Androsta-2,4-diene-6,17-dione

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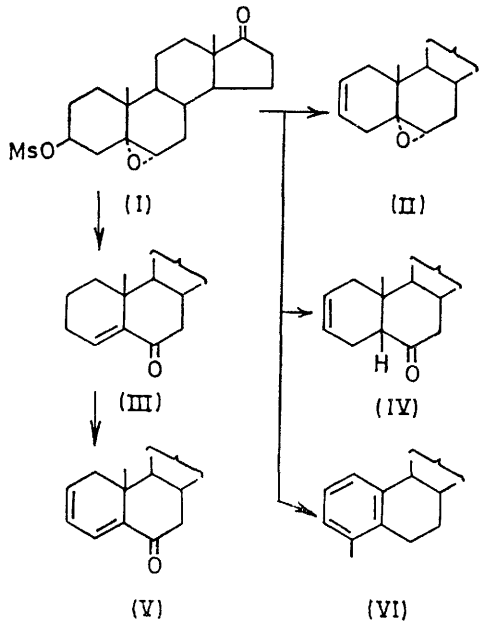
Treatment of 5α,6α-epoxy-3β-methylsulphonyloxyandrostan-17-one with lithium bromide and lithium carbonate in dimethylformamide afforded androst-4-ene-6,17-dione. Dehydrogenation of this with dichlorodicyanobenzoquinone gave androsta-2,4-diene-6,17-dione. This was also prepared by oxidation of the epoxide to the 5α-hydroxy-6-ketone followed by elimination of the methanesulphonate group with lithium carbonate and dehydration of the 5α-alcohol with thionyl chloride.

ANDROSTA-2,4-DIENE-6,17-DIONE (V) contains an interesting dienone system whose properties have not been fully studied. The preparation [1] of cholesta-2,4-dien-6-one utilizes the dehydrobromination of the relatively unstable 3β,5α-dibromocholestan-6-one. Hence we sought an alternative route in the androstane series. Elimination reactions of 3β-sulphonate esters provide [2] a method of generating steroidal Δ^2-olefins, and oxidation of 5α,6α-epoxides and subsequent dehydration of the resultant 5α-hydroxy-6-ketones [3] leads to Δ^4-6-ketones.



A combination of these reactions appeared to offer a simple route to androsta-2,4-diene-6,17-dione. During the development of this sequence a number of unexpected reactions were also encountered.

The methanesulphonate of 3β-hydroxyandrost-5-en-17-one was prepared by use of methanesulphonyl chloride in pyridine, and converted into the 5α,6α-epoxide with *m*-chloroperbenzoic acid. However only a low yield of 5α,6α-epoxyandrost-2-en-17-one (II) was obtained when the methanesulphonate (I) was treated with alumina.[2] Under more vigorous conditions 5β-androst-2-ene-6,17-dione (IV) was formed. This was isomerized by alkali to the known [4] 5α-androst-2-ene-6,17-dione.

Elimination of the toluene-*p*-sulphonate group from 17α-acetoxy-5α,6α-epoxy-3β-*p*-tolylsulphonyloxypregnan-20-one with lithium carbonate in dimethylacetamide has been successfully employed [5] in preparing a Δ^2-olefin. When the methanesulphonate of 5α,6α-epoxy-3β-hydroxyandrostan-17-one was treated with lithium carbonate in dimethylformamide, 5α,6α-epoxyandrost-2-en-17-one (II) was obtained. However more prolonged reaction also gave 4-methyloestra-1,3,5(10)-trien-17-one (VI) [6] and 5β-androst-2-ene-6,17-dione (IV). We reasoned that the addition of lithium bromide to the reaction mixture would facilitate the elimination of the methanesulphonate by prior inversion. In the event the reaction took a different path. The major product was androst-4-ene-6,17-dione ($\lambda_{max.}$ 242 nm.) (III), which was accompanied by 4-methyloestra-1,3,5(10)-trien-17-one (VI). Since our physical constants for the former (m.p. 189—191°, $[\alpha]_D^{20}$ +127°) were different from the literature values [7] (m.p. 179—181°, $[\alpha]_D$ +97°), an authentic sample was prepared from 3β-acetoxyandrost-4-ene-6,17-dione [4,8] by hydrogenolysis with a zinc–copper couple in acetic acid.[9]

The formation of both the aromatic compound and the unsaturated ketone was unexpected. In contrast to observations of Hora,[1] the C-10 methyl group was retained during the aromatization. The aromatic compound may have arisen through elimination of the methanesulphonate and cleavage of the epoxide to give a 2,4-dien-6-ol. Further dehydration of this might then afford a 1,3,5-triene which on protonation can give the cationic intermediate of the dienol–benzene rearrangement. Although the related cholesta-1,3,5-trien-7-one is known [10] to aromatize, the product is a 1-methyl aromatic steroid rather than a 4-methyl steroid. The formation of the Δ^4-6-ketone may be understood in terms of the prior isomerization of the epoxide to the 5β-androstan-6-one. 3β-Chloro-5β-cholestane is known to

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[10] J. P. Connolly, R. B. Dorchai, and J. B. Thomson, *J. Chem. Soc.* (*C*), 1968, 461.

undergo elimination to form both Δ^2- and Δ^3-olefins.[11] In this case the formation of the Δ^3-olefin is followed by the isomerization of the $\beta\gamma$-unsaturated ketone to the $\alpha\beta$-unsaturated ketone. The possibility that a 3α,5α-cyclosteroid might be involved in this reaction was ruled out by the stability of 3α,5α-cycloandrostane-6,17-dione [12] under our conditions.

Androsta-2,4-diene-6,17-dione (V) was obtained by acid-catalysed dehydrogenation of androst-4-ene-6,17-dione with dichlorodicyanobenzoquinone in benzene.[13] However the product was difficult to separate from the starting material. Alternative approaches using bromination and dehydrobromination were not successful.

A better procedure involved the following steps. Oxidation of the methanesulphonate of 5α,6α-epoxy-3β-hydroxyandrostan-17-one with chromium trioxide gave a high yield of the corresponding 5α-hydroxy-6-one. Treatment of this with lithium carbonate in dimethylformamide or (better) lithium carbonate and lithium bromide, afforded 5α-hydroxyandrost-2-ene-6,17-dione, which was then dehydrated with thionyl chloride to give a good yield of androsta-2,4-diene-6,17-dione.

EXPERIMENTAL

General experimental details have been described previously.[14]

3β-*Methylsulphonyloxyandrost-5-en-17-one*.— Methanesulphonyl chloride (5 ml.) was added to a solution of 3β-hydroxyandrost-5-en-17-one (10 g.) in pyridine (25 ml.). The solution was left at room temperature for 3 hr. and then poured into water. The *methanesulphonate* (12·5 g.) was filtered off and gave needles, m.p. 149—151° (from acetone–light petroleum), $[\alpha]_D^{20}$ −1° (*c* 0·7) (Found: C, 65·0; H, 8·25. $C_{20}H_{30}O_4S$ requires C, 65·55; H, 8·25%), τ 9·12 [3H, s, C(18)H_3], 8·95 [3H, s, C(19)H_3], 7·00 (3H, s, $CH_3{\cdot}SO_2$), 5·50br [1H, C(3)H], and 4·55 [1H, m, C(6)H], $\nu_{max.}$ 1737 and 1175 cm.$^{-1}$.

5α,6α-*Epoxy*-3β-*methylsulphonyloxyandrostan*-17-*one*.— The foregoing methanesulphonate (12 g.) in benzene (200 ml.) was treated with an excess of *m*-chloroperbenzoic acid (15 g.). The suspension was left for 4 hr., repeatedly shaken with saturated aqueous sodium hydrogen carbonate, washed with water, dried, and evaporated. The *epoxide* (13 g.) gave needles, m.p. 168—172° (from acetone), $[\alpha]_D^{20}$ −16° (*c* 0·8) (Found: C, 62·9; H, 7·7. $C_{20}H_{30}O_5S$ requires C, 62·8; H, 7·9%), τ 9·18 [3H, s, C(18)H_3], 8·93 [3H, s, C(19)H_3], 7·10 [1H, m, C(6)H], 7·04 (3H, s, $CH_3{\cdot}SO_2$), and 5·40br [1H, C(3)H], $\nu_{max.}$ 1735 and 1178 cm.$^{-1}$.

Elimination Reactions.—(i) *With alumina*. (*a*) 5α,6α-Epoxy-3β-methylsulphonyloxyandrostan-17-one (6·6 g.) in benzene (50 ml.) was adsorbed on alumina (50 g.) (Woelm, grade 1, neutral) and shaken for 72 hr. The alumina was placed on a column of alumina and fractions were eluted with increasing concentrations of ethyl acetate in light petroleum. The fractions eluted with 10—12% ethyl acetate gave 5α,6α-*epoxyandrost*-2-*en*-17-*one* (100 mg.), plates, m.p. 172—174° (from acetone), $[\alpha]_D^{20}$ +49° (*c* 0·8) (Found: C, 79·15; H, 8·95. $C_{19}H_{26}O_2$ requires C, 79·7; H, 9·15%), τ 9·15 [3H, s, C(18)H_3], 8·94 [3H, s, C(19)H_3], 7·06 [1H, d, *J* 3 Hz, C(6)H], and 4·38 [2H, m, C(2) and C(3)H], $\nu_{max.}$ 1740 and 1652 cm.$^{-1}$. No other crystalline material was recovered from this experiment.

(*b*) The methanesulphonate (6 g.) adsorbed on alumina as in (*a*), was heated at 120° for 20 hr. Chromatography on alumina gave, in the fractions eluted with 16% ethyl acetate in light petroleum, 5β-*androst*-2-*ene*-6,17-*dione* (80 mg.) needles, m.p. 194—195° (from acetone–light petroleum), $[\alpha]_D^{20}$ +36° (*c* 0·8) (Found: C, 79·6; H, 9·10. $C_{19}H_{26}O_2$ requires C, 79·7; H, 9·15%), τ 9·24 [3H, s, C(19)-H_3?], 9·12 [3H, s, C(18)H_3?], and 4·36 [2H, m, C(2) and C(3)H], $\nu_{max.}$ 1740, 1715, 1664, and 666 cm.$^{-1}$. Treatment with 10% methanolic potassium hydroxide gave 5α-androst-2-ene-6,17-dione, m.p. 194—195°, $[\alpha]_D^{20}$ +133° (*c* 0·7) (lit.,[4] m.p. 194°, $[\alpha]_D^{20}$ +123°).

(ii) *With lithium carbonate*. The methanesulphonate (5 g.) in dimethylformamide (250 ml.) was heated under reflux with lithium carbonate (5 g.) for 3·5 hr. The solution was poured into 2N-hydrochloric acid and the product was recovered in chloroform. The extract was washed with hydrochloric acid and water, dried (Na_2SO_4), and evaporated, and the residue was chromatographed on alumina. Elution with 12% ethyl acetate–light petroleum gave 5α,6α-epoxyandrost-2-en-17-one (1·27 g.), m.p. 172—174°, which was identified by its i.r. spectrum. Repetition of this experiment but with 15 hr. reflux, gave after chromatography, 4-methyloestra-1,3,5(10)-trien-17-one (50 mg.), m.p. 181—183°, 5α,6α-epoxyandrost-2-en-17-one (1·37 g.), m.p. 172—174°, and 5β-androst-2-ene-6,17-dione (300 mg.), m.p. 194—195°. Each of these was identified by comparison of its i.r. spectrum with that of an authentic sample.

(iii) *With lithium bromide and lithium carbonate*. The methanesulphonate (5 g.), dissolved in dimethylformamide (50 ml.), was heated under reflux for 16 hr. with lithium bromide (5 g.) and lithium carbonate (1·5 g.). The solution was poured into 2N-hydrochloric acid and the steroid was recovered in chloroform. The extract was washed with hydrochloric acid and water, dried (Na_2SO_4) and evaporated, and the residue was chromatographed on silica. Elution with 10% ethyl acetate–light petroleum gave 4-methyloestra-1,3,5(10)-trien-17-one (600 mg.), needles, m.p. 181—183° (from acetone), $[\alpha]_D^{20}$ +154° (*c* 0·8) (lit.,[6] m.p. 180—181°, $[\alpha]_D$ +150°). Elution with 20% ethyl acetate–light petroleum gave androst-4-ene-6,17-dione (1·6 g.), needles, m.p. 189—191° (from acetone), $[\alpha]_D^{20}$ +127° (*c* 0·8) (Found: C, 79·8; H, 9·4. Calc. for $C_{19}H_{26}O_2$: C, 79·7; H, 9·15%), $\lambda_{max.}$ 242 nm. (ε 6300), τ 9·15 [3H, s, C(18)H_3], 9·06 [3H, s, C(19)H_3], and 3·59 [1H, t, *J* 3 Hz, C(4)H], $\nu_{max.}$ 1735, 1685, and 1627 cm.$^{-1}$ (lit.,[7] m.p. 179—181°, $[\alpha]_D$ +97°, $\lambda_{max.}$ 244 nm.).

Androst-4-*ene*-6,17-*dione*.— 3β-Acetoxyandrost-4-ene-6,17-dione [4] (800 mg.) was dissolved in acetic acid (20 ml.) and stirred with zinc–copper couple [9] (5 g.) for 18 hr. at room temperature. The solution was filtered, diluted with water, and neutralized with sodium hydrogen carbonate. The steroid was recovered in ether. The solvent was evaporated off and the product was chromatographed on alumina to yield androst-4-ene-6,17-dione (500 mg.), needles, m.p. 190—192° (from acetone), $[\alpha]_D^{20}$ +135° (*c* 0·5), identical with the sample obtained before.

Androsta-2,4-*diene*-6,17-*dione*.—Androst-4-ene-6,17-dione

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[12] R. Beugelmans, *Bull. Soc. chim France*, 1967, 244.
[13] H. J. Ringold and A. B. Turner, *J. Chem. Soc.* (*C*), 1967, 1720.
[14] J. R. Hanson and T. D. Organ, *J. Chem. Soc.* (*C*), 1970, 513.

(1 g.) in benzene (100 ml.) containing dichlorodicyano-*p*-benzoquinone (800 mg.) and a trace of toluene-*p*-sulphonic acid, was heated under reflux for 18 hr. The hydroquinone was filtered off and the solution was evaporated to give a gum which was chromatographed on alumina. Elution with 20% ethyl acetate–light petroleum gave *androsta*-2,4-*diene*-6,17-*dione* (400 mg.), needles, m.p. 167—169° (from acetone–light petroleum), $[\alpha]_D^{20}$ +107° (*c* 1·0) (Found: C, 80·0; H, 8·5. $C_{19}H_{24}O_2$ requires C, 80·2; H, 8·5%), τ 9·12 [3H, s, C(18)H_3], 9·00 [3H, s, C(19)H_3], 3·90 [2H, m, C(2) and C(4)H], and 3·08 [1H, t, *J* 3Hz, C(3)H], $\nu_{max.}$ 1735, 1675, 1630, and 1565 cm.$^{-1}$, $\lambda_{max.}$ 314 nm. (ε 8750). Androst-4-ene-6,17-dione (300 mg.) was recovered from the mother liquors.

5α-*Hydroxy*-3β-*methylsulphonyloxyandrostane*-6,17-*dione*.—5α,6α-Epoxy-3β-methylsulphonyloxyandrostan-17-one (10 g.) was dissolved in methyl ethyl ketone (100 ml.) at 35—40° and treated with two portions of 75% aqueous chromium trioxide (5 ml.) during 20 min. The solution was poured into ice–water (1 l.) and the product was filtered off. It was chromatographed on alumina in ethyl acetate to yield the *dione* (9·2 g.), needles, m.p. 172—173° (from acetone), $[\alpha]_D^{20}$ 0° (*c* 1·0) (Found: C, 60·35; H, 7·7. $C_{20}H_{30}O_6S$ requires C, 60·3; H, 7·6%), τ 9·15 [6H, s, C(18)H_3 and C(19)H_3], 7·00 (3H, s, $CH_3{\cdot}SO_2$), and 5·10br [1H, C(3)H], $\nu_{max.}$ 3360, 1730, 1713, and 1182 cm.$^{-1}$.

5α-*Hydroxyandrost*-2-*ene*-6,17-*dione*.—The foregoing methanesulphonate (5 g.) in dimethylformamide (250 ml.) was heated under reflux with lithium carbonate (5 g.) for 3 hr. The solution was poured into 2N-hydrochloric acid and the product was recovered in chloroform. The extract was washed with hydrochloric acid and water, dried (Na_2SO_4), and evaporated, and the product was chromatographed on alumina. Elution with 60% ethyl acetate–light petroleum gave 5α-*hydroxyandrost*-2-*ene*-6,17-*dione* (1·2 g.), needles (from chloroform–light petroleum), m.p. 242—245°, $[\alpha]_D^{20}$ +48° (*c* 0·7) (Found: C, 75·05; H, 8·4. $C_{19}H_{26}O_3$ requires C, 75·45; H, 8·7%), τ 9·24 [3H, s, C(19)H_3?], 9·12 [3H, s, C(18)H_3?], and 4·32 [2H, m, C(2) and C(3)H], $\nu_{max.}$ 3440, 1740, 1700, and 1660 cm.$^{-1}$. Repetition with lithium carbonate and lithium bromide (5 g.) in dimethylformamide (100 ml.) gave the olefin (2·67 g.) from the methanesulphonate (5 g.).

Androsta-2,4-*diene*-6,17-*dione*.—Thionyl chloride (1·5 ml.) (freshly purified) in pyridine (5 ml.) was cooled to −20° and added to a solution of 5α-hydroxyandrost-2-ene-6,17-dione (500 mg.) in pyridine (15 ml.) at −20°. After 30 min. at −20°, the solution was allowed to warm to room temperature, left for 30 min., and then cooled to −20° and poured into saturated aqueous sodium hydrogen carbonate. The product was recovered in ethyl acetate and chromatographed on alumina. Elution with 14—16% ethyl acetate–light petroleum gave androsta-2,4-diene-6,17-dione (300 mg.), needles, m.p. 167—169° (from acetone–light petroleum), identical with the material already described.

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