Preparation of Steroidal 5β,6β-Epoxides and their Oxidation by Chromium Trioxide

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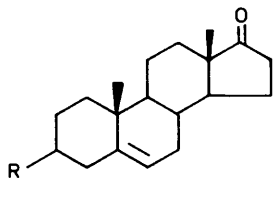
Reaction of 3α-chloroandrost-5-en-17-one with *m*-chloroperbenzoic acid affords the 5β,6β-epoxide. This is accompanied by some Baeyer-Villiger oxidation at C-17. The 3α-chlorine atom can be removed by hydrogenolysis with tributyltin hydride. Although the unsubstituted 5β,5β-epoxide is oxidized by chromium trioxide to the 5α-hydroxy 6-ketone, the 3α-chloro 5β,6β-epoxide is unreactive.

A 5β,6β-epoxide system is found in a number of biologically active steroids such as withaferin A,[1,2] withanolide D,[3] and jaborosalactone A.[4] Molecular models show that the geometry imposed by the 5β,6β-epoxide on rings *A* and *B* is quite different from that required by a 5α,6α-epoxide. However in the steroid series, the angular methyl group at C(10) normally dominates the stereochemistry of addition reactions to the Δ^5-alkene. Epoxidation with peroxy acid affords predominantly the 'α'-epoxide, with only relatively small amounts of the 'β' epoxide.[5] Consequently the chemistry of the 5β,6β-epoxides has been less widely studied.

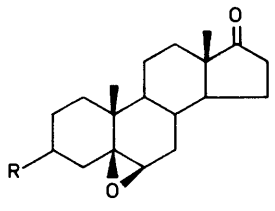
For our investigations we therefore required an efficient synthesis of the 'β'-epoxide. In a recent synthesis of withanolide D this was achieved[6] by utilizing the directing effect of a 4β-hydroxy group. However the proportions of 5α- and 5β-epoxides that are formed on epoxidation by peroxy acids are also dependent on the nature of the 3-substituent.[7] Thus an exception to the rule of 'α'-attack is provided[8] by the epoxidation of 3,3-ethylenedioxy-Δ^5-alkenes, which affords in addition to the 'α'-epoxide a substantial amount of the 'β'-epoxide. In this case the 'α'-face is partially shielded by the axial 3α-oxygen atom. The influence of a 3α-substituent on the stereochemical course of catalytic hydrogenation of a Δ^5-alkene has also been examined[9] and shown to lead to preferential and sometimes exclusive formation of the 5β-H steroid. In the cholestane series epoxidation of 3α-chlorocholest-5-ene with monoperphthalic acid has been reported[10] to give the 5β,6β-epoxide.

The ready availability of 3α-chloroandrost-5-en-17-one (**2**) from the reaction of dehydroisoandrosterone (**1**) with triphenylphosphine–carbon tetrachloride[11] permitted the preparation of the 5β-6β-epoxide (**3**). Reaction of (**2**) with *m*-chloroperbenzoic acid in dichloromethane was noticeably slower than the normal epoxidation of a 5-ene. It afforded an epoxide (**3**) and a second compound (**5**), $C_{19}H_{27}ClO_3$. The δ-lactone structure of the latter followed from its ^{13}C n.m.r. spectrum in which the C-17 carbonyl signal appeared at 170.8 p.p.m. and the C-13 resonance at 82.7 p.p.m. The corresponding 13α-methyl steroid (**6**), prepared from 3β-hydroxy-13α-androst-5-en-17-one,[12] also gave both an epoxide (**7**) and the δ-lactone (**8**) [δ_C 82.9 (C-13) and 171.1 (C-17)]. For comparison, 3α-chloro-5α,6α-epoxyandrostan-17-one (**10**) was prepared by treatment of 3β-hydroxy-5α,6α-epoxyandrostan-17-one (**9**) with triphenylphosphine–carbon tetrachloride.

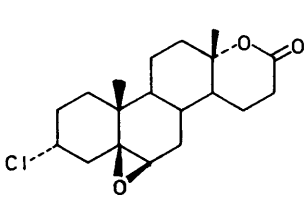
The assignment of the stereochemistry to the epoxides followed from their ^1H n.m.r. spectra. The 6β-H resonance of steroidal 5α,6α-epoxides appears in the range δ_H 2.82—2.86 (*J* 3.3—4.1 Hz), whilst the H-6α signal of the corresponding 5β,6β-epoxide is found in the range 3.05—3.10 (*J* 2.1—2.7 Hz).[13] Thus the epoxides [δ_H 3.14 (*J* 3 Hz)] obtained on treating the 3α-chloro-Δ^5-steroids with *m*-chloroperbenzoic acid were the 5β,6β-epoxides.



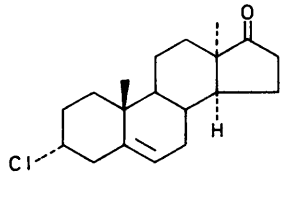
(**1**) R = α-H, β-OH
(**2**) R = α-Cl, β-H



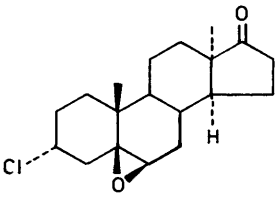
(**3**) R = α-Cl, β-H
(**4**) R = H



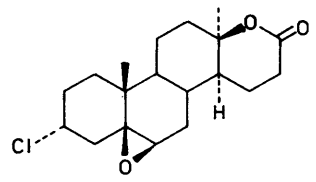
(**5**)



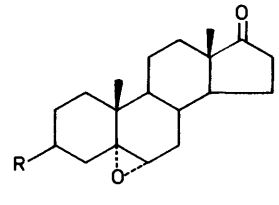
(**6**)



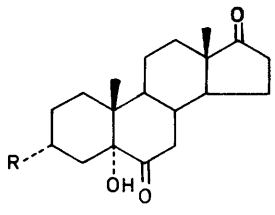
(**7**)



(**8**)



(**9**) R = α-H, β-OH
(**10**) R = α-Cl, β-H



(**11**) R = Cl
(**12**) R = H
(**13**) R = H; $\Delta^{2,3}$

Hydrogenolysis of the 3α-chlorine atom with tributyltin hydride gave 5β,6β-epoxyandrostan-17-one (**4**).

The oxidation of steroidal 5α,6α-epoxides with acidified chromium trioxide has provided a useful route to 5α-hydroxy

6-ketones. The application of this reaction to the 3α-chloro 5α,6α- and 5β,6β-epoxides (**10**) and (**3**) provided a revealing contrast in their reactivities. Oxidation of the 3α-chloro 5α,6α-epoxide (**10**) with acidified chromium trioxide in methyl ethyl ketone for 20 min at 35—40 °C gave 3α-chloro-5α-hydroxyandrostane-6,17-dione (**11**). The structure of this product was confirmed by its reduction with tributyltin hydride to 5α-hydroxyandrostane-6,17-dione (**12**),[15] identical with a sample obtained by catalytic hydrogenation of (**13**).[16] However the 3α-chloro 5β,6β-epoxide (**3**) was substantially unchanged even after prolonged reaction (4.5 h). Nevertheless the unsubstituted 5β,6β-epoxyandrostan-17-one (**4**) cleanly gave 5α-hydroxyandrostane-6,17-dione (**12**), identical with the material obtained previously. Hence the oxidation affords the 5α-hydroxy 6-ketone from both 5α,6α- and 5β,6β-epoxides. However there is steric hindrance to the reaction caused by the 3α-chloro substituent. A possible explanation is that the oxidation involves the initial hydrolysis of the epoxide to a *trans*-diol by the acidified chromium trioxide and this is followed by oxidation. The hydrolysis of a steroidal 5α,6α-epoxide leads to a 5α-hydroxy 6β-substituted product in which the nucleophile enters the 6β-position. On the other hand hydrolysis of the 5β,6β-epoxide leads[17] to a 6β-hydroxy 5α-substituted steroid in which the nucleophile has attacked the 5α-position. In the case of the 3α-chloro 5β,6β-epoxide, approach to the 5α-position would be hindered by interactions with the bulky 3α-chlorine atom. A similar explanation has been invoked.[8] to account for the resistance of the 5β,6β-epoxide to reduction by lithium aluminium hydride in the presence of a 3,3-ethylene acetal group.

Experimental

General.—Light petroleum refers to the fraction of b.p. 60—80 °C. Silica for chromatography was Merck 9385. Extracts were dried over sodium sulphate. ^{1}H N.m.r. spectra were determined at 90 MHz with a Perkin-Elmer R 32 spectrometer for solutions in deuteriochloroform. I.r. spectra were recorded for Nujol mulls.

Epoxidation of 3α-Chloroandrost-5-en-17-one (**2**).—The steroid (**2**) (500 mg) in dichloromethane (10 ml) was treated with *m*-chloroperbenzoic acid (400 mg) in dichloromethane (5 ml) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 24 h (t.l.c. monitor). It was diluted with dichloromethane and washed sequentially with aqueous 10% sodium sulphite (100 ml), aqueous sodium thiosulphate (100 ml), aqueous sodium hydrogen carbonate, and water. The organic layer was dried, the solvent evaporated off, and the residue chromatographed on silica. Elution with 10% ethyl acetate–light petroleum gave *3α-chloro-5β,6β-epoxyandrostan-17-one* (**3**) (253 mg), which crystallized from ethyl acetate–light petroleum as prisms, m.p. 143—146 °C (Found: C, 70.7; H, 8.65. $C_{19}H_{27}ClO_2$ requires C, 70.7; H, 8.4%); $\nu_{max.}$ 1 745 cm^{-1}; δ 0.85 (3 H, s, 18-H), 1.03 (3 H, s, 19-H), 3.14 (1 H, d, *J* 3 Hz, 6α-H), and 4.52 (1 H, $W_{\frac{1}{2}}$ 8 Hz, H-3β). Further elution gave *3α-chloro-5β,6β-epoxy-13α-hydroxy-13,17-secoandrostan-17-oic acid 17,13-lactone* (**5**) (230 mg), which crystallized from ethyl acetate as needles, m.p. 154—156 °C (Found: C, 67.6; H, 8.2. $C_{19}H_{27}ClO_3$ requires C, 67.3; H, 8.0%); $\nu_{max.}$ 1 710 cm^{-1}; δ 0.97 (3 H, s, 19-H), 1.29 (3 H, s, 18-H), 3.14 (1 H, d, *J* 3 Hz, 6α-H), and 4.52 (1 H, $W_{\frac{1}{2}}$ 7 Hz, 3β-H).

Under similar conditions 3α-chloro-13α-*epi*-androst-5-en-17-one (**6**)[18] (420 mg) in dichloromethane (8 ml) with *m*-chloroperbenzoic acid (600 mg) gave *3α-chloro-5β,6β-epoxy-13α-androstan-17-one* (**7**) (300 mg), m.p. 149—151 °C (Found: C, 70.85; H, 8.2. $C_{19}H_{27}ClO_2$ requires C, 70.7; H, 8.4%); $\nu_{max.}$ 1 740 cm^{-1}; δ 0.85 (3 H, s, 18-H), 0.95 (3 H, s, 19-H), 3.14 (1 H, d, *J* 3 Hz, 6α-H), and 4.5 (1 H, $W_{\frac{1}{2}}$ 7 Hz, 3β-H); and *3α-chloro-5β,6β-epoxy-13β-hydroxy-13,17-secoandrostan-17-oic acid 17,13-lactone* (**8**) (50 mg), m.p. 187—189 °C (Found: C, 67.2; H, 8.1. $C_{19}H_{27}ClO_3$ requires C, 67.3; H, 8.0%); $\nu_{max.}$ 1 705 cm^{-1}; δ 0.97 (3 H, s, 19-H), 1.27 (3 H, s, 18-H), 3.14 (1 H, d, *J* 3 Hz, 6α-H), and 4.53 (1 H, m, 3β-H). Similarly, dehydroisoandrosterone (1 g) gave the epoxide (**9**), m.p. 227—230 °C (lit.,[19] 229—230 °C); and *5α,6α-epoxy-3β,13α-dihydroxy-13,17-secoandrostan-17-oic acid 17,13-lactone* (320 mg), m.p. 212—216 °C (Found: C, 71.1; H, 8.85. $C_{19}H_{28}O_4$ requires C, 71.2; H, 8.8%); $\nu_{max.}$ 3 400 and 1 700 cm^{-1}; δ 1.02 (3 H, s, 19-H), 1.25 (3 H, s, 18-H), 2.90 (1 H, d, *J* 4 Hz, 6β-H), and 3.83 (1 H, $W_{\frac{1}{2}}$ 20 Hz, 3α-H).

Oxidation of the Epoxides with Chromium Trioxide.—(*a*) 3α-Chloro-5α,6α-epoxyandrostan-17-one (**10**), m.p. 194—197 °C (lit.,[20] 198—200 °C) was prepared as described previously.[20] The steroid (**10**) (250 mg) in methyl ethyl ketone (2.5 ml) was treated dropwise with aqueous 75% chromium trioxide (0.25 ml) for 20 min at 35—40 °C. The mixture was diluted with water and the product recovered in ethyl acetate. It was chromatographed on silica. Elution with 25% ethyl acetate–light petroleum gave *3α-chloro-5α-hydroxyandrostane-6,17-dione* (**11**) (135 mg), which crystallized from ethyl acetate–light petroleum as cubes, m.p. 195—197 °C (Found: C, 67.5; H, 8.3. $C_{19}H_{27}ClO_3$ requires C, 67.3; H, 8.0%); $\nu_{max.}$ 3 540, 1 740, and 1 710 cm^{-1}; δ 0.68 (3 H, s, 18-H), 0.77 (3 H, s, 19-H), 3.38 (1 H, s, 5α-OH; disappears on ^2H_2O wash), and 4.59 (1 H, $W_{\frac{1}{2}}$ 4 Hz, 3β-H).

(*b*) Under similar conditions 3α-chloro-5β,6β-epoxyandrostan-17-one (**3**) (100 mg) gave only starting material. When the reaction was repeated for 4.5 h (t.l.c. control), starting material (55 mg) was again recovered.

(c) 5β,6β-Epoxyandrostan-17-one (**4**) (300 mg) in methyl ethyl ketone (3 ml) was treated with aqueous 75% chromium trioxide (0.3 ml) over 20 min at 35—40 °C. The mixture was diluted with water and the product recovered in ethyl acetate and chromatographed. Elution with 20% ethyl acetate–light petroleum gave 5α-hydroxyandrostane-6,17-dione (**12**) (175 mg), identical with the material described later.

Hydrogenolysis Reactions.—(a) *3α-Chloro-5β,6β-epoxyandrostan-17-one.* Azoisobutyronitrile (120 mg) was added to a solution of the steroid (**3**) (480 mg) in benzene (40 ml) under nitrogen. Tributyltin hydride (4 ml) was then added and the mixture was heated under reflux for 1 h. The solvent was evaporated off and the residue was chromatographed on silica to give *5β,6β-epoxyandrostan-17-one* (**4**) (400 mg), which crystallized from ether as flakes, m.p. 113—115 °C (Found: C, 79.3; H, 9.9. $C_{19}H_{28}O_2$ requires C, 72.1; H, 9.8%); $\nu_{max.}$ 1 740 cm^{-1}; δ 0.83 (3 H, s, 18-H), 1.00 (3 H, s, 19-H), and 3.01 (1 H, d, *J* 2 Hz, 6α-H).

(b) *3α-Chloro-5α-hydroxyandrostane-6,17-dione* (**11**). Azoisobutyronitrile (28 mg) was added to a solution of the steroid (**11**) (100 mg) in dry benzene (9 ml) under nitrogen. Tributyltin hydride (0.85 ml) was then added and the mixture was heated under reflux for 1 h. The solvent was evaporated off and the residue chromatographed on silica. Elution with 30% ethyl acetate–light petroleum gave 5α-hydroxyandrostane-6,17-dione (**12**) (75 mg), which crystallized from ethyl acetate–light petroleum as cubes, m.p. 230—237 °C (lit.,[15] 236—238 °C) (Found: C, 75.1; H, 9.6. Calc. for $C_{19}H_{28}O_3$: C, 75.0; H, 9.3%); $\nu_{max.}$ 3 420, 1 740, and 1 700 cm^{-1}; δ 0.85 (3 H, s, 18-H) and 0.90 (3 H, s, 19-H). The identical product was obtained by hydrogenation of 5α-hydroxyandrost-2-ene-6,17-dione[16] (300 mg) in ethyl acetate (30 ml) over 10% palladium–charcoal (90 mg) at room temperature for 2 h.

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