# The Base-catalysed Epoxidation of Androst-4-en-6-ones

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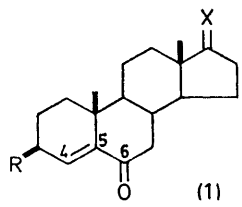
The products of base-catalysed epoxidation of androst-4-en-6-ones have been shown to be 4β,5β-epoxides The presence of a 3β-hydroxy-group facilitates epoxidation.

We required a method of preparing 3-substituted 4β,5β-epoxyandrostan-6-ones in high yield. 3β-Acetoxyandrost-4-ene-6,17-dione (1; R = OAc, X = O) may be prepared [1] from dehydroisoandrosterone acetate (3β-acetoxyandrost-5-en-17-one) by oxidation of the 5α,6α-epoxide to the 5α-hydroxy-6-ketone followed by dehydration with thionyl chloride. Epoxidation of 6-hydroxycholest-4-enes with perbenzoic acid has been reported [2] to give mixtures of the 4α,5α- and 4β,5β-epoxides irrespective of the C-6 stereochemistry. Oxidation of 3β-acetoxy-4β-hydroxycholest-5-ene with 8N-chromium trioxide has been reported [3,4] to give a mixture of 3β-acetoxy-5β,6β-epoxycholestan-4-one and 3β-acetoxy-4β,5β-epoxycholestan-6-one. However, base-catalysed epoxidation of testosterone with alkaline hydrogen peroxide yields predominantly the sterically less favoured 4β,5β-epoxy-17β-hydroxyandrostan-3-one.[5] Although there is steric hindrance by the C-10 methyl group to attack from the β face of the molecule at C-4, nevertheless we examined this method of epoxidation with 3β-acetoxyandrost-4-ene-6,17-dione.

Treatment of 3β-acetoxyandrost-4-ene-6,17-dione (1; R = OAc, X = O) with alkaline hydrogen peroxide gave 3β-hydroxy-4β,5β-epoxyandrostane-6,17-dione (2; R = OH, X = O). The n.m.r. signal for the C-4 proton in the 3β-alcohol and its acetate (τ 6·71 and 6·66, respectively) showed a coupling constant ($J_{3,4}$) of 2—3 Hz, as expected for an axial–equatorial coupling and hence a 'β' epoxide. The stereochemistry of epoxidation was firmly established in the 17-deoxy-series. 3β-Acetoxyandrost-5-ene [6] was converted into its epoxide and oxidized with chromium trioxide [7] to 3β-acetoxy-5α-hydroxyandrostan-6-one. Dehydration with thionyl chloride gave 3β-acetoxyandrost-4-en-6-one (1; R = OAc, X = $H_2$). On epoxidation with alkaline hydrogen peroxide this gave 4β,5β-epoxy-3β-hydroxyandrostan-6-one (2; R = OH, X = $H_2$). The reaction was followed by t.l.c. This revealed that a rapid hydrolysis of the acetoxy-group took place to give 3β-hydroxyandrost-4-en-6-one (1; R = OH, X = $H_2$) (identified by comparison with authentic material). This was followed by a slower epoxidation. Reduction of the epoxy-ketone with lithium aluminium hydride gave a 3β,5β,6β-triol, which was characterized as its 3β,6β-diacetate (3).

[1] L. Labler, F. Slama, and F. Sorm, *Coll. Czech. Chem. Comm.*, 1968, **33**, 2226.
[2] S. Greenfield, E. Glotter, D. Lavie, and Y. Kashman, *J. Chem. Soc.* (*C*), 1967, 1460.
[3] V. Petrow and W. W. Starling, *J. Chem. Soc.*, 1940, 60; O. Rosenheim, W. W. Starling, and V. Petrow, *ibid.*, 1937, 377; 1938, 677.
[4] E. Glotter, S. Greenfield, and D. Lavie, *J. Chem. Soc.* (*C*), 1968, 1646.
[5] H. B. Henbest and W. R. Jackson, *J. Chem. Soc.* (*C*), 1967, 2459.
[6] J. E. van Lier and L. L. Smith, *J. Org. Chem.*, 1970, **35**, 2627.
[7] L. Knof, *Annalen*, 1962, **657**, 171.

This differed from a sample of 3β,6β-diacetoxy-5α-hydroxyandrostane (4)[8] prepared by reduction and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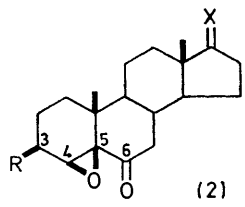
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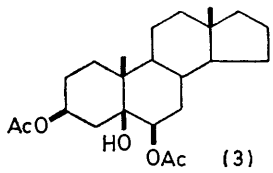
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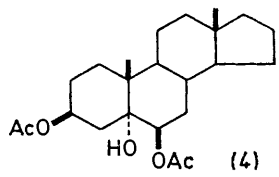
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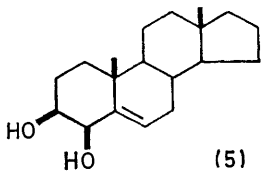
(5)

acetylation of 3β-acetoxy-5α-hydroxyandrostan-6-one. Treatment of the epoxy-ketone with hydrazine hydrate in refluxing ethanol gave 3β,4β-dihydroxyandrost-5-ene (5). The diacetate of this glycol was identical with material prepared by treatment of 3β-hydroxyandrost-5-ene with bromine and then silver acetate, followed by further acetylation.[9] The multiplicities of the C-3 and C-4 proton resonances were in accord with this stereochemistry. In the diacetate the C-4 proton resonance at τ 4·46 (τ 5·33 in the parent alcohol) appeared as a doublet ($J_{3,4}$ 3·5 Hz). The C-3 proton resonance at τ 5·25 (6·4 in the parent alcohol) was an eight-line multiplet which was analysed to give $J_{3\alpha,4\alpha}$ 3·5, $J_{3\alpha,2\alpha}$ 5·5, and $J_{3\alpha,2\beta}$ 10·5 Hz. The small 3,4-coupling constant implied an axial–equatorial interaction.

Two features may contribute to the formation of the 4β,5β-isomer. On the one hand there is the directing effect of the C-3β allylic oxygen function facilitating attack from the β face of the steroid by hydrogen bonding with the reagent. On the other hand the transition state for ring closure to the epoxide from the 4-hydroperoxy-enolate anion requires the existance of the hydroperoxy-group in a conformation where there is maximum overlap between the π-bond of the enolate and the hydroperoxide oxygen orbitals. A C-4β axial orientation of the hydroperoxide provides this feature, which is absent from a C-4α equatorial orientation. The contributions of these two features were revealed by comparing the epoxidation of 3β-hydroxyandrost-4-en-6-one (1; R = OH, X = $H_2$) with that of androst-4-en-6-one (1; R = H, X = $H_2$). Whereas the epoxidation of 3β-hydroxyandrost-4-en-6-one was essentially complete in 1·75 h (t.l.c.), the epoxidation of androst-4-en-6-one required *ca.* 16 h. Androst-4-en-6-one gave the 4β,5β-epoxide for which the C-4 proton resonance appeared as a triplet (*J* 2·5 Hz), in accordance with its 4-H equatorial conformation. Thus the 3β-hydroxy-group contributes to a rate enhancement but the orienting feature is probably the overlap between the hydroperoxide and the enolate.

Androst-4-en-6-one was prepared from androst-5-ene by epoxidation, oxidation of the 5,6-epoxide, and dehydration of the 5α-hydroxy-6-one with thionyl chloride.

## EXPERIMENTAL

General procedures have been described previously.[10]

*4β,5β-Epoxy-3β-hydroxyandrostane-6,17-dione.*— 3β-Acetoxyandrost-4-ene-6,17-dione [1] (1·0 g) in methanol (100 ml) was cooled to 0° and treated with 30% hydrogen peroxide (6·4 ml) followed by 4N-sodium hydroxide (4·3 ml). The temperature was maintained below 10° during these additions. The solution was then kept at 0° for 2 h, concentrated to 20 ml *in vacuo*, and poured into water (200 ml). The steroid was recovered in chloroform to give 4β,5β-*epoxy*-3β-*hydroxyandrostane*-6,17-*dione* (500 mg), which crystallized from ethyl acetate–light petroleum as needles, m.p. 174—175°, $[\alpha]_D^{20}$ +37° (*c* 0·2) (Found: C, 71·5; H, 8·4. $C_{19}H_{26}O_4$ requires C, 71·7; H, 8·2%), $\nu_{max.}$ 3490, 1735, and 1705 $cm^{-1}$, τ 9·08 (3H, s), 8·93 (3H, s), 6·71 (1H, d, *J* 3 Hz), and 5·95 (1H, m).

The *acetate*, prepared with acetic anhydride in pyridine, crystallized from acetate–light petroleum as needles, m.p. 211—212°, $[\alpha]_D^{20}$ −27° (*c* 0·2) (Found: C, 69·8; H, 7·75. $C_{21}H_{28}O_5$ requires C, 70·0; H, 7·75%), $\nu_{max.}$ 1740br $cm^{-1}$, τ 9·08 (3H, s), 8·91 (3H, s), 7·91 (3H, s), 6·66 (1H, d, *J* 2 Hz), and 4·92 (1H, m).

*3β-Acetoxy-5α,6α-epoxyandrostane.*— 3β-Acetoxyandrost-5-ene [6] (12·0 g) in benzene (200 ml) was treated with *m*-chloroperbenzoic acid (15·0 g) at room temperature overnight. The solution was diluted with benzene, washed with aqueous iron(II) sulphate, dil. hydrochloric acid, aqueous sodium hydrogen carbonate, and water, dried, and evaporated to give 3β-*acetoxy*-5α,6α-*epoxyandrostane* (11·4 g), which crystallized from methanol as needles, m.p. 118·5—120°, $[\alpha]_D^{20}$ −68° (*c* 0·2) (Found: C, 75·7; H, 9·6. $C_{21}H_{32}O_3$ requires C, 75·9; H, 9·7%), $\nu_{max.}$ 1740 $cm^{-1}$, τ 9·35 (3H, s), 8·92 (3H, s), 8·00 (3H, s), 7·13 (1H, d, *J* 4 Hz), and 5·07 (1H, m).

*3β-Acetoxy-5α-hydroxyandrostan-6-one.*— 3β-Acetoxy-5α,6α-epoxyandrostane (11·0 g) in ethyl methyl ketone (110 ml) was treated dropwise with aqueous 75% chromium trioxide (11·0 ml) during 20 min at 35—40°. The solution was poured into ice–water (1·1 l) and the product was filtered off. It was chromatographed on alumina; elution with 60% ether–light petroleum gave 3β-*acetoxy*-5α-*hydroxyandrostan*-6-*one* (6·3 g), which crystallized from light petroleum as needles, m.p. 220—221°, $[\alpha]_D^{20}$ −92° (*c* 0·2) (Found: C, 72·15; H, 9·1. $C_{21}H_{32}O_4$ requires C, 72·4; H, 9·3%), $\nu_{max.}$ 3420, 3360, 1735, and 1710 $cm^{-1}$, τ 9·32 (3H, s), 9·19 (3H, s), 8·01 (3H, s), and 5·00 (1H, m).

*3β-Acetoxyandrost-4-en-6-one.*—A solution of freshly distilled thionyl chloride (1·5 ml) in pyridine (5 ml) was cooled

[8] M. Fetizon and P. Foy, *Coll. Czech. Chem. Comm.*, 1970, **35**, 440.

[9] V. Petrow, O. Rosenheim, and W. W. Starling, *J. Chem. Soc.*, 1943, 135.

[10] J. R. Hanson and T. D. Organ, *J. Chem. Soc.* (*C*), 1970, 513.

to −20° and added to a solution of 3β-acetoxy-5α-hydroxyandrostan-6-one (500 mg) in pyridine (15 ml) at −20°. The solution was allowed to attain room temperature and stirred for 20 min. It was cooled to −20° and added to ice-cold dil. hydrochloric acid (150 ml). The steroid was recovered in ethyl acetate and chromatographed on alumina. Elution with 10% ethyl acetate–light petroleum gave 3β-*acetoxyandrost*-4-*en*-6-*one* (300 mg), which crystallized from light petroleum as needles, m.p. 109—111°, $[\alpha]_D^{20}$ −86° (*c* 0·2) (Found: C, 76·3; H, 9·2. $C_{21}H_{30}O_3$ requires, C, 76·3; H, 9·15%), $\nu_{max.}$ 1740, 1695, and 1640 cm$^{-1}$, τ 9·2 (3H, s), 8·91 (3H, s), 7·89 (3H, s), 4·66 (1H, m), and 3·9 (1H, m).

4β,5β-*Epoxy*-3β-*hydroxyandrostan*-6-*ones*.—A solution of 3β-acetoxyandrost-4-en-6-one (1·0 g) in methanol (100 ml) was cooled to 0° and treated with 30% hydrogen peroxide (6·4 ml) followed by 4N-sodium hydroxide (4·3 ml). The temperature was maintained below 10° during these additions. The mixture was kept at 0° for 2 h, concentrated to 20 ml *in vacuo*, and poured into water (200 ml). The steroid was recovered in ethyl acetate. The solvent was evaporated off to give 4β,5β-*epoxy*-3β-*hydroxyandrostan*-6-*one* (550 mg), which crystallized from light petroleum as needles, m.p. 147—149°, $[\alpha]_D^{20}$ −58° (*c* 0·2) (Found: C, 75·0; H, 9·2. $C_{19}H_{28}O_3$ requires C, 75·0; H, 9·3%), $\nu_{max.}$ 3400 and 1710 cm$^{-1}$, τ 9·19 (3H, s), 8·90 (3H, s) 6·69 (1H, d, *J* 3 Hz), and 5·93 (1H, m).

The *acetate*, prepared with acetic anhydride–pyridine, crystallized from light petroleum as needles, m.p. 109—110°, $[\alpha]_D^{20}$ −113° (*c* 0·2) (Found: C, 73·0; H, 8·7. $C_{21}H_{30}O_4$ requires C, 72·8; H, 8·7%), $\nu_{max.}$ 1740 and 1725 cm$^{-1}$, τ 9·24 (3H, s), 8·93 (3H, s), 7·91 (3H, s), 6·68 (1H, d, *J* 4 Hz), and 4·9 (1H, m).

*Androst*-5-*ene*-3β,4β-*diol*.— 4β,5β-Epoxy-3β-hydroxyandrostan-6-one (250 mg) and hydrazine hydrate (1 ml) in ethanol (10 ml) were heated under reflux for 2 h. The solution was poured into water and the steroid recovered in methylene chloride. The solvent was evaporated to give the *diol* (150 mg), which crystallized from light petroleum as plates, m.p. 163—165°, $[\alpha]_D^{20}$ −83° (*c* 0·1) (Found: C, 79·0; H, 10·3. $C_{19}H_{30}O_2$ requires C, 78·6; H, 10·4%), $\nu_{max.}$ 3530, 3430, 3380, and 3240 cm$^{-1}$, τ 9·28 (3H, s), 8·75 (3H, s), 6·4 (1H, m), 5·33 (1H, d, *J* 3·5 Hz), and 4·3 (1H, m).

The *diacetate*, prepared with acetic anhydride in pyridine, crystallized from methanol as needles, m.p. 163—164°, $[\alpha]_D^{20}$ −114° (*c* 0·2) (Found: C, 74·0; H, 9·2. $C_{23}H_{34}O_4$ requires C, 73·8; H, 9·15%), $\nu_{max.}$ 1745 and 1735 cm$^{-1}$, τ 9·25 (3H, s), 8·81 (3H, s), 7·96 (3H, s), 7·90 (3H, s), 5·25 (1H, m; see text), 4·46 (1H, d, *J* 3·5 Hz), and 4·15 (1H, m).

3β,4β-*Diacetoxyandrost*-5-*ene*.—Bromine (0·38 ml) was added to a solution of androst-5-en-3β-ol (1·9 g) in chloroform (20 ml). The solvent was removed *in vacuo* at room temperature. The residue was dissolved in pyridine (10 ml) and ether (20 ml) and treated with silver acetate (2·3 g) in pyridine (10 ml) for 20 min in the dark. Ether (250 ml) was added and the silver bromide was filtered off. The solution was washed with dil. hydrochloric acid and water, dried, and evaporated; the residue (2·0 g) was taken up in pyridine (60 ml) and treated with acetic anhydride (10 ml) overnight. The solution was poured into dil. hydrochloric acid (500 ml) and the steroid was recovered in ethyl acetate and chromatographed on alumina. Elution with 4% ethyl acetate–light petroleum gave 3β,4β-diacetoxyandrost-5-ene (750 mg), which crystallized from methanol as needles, m.p. 163—164°, identical (i.r. and t.l.c.) with the material already described.

3β,6β-*Diacetoxyandrostan*-5β-*ol*.— 4β,5β-Epoxy-3β-hydroxyandrostan-6-one (180 mg) in tetrahydrofuran (20 ml) was treated with lithium aluminium hydride (100 mg) at room temperature for 1 h. Water was added and the organic product was recovered in ethyl acetate. The product (100 mg) in pyridine (2 ml) was treated with acetic anhydride (1 ml) overnight. The solution was poured into dil. hydrochloric acid and the steroid was recovered in ethyl acetate. Evaporation of the solvent gave 3β,6β-*diacetoxyandrostan*-5β-*ol* (60 mg), which crystallized from light petroleum as needles, m.p. 210—212°, $[\alpha]_D^{20}$ +40° (*c* 0·2) (Found: C, 70·2; H, 9·4. $C_{23}H_{36}O_5$ requires C, 70·4; H, 9·2%), $\nu_{max.}$ 3590, 3480, and 1733 cm$^{-1}$, τ 9·30 (3H, s), 8·99 (3H, s), 7·93 (3H, s), 7·90 (3H, s), and 4·8 (2H, m).

3β,6β-*Diacetoxyandrostan*-5α-*ol*.— 3β-Acetoxy-5α-hydroxyandrostan-6-one (300 mg) in tetrahydrofuran (20 ml) was treated with lithium aluminium hydride (100 mg) at room temperature for 1 h. Water was added and the steroid was recovered in ethyl acetate. The solvent was evaporated to give *androstane*-3β,5α,6β-*triol* (150 mg), which crystallized from ethyl acetate as needles, m.p. 222—224°, $[\alpha]_D^{20}$ −29° (*c* 0·2) (Found: C, 74·0; H, 10·1. $C_{19}H_{32}O_3$ requires C, 74·0; H, 10·5%), $\nu_{max.}$ 3620sh, 3550sh, and 3430br cm$^{-1}$.

The 3β,6β-diacetate, prepared with acetic anhydride in pyridine, crystallized from light petroleum as needles, m.p. 187—189°, $[\alpha]_D^{20}$ −75° (*c* 0·2) (lit.,[8] m.p. 187—189°, $[\alpha]_D$ −70°) (Found: C, 70·4; H, 9·2. Calc. for $C_{23}H_{36}O_5$: C, 70·4; H, 9·2%), $\nu_{max.}$ 3440, 1740, and 1715 cm$^{-1}$, τ 9·28 (3H, s), 8·82 (3H, s), 7·93 (3H, s), 5·3 (1H, m), and 4·9 (1H, m).

3β-*Hydroxyandrost*-4-*en*-6-*one*.— 3β-Acetoxyandrost-4-en-6-one (330 mg) in methanol (40 ml) was treated with 4N-sodium hydroxide (1·5 ml) at 0° for 15 min. The solution was concentrated *in vacuo* and poured into water (75 ml). The steroid was recovered in ethyl acetate. Evaporation left 3β-*hydroxyandrost*-4-*en*-6-*one*, which crystallized from light petroleum as needles, m.p. 177—179°, $[\alpha]_D^{20}$ −47° (*c* 0·2) (Found: C, 79·2; H, 9·45. $C_{19}H_{28}O_2$ requires C, 79·1; H, 9·8%), $\nu_{max.}$ 3420, 1690, 1680, and 1630 cm$^{-1}$, τ 9·21 (3H, s), 8·95 (3H, s), 5·8 (1H, m), and 3·8 (1H, m).

5α-*Hydroxyandrostan*-6-*one*.—Androst-5-ene [11] (2·5 g) in chloroform (40 ml) was treated with *m*-chloroperbenzoic acid (2·5 g) overnight. The solution was diluted with chloroform, washed with aqueous iron(II) sulphate, water, aqueous sodium hydrogen carbonate, and water, dried, and evaporated to give a gum (2·4 g), which was dissolved in acetone (30 ml) and treated with chromium trioxide (4 g) in water (6 ml) for 20 min. Methanol (10 ml) was added and the solution was then poured into water and the product recovered in ether. It was chromatographed on alumina. Elution with 20—30% ether–light petroleum gave 5α-*hydroxyandrostan*-6-*one* (570 mg), which crystallized from acetone–light petroleum as needles, m.p. 182—183°, $[\alpha]_D^{20}$ −88° (*c* 0·2) (Found: C, 78·5; H, 10·2. $C_{19}H_{30}O_2$ requires C, 78·6; H, 10·4%), $\nu_{max.}$ 3520, 3500, and 1703 cm$^{-1}$, τ 9·27 (3H, s) and 9·17 (3H, s).

*Androst*-4-*en*-6-*one*.—5α-Hydroxyandrostan-6-one (380 mg) in pyridine (5 ml) was treated with thionyl chloride (1·5 ml) in pyridine (5 ml) at 0° for 1 h. The solution was poured on ice and the product was recovered in ethyl acetate and chromatographed on alumina. Elution with light

[11] J. E. Bridgeman, P. C. Cherry, A. S. Clegg, Sir Ewart R. H. Jones, A. Kasai, V. Kumar, G. D. Meakins, Y. Morisawa, Mrs. E. E. Richards, and P. D. Woodgate, *J. Chem. Soc.* (*C*), 1970, 250.

petroleum gave androst-4-en-6-one (130 mg), which crystallized from light petroleum as plates, m.p. 130—131°, $[\alpha]_D^{20}$ +20° (*c* 0·2) (lit.,[12] m.p. 135°, $[\alpha]_D$ +24°) (Found: C, 83·5; H, 10·2. Calc. for $C_{19}H_{28}O$: C, 83·8; H, 10·4%), $\nu_{max.}$ 1685 $cm^{-1}$, $\tau$ 9·25 (3H, s), 9·03 (3H, s), and 4·82 (1H, t, *J* 3 Hz).

4β,5β-*Epoxyandrostan*-6-*one*.—Androst-4-en-6-one (250 mg) in methanol (25 ml) was treated at 0° with 30% hydrogen peroxide (1·6 ml) followed by 4N-sodium hydroxide (1·1 ml) below 10°. The solution was left at 0° for 3 h, and then stirred at room temperature overnight. The methanol was removed *in vacuo*, water (50 ml) was added, and the steroid was recovered in ethyl acetate. 4β,5β-*Epoxyandrostan*-6-*one* (130 mg) crystallized from light petroleum as needles, m.p. 155—160°, $[\alpha]_D^{20}$ −43° (*c* 0·2) (Found: C, 79·2; H, 9·5. $C_{19}H_{28}O_2$ requires C, 79·1; H, 9·8%), $\nu_{max.}$ 1720 $cm^{-1}$, $\tau$ 9·24 (3H, s), 8·97 (3H, s), and 6·95 (1H, t, *J* 2·5 Hz).

A second epoxidation was run in parallel at 0° with an epoxidation of 3β-hydroxyandrost-4-en-6-one and assayed by t.l.c. on silica (40% ethyl acetate–light petroleum as the mobile phase). The epoxidation of 3β-hydroxyandrost-4-en-6-one was complete after 1·75 h whereas that of androst-4-en-6-one required *ca.* 16 h.

We thank Schering Chemicals Ltd. for financial support.

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[12] R. Beugelmans, *Bull. Soc. chim. France*, 1967, 244.