Reactions of Androsta-3,5-dienes with *m*-Chloroperbenzoic Acid

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The reactions of androsta-3,5-diene and of androsta-3,5-dien-17-one with one or 2 molar equiv. of *m*-chloroperbenzoic acid give complex mixtures of products. Only low yields of diepoxides are formed using 2 equiv. of peracid in ether as solvent, unsaturated *vic*-3,4-diols being the major products. Use of 1 equiv. of peracid leads, *inter alia*, to unsaturated hydroxy-*m*-chlorobenzoates. The formation of these and other products are discussed.

WHILST the stereochemistry of epoxidation of steroidal olefins has been thoroughly investigated,[1] conjugated dienes have been rarely studied. We have examined the reactions of androsta-3,5-diene (1) and androsta-3,5-dien-17-one (2) with *m*-chloroperbenzoic acid. In this system the initial axial electrophilic attack, *i.e.* at 3α,4β, 5α, or 6β, may be directed to the α-face by interactions on the β-face between the reagent and C-19. Whereas simple allylic stabilization of a carbocation might favour reaction at C-3 or C-6, homoallylic participation of the Δ⁵-double bond with a developing cationic centre at C-3 involving a 3α,5-cyclo-steroid type of intermediate, might favour initial reaction at C-4β. The stereochemistry of the second epoxidation may, in part, be determined by a repulsive interaction between the non-bonding p-electrons of the epoxide and the olefin, leading to a higher electron density on the olefinic face *trans* to the epoxide. It has been our object to study the relative importance of these features in the 3,5-diene system.

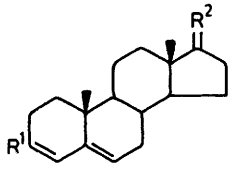
Although mono-epoxidation of simple alicyclic dienes is not generally possible,[2] this has been observed in some steroidal systems. Thus, for steroidal 5,7-dienes where both double bonds are trisubstituted, the 5(6)-double bond is attacked preferentially,[3] while for 7,9(11)-dienes, the 9(11)-double bond is usually attacked first by peracids.[4] Preferential epoxidation of the 5(10)-double bond of 5(10),9(11)-dienes [5] and of a 14(15)-double bond of 17-methoxycarbonyl-5α-androsta-14,16-dien-3β-yl acetate,[6] has been observed. The trisubstituted 4(5)-double bond of cholesta-2,4-diene is also attacked preferentially by perbenzoic acid but in this case the epoxide was not isolated owing to rapid hydrolysis to cholest-2-ene-4β,5α-diol.[7] The 3,5-dienol-esters of steroidal 4-en-3-ones have been reported [8] to give 6β-hydroxy-4-en-3-ones and, in some circumstances, the 5-*m*-chlorobenzoates of 3-acetoxy-5,6-dihydroxyandrost-3-enes.

Initial experiments with either of the dienes (1) or (2) using 1 or 2 molar equiv. of peracid in dichloromethane, chloroform, benzene, or ether, for various times, indicated the formation of a complex mixture of products in which mono- or di-epoxides were usually only minor components. Attempts to minimise epoxide opening by the *m*-chlorobenzoic acid produced during the reactions by carrying them out in the presence of a phosphate buffer, resulted in no significant increase in the amount of epoxides isolated. In subsequent experiments reactions were carried out for 3.5 h at 20 °C in ether since less attack by *m*-chlorobenzoate anion occurred in this solvent, possibly as a result of greater competitive solvation of the *m*-chlorobenzoic acid. However reproducible results were difficult to achieve and the ratio and diversity of products appeared to depend on minor changes in reaction conditions.

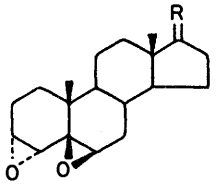
Three products were isolated by preparative t.l.c. from the reaction of androsta-3,5-diene (1) with 2 equiv. of *m*-chloroperbenzoic acid. These were (in order of decreasing R_F value) 3α,4α;5β,6β-diepoxyandrostane (3) (8%), androst-5-ene-3α,4β-diol (4) (26%), and androst-5-ene-3α,4α-diol (5) (10%). Although contiguous functional groups are better treated as a unit when calculating chemical-shift increments,[9] assignment of the configuration of the epoxy-groups in the diepoxide (3) followed from a consideration of ^{1}H n.m.r. 19-H_3 and 18-H_3 substituent increments [10–13] for steroidal 3(4) and 5(6)-monoepoxides (see Table 1). Although they have been prepared,[14] no ^{1}H n.m.r. data appears to be recorded for 3α,4α-epoxides in the 5β-series. Combination of the increments gives the calculated 19-H_3 and 18-H_3 chemical shifts for all of the possible 3(4);5(6)-diepoxides with the exception of the 3α,4α;5β,6β-epoxide. However, Lavie *et al.*[9] have pointed out that an α-substituent at C-4 in both the 5α- and 5β-series should have only a minor effect on the chemical shift of the 19-protons. A similar situation should hold for 3α-substituents and thus a 3α,4α-epoxide in the 5β-series should have substituent increments similar to those for the same group in the 5α-series. Tori and his co-workers [10] have found not only that the epoxy-proton signals in the ^{1}H n.m.r. spectra of α-isomers generally occur at higher field than those of β-isomers, but also that their patterns are characteristic of their locations and configurations. The pattern of a doublet at δ 2.51 (J 4.4 Hz) in the ^{1}H n.m.r. spectrum of the diepoxide (3) was similar to that recorded for the 6α-proton signal of a 5β,6β-epoxide while a two-proton multiplet at δ 3.18 was assigned to the 3β- and 4α-protons. These analyses lead to the 3α,4α;5β,6β-configuration for the diepoxide (3).

In the ^{1}H n.m.r. spectrum of the diol (4) the vinylic proton signal occurred as a doublet at δ 5.74 ($J_{6,7}$ 4.8 Hz) and the C-3 and C-4 proton signals occurred as a multiplet in the region, δ 3.78—4.32. Comparison of the observed chemical shifts of the 19-H_3 and 18-H_3

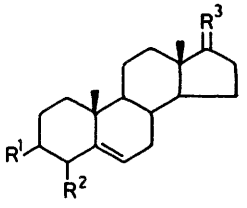
protons with those of the known isomeric 3β,4β-diol (6) [15] and with those calculated using substituent increments permitted assignment of the stereochemistry of the vicinal hydroxy-groups of (4) as 3α,4β (Table 2). In the ^{1}H n.m.r. spectrum of the diol (5) the vinylic proton gave rise to a multiplet centred at δ 5.88 while the C-3 and C-4 protons resonated as a multiplet in the region δ 4.01—4.40. Similar analysis (Table 2) to that



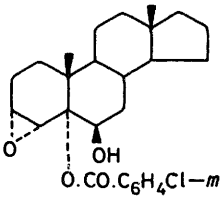
(1) R^1 = H, R^2 = H_2
(2) R^1 = H, R^2 = O
(13) R^1 = O·CO·C_6H_4Cl—*m*, R^2 = O



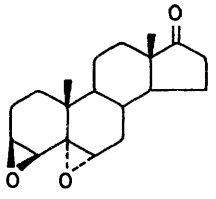
(3) R = H_2
(10) R = O



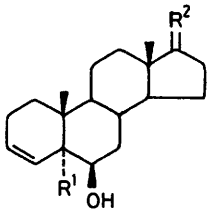
(4) R^1 = α—OH, R^2 = β—OH, R^3 = H_2
(5) R^1 = R^2 = α—OH, R^3 = H_2
(6) R^1 = β—OH, R^2 = β—OH, R^3 = H_2
(9) R^1 = α—OH, R^2 = β—O·CO·C_6H_4Cl—*m*, R^3 = H_2
(11) R^1 = α—OH, R^2 = β—OH, R^3 = O
(16) R^1 = β—O·CO·C_6H_4Cl—*m*, R^2 = β—OH, R^3 = O



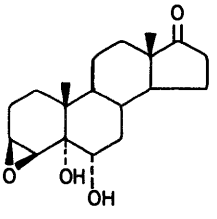
(7)



(14)



(8) R^1 = O·CO·C_6H_4Cl—*m*, R^2 = H_2
(12) R^1 = OH, R^2 = O



(15)

for the diol (4) showed that the vicinal hydroxy-groups of compound (5) possessed a *cis*-3α,4α-configuration. These stereochemical assignments were consistent with the expectation that the major product (4) would arise from the *trans*-diaxial opening [16] of a 3α,4α-epoxide. Moreover since an axial alcohol runs faster on a p.l.c. plate than an equatorial one, the axial-axial 3α,4β-diol should travel faster than an axial-equatorial 3α,4α-diol, as was observed.

In one experiment in which the epoxidation was carried out with 2 equiv. of peracid in dichloromethane for 12 h, the diepoxide (3) (49%) and a further product tentatively identified as 5α-(*m*-chlorobenzoyloxy)-3α,4α-epoxyandrostan-6β-ol (7) (28%) were isolated. The latter compound was not obtained crystalline although its analysis was consistent for the formulation $C_{26}H_{33}ClO_4$. The presence of hydroxy (3 480 cm^{-1}) and benzoyloxycarbonyl (1 722 cm^{-1}) groups was indicated by

TABLE 1

Substituent effects of 3,4- and 5,6-epoxides on the 19-H_3 and 18-H_3 proton signals

Δδ 5α-Series	19-H_3	18-H_3
3α,4α-Epoxide	−0.01	0.00
3β,4β-Epoxide	0.17	−0.01
5α,6α-Epoxide	0.25	−0.02
Δδ 5β-Series		
3β,4β-Epoxide	−0.04	−0.02
5β,6β-Epoxide	0.04	0.00
Calculated values [a]		
3α,4α; 5α,6α-Diepoxide	1.02	0.66
3α,4α; 5β,6β-Diepoxide [b]	0.95	0.68
3β,4β; 5α,6α-Diepoxide	1.20	0.66
3β,4β; 5β,6β-Diepoxide	0.92	0.69
Observed for (3)	0.96	0.67

[a] Based on 5α-androstane 19-H_3 = 0.78 and 18-H_3 = 0.69; and 5β-androstane 19-H_3 = 0.92 and 18-H_3 = 0.69. [b] Calc. on the basis of a 3α,4α-epoxide in the 5α-series.

the i.r. spectrum. The ^{1}H n.m.r. spectrum contained no signals below δ 4.5 other than those of aryl protons and thus the *m*-chlorobenzoyloxy-group was attached to a fully substituted carbon atom, *i.e.* C-5. A multiplet centred at δ 4.05 was assigned to a 6α-proton geminal to a hydroxy-group while a further multiplet in the region δ 3.1—3.6 could be assigned to the C-3 and C-4 protons. The 19-H_3 signal (δ 1.25) showed a large downfield shift relative to that of 5α-androstane (δ 0.78) reflecting the large substituent increments of a 6β-hydroxy (Δδ +0.23) and of that expected for a 5α-benzoyloxy-group (*cf.* Δδ +0.20 for 5α-OAc [11]). The assignment of structure (7) is supported by the fact that *trans*-diaxial opening of a 5β,6β-epoxide would be

TABLE 2

Chemical shifts for 19-H_3 and 18-H_3 in androst-5-ene-3,4-diols

Compound	19-H_3	18-H_3	6-H
5-Ene-3α,4α-diol (calc.)	1.02	0.73	
5-Ene-3α,4α-diol (5)	0.98	0.72	5.88
5-Ene-3α,4β-diol (calc.)	1.24	0.73	
5-Ene-3α,4β-diol (4)	1.20	0.80	5.74
5-Ene-3β,4β-diol (calc.)	1.27	0.73	
5-Ene-3β,4β-diol (6) [15]	1.25	0.72	5.70
5-Ene-3β,4α-diol (calc.)	1.27	0.73	

expected to lead to the observed product since any carbocationic character generated during the acid-catalysed epoxide opening is more likely to be centred on C-5 rather than on C-6.

Attempts to achieve monoepoxidation of androsta-3,5-diene using 1 equiv. of *m*-chloroperbenzoic acid in ether were unsuccessful. T.l.c. analysis showed that a considerable amount of starting material was still present after reaction for 24 h. Work-up after 8 days

gave the diepoxide (3) in low yield (2%), the 3α,4β-diol (4) (43%), and two isomeric *m*-chlorobenzoates which were assigned the structures 5α-(*m*-chlorobenzoyloxy)-androst-3-en-6β-ol (8) (12%) and 4β-(*m*-chlorobenzoyloxy)androst-5-en-3α-ol (9) (7%), from their spectral parameters. The ^{1}H n.m.r. spectrum of the less-polar ester (8) showed a two-proton multiplet at δ 5.30—5.65 due to the C-3 and C-4 vinylic protons while the equatorial 6α-proton appeared as a multiplet at δ 4.25 ($w_{\frac{1}{2}}$ 7 Hz). Assignment of a 5α-configuration for the *m*-chlorobenzoate group follows from the absence of a signal in the ^{1}H n.m.r. spectrum corresponding to a proton geminal to an ester group and from the assumption that the hydroxy-ester arises by *trans*-diaxial opening of a 5β,6β-epoxide. In such a case a C-5 carbocation would be stabilised by conjugation with the 3(4)-double bond. The ^{1}H n.m.r. spectrum of the more-polar ester (9) showed a one-proton multiplet at δ 5.95 ($w_{\frac{1}{2}}$ 9 Hz) corresponding to the C-6 vinylic proton. A doublet at δ 5.35 (J 3.5 Hz) corresponded to a proton geminal to an ester group which was coupled to one other proton and hence the *m*-chlorobenzoyloxy-group was assigned to the C-4 position. A multiplet at δ 4.02 ($w_{\frac{1}{2}}$ 5 Hz) was consistent with the signal expected for a C-3 equatorial proton which was geminal to a hydroxy-group. The origin of (9) may lie in the acid-catalysed *trans*-diaxial opening of the 3α,4α-epoxide.

Reaction of androsta-3,5-dien-17-one (2) with 2 equiv. of *m*-chloroperbenzoic acid in ether also afforded three isolable products. ^{1}H N.m.r. studies (see Table 3) showed that two of these, the diepoxide (10) (4%) and the 3α,4β-diol (11) (36%), were the 17-keto-analogues of the products (3) and (4) isolated from the diene (1). However the third product (13%) was identified as 5α,6β-dihydroxyandrost-3-en-17-one (12). The ^{1}H n.m.r. spectrum showed a two-proton multiplet at δ 5.85 ($w_{\frac{1}{2}}$ 2.5 Hz) (3-H and 4-H) and a one-proton multiplet at δ 3.90 ($w_{\frac{1}{2}}$ 6 Hz) corresponding to an equatorial 6-H. The observed chemical shifts for the 19-H_3 and 18-H_3 signals (δ 1.12 and 0.87) were in agreement with those (δ 1.18 and 0.84) calculated from substituent increments [9] that for a 3(4)-double bond obtained from the spectrum of 5α-cholest-3-ene.[17]

TABLE 3

Chemical shifts for androstan-17-ones (10) and (11)

Substituent	19-H_3	18-H_3
3α,4α;5β,6β-Diepoxide (calc.)	0.95	0.84
Observed for (10)	0.91	0.82
5-Ene-3α-4β-diol (calc.)	1.22	0.97
Observed for (11)	1.20	0.92

Treatment of androsta-3,5-dien-17-one with 1 equiv. of *m*-chloroperbenzoic acid in ether afforded the same products, (10) (4%), (11) (34%), and (12) (15%) as those formed with 2 equiv. of per-acid. In one experiment in which the solvent was benzene and the reaction was carried out for 5 days, the diepoxide (10) (10%) and a new compound, $C_{26}H_{29}ClO_3$ (14%) were obtained. The latter was assigned the structure 3-(*m*-chlorobenzoyloxy)-androsta-3,5-dien-17-one (13) since its n.m.r. spectrum showed two olefinic signals, δ 5.52 (m) and 5.64br (s). Alkaline hydrolysis of the compound followed by acidification yielded androst-4-ene-3,17-dione which was identical with a sample prepared by mild oxidation of testosterone.[18]

In one experiment in which androsta-3,5-dien-17-one was treated with 3 equiv. of *m*-chloroperbenzoic acid in benzene at 20 °C for 5 days, different results from those above were obtained. The major product (81%) was a new diepoxide, tentatively identified as 3β,4β;5α,6α-diepoxyandrostan-17-one (14). Its 19-H_3 and 18-H_3 signals in the ^{1}H n.m.r. spectrum (δ 1.30 and 0.89) correspond more closely with those expected for a 3β,4β;5α,6α-diepoxide (δ 1.23 and 0.83) than with those for the remaining two possibilities, *viz.* 3β,4α;5α,6α- or 3β,4β;5β,6β-diepoxides. Hydrolysis of the diepoxide (14) with sulphuric acid [19] gave an epoxydiol which was identical with a minor product isolated from the epoxidation and formulated as 3β,4β-epoxy-5α,6α-dihydroxy-androstan-17-one (15). Its 19-H_3 signal in the ^{1}H n.m.r. spectrum showed an upfield shift to give 19-H_3 and 18-H_3 chemical shifts in closer agreement with those calculated for a 5α,6α-dihydroxy-3β,4β-epoxide from substituent increments [9] than for any of the other possibilities (see Table 4). A signal at δ 2.42 (J 4 Hz) corresponded to a 3α-proton while a one-proton doublet at δ 2.97 (J 4 Hz) and a one-proton multiplet centred at δ 4.11 were assigned to H-4α and H-6β, respectively.

TABLE 4

Chemical shifts for 3,4-dihydroxy-5,6-epoxyandrostan-17-ones

Compound	19-H_3	18-H_3
3α,4β-Diol, 5α,6α-epoxide [a]	1.30	0.85
3β,4β-Diol, 5α,6α-epoxide [a]	1.33	0.87
5α,6β-Diol, 3β,4β-epoxide [a]	1.38	0.89
5α-6α-Diol, 3β,4β-epoxide [a]	1.08	0.87
Observed for (15)	1.12	0.82

[a] Calculated.

The products of the reactions may be rationalized as follows. In ether or methylene chloride, androsta-3,5-diene and its 17-ketone undergo initial axial attack at C-3α. The diols (4), (5), and (11) may arise by sufficient stabilization of an allylic carbocation to allow nucleophilic attack at C-4. The 3α,4α-diol (5) might arise by the internal return of the *m*-chlorobenzoate ion during epoxidation followed by hydrolysis whilst the 3α,4β-diols (4) and (11) would be the normal products of diaxial opening of a 3α,4α-epoxide.[1] Alternatively the 3α,4α-diol might have arisen by *cis*-cleavage of the steroidal epoxide (*cf.* ref. 20). Mechanistic studies [21] show that in acid-catalysed epoxide opening one of the oxiran carbon atoms can have a high degree of carbocation character. In the present case the 5(6) double-bond would stabilize a C-4 carbocation thereby assisting the formation of the *cis*-diol (5) with attack occurring at C-4 from the less-hindered face of the molecule. Some reaction occurs at C-6β facilitated by allylic stabilization of a C-5 carbocation. The 5α-*m*-chlorobenzoates (7)

and (8) may arise by hydrolysis of the 5β,6β-epoxide. The diepoxides, (3), (10), and (14), which are *trans*, demonstrate the possibility of a directing effect of the first epoxide on the formation of the second. The formation of the diepoxide (14) in benzene may show the influence of an initial cyclo-steroid dominated attack. This would favour initial axial attachment of the oxygen ar C-4β with the formation of the 3β,4β-epoxide and thence the 3β,4β;5α,6α-diepoxide. Alternatively the hydroxy-benzoate (16) might be formed from which the diaxial elimination of water would afford the dienol-benzoate (13).

Androsta-3,5-diene (1) [22] used in the above reactions was prepared from 3β-hydroxyandrost-5-en-17-one by Wolff-Kishner reduction of the 17-oxo-group, conversion of the 3β-hydroxy into a 3β-chloro-group and then dehydrohalogenation with lithium bromide–lithium carcarbonate in dimethylformamide. Phosphorus pentachloride [23] rather than thionyl chloride, gave a high yield of the chloro-compound. Dehydration of androst-5-en-3β-ol with phosphorus pentaoxide [24] gave a dimer, $C_{38}H_{58}$, and only a trace of androsta-3,5-diene.

EXPERIMENTAL

General experimental details have been described previously.[25]

Androsta-3,5-diene (1).—(*a*) Androsta-3,5-dien-17-one (4.0 g) (prepared in 100% yield by dehydrohalogenation of 3β-chloroandrost-5-en-17-one with lithium bromide and lithium carbonate in dimethylformamide) in digol (50 ml) was reduced with 64% aqueous hydrazine hydrate (10 ml) and potassium hydroxide (5.4 g). Crystallization of the product from hexane–acetone or chromatography from light petroleum on alumina gave androsta-3,5-diene as needles (3.0 g, 79%), m.p. 50—51 °C (lit.,[22] 52.5 °C, $[\alpha]_D^{20}$ −130°) (Found: C, 88.6; H, 11.0. Calc. for $C_{19}H_{28}$: C, 89.0; H, 11.0%), $\nu_{max.}$ 1 650 and 830 cm^{-1}; δ 0.81 (3 H, s, 18-H), 0.99 (3 H, s, 19-H), 5.40 (1 H, d, $J_{6,7}$ 4.5 Hz, 6-H), 5.52 (1 H, d, $J_{3,4}$ 10 Hz, 4-H), and 5.94 (1 H, dd, $J_{3,4}$ 10 Hz, $J_{2,3}$ 2.5 Hz, 3-H).

(*b*) Androst-5-en-3β-ol (4.15 g) was heated under reflux with phosphorus pentaoxide (10 g) in benzene (200 ml) for 30 min while water was removed with a Dean and Stark apparatus. Chromatography of the product from light petroleum on alumina yielded androsta-3,5-diene (0.10 g), m.p. and mixed m.p. 50—51 °C. Further elution with light petroleum gave a *dimer* which crystallized from acetone–light petroleum as needles (3.16 g, 81%), m.p. 244—246 °C, $[\alpha]_D^{20}$ −164° (*c* 0.2) (Found: $M^{+\bullet}$ 514.452 9. $C_{38}H_{58}$ requires *M*, 514.453 6), $\lambda_{max.}$ 274 nm (ε 43), δ 0.71 (6 H, s, 18-H), 1.04 (6 H, s, 19-H), and 6.76 (1 H, s, olefinic-H).

Reaction of Androsta-3,5-diene with m-*Chloroperbenzoic Acid.*—(a) *With 2 equiv.* A solution of 91% *m*-chloroperbenzoic acid (0.82 g) in ether (5 ml) was added to a stirred solution of androsta-3,5-diene (1) (0.60 g) in ether (15 ml) at 20 °C. The mixture was stirred for 3.5 h and then washed with sodium metabisulphite solution, water, and saturated sodium hydrogen carbonate solution. Solvent was removed from the dried solution to give an oil (0.67 g) which was separated by p.l.c. with ether–hexane (5 : 1) to yield (i) 3α,4α;5β,6β-*diepoxyandrostane* (3) (51 mg, 8%), which crystallized from acetone as needles, m.p. 75—78 °C, $[\alpha]_D^{19}$ −9° (*c* 1.1) (Found: C, 78.9; H, 9.8. $C_{19}H_{28}O_2$ requires C, 79.2; H, 9.7%), $\nu_{max.}$ 906 cm^{-1}, δ 0.67 (3 H, s, 18-H), 0.96 (3 H, s, 19-H), 2.51 (1 H, d, *J* 4.4 Hz, 6-H), and 3.18 (2 H, m, $W_{\frac{1}{2}}$ 5 Hz, 3- and 4-H), *m/e* 288 (11, $M^{+\bullet}$), 273 (5, $M^{+\bullet} - CH_3$), 270 (10, $M^{+\bullet} - H_2O$), 260 (8, $M^{+\bullet} - CO$), and 135 (100); (ii) *androst-5-ene-3α,4β-diol* (4) (0.18 g, 26%), which crystallized from acetone as needles, m.p. 192—193 °C, $[\alpha]_D^{19}$ +58° (*c* 1.2) (Found: C, 78.4; H, 10.5. $C_{19}H_{28}O_2$ requires C, 79.2; H, 9.7%), $\nu_{max.}$ 3 610 and 3 540—3 200 cm^{-1}; δ 0.80 (3 H, s, 18-H), 1.20 (3 H, s, 19-H), 1.71 (2 H, m, 2 × OH, exchanged with D_2O), 3.82—4.35 (2 H, m, 3β- and 4α-H), and 5.74 (1 H, d, *J* 4.8 Hz, 6-H); *m/e* 290 (14, $M^{+\bullet}$), 275 (52, $M^{+\bullet} - CH_3$), 272 (80, $M^{+\bullet} - H_2O$), 257 (100, 272 − CH_3), 254 (20, 272 − H_2O), and 239 (39, 257 − H_2O, 254 − CH_3); and (iii) *androst-5-ene-3α,4α-diol* (5) (69 mg, 10%) which crystallized from acetone as needles, m.p. 190—195° (Found: C, 78.5; H, 10.6. $C_{19}H_{30}O_2$ requires C, 78.6; H, 10.3%), $\nu_{max.}$ 3 610 and 3 510—3 200 cm^{-1}; δ 0.72 (3 H, s, 18-H), 0.98 (3 H, s, 19-H), 1.50 (2 H, s, 2 × OH, exchanged with D_2O), 2.05 (1 H, d, *J* 6 Hz, 7-H), 4.01—4.40 (2 H, m, 3β- and 4β-H), and 5.88 (1 H, m, 6-H); *m/e* 290 (8, $M^{+\bullet}$), 272 (69, $M^{+\bullet} - H_2O$), 257 (100, 272 − CH_3), 254 (23, 272 − H_2O), and 293 (28, 257 − H_2O, 254 − CH_3).

(b) *With 2 equiv. in dichloromethane.* Androsta-3,5-diene (0.33 g) was treated as above with *m*-chloroperbenzoic acid (0.47 g) in dichloromethane (50 ml) for 12 h. Chromatography of the resulting gum on alumina and elution with benzene gave 3α,4α;5β,6β-diepoxyandrostane (3) (0.18 g, 49%). Further elution of the column with benzene gave 5α-(m-*chlorobenzoyloxy*)-3α,4α-*epoxyandrostan*-6β-*ol* (7) as a clear gum (0.16 g, 28%) which could not be obtained crystalline (Found: C, 69.7; H, 7.5. $C_{26}H_{33}ClO_4$ requires C, 70.2; H, 7.5%), $\nu_{max.}$ 3 480, 1 722, 1 256, and 1 125 cm^{-1}; δ 0.75 (3 H, s, 18-H), 1.25 (3 H, s, 19-H), 3.1—3.6 (2 H, m, 3- and 4-H), 4.05 (1 H, m, 6α-H), and 7.44—8.15 (4 H, m, ArH).

(c) *With 1 equiv.* Androsta-3,5-diene (0.59 g) was treated as above with *m*-chloroperbenzoic acid (0.40 g) in ether (15 ml) for 8 days. P.l.c. of the resulting oil (0.83 g) with ether–hexane (5 : 1) afforded (i) 3α,4α;5β,6β-diepoxyandrostane (3) (13 mg, 2%); (ii) 5α-(m-*chlorobenzoyloxy*)-*androst*-3-*en*-6β-*ol* (8) (68 mg, 7%) which crystallized from acetone as needles, m.p. 92—95 °C (Found: C, 70.8; H, 7.8. $C_{26}H_{33}ClO_3 \cdot 2CH_3COCH_3$ requires C, 70.5; H, 8.3%), $\nu_{max.}$ 3 610, 3 560—3 300, 1 730, 1 260, and 1 135 cm^{-1}, δ 0.78 (3 H, s, 18-H), 1.32 (3 H, s, 19-H), 1.73br (1 H, s, OH, exchanged with D_2O), 4.25 (1 H, m, $W_{\frac{1}{2}}$ 7 Hz, 6α-H), 5.30—5.65 (2 H, m, 3- and 4-H), and 7.25—8.02 (4 H, m, ArH), *m/e* 428 (0.3, $M^{+\bullet}$), 410 (4, $M^{+\bullet} - H_2O$), 272 (19, $M^{+\bullet}$ − *m*-$ClC_6H_4CO_2H$), 254 (11, 272 − H_2O), 242 (9, 257 − CH_3), 239 (5, 254 − CH_3), 155 (32, *m*-$ClC_6H_4CO_2^{+\bullet}$), and 96 (100); (iii) 4β-(m-*chlorobenzoyloxy*)*androst*-5-*en*-3α-*ol* (9) (68 mg, 7%) which crystallized from acetone as needles, m.p. 143—146° (Found: C, 72.4; H, 7.9. $C_{26}H_{33}ClO_3$ requires C, 72.9; H, 7.7%), $\nu_{max.}$ 3 710, 1 720, 1 605, 1 255, and 1 125 cm^{-1}; δ 0.73 (3 H, s, 18-H), 1.25 (3 H, s, 19-H), 2.87 (1 H, s, OH, exchanged with D_2O), 4.02 (1 H, m, $W_{\frac{1}{2}}$ 5 Hz, 3β-H), 5.35 (1 H, d, *J* 3.5 Hz, 4α-H), 5.95 (1 H, m, $W_{\frac{1}{2}}$ 9 Hz, 6-H), and 7.30—8.09 (4 H, m, ArH), *m/e* 428 (2, $M^{+\bullet}$), 410 (26, $M^{+\bullet} - H_2O$), 395 (1, 410 − CH_3), 272 (71, $M^{+\bullet}$ − *m*-$ClC_6H_4CO_2H$), 257 (46, 272 − CH_3), 254 (18, 272 − H_2O), 239 (21, 257 − H_2O, 254 − CH_3), 156 (24, *m*-$ClC_6H_4CO_2H$), and 139 (100, *m*-$ClC_6H_4CO^{+\bullet}$); and (iv) androst-5-ene-3α,4β-diol (4) (0.29 g, 43%), m.p. and mixed m.p. 186—187 °C.

Reaction of Androsta-3,5-dien-17-one with m-Chloroperbenzoic Acid.—(a) *With 2 equiv.* Androsta-3,5-dien-17-one [26] (2) (1.0 g) was treated as above with *m*-chloroperbenzoic acid (1.4 g) in ether (35 ml) for 15 min. P.l.c. of the resulting foam (1.23 g) with benzene–ethyl acetate (1 : 1) afforded (i) 3α,4α;5β,6β-*diepoxyandrostan*-17-*one* (10) (41 mg, 4%) which crystallized from dichloromethane–hexane as needles, m.p. 178—180 °C, $[\alpha]_D^{19}$ +73° (*c* 0.1) (Found: C, 75.3; H, 8.6. $C_{19}H_{26}O_3$ requires C, 75.5; H, 8.7%), $\nu_{max.}$ 1 725 cm^{-1}; δ 0.82 (3 H, s, 18-H), 0.91 (3 H, s, 19-H), 2.58 (1 H, d, *J* 3.5 Hz, 6-H), and 3.28 (2 H, m, $W_{\frac{1}{2}}$ 6 Hz, 3- and 4-H); *m/e* 302 (35, $M^{+\bullet}$), 287 (13, $M^{+\bullet} - CH_3$), 284 (16, $M^{+\bullet} - H_2O$), 274 (18, $M^{+\bullet} - CO$), 259 (25, 287 − CO, 274 − CH_3), and 41 (100); (ii) 5α,6β-*dihydroxyandrost*-3-*en*-17-*one* (12) (0.14 g, 13%) which crystallized from acetone as needles, m.p. 239—241 °C (sealed tube), $[\alpha]_D^{19}$ −6° (*c* 1.2) (Found: C, 75.1; H, 9.4. $C_{19}H_{28}O_3$ requires C, 75.0; H, 9.3%), $\nu_{max.}$ 3 550—3 175, 2 625—2 475, and 1 730 cm^{-1}; δ 0.87 (3 H, s, 18-H), 1.12 (3 H, s, 19-H), 1.56br (2 H, s, 2 × OH, exchanged with D_2O), 3.80 (1 H, m, $W_{\frac{1}{2}}$ 6 Hz, 6α-H) and 5.85 (2 H, m, $W_{\frac{1}{2}}$ 2.5 Hz, 3- and 4-H); *m/e* 304 (15, $M^{+\bullet}$), 286 (95, $M^{+\bullet} - H_2O$), 271 (78, 286 − CH_3), 268 (41, 286 − H_2O), 253 (25, 271 − H_2O, 268 − CH_3), and 77 (100); and (iii) 3α,4β-*dihydroxyandrost*-5-*en*-17-*one* (11) (0.41 g, 36%) which crystallized from acetone as needles, m.p. 213—215.5 °C (sealed tube), $[\alpha]_D^{19}$ +149° (*c* 1.2) (Found: C, 74.6; H, 9.4. $C_{19}H_{28}O_3$ requires C, 75.0; H, 9.3%), $\nu_{max.}$ 3 550—3 200 and 1 725 cm^{-1}; δ 0.92 (3 H, s, 18-H), 1.20 (3 H, s, 19-H), 1.58br (2 H, s, 2 × OH, exchanged with D_2O), 4.00—4.35 (2 H, m, 3β- and 4β-H), and 5.75 (1 H, d, *J* 4.8 Hz, 6-H), *m/e* 304 (14, $M^{+\bullet}$), 289 (21, $M^{+\bullet} - CH_3$), 287 (28, $M^{+\bullet} - OH$), 286 (100, $M^{+\bullet} - H_2O$), 271 (93, 289 − H_2O, 286 − CH_3), 268 (51, 286 − H_2O), and 253 (30, 268 − CH_3).

(b) *With 1 equiv.* Androsta-3,5-dien-17-one (1.0 g) was treated as above with *m*-chloroperbenzoic acid (0.71 g) in ether (35 ml) for 3.5 h. P.l.c. of the resulting solid (1.24 g) with benzene–ethyl acetate (1 : 1) afforded in order of decreasing R_F value (i) 3α,4α;5β,6β-diepoxyandrostan-17-one (10) (43 mg, 4%); (ii) 5α,6β-dihydroxyandrost-3-en-17-one (12) (0.16 g, 15%); and (iii) 3α,4β-dihydroxyandrost-5-en-17-one (11) (0.38 g, 34%).

(c) *With 1 equiv. in benzene.* Androsta-3,5-dien-17-one (3.1 g) was treated as above with 85% *m*-chloroperbenzoic acid (2.4 g) in benzene (100 ml) for 5 days. Chromatography of the resulting gum on alumina and elution with benzene–ether (1 : 1) gave 3-(*m*-*chlorobenzoyloxy*)*androsta*-3,5-*dien*-17-*one* (13) (0.64 g, 14%) which crystallized from aqueous acetone as needles, m.p. 146—148 °C with softening from 131 °C, $[\alpha]_D^{20}$ +78° (*c* 0.7) (Found: $M^{+\bullet}$ 424.176 2. $C_{26}H_{29}ClO_3$ requires *M* 424.179 7), $\nu_{max.}$ 1 740, 1 700, and 758 cm^{-1}; δ 0.94 (3 H, s, 18-H), 1.37 (3 H, s, 19-H), 5.52 (1 H, m, 6-H), 5.64br (1 H, s, 4-H), and 7.20—8.10 (4 H, m, ArH).

Elution of the column with ether gave oils; elution with ethyl acetate gave 3α,4α;5β,6β-diepoxyandrostan-17-one (10) (0.18 g, 10%).

(d) *With 3 equiv. in benzene.* In one experiment androsta-3,5-dien-17-one (2.9 g) was treated as above with 85%-*m*-chloroperbenzoic acid (6.1 g) in benzene (100 ml) for 5 days. Chromatography of the resulting oil on alumina and elution with benzene–ether gave a gum. Elution with ethyl acetate gave 3β,4β;5α,6α-*diepoxyandrostan*-17-*one* (14) (2.6 g, 81%), which crystallized from aqueous methanol as needles, m.p. 261—263 °C, $[\alpha]_D^{20}$ −64° (*c* 1.0) (Found: C, 75.15; H, 8.5. $C_{19}H_{26}O_3$ requires C, 75.4; H, 8.5%), $\nu_{max.}$ 1 740 cm^{-1}; δ 0.89 (3 H, s, 18-H), 1.30 (3 H, s, 19-H), 2.58 (2 H, m, 3- and 6-H), and 3.35 (1 H, d, *J* 3.5 Hz, 4-H).

The gum from above was re-chromatographed on alumina. Elution of the column with benzene gave 3β,4β-*epoxy*-5α,6α-*dihydroxyandrostan*-17-*one* (15) (20 mg) which crystallized from aqueous acetone as rods, m.p. 181—184 °C, $[\alpha]_D^{20}$ +168° (*c* 1.2) (Found: C, 71.8; H, 8.7. $C_{19}H_{28}O_4$ requires C, 71.2; H, 8.8%), $\nu_{max.}$ 3 430, 1 735, and 1 115 cm^{-1}; δ 0.82 (3 H, s, 18-H), 1.12 (3 H, s, 19-H), 1.58 (2 H, s, OH, exchanged with D_2O), 2.42 (1 H, m, 3α-H), 2.97 (1 H, d, *J* 4 Hz, 4α-H), and 4.11 (1 H, m, 6β-H).

Androst-4-*ene*-3,17-*dione.*—A solution of 3-(*m*-chlorobenzoyloxy)androsta-3,5-dien-17-one (13) (80 mg) in 10% methanolic potassium hydroxide (10 ml) was heated under reflux for 1 h. Most of the methanol was removed by distillation and water (30 ml) and concentrated hydrochloric acid (1 ml) were added to the cooled solution. Extraction of the mixture with ether gave androst-4-ene-3,17-dione (40 mg, 74%), which crystallized from aqueous acetone as needles, m.p. 168—174 °C, undepressed by a sample prepared by oxidation of testosterone with chromium trioxide.[18]

Hydrolysis of 3β,4β;5α,6α-*Diepoxyandrostane.*—The diepoxide (14) was hydrolysed with sulphuric acid by Weinman and Weinman's method.[19] Work-up gave 3β,4β-epoxy-5α,6α-dihydroxyandrostan-17-one (15) (81%), m.p. and mixed m.p. 181—184 °C (correct i.r. spectrum).

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