1:3-Rearrangement of Steroidal Allylic Acetoxy Groups during Epoxidation

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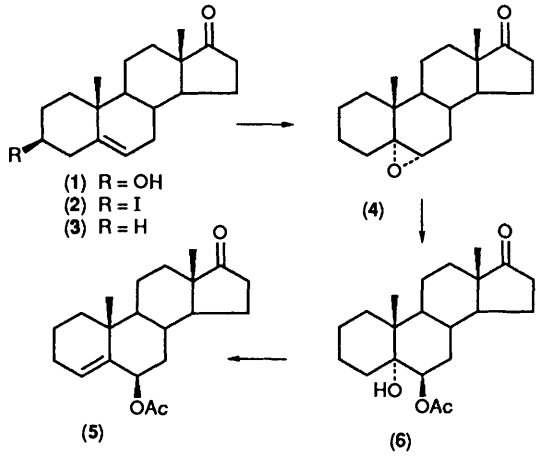
Epoxidation of both 4β-acetoxyandrost-5-en-17-one and 6β-acetoxyandrost-4-en-17-one by *m*-chloroperbenzoic acid affords a similar mixture of 4β-acetoxy-5α,6α-epoxy- and 6β-acetoxy-4α,5α-epoxyandrostan-17-one. This is interpreted in terms of a symmetrical 'acetoxylinium' (1,3-dioxan-2-ylium) ion and a degree of charge separation in the transition state for epoxidation.

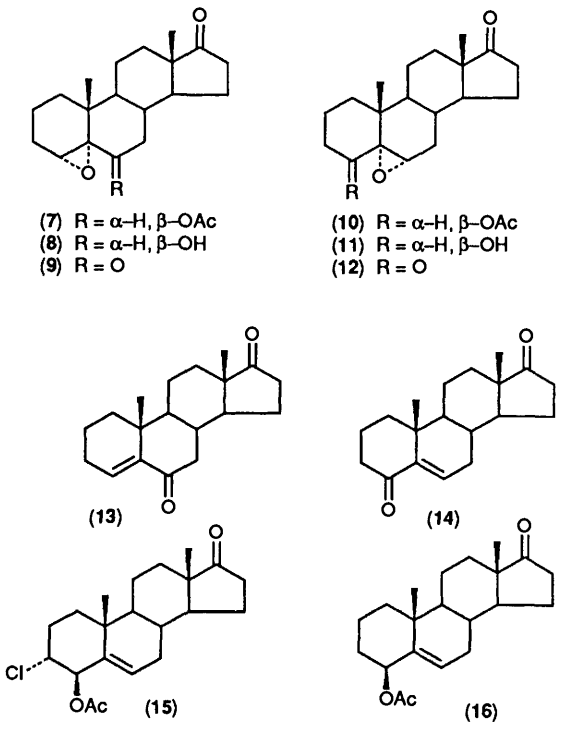
The epoxidation of 6β-acetoxycholest-4-ene with perbenzoic acid has been reported[1] to give solely the 4α,5α-epoxide. In the course of other work we carried out the epoxidation of 6β-acetoxyandrost-4-en-17-one (**5**) with *m*-chloroperbenzoic acid (MCPBA) and have found that the reaction is accompanied by some 1:3-allylic rearrangement of the acetoxy group. This rearrangement, which sheds some light on the possible extent of charge separation in the transition state for epoxidation, forms the subject of this paper.

The 6β-acetoxyandrost-4-en-17-one (**5**) required for the present study was obtained from dehydroisoandrosterone (**1**). Hydrogenolysis of the 3β-iodo compound (**2**) afforded the 3-deoxy-5-ene (**3**),[2] which was epoxidized with MCPBA. Hydrolysis of the resultant epoxide (**4**) in refluxing acetic acid then gave 6β-acetoxy-5α-hydroxyandrostan-17-one (**6**). Elimination of the hydroxy group with thionyl chloride produced the required 4-ene (**5**) (Scheme 1). Epoxidation of compound (**5**) with MCPBA in chloroform gave a mixture of 6β-acetoxy-4α,5α-epoxyandrostan-17-one (**7**) and 4β-acetoxy-5α,6α-epoxyandrostan-17-one (**10**) (10:1), which were separated by careful chromatography. Examination of the multiplicity of their ^{1}H NMR signals suggested that these compounds were regio- rather than stereo-isomers. The compounds were identified by hydrolysis to the alcohols (**8**) and (**11**) followed by oxidation to the corresponding ketones (**9**) and (**12**) with chromium trioxide in pyridine. These were compared to authentic samples which were obtained by epoxidation of the corresponding unsaturated ketones (**13**) and (**14**) with MCPBA.[3-5]

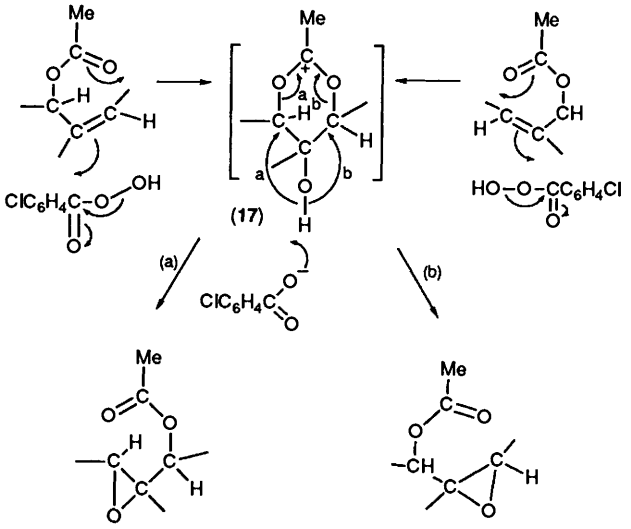


Scheme 1.

The rearrangement implies the intervention of a symmetrical ion as shown in Scheme 2. The intermediates may be approached either from a 6β-acetate or from a 4β-acetate such as compound (**16**). The latter was prepared by reduction of the 4β-acetoxy-3α-chloro-Δ^5-steroid (**15**)[6] with tributyltin hydride. The product had spectral data consistent with the structure (**16**). Epoxidation with MCPBA gave mixture of compounds (**7**) and (**10**) (4:1) comparable to that which was obtained on epoxidation of compound (**5**). In both epoxidations the ring-A epoxide predominated. There was no evidence (^{1}H NMR assay) for isomerization of the acetoxy epoxide in chloroform in the presence of MCPBA catalysis during the period of the epoxidation. The epoxidation of 4β-acetoxycholest-5-ene with peracid has been reported[7] to give a mixture of 5α,6α- and 5β,6β-stereoisomers in the similar ratio. It is possible that positional rather than stereoisomers were also involved in this case.



The neighbouring-group participation by the adjacent axial acetoxy groups in the epoxidation reaction is represented in Scheme 2. The formation of an intermediate such as (**17**) would suggest that there is more charge separation in the transition state for epoxidation than is envisaged in the Bartlett mechanism for epoxidation, and is more consistent with the data of both Dryuk[8] and Hanzlik and Shearer.[9] Indeed, a modification of their mechanism in this case involving a close ion-pair may be a possibility. The ready fission of the oxygen-



Scheme 2.

oxygen bond in the first step may be driven by the lone-pair repulsions. The participation of a steroidal 6β-acetoxy group in stabilizing a C-5 carbocation is well documented and has recently been reported in a study of the isomerization of steroidal hydroxy epoxides.[10]

Experimental

IR spectra were determined as Nujol mulls and ^{1}H NMR spectra were obtained for solutions in deuteriochloroform on a Bruker WM 360 spectrometer. Extracts were dried over sodium sulphate. Silica for chromatography was Merck 9385. Light petroleum refers to the fraction boiling in the range 60–80 °C.

Epoxidation of Androst-5-en-17-one (**3**).—A solution of androst-5-en-17-one[2] (7 g) in chloroform (150 ml) was treated with MCPBA (8 g) at 0 °C. The mixture was then allowed to attain room temperature and was stirred for 1 h, washed successively with aq. sodium sulphite, aq. sodium hydrogen carbonate, and water, and dried. The solvent was evaporated off to give *5α,6α-epoxyandrostan-17-one* (**4**) (6.1 g), which crystallized from diethyl ether as plates, m.p. 140–143 °C (Found: C, 79.2; H, 9.8. $C_{19}H_{28}O_2$ requires C, 79.1; H, 9.8%); ν_{max} 1 744 cm^{-1}; δ 0.84 (3 H, s, 18-H$_3$), 1.09 (3 H, s, 19-H$_3$), and 2.92 (1 H, d, *J* 4 Hz, 6-H).

6β-Acetoxy-5α-hydroxyandrostan-17-one[a] (**6**).—5α,6α-Epoxyandrostan-17-one (**4**) (4 g) was heated under reflux in acetic acid (200 ml) for 2 h. The solution was cooled, neutralized with aq. sodium hydrogen carbonate, and the products were recovered in ethyl acetate. The extract was washed with water, dried, and the solvent was evaporated off to give a residue, which was chromatographed on silica. Elution with 10% ethyl acetate–light petroleum gave *6β-acetoxy-5α-hydroxyandrostan-17-one* (**6**) (2.2 g), m.p. 156–159 °C (Found: C, 72.2; H, 9.3. $C_{21}H_{32}O_4$ requires C, 72.4; H, 9.3%); ν_{max} 3 512, 1 736, and 1 732 cm^{-1}; δ 0.89 (3 H, s, 18-H$_3$), 1.14 (3 H, s, 19-H$_3$), 2.09 (3 H, s, OAc), and 4.72 (1 H, t, *J* 2.5 Hz, 6-H).

6β-Acetoxyandrost-4-en-17-one[b] (**5**).—Thionyl chloride (6 ml) (freshly distilled from triphenyl phosphite) was dissolved in dry, freshly redistilled pyridine (25 ml) and the solution was cooled to −20 °C. This solution was added to a stirred solution of 6β-acetoxy-5α-hydroxyandrostan-17-one (**6**) (2 g) in dry, freshly redistilled pyridine (70 ml) at −20 °C. After 30 min the mixture was allowed to attain room temperature, and was stored for 30 min. The mixture was then recooled, poured into water, and the products were recovered in ethyl acetate. The extract was washed successively with dil. hydrochloric acid and aq. sodium hydrogen carbonate, then dried, and the solvent was evaporated off to give a residue, which was chromatographed on silica. Elution with 5% ethyl acetate–light petroleum gave *6β-acetoxyandrost-4-en-17-one* (**5**) (1.8 g), which crystallized from light petroleum as needles, m.p. 96–98 °C (Found: C, 76.2; H, 9.3. $C_{21}H_{30}O_3$ requires C, 76.3; H, 9.2%); ν_{max} 1 745 and 1 740 cm^{-1}; δ 0.94 (3 H, s, 18-H$_3$), 1.13 (3 H, s, 19-H$_3$), 2.04 (3 H, s, OAc), 5.33 (1 H, t, *J* 2.9 Hz, 6-H), and 5.77 (1 H, dd, *J* 2.4 and 5 Hz, 4-H).

Action of MCPBA on 6β-Acetoxyandrost-4-en-17-one (**5**).—A solution of 6β-acetoxyandrost-4-en-17-one (**5**) (1.2 g) in chloroform (70 ml) was treated with MCPBA (1.2 g) at 0 °C. The mixture was allowed to attain room temperature and was stirred for 2 days, washed successively with aq. sodium sulphite, aq. sodium hydrogen carbonate, and water, and dried. The solvent was evaporated off and the residue was chromatographed on silica. Elution with 2% ethyl acetate–light petroleum gave the starting material (85 mg recovery). Elution with 3% ethyl acetate–light petroleum gave *6β-acetoxy-4α,5α-epoxyandrostan-17-one*[c] (**7**) (780 mg), which crystallized from ethyl acetate–light petroleum as needles, m.p. 172–173 °C (Found: C, 72.7; H, 8.7. $C_{21}H_{30}O_4$ requires C, 72.8; H, 8.7%); ν_{max} 1 735 cm^{-1}; δ 0.93 (3 H, s, 18-H$_3$), 1.18 (3 H, s, 19-H$_3$), 2.10 (3 H, s, OAc), 3.25 (1 H, d, *J* 3.8 Hz, 4-H), and 4.32 (1 H, t, *J* 3 Hz, 6-H). Elution with 6% ethyl acetate–light petroleum gave *4β-acetoxy-5α,6α-epoxyandrostan-17-one*[d] (**10**) (74 mg), which crystallized from ethyl acetate–light petroleum as needles, m.p. 186–188 °C (Found: C, 72.7; H, 8.7%); ν_{max} 1 736 cm^{-1}; δ 0.93 (3 H, s, 18-H$_3$), 1.16 (3 H, s, 19-H$_3$), 2.11 (3 H, s, OAc), 3.04 (1 H, dd, *J* 0.6 and 3.7 Hz, 6-H), and 4.54 (1 H, t, *J* 3 Hz, 4-H).

Hydrolysis of 6β-Acetoxy-4α,5α-epoxyandrostan-17-one (**7**).—A solution of 6β-acetoxy-4α,5α-epoxyandrostan-17-one (**7**) (560 mg) in methanol (15 ml) was treated with aq. sodium hydroxide (0.6 g in 4 ml) at room temperature for 45 min. The solution was neutralized with acetic acid, concentrated, and poured into water. The product was recovered in ethyl acetate, and the extract was washed successively with aq. sodium hydrogen carbonate and water, and dried. The solvent was evaporated off to give *4α,5α-epoxy-6β-hydroxyandrostan-17-one* (**8**) (480 mg), which crystallized from ethyl acetate–light petroleum as needles, m.p. 204–206 °C (Found: C, 75.1; H, 9.2. $C_{19}H_{28}O_3$ requires C, 75.0; H, 9.3%); ν_{max} 3 412 and 1 725 cm^{-1}; δ 0.89 (3 H, s, 18-H$_3$), 1.25 (3 H, s, 19-H$_3$), 3.03 (1 H, t, *J* 2.2 Hz, 4-H), and 3.26 (1 H, t, *J* 2.9 Hz, 6-H).

Oxidation of 4α,5α-Epoxy-6β-hydroxyandrostan-17-one (**8**).—A solution of 4α,5α-epoxy-6β-hydroxyandrostan-17-one (**8** (400 mg) in pyridine (8 ml) was added to a stirred solution of chromium trioxide (1.2 g) in pyridine (16 ml). The mixture was stirred for 2.5 h and was then poured into diethyl ether (100 ml). Insoluble inorganic salts were removed by filtration through Celite. The filtrate was washed successively with dil. hydrochloric acid, aq. sodium hydrogen carbonate, and water, and dried. The solvent was evaporated off to afford *4α,5α-epoxyandrostane-6,17-dione* (**9**) (309 mg), which crystallized from ethyl acetate as needles, m.p. 207–208 °C (Found: C, 75.4; H, 8.8.

[a] *Alternative name:* 17-oxoandrostane-5α,6β-diol 6-acetate.
[b] *Systematic name:* 17-oxoandrost-4-en-6β-yl acetate.
[c] *Systematic name:* 4α,5α-epoxy-17-oxoandrostan-6β-yl acetate.
[d] *Systematic name:* 5α,6α-epoxy-17-oxoandrostan-4β-yl acetate.

$C_{19}H_{26}O_3$ requires C, 75.6; H, 8.7%); ν_{max} 1 739 and 1 725 cm^{-1}; δ 0.91 (3 H, s, 18-H_3), 1.03 (3 H, s, 19-H_3), and 3.64 (1 H, d, *J* 4.4 Hz, 4-H).

Epoxidation of Androst-4-ene-6,17-dione (**13**).—A solution of androst-4-ene-6,17-dione[3] (**13**) (100 mg) (obtained by treatment of 5α,6α-epoxy-3β-methylsulphonyloxyandrostan-17-one with hydrobromic acid[4]) in chloroform (10 ml) was treated with MCPBA (100 mg) at room temperature. After 24 h the mixture was washed successively with aq. sodium sulphite, aq. sodium hydrogen carbonate, and water, and dried. The solvent was evaporated off and the residue was recrystallized to give 4α,5α-epoxyandrostane-6,17-dione (**9**) (75 mg), identical (IR, NMR) with the material described above.

Hydrolysis of 4β-*Acetoxy*-5α,6α-*epoxyandrostan*-17-*one* (**10**).—A solution of 4β-acetoxy-5α,6α-epoxyandrostan-17-one (**10**) (60 mg) in methanol (3 ml) was treated with aq. sodium hydroxide (60 mg in 0.5 ml) at room temperature for 1 h. The solution was neutralized with acetic acid, concentrated under reduced pressure, and poured into water. The steroid was recovered in ethyl acetate, and the extract was washed with aq. sodium hydrogen carbonate and dried. The solvent was evaporated off to afford 5α,6α-*epoxy*-4β-*hydroxyandrostan*-17-*one* (**11**) (52 mg), which was crystallized from ethyl acetate–light petroleum as needles, m.p. 153–155 °C (Found: C, 75.3; H, 9.6. $C_{19}H_{28}O_3$ requires C, 75.0; H, 9.3%); δ 0.91 (3 H, s, 18-H_3), 1.19 (3 H, s, 19-H_3), 3.05 (1 H, dd, *J* 1.8 and 3.2 Hz, 6-H), and 3.35 (1 H, t, *J* 3 Hz, 4-H).

Oxidation of 5α,6α-*Epoxy*-4β-*hydroxyandrostan*-17-*one* (**11**).—A solution of 5α,6α-epoxy-4β-hydroxyandrostan-17-one (**11**) (40 mg) in pyridine (2 ml) was added to a stirred solution of chromium trioxide (120 mg) in pyridine (2 ml). The mixture was left for 2.5 h at room temperature and was then poured into diethyl ether (15 ml). The mixture was filtered through Celite, and the filtrate was washed successively with dil. hydrochloric acid, aq. sodium hydrogen carbonate, and water, and dried. The solvent was evaporated off to give 5α,6α-epoxyandrostane-4,17-dione (**12**) (25 mg), which was crystallized from diethyl ether as needles, m.p. 190–191 °C (lit.,[5] 193–195 °C), identical with the material prepared by epoxidation of androst-5-ene-4,17-dione (**14**).

Reduction of 4β-*Acetoxy*-3α-*chloroandrost*-5-*en*-17-*one*[e] (**15**).—A solution of 4β-acetoxy-3α-chloroandrost-5-en-17-one[6] (750 mg) in dry benzene (40 ml) was treated with azoisobutyronitrile (150 mg) and tributyltin hydride (2 ml) under reflux for 3 h. The solution was cooled, the solvent was evaporated off, and the residue was chromatographed on silica. Elution with 1% ethyl acetate–light petroleum gave 4β-*acetoxyandrost*-5-*en*-17-*one*[f] (**16**) (410 mg), which crystallized from light petroleum as plates, m.p. 120–122 °C (Found: C, 76.2; H, 9.2. $C_{21}H_{30}O_3$ requires C, 76.3; H, 9.2%); ν_{max} 1 742 cm^{-1}; δ 0.89 (3 H, s, 18-H_3), 1.15 (3 H, s, 19-H_3), 2.02 (3 H, s, OAc), 5.32 (1 H, t, *J* 3 Hz, 4-H), and 5.77 (1 H, t, *J* 3 Hz, 6-H).

Action of MCPBA on 4β-*Acetoxyandrost*-5-*en*-17-*one* (**16**).—A solution of 4β-acetoxyandrost-5-en-17-one (**16**) (100 mg) in chloroform (7 ml) was treated with MCPBA (120 mg) at 0 °C. The mixture was allowed to attain room temperature and was then stirred for 36 h before being washed successively with aq. sodium sulphite, aq. sodium hydrogen carbonate, and water, and dried. The solvent was evaporated off and the residue was chromatographed on silica. Elution with 3% ethyl acetate–light petroleum gave 6β-acetoxy-4α,5α-epoxyandrostan-17-one (**7**) (80 mg), identified by its NMR spectrum. Further elution, with 6% ethyl acetate–light petroleum, gave 4β-acetoxy-5α,6α-epoxyandrostan-17-one (**10**) (18 mg), which was also identified by its NMR spectrum.

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[e] *Systematic name:* 3α-chloro-17-oxoandrost-5-en-4β-yl acetate.
[f] *Systematic name:* 17-oxoandrost-5-en-4β-yl acetate.

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