Preparation of Androsta-2,5-dien-4-ones

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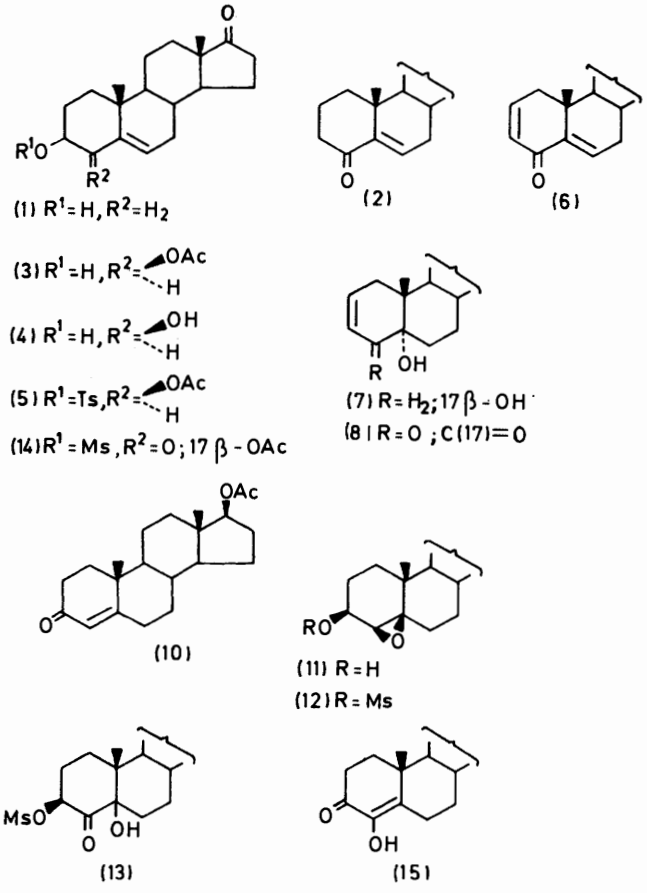
Simple sequences are described for the preparation of the title compounds from dehydroisoandrosterone(3β-hydroxyandrost-5-en-17-one) and testosterone (17β-hydroxyandrost-4-en-3-one).

THE preparation and chemistry of steroidal 1,4-dien-3-ones are well documented.[1] In contrast, the isomeric 2,5-dien-4-ones are relatively inaccessible and have been little studied. We describe here simple syntheses of this system from the readily available dehydroisoandrosterone (1) and testosterone acetate (10) *via* the androst-5-en-4-ones (2).[2-4]

Dehydroisoandrosterone (1), on treatment with bromine in chloroform at −60 °C followed by silver acetate in pyridine under dry conditions (*cf.* ref. 5) was converted into its 4β-acetate (3) [δ 5.34 ($J_{3,4}$ 3.5 Hz, 4-H)]. This was then carefully hydrolysed to the 3β,4β-diol (4). The equatorial 3β-hydroxy-group may be esterified selectively to form a monomethanesulphonate or monotoluene-*p*-sulphonate by treatment with the corresponding acid chloride in pyridine. Careful treatment of the monotoluene-*p*-sulphonate (t.l.c. control) with sodium hydride in freshly purified tetrahydrofuran [6] gave androst-5-ene-4,17-dione (2) [δ 6.56 (q, *J* 2.5 and 5 Hz, 6-H)]. This compound was also obtained, in lower yield, by treatment of the 4β-acetoxy-3-toluene-*p*-sulphonate (5) with aqueous ethanolic potassium hydroxide.[4] Dehydrogenation of androst-5-ene-4,17-dione with dichlorodicyanobenzoquinone in benzene gave the required androsta-2,5-diene-4,17-dione (6) rather than the 5,7-diene-4,17-dione. The 3-H n.m.r. signal (δ 6.12), apart from showing the expected vicinal coupling (10 Hz) to the 2-H, also showed a W-type long-range coupling to the 1-protons (*J* 1 and 3 Hz).

An alternative short sequence which, however, did not proceed in comparable yield, also started from dehydroisoandrosterone (1). This was converted into the 3β-methylsulphonoxy-5α,6α-epoxide and thence into 5α,6α-epoxyandrost-2-en-17-one.[7] Elimination of the 3β-methanesulphonate group with either alumina or lithium carbonate proved a capricious reaction affording on occasion the 3α-alcohol [8] or a formate ester. Reduction of 5α,6α-epoxyandrost-2-en-17-one with lithium aluminium hydride afforded androst-2-ene-5α,17β-diol (7),[9] which was readily oxidized with 8N-chromium trioxide to form 5α-hydroxyandrost-2-ene-4,17-dione (8).[10] Cautious dehydration of this with thionyl chloride in pyridine gave androsta-2,5-diene-4,17-dione in modest yield.



A third route, applicable to compounds possessing a 17β-acetoxy-group, started with testosterone acetate

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(10). This was reduced with sodium borohydride to the 3β-alcohol and the product epoxidized with *m*-chloroperbenzoic acid to form the 4β,5β-epoxide (11).[11] This readily formed a methanesulphonate (12) which was oxidized with chromium trioxide in ethyl methyl ketone [12] to form the 5β-hydroxy-4-ketone (13). Although the 3β-methylsulphonyloxy-grouping in similar 5-hydroxy-steroids is readily eliminated by refluxing collidine,[13] no reaction was observed after 5 h. In this case the C-4 carbonyl group destabilizes the incipient C-3 carbocation. On the other hand, elimination of the 5-hydroxy-group with thionyl chloride in pyridine gave a 5-en-4-one (14), from which the methanesulphonate could then be eliminated with collidine to afford the required 17β-acetoxyandrosta-2,5-diene-4-one. In this case the known participation of a 5,6-double bond in displacement reactions at C-3 must outweigh the effect of the C-4 carbonyl group. When lithium carbonate in dimethylformamide was used for the elimination reaction, the main product was the diosphenol (15);[14] use of alumina or lithium iodide gave mixtures of the dienone and the diosphenol.

EXPERIMENTAL

General experimental details have been described previously.[15]

4β-Acetoxy-3β-hydroxyandrost-5-en-17-one (3).—This was prepared by a modification of the method of Petrow.[5] 3β-Hydroxyandrost-5-en-17-one (1) (40 g) in dry chloroform (300 ml) was cooled to −60 °C in an acetone–solid carbon dioxide bath and treated with bromine (22.2 g). The solution was swirled until the colour was discharged and fresh, dry silver acetate (50 g) in dry pyridine (75 ml) was added. The solution was allowed to attain room temperature in the dark over 5 h. The silver bromide was filtered off and the solution was diluted with chloroform, washed with dilute hydrochloric acid, water, and sodium hydrogen carbonate solution, dried, and evaporated to afford a gum which was triturated with ether (100 ml). The slurry was filtered and the 4β-acetoxy-3β-hydroxyandrost-5-en-17-one (3) (25 g) crystallized from acetone as needles, m.p. 191—193°, $[\alpha]_D$ −58° (*c* 0.2) (lit.,[5] 192—193°, $[\alpha]_D$ −60.7°), $\nu_{max.}$ 3 520, 1 735, and 1 730 cm^{-1} δ 0.88 (3 H, s), 1.14 (3 H, s), 2.06 (3 H, s), 3.59 (1 H, m), 5.34 (1 H, d, *J* 3.5 Hz), and 5.84 (1 H, q, *J* 2 and 5 Hz).

3β,4β-Dihydroxyandrost-5-en-17-one (4).—The acetate (3) (20 g) in warm methanol (600 ml) was diluted with water (600 ml) and saturated aqueous sodium hydroxide (10 ml) was added. After 2 h, glacial acetic acid (5 ml) was added and the solution was concentrated *in vacuo*. The steroid was recovered in chloroform; the solution was washed with aqueous sodium hydrogen carbonate, dried, and evaporated to give 3β,4β-dihydroxyandrost-5-en-17-one (4) (15 g) which crystallized from acetone as plates, m.p. 204—205° (lit.,[5] 204—205°), $\nu_{max.}$ 3 520, 3 330, and 1 746 cm^{-1}, δ 0.87 (3 H, s), 1.20 (3 H, s), 3.60 (1 H, m), 4.15 (1 H, d, *J* 3.5 Hz), and 5.70 (1 H, m). The monotoluene-*p*-sulphonate, prepared with toluene-*p*-sulphonyl chloride in pyridine for 15 h, crystallized from light petroleum–acetone as needles, m.p. 116—118° (decomp.), $[\alpha]_D$ −110° (*c* 0.2) (lit.,[4] 112°, $[\alpha]_D$ −52°), $\nu_{max.}$ 3 595, 1 740, and 1 602 cm^{-1}, δ 0.88 (3 H, s), 1.22 (3 H, s), 2.48 (3 H, s), 4.45 (2 H, m), 5.75 (1 H, m), and 2.61 and 2.12 (2 H each, d, *J* 8.5 Hz).

Androst-5-ene-4,17-dione (2).—(*a*) 4β-Hydroxy-3β-*p*-tolylsulphonyloxyandrost-5-en-17-one (3.50 g) was dissolved in freshly purified tetrahydrofuran (100 ml). Sodium hydride (60% dispersion in mineral oil) (400 mg) was added under nitrogen. The mixture was heated under reflux for 3 h, then cooled, and water (0.25 ml) was added with vigorous stirring. The solution was filtered and evaporated. The residual gum was taken up in ether; the solution was washed thoroughly with water and aqueous sodium hydrogen carbonate, dried, and evaporated to give a gum which was chromatographed on alumina. Elution with 10% ethyl acetate–light petroleum gave androst-5-ene-4,17-dione (2) (1.66 g), which crystallized from light petroleum as needles, m.p. 122—123°, $[\alpha]_D$ +6° (*c* 0.2) (lit.,[2] 128°, $[\alpha]_D$ +5°), $\nu_{max.}$ 1 748, 1 692, and 1 640 cm^{-1}, δ 0.84 (3 H, s), 1.03 (3 H, s), and 6.56 (1 H, q, *J* 2.5 and 5 Hz), $\lambda_{max.}$ 241 nm (ε 6 900).

(*b*) 4β-Acetoxy-3β-*p*-tolylsulphonyloxyandrost-5-en-17-one [4] (5) (500 mg) in ethanol (25 ml) and aqueous potassium hydroxide (0.1M; 30 ml) was heated under reflux for 30 min. The solution was cooled, neutralized with dilute hydrochloric acid, and diluted with water, and the steroid was recovered in ethyl acetate. The extract was washed with dilute hydrochloric acid, aqueous sodium hydrogen carbonate, and water, dried, and evaporated to leave a gum. Preparative layer chromatography on silica in 30% ethyl acetate–light petroleum gave androst-5-ene-4,17-dione (2) (41 mg), which crystallized from light petroleum as needles, m.p. 122—124°, identified by its i.r. and n.m.r. spectra.

Androsta-2,5-diene-4,17-dione (6).—(*a*) Androst-5-ene-4,17-dione (2) (1 g) and dichlorodicyanobenzoquinone (1 g) in benzene (50 ml) were heated under reflux for 5 h. The solution was cooled and filtered. The precipitate was washed with benzene and the washings were combined with the filtrate and evaporated to afford a gum which was chromatographed on alumina. Elution with 30% ethyl acetate–light petroleum gave *androsta-2,5-diene-4,17-dione* (6) (583 mg), which crystallized from acetone–light petroleum as needles, m.p. 169—170°, $[\alpha]_D$ +96° (*c* 0.2) (Found: C, 80.3; H, 8.6. $C_{19}H_{24}O_2$ requires C, 80.2; H, 8.5%), $\nu_{max.}$ 1 735, 1 665, 1 635, and 1 614 cm^{-1}, $\lambda_{max.}$ 242 (ε 7 850) and 268sh nm (ε 5 350), δ 0.92 (3 H, s), 1.13 (3 H, s), 6.12 (1 H, octet, *J* 10, 3, and 1 Hz), and 6.90 (2 H, m).

(*b*) 5α-Hydroxyandrost-2-ene-4,17-dione (8) [10] (200 mg) in dry pyridine (10 ml) was treated with thionyl chloride (1 ml) (freshly distilled from triphenyl phosphite) at −20 °C for 30 min. The solution was left to attain room temperature over 30 min, then cooled and poured into water. The organic product was recovered in ethyl acetate. The solvent was evaporated off and the product chromatographed to afford androsta-2,5-diene-4,17-dione (6) (55 mg), identified by its n.m.r. spectrum.

17β-Acetoxy-4β,5β-epoxy-3β-methylsulphonyloxyandrostane (12).—17β-Acetoxy-4β,5β-epoxyandrostan-3β-ol [11] (11) (7 g) in dry pyridine (50 ml) was treated with methanesulphonyl chloride (4.0 ml) at 0 °C for 2 h. The solution was poured into water and the organic product recovered in ethyl acetate. The extract was washed with dilute hydrochloric acid, aqueous sodium hydrogen carbonate, and water,

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dried, and evaporated to afford the *methanesulphonate* (12) (7.2 g), which crystallized from acetone–light petroleum as needles, m.p. 95—96°, $[\alpha]_D$ −64° (*c* 0.2) (Found: C, 61.9; H, 7.9. $C_{22}H_{34}O_6S$ requires C, 61.9; H, 8.0%), $\nu_{max.}$ 1 722 and 1 171 cm^{-1}, δ 0.82 (3 H, s), 1.07 (3 H, s), 2.04 (3 H, s), 3.10 (3 H, s), 3.20 (1 H, d, *J* 5 Hz), 4.65 (1 H, m), and 5.10 (1 H, m).

17β-*Acetoxy*-5β-*hydroxy*-3β-*methylsulphonyloxyandrostan*-4-*one* (13).—Chromium trioxide (10 g) in water (15 ml) was added dropwise with vigorous stirring to a solution of the methanesulphonate (12) (7 g) in ethyl methyl ketone (100 ml). After 3 h the solution was poured into water (500 ml) and the product was recovered in ethyl acetate. The extract was washed with water, dried, and evaporated to afford a gum, which was purified by filtration through a short column of alumina in ethyl acetate. The 4-*one* (13) (4.66 g) crystallized from acetone as needles, m.p. 233—234° (decomp.), $[\alpha]_D$ −7.0° (*c* 0.2) (Found: C, 60.0; H, 7.3. $C_{22}H_{34}O_7S$ requires C, 59.7; H, 7.7%), $\nu_{max.}$ 3 380, 1 735, 1 706, and 1 173 cm^{-1}, δ 0.77 (3 H, s), 0.81 (3 H, s), 2.03 (3 H, s), 2.50 (1 H, s, removed on shaking with deuterium oxide), 3.16 (3 H, s), 4.60 (1 H, t, *J* 7 Hz), and 5.92 (1 H, t, *J* 5 Hz).

17β-*Acetoxy*-3β-*methylsulphonyloxyandrost*-5-*en*-4-*one* (14).—Thionyl chloride (13.5 ml) (freshly redistilled from triphenyl phosphite) dissolved in dry freshly redistilled pyridine (45 ml) was cooled to −20 °C. The methanesulphonate (13) (4.5 g) in pyridine (135 ml) was also cooled to −20 °C and the solution of thionyl chloride was slowly added. After 30 min the mixture was allowed to attain room temperature over 30 min. It was then re-cooled and poured into water (500 ml), and the steroid was recovered in ethyl acetate. The extract was washed with dilute hydrochloric acid, aqueous sodium hydrogen carbonate, and water, dried (Na_2SO_4), and evaporated to afford the 5-*en*-4-*one* (14) (3.35 g), which crystallized from acetone–light petroleum as needles, m.p. 158—160° (decomp.), $[\alpha]_D$ −135° (*c* 0.2) (Found: C, 62.4; H, 7.6. $C_{22}H_{32}O_6S$ requires C, 62.3; H, 7.6%), $\nu_{max.}$ 1 735, 1 675, 1 630, and 1 173 cm^{-1}, δ 0.81 (3 H, s), 1.00 (3 H, s), 2.04 (3 H, s), 3.24 (3 H, s), 4.62 (1 H, t, *J* 8 Hz), 5.03 (1 H, q, *J* 8 and 10 Hz), and 6.46 (1 H, q, *J* 2 and 6 Hz).

17β-*Acetoxyandrosta*-2,5-*dien*-4-*one*.—The methanesulphonate (14) (3 g) in freshly redistilled collidine (50 ml) was heated under reflux for 2 h. The solution was cooled and poured into dilute hydrochloric acid (500 ml), and the steroid was recovered in ethyl acetate. The extract was washed with dilute hydrochloric acid, aqueous sodium hydrogen carbonate, and water, and dried. Evaporation gave a gum which was chromatographed on alumina. Elution with 8% ethyl acetate–light petroleum gave the 2,5-*dien*-4-*one* (1.21 g), which crystallized from light petroleum as needles, m.p. 179—181°, $[\alpha]_D$ −18° (*c* 0.2) (Found: C, 77.2; H, 8.6. $C_{21}H_{28}O_3$ requires C, 76.8; H, 8.6%), $\nu_{max.}$ 1 736, 1 672, 1 630, and 1 615 cm^{-1}, δ 0.82 (3 H, s), 1.10 (3 H, s), 2.04 (3 H, s), 4.64 (1 H, m), 6.10 (1 H, q, *J* 10 and 4 Hz), and 6.90 (2 H, m).

17β-*Acetoxy*-4-*hydroxyandrost*-4-*en*-3-*one* (15).—The methanesulphonate (14) (500 mg) in freshly distilled dimethylformamide (50 ml) containing lithium carbonate (500 mg) was heated under reflux for 5 h. Benzene (250 ml) was added and the inorganic salts were filtered off. The filtrate was diluted with light petroleum, washed with water, dried, and evaporated to afford the diosphenol (15) (235 mg), which crystallized from light petroleum as needles, m.p. 184—186°, $[\alpha]_D$ +82° (*c* 0.2) (lit.,[14] m.p. 194—196°, $[\alpha]_D$ +83°) (Found: C, 72.7; H, 8.8. Calc. for $C_{21}H_{30}O_4$: C, 72.8; H, 8.7%), $\nu_{max.}$ 3 435, 3 360, 1 742, 1 672, and 1 620 cm^{-1}, δ 0.83 (3 H, s), 1.19 (3 H, s), 2.04 (3 H, s), 4.62 (1 H, m), and 6.08 (1 H, s, removed by washing with deuterium oxide).

Under similar conditions but with lithium iodide (500 mg) and lithium carbonate (500 mg), the methanesulphonate (14) (500 mg) gave the diosphenol (15) (217 mg) and the dienone (6) (37 mg).

On heating with alumina (Woelm, grade 1; 10 g) in benzene (100 ml) for 5 h, the diosphenol (45 mg) and the dione (230 mg) were obtained.

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