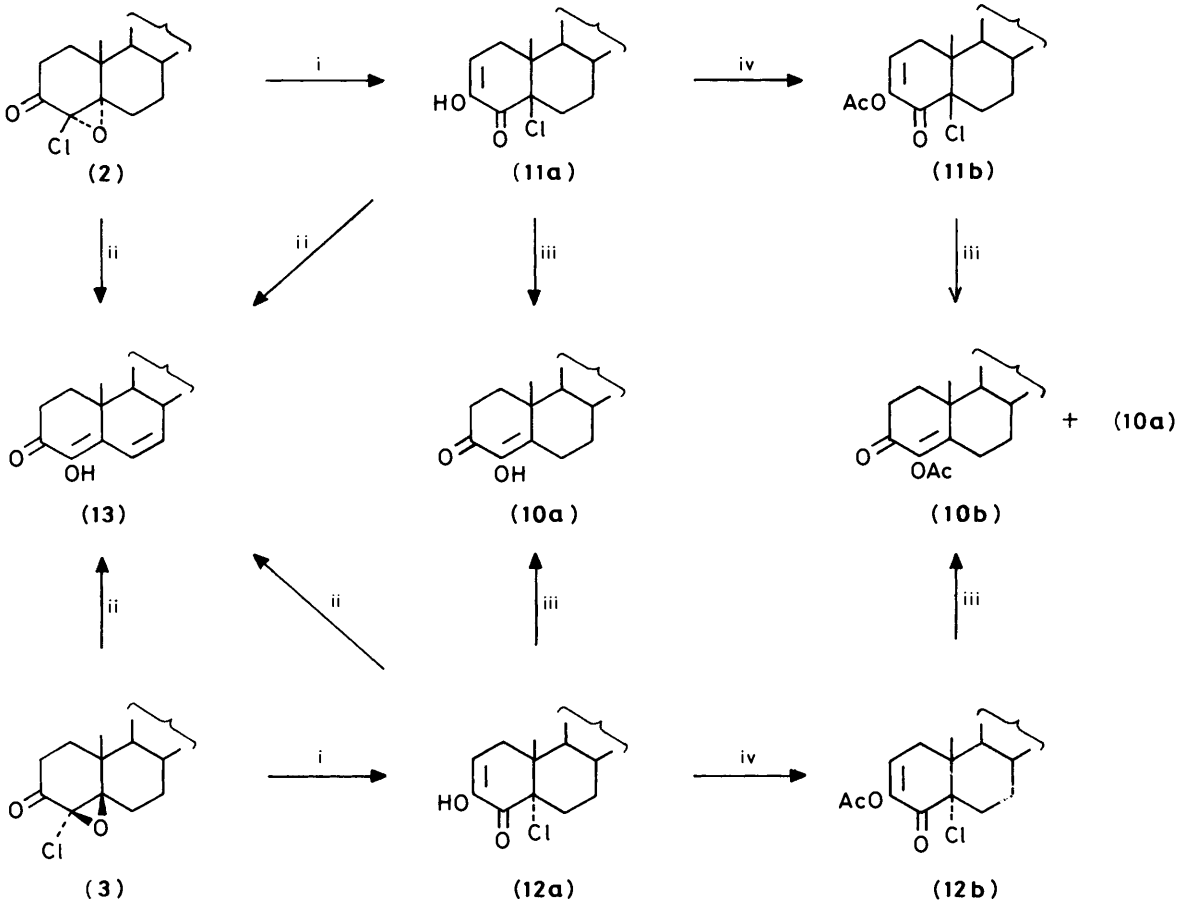
Thermolysis of each of the epoxy alcohols (**6a**), (**7a**), (**8a**), and (**9a**) at 190—200 °C resulted in rearrangement, in high yield, to give the diosphenol (**10a**) (Scheme 4). This novel rearrangement of all four isomers suggests a common intermediate such as the α-oxocarbenium ion–chloride ion pair,[5] although acid-catalysed ring opening is also possible. Epoxide



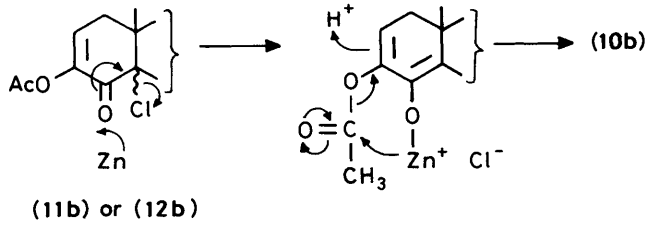
Scheme 1. *Reagents:* i, H_2O_2–NaOH; ii, LTBA; iii, *m*CPBA; iv, Jones reagent; v, Ac_2O–pyridine; vi, Bu^{t}Me$_2$SiCl–imidazole–DMF; vii, Bu_4NF

ring opening to form the tertiary C-5 carbocation, accompanied by loss of the alcohol hydrogen atom, with migration of the C-3 hydrogen atom and elimination of HCl, would yield the 3,4-dioxo derivative which is enolized to the diosphenol (**10a**). This is a novel synthesis of this system.

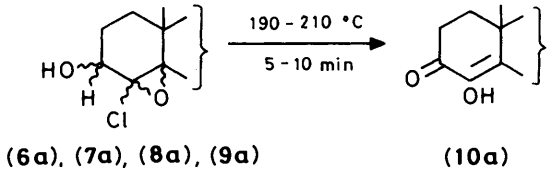
Thermolysis of the chloro epoxides (**6b**), (**7b**), (**8b**), and (**9b**) gave, in some cases, the expected chloro ketones; alternative rearrangements and eliminations occurred with others (see Scheme 5). The 3β-acetoxy-5β-chloro epoxide (**9b**) cleanly rearranged to the expected product, the 5α-chloro 4-one (**21**). In this case all of the stereochemical changes are energetically favourable: the acetoxy function goes from an axial to an equatorial configuration and the ring junction from 5β-(*cis*) to 5α-(*trans*) stereochemistry; furthermore, the product has no 1,3-diaxial interaction between the chloro and acetoxy substituents. Treatment of the 5α-chloro 4-one (**21**) with Zn–Cu couple selectively reduced the chlorine to give the 3β-acetoxy ketone (**22**). Similarly the 3α-acetoxy-5α-chloro epoxide (**8b**) gave the 3α-acetoxy-5β-chloro 4-one (**20**), in which an energetically favourable axial-to-equatorial change of the acetoxy function



Scheme 2. *Reagents and conditions:* i, pyridine, reflux; ii, 240 °C, 5 min; iii, Zn–Cu couple; iv, Ac_2O–pyridine



Scheme 3. Mechanism of Zn reduction and acetyl rearrangement

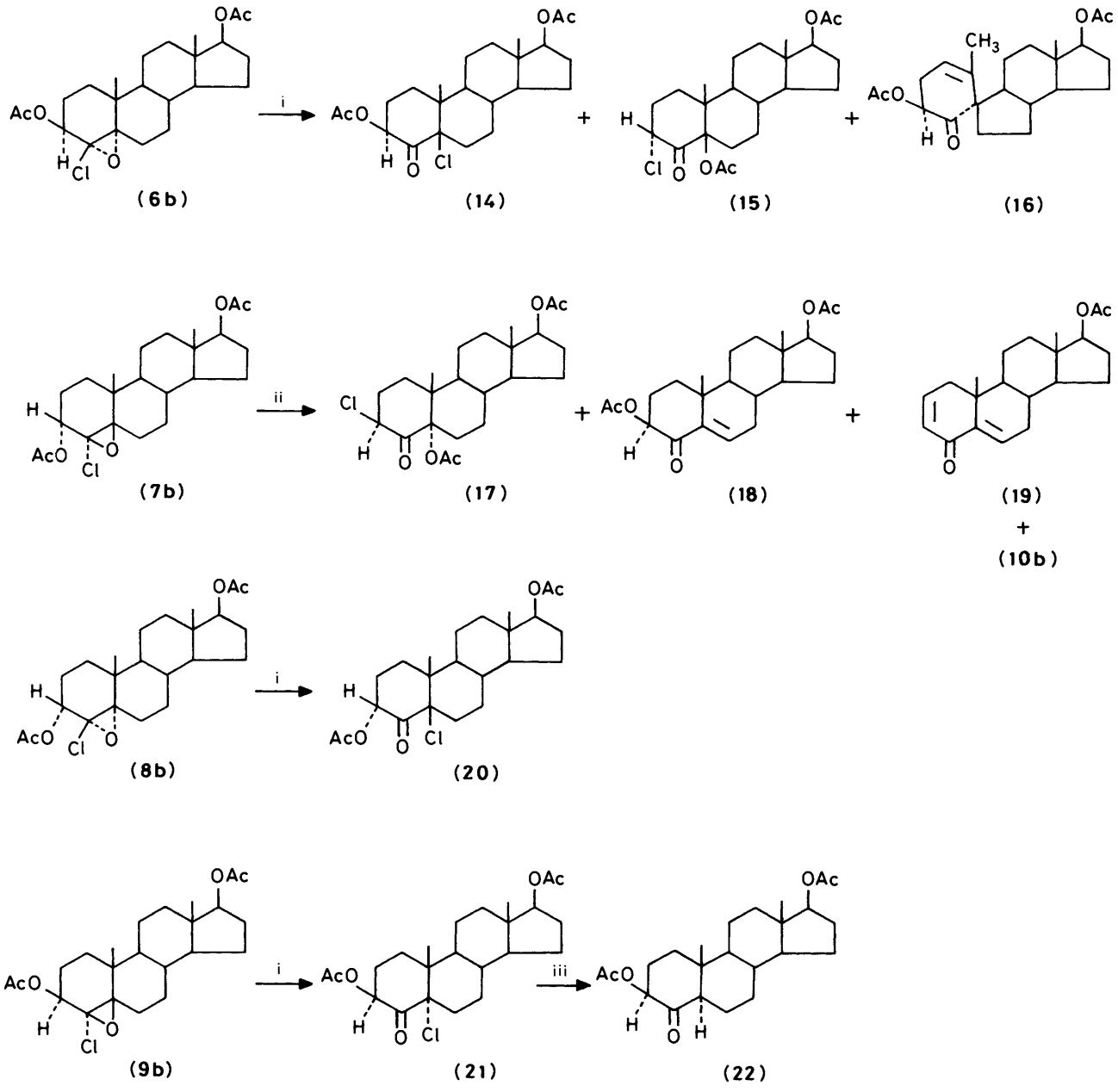


Scheme 4.

occurs and no 1,3-diaxial interaction is produced; nevertheless, in this case an unfavourable 5α to 5β change in stereochemistry does occur at the ring junction.

Whether thermolysis of the chloro epoxides gives the normal chloro ketone rearrangement product or leads to rearrangement of the acetoxy function depends upon the availability of the C-3 acetoxy function for intramolecular rearrangement. Rearrangement of the acetoxy function depends on a balance of the interactions present in the starting chloro epoxide and the chloro ketone product. When intramolecular rearrangement of acetate can occur as in (**6b**) and (**7b**) (see Scheme 6), it is energetically favoured because of the relief of strain induced by unfavourable steric interactions in the normal rearrangement products. Examination of the changes which occur in the formation of the normal rearrangement product (**14**) from the 3β-acetoxy-5α-chloro epoxide (**6b**) shows that three are energetically unfavourable, *viz.* the change of the acetoxy function from equatorial to axial, that of the ring junction from 5α to 5β, and the occurrence of a 1,3-diaxial interaction between the chloro and acetoxy substituents. The first two interactions can be relieved by an alternative rearrangement to the 3α-chloro-5β-acetoxy 4-one (**15**). This rearrangement can be envisaged as an internal attack of the acetoxy carbonyl on a developing or formed charge at C-5, accompanied by chloride ion attack at C-3 rather than C-5. Both products (**14**) and (**15**) are obtained. Another rearrangement, initiated by a positive charge at C-5, results in the loss of a C-1 proton and migration of the 9,10-bond, giving the spiro derivative (**16**).

The 3α-acetoxy-5β-chloro epoxide (**7b**) on thermolysis forms principally the product of C-3 to C-5 acetoxy rearrangement (**17**). The normal rearrangement product would undergo a change from 5β- to 5α-stereochemistry but the acetoxy function would go from equatorial to axial, and the product would have a 1,3-diaxial interaction of the chloro and acetoxy groups. The acetoxy rearrangement gives an energetically more favoured product with an unchanged stereochemistry for the acetoxy function and a 5β to 5α change at the ring junction, and the 1,3-diaxial interaction is removed in forming the 3β-chloro-5α-



Scheme 5. *Reagents and conditions:* i, 190—200 °C, 5—10 min; ii, 130 °C, 3.5 min; iii, Zn–Cu, HOAc

acetoxy 4-one (**17**). Although the ketone (**17**) was a major product from thermolysis of the epoxide (**7b**), the 5,6-unsaturated ketone (**18**), the 2,5-dien-4-one (**19**), and the diosphenol acetate (**10b**) were also isolated. Formation of (**10b**), (**18b**), and (**19**) can be rationalized as shown in Scheme 7, in which an intermediate C-3 axial acetate formed through epoxide ring opening and loss of HCl can undergo thermal elimination or enolization to give the observed products.

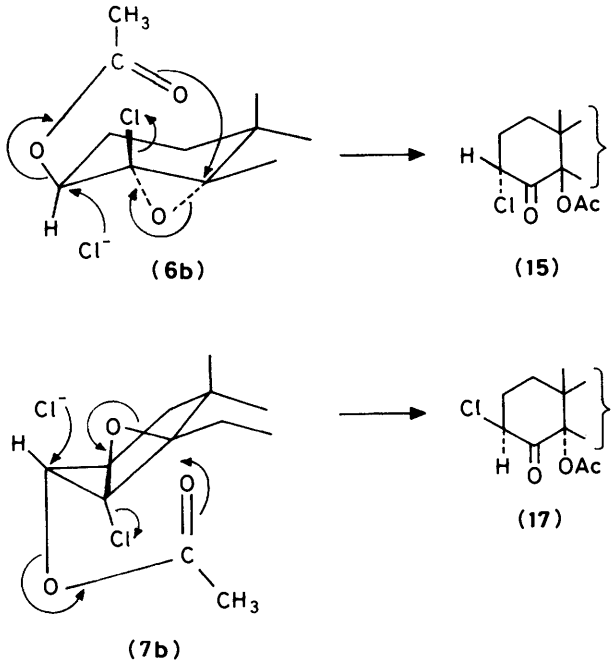
The rearrangement products of (**8b**) and (**9b**) are not consistent with an α-oxocarbenium ion–chloride ion pair as an intermediate. The 5α-chloro product (*trans* ring junction) would be expected from chloride ion attack on an intermediate C-5 carbocation unless a concerted rearrangement operated which retained the stereochemistry. Alternatively, an intermediate oxiranyl cation–chloride ion pair would, as a result of chloride ion attack at C-5, lead to the observed products (**14**) and (**12**). Thermolysis products of the chloro epoxides (**6b**) and (**7b**) may be formed from either intermediate as the geometry of the acetate requires transfer on the face of the molecule to which it is attached, with chloride ion attack from the opposite face.

N.m.r. Structural Assignments.—^{1}H N.m.r. data of the synthetic compounds are given in Tables 1—6 and are in general agreement with the structures assigned.[7] The chloro epoxy ketones (**2**) and (**3**) can be distinguished by small differences in the ^{13}C chemical shifts and in the ^{1}H shifts for the 10-Me protons, as well as by the four-bond 10-Me, 1α-H coupling seen in (**2**) but not in (**3**) (see later). For the isomeric chloro epoxy alcohols larger coupling constants are observed for the pseudo-axial 3-H in (**6a**) and (**7a**) than for the pseudoequatorial 3-H derivatives (**8a**) and (**9a**). The rearrangement products (**11a**) and (**12a**) show a vinylic 2-H, and their 10-Me proton shifts are in agreement with estimated values. A four-bond coupling between the 10-Me protons and 1α-H, and the downfield shift of

Table 1. ^{1}H Chemical shifts (J and half-height width, $w_{\frac{1}{2}}$, in Hz)[a]

Compound	13-Me	10-Me	17-OAc	3-OAc	17-H	3-H	Other
(**1**)	0.84	1.23	2.04		4.60dd (J 7.7, 9.1)		3.25ddd (J 2.6, 4.1, 15.0) (6α-H)
(**4**)	0.81	1.04	2.04		4.58dd (J 7.7, 9.1)	4.14 ($w_{\frac{1}{2}}$ 8)	2.94ddd (J 2.7, 4.1, 14.3) (6α-H)
(**5a**)	0.81	1.10	2.03		4.58dd (J 7.8, 9.1)	4.14 ($w_{\frac{1}{2}}$ 16)	2.40d (J 3) (3-OH); 2.92ddd (J 2.7. 4.1, 14.4) (6α-H)
(**5b**)	0.82	1.11	2.03	2.10	4.58dd (J 7.7, 9.1)	5.40 ($w_{\frac{1}{2}}$ 16)	2.99ddd (J 2.7, 4.1, 14.2) (6α-H)
(**5c**)	0.80	1.09	2.04		4.58dd (J 7.7, 9.1)	4.15ddd (J 1.7, 6.8, 6.8)	0.11, 0.15, 0.92 (Bu^{t}M eSiO); 2 .98ddd (J 2.8, 4.0, 14.2) (6α-H)
(**6a**)	0.81	1.13	2.04		4.60dd (J 7.7, 9.1)	4.05t (J 8.5)	
(**6b**)	0.81	1.14	2.03	2.12	4.60dd (J 7.8, 9.2)	5.25t (J 8.6)	
(**6c**)	0.81	1.12	2.03		4.60dd (J 7.8, 9.1)	3.99t (J 8.2)	0.11, 0.15, 0.92 (Bu^{t}MeSiO)
(**7a**)	0.80	1.02	2.03		4.58dd (J 7.7, 9.2)	4.10t (J 6.6)	2.37br s (3-OH)
(**7b**)	0.82	1.04	2.04	2.14	4.62dd (J 7.7, 9.1)	5.33t (J 6.2)	
(**8a**)	0.81	1.08	2.04		4.61dd (J 7.8, 9.1)	4.30d (J 5.7)	
(**8b**)	0.81	1.09	2.04	2.17	4.61dd (J 7.7, 9.1)	5.52d (J 6.6)	
(**9a**)	0.81	1.04	2.05		4.60dd (J 7.7, 9.1)	4.30dd (J 3.1, 5.4)[b]	
(**9b**)	0.82	1.06	2.05	2.17	4.61dd (J 7.7, 9.2)	5.49dd (J 3.9, 5.8)	
(**10a**)	0.83	1.18	2.04		4.60dd (J 7.7, 9.1)		3.01ddd (J 2.4, 4.6, 15.1) (6α-H); 6.06s (4-OH)
(**10b**)	0.84	1.25	2.04	2.23	4.60dd (J 7.8, 9.1)		2.68ddd (J 2.5, 4.2, 14.9) (6α-H); 2.09s (4-OAc)
(**11a**)	0.77	1.23	2.02		4.53dd (J 7.8, 9.1)		5.85br s (3-OH); 5.93dd (J 2.9, 7.1) (2-H)
(**12a**)	0.80	1.06	2.04		4.63dd (J 7.7, 9.1)		5.68br s (3-OH); 5.94dd (J 2.8, 6.8) (2-H)
(**13**)	0.88	1.10	2.05		4.64dd (J 7.2, 8.9)		6.00dd (J 2.1, 9.9) (6-H); 6.20s (4-OH); 6.65dd (J 2.8, 9.9) (7-H)
(**18**)	0.82	1.00	2.05	2.17	4.63dd (J 7.7, 9.1)	5.20dd (J 7.3, 12.4)	6.36dd (J 2.6, 5.0) (5-H)
(**19**)	0.82	1.09	2.04		4.63dd (J 7.8, 9.1)	6.11dd (J 2.8, 10.2)	6.78dd (J 2.6, 5.3) (6-H); 6.87ddd (J 2.3, 6.4, 10.0) (2-H)

[a] For solutions in $CDCl_3$ ($SiMe_4$ internal standard); a Bruker AM300 Instrument. [b] Decoupled from 3-OH.



Scheme 6. 3,5-Acetoxy rearrangement

the 9-H signal confirms the 5α-stereochemistry of (**12b**) (see later). The chloro epoxy ketones (**2**) and (**3**) and the thermal rearrangement products (**11b**), (**12b**), (**14**)—(**17**), and (**20**)—(**22**) were analysed in greater detail as shown in Tables 2—6.

The C-5 stereochemistry of the 3α-acetoxy ketone (**22**) can be determined directly as α from $^3J_{5,6\beta}$ (Table 4). For the C-5 substituted compounds the stereochemistry had to be established by more indirect methods. In 5α-steroids the 1α-H is axial and has a four-bond W coupling of *ca.* 0.5 Hz with the 10-Me protons. This coupling can be observed as a broadening of the 1α-H signal, a splitting of the 10-Me signal (especially when resolution is enhanced), and a cross-peak in the COSY spectrum. In 5β-steroids, however, the 1α-H is equatorial and does not couple significantly with the 10-Me. This absence of coupling leaves the 10-Me signal measurably sharper and more intense than the 10-Me signal in the corresponding 5α-derivative. This absence of coupling can also be observed in the COSY spectrum. The different substituent effects of chlorine *versus* acetate in the ^{13}C spectrum allow a distinction to be made between 3-Cl,5-OAc and 3-OAc,5-Cl substitution.

Nuclear Overhauser effect (n.O.e.) measurements also provide evidence regarding the C-5 stereochemistry (Table 6). In the 5α-compounds an n.O.e. is observed between the 2β-H and the 10-Me. In the 5β-compounds these protons are too remote for a significant n.O.e. In 5,17β-diacetoxy-3α-chloro-5β-androstan-4-one (**15**), however, there is an n.O.e. between the 10-Me and the 5-OAc. This n.O.e. is possible only with a 5β-stereochemistry. Once the C-5 stereochemistry has been established the C-3 stereochemistry may easily be deduced from the ring-*A* coupling constants (Table 4). Furthermore, a downfield shift of the 1α-H, 3α-H, 7α-H, and 9α-H signals in (**21**) as compared with (**22**) is observed, which probably results from 1,3-diaxial interaction with the axial 5α-Cl. A similar but smaller effect is observed in (**17**), with axial 5α-OAc.

The spiro compound (**16**) showed a n.O.e. from the 10-Me to the 13-Me and 11β-H which confirms the stereochemistry at C-5. The 3-H shows an axial coupling and a positive n.O.e. to the equatorial 2-H, and a negative n.O.e. to the axial 2-H. A positive n.O.e. is observed from 3-H to 9-H and 11α-H, and a negative n.O.e. from 3-H to 11β-H; therefore the 3-H is adjacent to the 11α-H. The conformation of (**16**) is probably either a C-3 sofa or a C-2,C-3 half-chair, or some intermediate geometry. Difference double resonance[8] from 13-Me isolates the 12α-H signal; all other C and H signals were assigned by COSY[9] and heteronuclear correlation experiments[10] (Tables 2, 3, and 5).

Table 2. ^{13}C Chemical shifts

	5α					5β					
Carbon No.	**(2)** 5α-Epoxide	**(12b)** 3-OAc, 5α-Cl	**(17)** 3β-Cl, 5α-OAc	**(21)** 3β-OAc, 5α-Cl	**(22)** 3β-OAc, 5α-H	**(3)** 5β-Epoxide	**(11b)** 3-OAc, 5β-Cl	**(14)** 3β-OAc, 5β-Cl	**(15)** 3α-Cl, 5β-OAc	**(16)** Spiro	**(20)** 3α-OAc, 5β-Cl
1	28.91	35.94	31.18	30.51	35.96	26.08	31.89	29.14	30.28	119.98	28.90
2	32.71	132.05	34.50	27.21	28.45	32.27	131.68	(26.91)	33.48	30.54	25.59
3	196.85	142.43	61.13	72.09	76.15	196.42	143.03	73.16	61.88	73.50	72.11
4	83.8	186.36	199.48	200.20	205.49	83.05	185.43	198.41	199.37	206.45	198.82
5	74.76	78.10	89.08	81.51	57.35	74.46	77.20	*ca.* 77[a]	88.41	61.11	79.11
6	26.14	25.30	23.08	24.84	20.08	26.12	28.73	(26.91)	26.79	31.12	32.09
7	28.42	27.93	25.09	28.65	29.81	29.10	30.91	32.48	27.09	30.15	28.90
8	34.67	34.13	34.12	34.19	34.76	34.74	33.99	33.93	33.48	45.31	33.85
9	49.94	45.60	46.53	45.40	54.20	46.54	43.93	45.56	41.45	57.96	44.48
10	37.46	43.50	45.30	44.51	(42.69)	37.96	45.05	44.03	45.27	138.05	44.76
11	20.78	20.21	21.16	21.12	21.21	21.09	22.54	21.27	20.06	23.02	21.10
12	36.59	36.59	36.85	36.85	36.82	36.39	36.55	36.62	36.38	36.72	36.55
13	42.56	42.70	42.75	42.80	(42.63)	42.69	42.32	42.27	42.37	43.77	42.22
14	50.45	50.06	50.30	50.16	50.45	50.14	50.31	50.45	50.27	50.73	50.34
15	23.41	23.31	23.32	23.34	23.45	23.41	23.28	23.36	23.41	23.86	23.33
16	27.46	27.50	27.49	27.58	27.50	27.41	27.47	27.46	27.54	27.45	27.46
17	82.43	82.49	82.49	82.53	82.64	82.31	82.27	82.34	82.50	82.10	82.36
18	12.02	12.17	12.19	12.21	12.12	12.03	11.98	11.90	11.96	12.64	11.88
19	16.43	15.77	14.63	16.37	13.71	19.26	17.66	17.95	17.31	22.12	17.48
3-O*C*OCH$_3$		20.32		169.78	170.14		20.27	169.76		170.17	169.77
3-OCO*C*H$_3$		168.97		20.68	20.74		168.90	(21.07)		20.66	20.71
5-O*C*OCH$_3$			169.95						170.18		
5-OCO*C*H$_3$			21.16						(21.14)		
17-O*C*OCH$_3$	21.12	21.15	171.17	171.03	171.17	21.09	21.10	171.02	171.03	170.97	171.06
17-OCO*C*H$_3$	171.08	171.11	21.16	21.18	21.17	171.02	170.96	(21.11)	(21.18)	21.12	21.12

[a] Not observed, probably under $CDCl_3$ peak.

Table 3. Chemical shifts

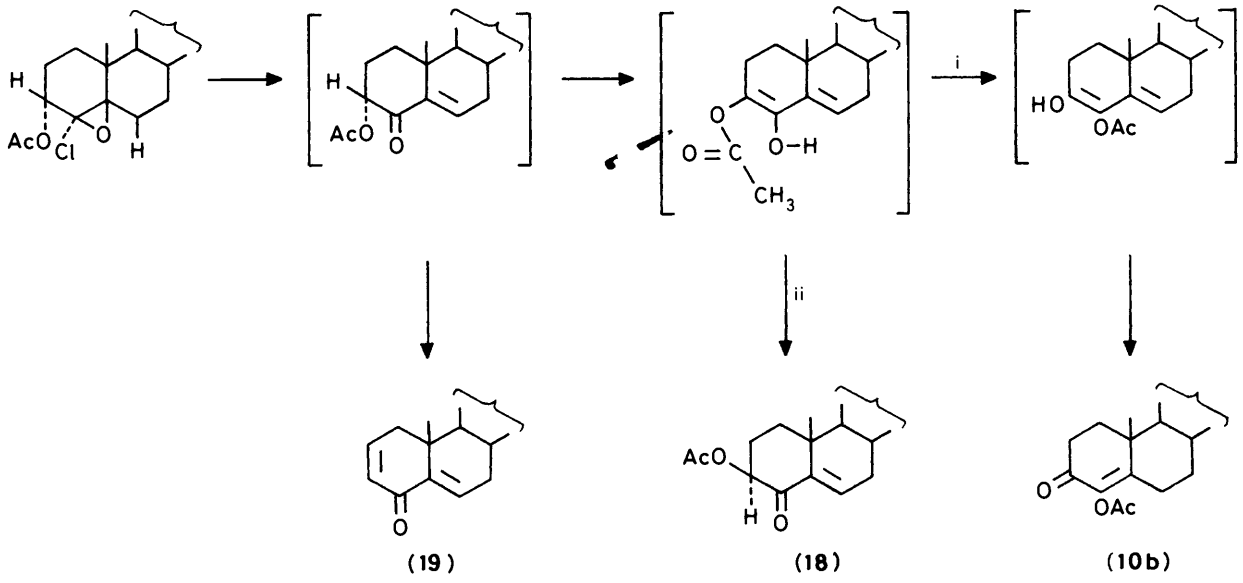
	5α					5β					
H	**(2)** 5α-Epoxide	**(12b)** 3-OAc, 5α-Cl	**(17)** 3β-Cl, 5α-OAc	**(21)** 3β-OAc, 5α-Cl	**(22)** 3β-OAc, 5α-H	**(3)** 5β-Epoxide	**(11b)** 3-OAc, 5β-Cl	**(14)**[a] 3β-OAc, 5β-Cl	**(15)** 3α-Cl, 5β-OAc	**(16)** Spiro	**(20)** 3α-OAc, 5β-Cl
1α[b]	1.70	2.57	1.92	2.06	1.54	1.61[c,d,e]	2.42		1.69	For	1.74
1β[b]	1.62	2.26	1.56	1.66	1.96	1.66[c,d,e]	2.66		1.92	Ring *A*	2.14
2α/2[b]	2.55	6.39	2.39	2.22	2.22	2.28	6.39		1.84	data	1.78
2β[b]	2.37		1.94	1.85	1.88	2.45			2.23	see	2.06
3α[b]			4.67	6.17	5.16			5.12		Table 5	
3β[b]									4.60		5.96
5					2.20[c,d,f]						
6α	1.86[d]	1.69[c,d]	2.11[d]	1.65[d]	1.63[d,f]	1.92[d]	1.63[c]	2.45	2.59	2.55[c,d]	2.43
6β	2.08[d]	1.35[c,d]	1.92[d]	1.48[d]	1.45[c,d]	2.14[d]	0.95[c]		1.48[c,f]	1.65[c,d,f]	1.93[c,d,f]
7α	1.22[d]	1.91[d]	0.96[d]	1.86[d]	0.83[d]	1.09[d]	1.92		1.60[c,d]	1.21[c,d]	1.25[c,d]
7β	1.83[d]	2.15[d]	1.55[c,d]	2.03[d]	1.76[d]	1.87[d]	2.63		1.64[d]	1.81[c,d]	1.62[c,d]
8	1.52[d]	1.45[d]	1.43[d]	1.46[d,f]	1.32[d,f]	1.65[d]	1.51[d]		1.49[d,f]	1.72[d,f]	1.50[d,f]
9	1.15[d]	1.70[d]	1.57[d]	1.72[d]	0.94[d]	1.17[d]	1.54[d]		0.98[d]	1.13[d,f]	0.97[c,d]
11α	1.50[d]	1.49[d]	1.45[d]	1.52[d]	1.61[d]	1.45[d]	1.4[d]		1.32[d]	1.65[d,f]	1.48[d]
11β	1.33[d]	1.32[d]	1.28[d]	1.24[d]	1.26[d]	1.3[d]	1.4[d]		1.32[d]	1.46[d,f]	1.37[d,f]
12α	1.21[c]	1.27[c,d]	1.23[c,d]	1.26[c,d,g]	1.21[c,d,f]	1.19[c]	1.22[c,d]		1.13[c,d]	1.20[c,d,f,g]	1.15[c,f]
12β	1.77[d]	1.79[d]	1.77[d]	1.80[d,f]	1.76[d]	1.78[c,d]	1.72		1.74[d,f]	1.81	1.75[c,d,f]
14	1.20[d]	1.18[d]	1.11[d]	1.03[d]	1.05[d,f]	1.12[d]	0.98		1.04[d]	1.12[d,f]	0.98[c,d,f]
15α	1.73[c]	1.68[c]	1.60[d]	1.66[d]	1.64[d]	1.69[c]	1.55[c]		1.66[d]	1.68[d]	1.60[d]
15β	1.38[c]	1.35[d]	1.31[d]	1.33[d]	1.32[d]	1.38[d]	1.26[c]		1.28[d]	1.42[d]	1.28[d]
16α	2.18[c]	2.18[c]	2.15[c,d]	2.20[c,d]	2.16[c,d]	2.18[c]	2.13[c]		2.17[c,d]	2.20[c,d]	2.15[c,d]
16β	1.52[c]	1.51[c]	1.51[c,d]	1.53[c,d]	1.51[c,d,f]	1.52[c]	1.50[c]		1.51[c,d]	1.50[c,d]	1.50[c,d]
17α	4.62	4.63	4.62	4.61	4.60	4.59	4.56	4.55	4.54	4.58	4.56
10-Me	1.100	1.130	0.852	0.944	0.754	1.163	1.248	1.20	1.126	1.810	1.203
13-Me	0.822	0.795	0.790	0.772	0.772	0.813	0.766	0.77	0.747	0.73	0.768
3-OAc		2.234		2.146	2.213		2.237	2.087		2.152	2.170
5-OAc			2.148						2.086		
17-OAc	2.033	2.037	2.029	2.025	2.028	2.029	2.012	2.030	2.015	2.031	2.027

[a] Insufficient material for detailed analysis. [b] Ring *A* shifts are the result of iterative simulation. [c] Shift obtained from COSY spectrum. [d] Shift obtained from heteronuclear correlation spectrum. [e] Not iterated; lines highly overlapped. [f] Shift obtained from n.O.e. difference experiment. [g] Shift obtained from difference double-resonance experiment.

Table 4. ^{1}H–^{1}H Couplings[a]

	5α					5β				
	(2) 5α-Epoxide	(12b) 3-OAc, 3α-Cl	(17) 3β-Cl, 5α-OAc	(21) 3β-OAc, 5α-Cl	(22) 3β-OAc, 5α-H	(3) 5β-Epoxide	(11) 3-OAc, 5β-Cl	(14) 3β-OAc, 5β-Cl	(15) 3α-Cl, 5β-OAc	(20) 3α-OAc, 5β-Cl
^2J(1α,1β)	−13.48	−18.73	−13.93	−14.00	−13.66	−13.5[b]	−19.00		−14.75	−15.25
^3J(1α,2α)	6.24	2.48[c]	4.99	4.72	4.01	6.22	7.08[c]		3.00	4.04
^3J(1α,2β)	12.78		13.88	13.70	13.67	2.63			3.09	3.04
^3J(1β,2α)	1.80	6.42[d]	2.48	2.47	2.80	13.70	2.39[d]		14.63	14.96
^3J(1β,2β)	7.22		4.56	5.21	4.35	4.94			3.79	4.05
^2J(2α,2β)	−19.54		−13.77	−13.80	−12.80	−18.67			−13.27	−12.41
^3J(2α,3)			7.17	8.16	7.35			3.3[e]	12.61	12.63
^3J(2β,3)			12.65	12.10	12.56			3.4[e]	6.47	7.41
^4J(3,5)					1.21					
^3J(5,6α)					3.16					
^3J(5,6β)					12.40					

[a] Root mean square deviation 0.05—0.20 Hz; standard errors 0.03—0.20 Hz. [b] Not iterated; lines highly overlapped. [c] J(1α,2). [e] Insufficient material for detailed analysis; first-order approximation.



Scheme 7. i, 3,4-Acetoxy shift; ii, C-3 protonation

Experimental

^{1}H N.m.r. spectra were recorded for solutions (30—100mM) in deuteriochloroform with a Bruker AM 300 spectrometer, using a 5 mm dual ^{13}C/^{1}H probe. Proton and carbon spectra were recorded for each compound, and carbon multiplicities were determined with the DEPT[11] sequence. Homonuclear correlation (COSY)[9] and heteronuclear correlation (C–H)[10] spectra were recorded for all compounds except (**15**). Proton and carbon shifts were assigned by complementary analysis of the COSY and heteronuclear correlation spectra (Tables 2 and 3). N.O.e. difference spectroscopy[8] and difference double-resonance techniques[8] were used to confirm the shift assignments and to confirm or establish some of the stereochemical assignments. Individual proton multiplets observed with these techniques had structures consistent with the proposed assignments in every case. Because the ring *A* protons are tightly coupled, the ring *A* proton spectra were analysed with the PANIC program[12] on an ASPECT 3000 computer using previously reported techniques.[13] This analysis was necessary to ensure reliable ring *A* coupling constants. Tables 1 and 2 give the ^{1}H and ^{13}C n.m.r. data.

H.p.l.c. was carried out on a Waters μ-Porasil (10 μm) column in 10% ethyl acetate–hexane (unless otherwise stated) with a 1.5 ml min^{-1} flow rate (Waters M45 instrument and RI detector). Thin-layer chromatography refers to precoated silica gel plates (Merck 60 F254) run in 10—25% ethyl acetate–hexane unless otherwise stated; plates were sprayed with 4% concentrated sulphuric acid in ethanol and heated 5—10 min at 110 °C to produce a characteristic colour. Column chromatography was carried out on either neutral alumina or silica gel (Merck type 60 H for t.l.c.). Elemental analyses were performed by Mr. W. Baldeo, School of Pharmacy, University of London, England.

4-Chlorotestosterone Acetate (**1**).—The acetate (**1**), m.p. 228—231 °C (lit.,[14] 228—230 °C), was prepared from testosterone acetate by the method of Mori.[15]

17β-Acetoxy-4β-chloro-4,5-epoxy-5α-androstan-3-one (**2**).—The 5α-epoxy 3β-alcohol (**6a**) (300 mg) in acetone was treated with an excess of Jones reagent for 5 min to give the *5α-epoxy ketone* (**2**) (225 mg), m.p. 161—163 °C (Found: C, 66.2; H, 7.6; Cl, 9.3. $C_{21}H_{29}ClO_4$ requires C, 66.2; H, 7.7; Cl, 9.3%).

17β-*Acetoxy*-4α-*chloro*-4,5-*epoxy*-5β-*androstan*-3-*one* (**3**).—(a) *From* 4-*chlorotestosterone acetate* (**1**). To the acetate (**1**) (1.1 g) in methanol (105 ml) cooled to 5 °C were added 4M NaOH (4.5 ml) and 10% H_2O_2 (4.5 ml), and cooling was maintained for 18 h. The mixture was acidified with HOAc, diluted with water, and extracted with ether to give a crystalline product, which was dissolved in pyridine (10 ml). Acetic anhydride (5 ml) was added. The mixture was set aside overnight at 20 °C then poured into ice–water, acidified, and extracted with ether. The crystalline product (1.0 g) consisted of two components (t.l.c.), separated by two solvent developments (5α:5β 2:3 by h.p.l.c. in dichloromethane). Recrystallization gave the 5β-*epoxide* (**3**) (230 mg), m.p. 153—162 °C (from dichloromethane–acetone). Several recrystallizations gave a sample of m.p. 162—166 °C (Found: C, 66.0; H, 7.7; Cl, 9.1. $C_{21}H_{29}ClO_4$ requires C, 66.2; H, 7.7; Cl, 9.3%). The h.p.l.c. fraction containing the 5α-epoxide (**2**) gave a ^1H n.m.r. spectrum identical with that of the product from (**6a**).

(b) *From the* 5β-*epoxy* 3α-*alcohol* (**9a**). The alcohol (**9a**) (100 mg) in acetone was treated with an excess of Jones reagent for 5 min to give the 5β-epoxy ketone (**3**) (70 mg), m.p. 160—165 °C; the ^1H n.m.r. spectrum was the same as that of the product from (**1**).

17β-*Acetoxy*-3α-*hydroxy*- (**4**) *and* 17β-*Acetoxy*-3β-*hydroxy*-(**5a**) 4-*chloroandrost*-4-*ene*.—4-Chlorotestosterone acetate (**1**) (10 g) and 85% w/w lithium hydrido tri-(t-butoxy)aluminate (16.8 g) were dissolved in freshly distilled tetrahydrofuran (450 ml) in an ice-bath under argon. The mixture was stirred for 3 h, after which no starting material remained (t.l.c.; 2% acetone–dichloromethane). The mixture was poured into an excess of cold dilute hydrochloric acid and extracted with dichloromethane. The organic layer was washed with water, dried (Na_2SO_4), and evaporated. T.l.c. of the crystalline residue showed one minor and one major component (2% acetone–dichloromethane) (3α:3β 0.7:9.3 by h.p.l.c.). Column chromatography over silica gel in 10% dichloromethane–cyclohexane (elution with 15% dichloromethane–hexane, with 5% increments of CH_2Cl_2) gave the 3β-*alcohol* (**5a**) (6.7 g), m.p. 172—174 °C (from dichloromethane–ethyl acetate) (Found: C, 68.5; H, 8.7; Cl, 9.7. $C_{21}H_{31}ClO_3$ requires C, 68.7; H, 8.5; Cl, 9.7%). Elution with 2—3% acetone–dichloromethane gave fractions (0.51 g) which on three recrystallizations afforded the 3α-*alcohol* (**4**) (250 mg), m.p. 177—179 °C (from dichloromethane–ethyl acetate) (Found: C, 68.6; H, 8.6; Cl, 9.5. $C_{21}H_{31}ClO_3$ requires C, 68.7; H, 8.5; Cl, 9.7%).

3β,17β-*Diacetoxy*-4-*chloroandrost*-4-*ene* (**5b**). The 3β-alcohol (**5a**) (400 mg) was dissolved in dry pyridine (4 ml), acetic anhydride (2 ml) was added, and the mixture was kept at room temperature overnight. Dilution with ice–water, acidification, extraction with ether, and evaporation of the solvent left a residue, which gave the 3β-acetate (**5b**) (315 mg), m.p. 145—147 °C (from dichloromethane–methanol) (lit.,[16] 145—147 °C).

17β-*Acetoxy*-4-*chloro*-3β-*t*-*butyldimethylsilyloxyandrost*-4-*ene* (**5c**).—To a stirred mixture of the 3β-alcohol (**5a**) (6.7 g) and dry dimethylformamide (DMF) (13.4 ml) were added Bu^tMe_2SiCl (3.3 g) and imidazole (3.1 g) as described by Corey.[17] After 20 min at room temperature the mixture was diluted with sodium hydrogen carbonate solution and extracted with ether. Recrystallization from acetone gave the *siloxane* (**5c**) (6.4 g), m.p. 146—149 °C (Found: C, 67.5; H, 9.4; Cl, 7.2. $C_{27}H_{45}ClO_3Si$ requires C, 67.4; H, 9.4; Cl, 7.4%).

17β-*Acetoxy*-4β-*chloro*-3β-*hydroxy*-4,5-*epoxy*-5α-*androstane* (**6a**).—(a) *From the* 5α-*epoxy ketone* (**2**). To a solution of the 5α-epoxy ketone (**2**) (50 mg) in dry ether (50 ml) was added 85% w/w LTBA (72 mg). The mixture was stirred at room temperature for 2 h and acetone (2 ml) was added. The mixture was poured into an excess of cold dilute HCl and extracted with ether to yield a crystalline product (49 mg), m.p. 115—123 °C. The ^1H n.m.r. spectrum showed a mixture of 3-epimers (α:β 1:11). Recrystallization gave the 5α-epoxy 3β-alcohol (**6a**) (20 mg), m.p. 123—125 °C (from ether–acetone), identical (^1H n.m.r.) with that obtained from (**6c**).

(b) *From the* 5α-*epoxy siloxane* (**6c**). To a solution of the 5α-epoxy siloxane (**6c**) (196 mg) in dry tetrahydrofuran (2.5 ml) was added tetrabutylammonium fluoride (1 ml; 1M solution in tetrahydrofuran), as described by Corey.[17] After 30 min the mixture was diluted with water and extracted with ether to give the 5α-*epoxy* 3β-*alcohol* (**6a**) (94 mg), m.p. 119—123 °C (from dichloromethane–methanol) (Found: C, 66.0; H, 8.3; Cl, 9.15. $C_{21}H_{31}ClO_4$ requires C, 65.9; H, 8.2; Cl, 9.3%).

3β,17β-*Diacetoxy*-4β-*chloro*-4,5-*epoxy*-5α-*androstane* (**6b**).—The 3β-acetate (**5b**) (1 g) was dissolved in dichloromethane (50 ml) and 85% *m*CPBA (987 mg) was added at room temperature.

Table 5. Ring *A* ^1H data (δ values; *J* in Hz) for spiro compound (**16**)[a]

H-1	5.498	$^3J(1,2eq)$	6.14 ± 0.04
H-2*eq*	2.645	$^3J(1,2ax)$	2.01 ± 0.04
H-2*ax*	2.415	$^2J(2eq,2ax)$	−16.32 ± 0.04
H-3*ax*	5.347	$^3J(2eq,3ax)$	7.94 ± 0.04
		$^3J(2ax,3ax)$	11.81 ± 0.04

[a] Uncertainties are 2 × probable errors; root mean square deviation 0.032 Hz.

Table 6. Nuclear Overhauser effects

	Protons showing n.O.e.					
	5α				5β	
Protons irradiated	(**2**) 5α-Epoxide	(**17**) 3β-Cl,5α-OAc	(**21**) 3β-OAc,5α-Cl	(**22**) 3β-OAc,5α-H	(**15**) 3α-Cl,5β-OAc	(**20**) 3α-OAc,5β-Cl
2α	2β, 1α	2β, 3β				
2β	2α				2α, 3β	
3		2α, 1α	2α	1α, 5	2α	2β
6α					6β	6β, 7β
17α			16α, 12α	12α, 14, 16α		12α, 14, 16α
10-Me	2β, 6β, 8	1β, 2β, 6β, 8	1β, 2β, 8, 11β	2β, 8, 11β	5-OAc, 6β	1β, 11β, 13-Me
13-Me					8, 13-Me	
			8, 12β	8, 11β	8, 11β, 12β	8, 11β, 12β
			17-OAc		10-Me, 17-OAc	17-OAc

Next day t.l.c. showed no starting material and the formation of two products (5α:5β 2:1 by h.p.l.c.). The mixture was washed thoroughly with an excess of 10% sodium sulphite, 5% sodium carbonate, and water to give, after evaporation at reduced pressure, a crystalline product. Several recrystallizations from dichloromethane–methanol gave the *epoxide* (**6b**) (381 mg), m.p. 158—160 °C (Found: C, 64.9; H, 7.7; Cl, 8.5. $C_{23}H_{33}ClO_5$ requires C, 65.0; H, 7.8; Cl, 8.3%).

17β-*Acetoxy*-4β-*chloro*-3β-*t-butyldimethylsilyloxy*-4,5-*epoxy*-5α-*androstane* (**6c**).—To a solution of the siloxane (**5c**) (6.0 g) in dichloromethane (120 ml) was added 85% w/w *m*CPBA (5.1 g). After 18 h at room temperature the reaction was worked up as for the 5β-epoxy alcohol (**9a**) to give the 5α-epoxy siloxane (**6c**) (2.9 g), m.p. 170—173 °C (Found: C, 65.2; H, 9.0; Cl, 7.0. $C_{27}H_{45}ClO_4Si$ requires C, 65.2; H, 9.1; Cl, 7.1%).

17β-*Acetoxy*-4α-*chloro*-3α-*hydroxy*-4,5-*epoxy*-5β-*androstane* (**7a**).—To a solution of the 5β-epoxy ketone (**3**) (83 mg) in dry ether (28 ml) was added 85% w/w LTBA (103 mg) and the mixture was stirred for 2 h at room temperature. After work-up as described for the conversion of (**2**) into (**5a**), the ^1H n.m.r. spectrum of the crude crystalline product (83 mg) showed a mixture of 3-epimers (α:β 12:1). Recrystallization gave the 5β-epoxy 3α-alcohol (**7a**) (52 mg), m.p. 207—209 °C (from dichloromethane–ethyl acetate). Reduction of (**3**) with 1 mol equiv. of $NaBH_4$ in ethanol gave a mixture of 3-epimers (α:β 4:1 by ^1H n.m.r.). Satisfactory elemental analyses were not obtained for this thermolabile compound.

3α,17β-*Diacetoxy*-4α-*chloro*-4,5-*epoxy*-5β-*androstane* (**7b**).—The 5β-epoxy 3α-alcohol (**7a**) (500 mg) in dry pyridine (10 ml) was treated with acetic anhydride (5 ml) at room temperature. After 30 min reaction (monitored by t.l.c.) was complete and the mixture was diluted with ice–water, acidified with dilute HCl, and extracted with ether. Evaporation left a crystalline residue (510 mg), m.p. 125—129 °C. Recrystallization gave the 5β-*epoxy* 3α-*acetate* (**7b**) (387 mg), m.p. 127—130 °C (from dichloromethane–acetone) (Found: C, 64.2; H, 7.8; Cl, 10.1. $C_{23}H_{33}ClO_5 \cdot 0.25CH_2Cl_2$ requires C, 63.9; H, 7.7; Cl, 10.1%; sample dried at 25 °C).

17β-*Acetoxy*-4β-*chloro*-3α-*hydroxy*-4,5-*epoxy*-5α-*androstane* (**8a**).—The 3α-alcohol (**4**) (254 mg) in dichloromethane (2 ml) was cooled in an ice-bath and 85% w/w *m*CPBA (447 mg) was added. After 24 h reaction was not complete (t.l.c.); a second portion of *m*CPBA (152 mg) was added and the reaction continued for a further 24 h. The mixture was worked up as for the 5β-epoxy alcohol (**9a**) to give the 5α-*epoxy alcohol* (**8a**) (68 mg), m.p. 128—133 °C (from dichloromethane–methanol); further recrystallization gave a pure sample (25 mg), m.p. 131—134 °C (Found: C, 65.6; H, 8.1; Cl, 9.4. $C_{21}H_{31}ClO_4$ requires C, 65.9; H, 8.2; Cl, 9.3%).

3α,17β-*Diacetoxy*-4β-*chloro*-4,5-*epoxy*-5α-*androstane* (**8b**).—The 5α-epoxy 3α-acetate (**8a**) (68 mg) was treated with acetic anhydride and pyridine as described for the acetylation of (**7a**), to give the 5α-*epoxy* 3α-*acetate* (**8b**) (50 mg), m.p. 206—210 °C (from dichloromethane–methanol) (Found: C, 64.8; H, 7.8; Cl, 8.6. $C_{23}H_{33}ClO_5$ requires C, 65.0; H, 7.8; Cl, 8.3%).

17β-*Acetoxy*-4α-*chloro*-3β-*hydroxy*-4,5-*epoxy*-5β-*androstane* (**9a**).—To the 3β-alcohol (**5a**) (250 mg) in dichloromethane (50 ml) was added 85% w/w *m*CPBA (275 mg), and the solution was kept at room temperature until no starting material remained (t.l.c.; 18 h). The organic layer was washed thoroughly with aqueous 10% sodium sulphite, aqueous 5% sodium carbonate, dried (Na_2SO_4), and evaporated at reduced pressure and room temperature. The crystalline residue showed two components on t.l.c. (5α:5β 1:2.5 by h.p.l.c.). Recrystallization gave the 5β-*epoxy* 3β-*alcohol* (**9a**) (200 mg), m.p. 130—133 °C (from dichloromethane–ethyl acetate) (Found: C, 65.9; H, 8.5; Cl, 9.3. $C_{21}H_{31}ClO_4$ requires C, 65.9; H, 8.2; Cl, 9.3%). The ^1H n.m.r. spectrum of the reaction mixture showed (by difference) the presence of the 5α-epoxy 3β-alcohol (**6a**).

3β,17β-*Diacetoxy*-4α-*chloro*-4,5-*epoxy*-5β-*androstane* (**9b**).—The 5β-epoxy 3β-alcohol (**9a**) (253 mg) was dissolved in dry pyridine (2.5 ml) and acetic anhydride (1.25 ml) was added. After 3 h at room temperature t.l.c. showed no starting material and the mixture was diluted with ice–water, acidified, and extracted with dichloromethane. The product gave the 5β-*epoxy* 3β-*acetate* (**9b**) (228 mg), m.p. 121—123 °C (from cyclohexane); further recrystallization gave material of m.p. 123—125 °C (Found: C, 65.0; H, 7.9; Cl, 8.6. $C_{23}H_{33}ClO_5$ requires C, 65.0; H, 7.8; Cl, 8.3%).

17β-*Acetoxy*-4-*hydroxyandrost*-4-*en*-3-*one* (**10a**).—(a) *By thermolysis.* (i) A flask containing the 5β-epoxy 3β-alcohol (**9a**) (200 mg) attached to a water pump was immersed in an oil-bath preheated to 200 °C and the temperature was maintained at 190—200 °C until effervescence ceased (10 min). The residue was recrystallized to give the diosphenol (**10a**) (111 mg), m.p. 191—192 °C (from dichloromethane–methanol) (lit.,[14] 194—196 °C). A preparation from 4-chlorotestosterone (7.5 g) without isolation of intermediate gave (**10a**) (3 g), m.p. 182—187 °C.

(ii) When the 5α-epoxy 3α-alcohol (**8a**) (22 mg) was treated as in (i), the diosphenol (**10a**) (14 mg), m.p. 190—192 °C was obtained.

(iii) When the 5β-epoxy 3α-alcohol (**7a**) (24 mg) was treated as in (i), the diosphenol (**10a**) (12 mg), m.p. 189—190 °C was obtained.

(iv) When the 5α-epoxy 3β-alcohol (**6a**) (100 mg) was treated as in (i) the diosphenol (**10a**) (55 mg), m.p. 184—186 °C was obtained.

All products showed identical ^1H n.m.r. spectra, in agreement with expectation for the diosphenol (**10a**).

(b) *By treatment with zinc–copper couple.* (i) To the 5β-chloro diosphenol (**11a**) (100 mg) in ethanol (5 ml) was added Zn–Cu couple[18] (1.3 g) and the mixture was heated to reflux for 30 min to give the diosphenol (**10a**) (40 mg), m.p. 188—193 °C (lit.,[14] m.p. 194—196 °C).

(ii) Treatment of the 5α-chloro diosphenol (**12a**) (70 mg) with Zn–Cu couple (900 mg) in ethanol (3 ml) gave the diosphenol (**10a**) (30 mg), m.p. 189—192 °C, identical (^1H n.m.r.) with that obtained in (i).

(iii) To the 5β-chloro diacetate (**11b**) (100 mg) in ethanol (5 ml) was added freshly prepared Zn–Cu couple[18] (1.3 g). The mixture was heated to reflux for 30 min, filtered, and evaporated at reduced pressure. The product was passed over neutral alumina in dichloromethane–hexane to give the diosphenol diacetate (**10b**) (54 mg), m.p. 168—171 °C (from acetone) (lit.,[14] 170—172 °C); and the diosphenol (**10a**) (22 mg), m.p. 189—192 °C (from dichloromethane–methanol) (lit.,[14] 194—196 °C).

(iv) Similar treatment of the 5α-chloro diosphenol (**12b**) (100 mg) gave the diosphenol acetate (**10b**) (53 mg), m.p. 168—171 °C, and the diosphenol (**10a**) (23 mg), m.p. 186—190 °C.

17β-*Acetoxy*-5-*chloro*-3-*hydroxy*-5β-*androst*-2-*en*-4-*one* (**11a**).—The 5β-epoxy ketone (**3**) (200 mg) was heated to reflux in pyridine for 45 min, after which no starting material remained (t.l.c.; two developments). The solution was poured into ice–water and extracted with ether to give the 5β-*chloro diosphenol* (**11a**) (120 mg), m.p. 162—166 °C (from cyclohexane) (Found: C, 66.5; H, 7.6; Cl, 9.1. $C_{21}H_{29}ClO_4$ requires C, 66.2; H, 7.7; Cl, 9.3%).

3,17β-*Diacetoxy*-5-*chloro*-5β-*androst*-2-*en*-4-*one* (**11b**).—The 5β-chloro diosphenol (**11a**) (100 mg) on treatment with acetic anhydride–pyridine (1:2) (1.5 ml) gave the 5β-*chloro diacetate* (**11b**) (70 mg), m.p. 198—201 °C (from dichloromethane–acetone) (Found: C, 65.6; H, 7.4; Cl, 8.1. $C_{23}H_{31}ClO_5$ requires C, 65.35; H, 7.4; Cl, 8.4%).

17β-*Acetoxy*-5-*chloro*-3-*hydroxy*-5α-*androst*-2-*en*-4-*one* (**12a**).—The 5α-epoxy ketone (**2**) (60 mg) was heated to reflux in pyridine for 45 min, after which no starting material remained (t.l.c.) and a more polar component had been formed. The solution was diluted with water and extracted with ether to give the *diosphenol* (**12a**), m.p. 178—184 °C (from acetone) (Found: C, 66.0; H, 7.6; Cl, 9.4. $C_{21}H_{29}ClO_4$ requires C, 66.2; H, 7.7; Cl, 9.3%).

3,17β-*Diacetoxy*-5-*chloro*-5α-*androst*-2-*en*-4-*one* (**12b**).—The 5α-chloro diosphenol (**12a**) (200 mg) on treatment with acetic anhydride–pyridine (1:2; 3 ml) gave the *diacetate* (**12b**) (150 mg), m.p. 207—210 °C (from dichloromethane–acetone) (Found: C, 65.0; H, 7.45; Cl, 8.5. $C_{23}H_{31}ClO_5$ requires C, 65.25; H, 7.4; Cl, 8.4%).

17β-*Acetoxy*-4-*hydroxyandrosta*-4,6-*dien*-3-*one* (**13**).—(i) A flask containing the 5α-epoxy ketone (**2**) (600 mg) attached to a water pump was immersed in an oil-bath preheated to 240 °C for 5 min. The residue was recrystallized to give the *dienol* (**13**) (150 mg), m.p. 197—198 °C (from dichloromethane–acetone) (Found: C, 73.1; H, 8.4. $C_{21}H_{28}O_4$ requires C, 73.2; H, 8.2%).

(ii) When the 5β-epoxy ketone (**3**) (200 mg) was treated as in (i) the *dienol* (**13**) (105 mg), m.p. 188—194 °C, was obtained.

(iii) When the 5β-chloro diosphenol (**11a**) (240 mg) was treated as in (i) the dienol (**13**) (123 mg), m.p. 189—193 °C, was isolated.

(iv) When the 5α-chloro diosphenol (**12a**) (350 mg) was treated as in (i) the dienol (**13**) (220 mg), m.p. 186—190 °C, was isolated.

All products gave ^{1}H n.m.r. spectra corresponding to the dienol (**13**).

Thermolysis of 3β,17β-*Diacetoxy*-4β-*chloro*-4,5-*epoxy*-5α-*androstane* (**6b**).—A flask containing the 5α-epoxy 3β-acetate (**6b**) (40 mg) attached to a water pump was immersed in a preheated oil-bath (210 °C) maintained at 190—210 °C for 10 min. Three major components were separated by h.p.l.c. The least polar fraction (13.6 mg) gave 5,17β-*diacetoxy*-3β-*chloro*-5β-*androstan*-4-*one* (**14**), m.p. 235—236.5 °C (from dichloromethane–methanol) (Found: C, 65.1; H, 7.8; Cl, 8.6. $C_{23}H_{33}ClO_5$ requires C, 65.0; H, 7.8; Cl, 8.3%). The most polar fraction (12.4 mg) gave 5,17β-*diacetoxy*-3α-*chloro*-5β-*androstan*-4-*one* (**15**), m.p. 136—137 °C (from dichloromethane–methanol) (Found: C, 64.75; H, 7.8; Cl, 8.3. $C_{23}H_{33}ClO_5$ requires C, 65.0; H, 7.8, Cl, 8.3%). The fraction of intermediate polarity (7 mg) gave (1′S,5′S)-5′17β-*diacetoxy*-2′-*methylspiro*-[7,19-*dinordes*-A-*androstane*-10,1′-*cyclohex*-2′-*en*]-6′-*one* (**16**), m.p. 193—194.5 °C (from dichloromethane–methanol) (Found: C, 71.25; H, 8.2. $C_{23}H_{32}O_5$ requires C, 71.1; H, 8.3%).

Thermolysis of 3α.17β-*Diacetoxy*-4α-*chloro*-4,5-*epoxy*-5β-*androstane* (**7b**).—A flask containing the 5β-epoxy 3α-acetate (**7b**) (445 mg) attached to a water pump was immersed in a preheated oil-bath (130 °C) until melting and evolution of gas was complete (3.5 min). The major components were separated by column chromatography over silica gel in dichloromethane; components were eluted in the following order.

Combined fractions (180 mg) were recrystallized to give 5,17β-*diacetoxy*-3β-*chloro*-5α-*androstan*-4-*one* (**17**) (56 mg), m.p. 258—259 °C (from dichloromethane–acetone) (Found: C, 65.0; H, 7.8; Cl, 8.5. $C_{23}H_{33}ClO_5$ requires C, 65.0, H, 7.8; Cl, 8.3%).

Fractions (22 mg) were further purified by h.p.l.c. (15 mg) and recrystallized to give 17β-*acetoxyandrosta*-2,5-*dien*-4-*one* (**19**) (11 mg), m.p. 180—183 °C [from light petroleum (b.p. 60—80 °C)] (lit.,[19] 179—181 °C); ^{1}H n.m.r. spectrum in agreement with published values.[19]

Fractions (156 mg) were recrystallized to give 3β,17β-*diacetoxyandrost*-5-*en*-4-*one* (**18**) (60 mg), m.p. 102—103 and 125—128 °C (from ether–acetone) (Found: C, 70.9; H, 8.2. $C_{23}H_{32}O_5$ requires C, 71.1; H, 8.3%).

Fractions (21 mg) were recrystallized to give 4,17β-*diacetoxyandrost*-4-*en*-3-*one* (**10b**) (15 mg), m.p. 171—173 °C (from acetone) (lit.,[14] 170—172 °C). When the reaction was carried out at 190—200 °C a larger proportion of (**10b**) and (**19**) was obtained.

3α-17β-*Diacetoxy*-5-*chloro*-5β-*androstane* (**20**).—The 5α-epoxy 3α-acetate (**8b**) (40 mg) attached to a water pump was immersed in a preheated oil-bath (210 °C) maintained at 190—210 °C for 10 min. The residue was recrystallized to yield the 3α-*acetoxy*-5β-*chloro* 4-*ketone* (**20**) (24 mg), m.p. 208—210 °C (from dichloromethane–methanol) (Found: C, 65.3; H, 7.8; Cl, 8.5. $C_{23}H_{33}ClO_5$ requires C, 65.0; H, 7.8; Cl, 8.3%).

3β,17β-*Diacetoxy*-5-*chloro*-5α-*androstan*-4-*one* (**21**).—A flask containing the 5β-epoxy 3β-acetate (**9b**) (8.2 g) attached to a water pump was immersed in a preheated oil-bath (210 °C) maintained at 190—210 °C for 10 min. The crystalline residue gave the 3β-*acetoxy*-5α-*chloro* 4-*ketone* (**21**) (7.2 g), m.p. 172—173 °C (analytical sample, m.p. 173—173.5 °C) (from dichloromethane–methanol) (Found: C, 65.0; H, 7.8; Cl, 8.5. $C_{23}H_{33}ClO_5$ requires C, 65.0; H, 7.8; Cl, 8.3%). A preparation from 4-chlorotestosterone acetate (1.8 g) without isolation of intermediates gave (**21**) (760 mg), m.p. 165—168 °C.

3β,17β-*Diacetoxy*-5α-*androstan*-4-*one* (**22**).—The 3β-acetoxy-5α-chloro 4-ketone (**21**) (518 mg) was dissolved in ethanol (25 ml) and Zn–Cu couple[18] (5 g) was added. The mixture was stirred for 5 min at room temperature, then filtered, and the filtrate was evaporated to dryness. Chromatography of the crude product over neutral alumina in benzene–hexane mixtures gave the *diacetate* (**22**) (154 mg), m.p. 137—139 °C (Found: C, 70.5; H, 8.7. $C_{23}H_{34}O_5$ requires C, 70.7; H, 8.8%).

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