Androsta-2,4-diene-1,17-dione

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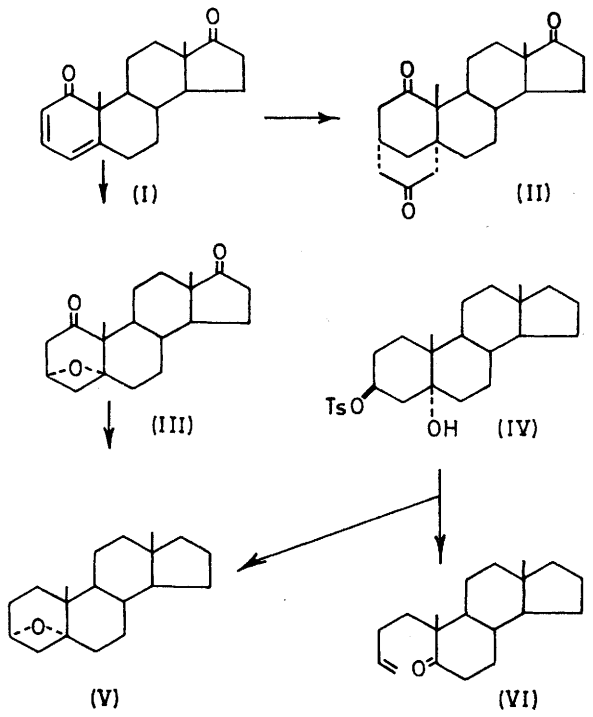
Bromination of 5α-androst-2-ene-1,17-dione and dehydrobromination of the product afforded androsta-2,4-diene-1,17-dione. Treatment of this with alkali afforded 3α,5α-epoxyandrostane-1,17-dione. This structure was confirmed by reduction to 3α,5α-epoxyandrostane, which was also prepared from androstane-3β,5α-diol. Androsta-2,4-diene-1,17-dione on treatment with acetone and hydrochloric acid gives a 3α,5α-adduct.

THE chemistry of steroidal cross-conjugated dienones has been thoroughly studied,[1] but considerably less is known of steroidal 2,4-diene 1-ketones. We report here the preparation of the hitherto unknown title compound (I) from 5α-androst-2-ene-1,17-dione. The literature procedure,[2] for synthesis of 17β-hydroxy-5α-androst-1-en-3-one, by bromination of 17β-hydroxy-5α-androstan-3-one in the presence of hydrobromic acid



followed by dehydrobromination with lithium carbonate and lithium chloride, was unreliable; the product could be separated in, at best, 50% yield from the starting material, testosterone, and 1-dehydrotestesterone. An improvement involved the prior conversion of 17β-hydroxy-5α-androstan-3-one into its 2-hydroxymethylene derivative with sodium methoxide and ethyl formate. The product was brominated to give the unstable 2-bromo-2-formyl-3-ketone. Treatment with 0·05N-sodium hydroxide to remove the formyl group followed immediately by dehydrobromination with lithium carbonate and lithium chloride then gave 17β-hydroxy-5α-androst-1-en-3-one in 80% overall yield. This was converted by way of its epoxide, by Wolff–Kishner reduction and subsequent oxidation, into 5α-androst-2-ene-1,17-dione.[3-5] Attempted dehydrogenation of this with dichlorodicyanobenzoquinone [6] was unsuccessful. However bromination with *N*-bromosuccinimide afforded the 4α-bromo-steroid, the stereo-chemistry of which was ascertained by *X*-ray analysis.[7] Dehydrobromination with lithium carbonate in dimethylformamide afforded androsta-2,4-diene-1,17-dione (I), $\lambda_{max.}$ 321 nm. (ε 2000), τ 4·01 (d, *J* 9 Hz), 3·98 (d, *J* 6 Hz), and 3·02 (q, *J* 6 and 9 Hz).

Treatment of the dienone with dilute aqueous methanolic alkali gave a compound, $C_{19}H_{26}O_3$. This lacked the u.v. absorption of the dienone, and there were no olefinic proton signals in the n.m.r. spectrum and no hydroxy-absorption in the i.r. spectrum. However carbonyl absorptions at 1740 and 1710 cm.$^{-1}$ (saturated cyclopentanone and cyclohexanone respectively) agreed with the structure, 3α,5α-epoxyandrostan-1,17-dione (III). Confirmation of this identification, together with assignment of the stereo-chemistry of the oxide ring, was obtained by Wolff–Kishner reduction of the carbonyl groups to give 3α,5α-epoxyandrostane (V), also prepared from androstane-3β,5α-diol.[8] The diol gave a 3β-monotoluene-*p*-sulphonate (IV) with toluene-*p*-sulphonyl chloride in pyridine, which, when treated with potassium t-butoxide in t-butyl alcohol [9] afforded the 3α,5α-oxide (V) and a fragmentation product (VI). The products were separated by reduction with lithium aluminium hydride and chromatography, which gave the fragmentation product as the corresponding alcohol.

Reduction of androsta-2,4-diene-1,17-dione with sodium borohydride gave a compound $C_{19}H_{30}O_3$ lacking olefinic proton resonances in the n.m.r. spectrum. This compound was identical with the sodium borohydride reduction product of 3α,5α-epoxyandrostane-1,17-dione. The overlap of the various CH·O resonances does not permit a confident assignment of the stereo-chemistry at C-1. This reaction further exemplifies the ready 3α,5α-ether formation shown by androsta-2,4-diene-1,17-dione.

[1] For a recent review see D. N. Kirk and M. P. Hartshorn, 'Steroid Reaction Mechanisms,' Elsevier, London, 1968, p. 277.
[2] R. E. Counsell, P. D. Klimstra, and F. B. Colton, *J. Org. Chem.*, 1962, **27**, 248.
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[7] G. A. Sim, personal communication.
[8] J. Weinman and S. Weinman, *Steroids*, 1965, **6**, 683.
[9] R. B. Clayton, H. B. Henbest, and M. Smith, *J. Chem. Soc.*, 1957, 1982.

Androsta-2,4-diene-1,17-dione was relatively stable under conditions which lead to the dienone-phenol rearrangement of androsta-1,4-dien-3-ones. However treatment with acetone containing a catalytic amount of concentrated hydrochloric acid gave as the major product a saturated triketone ($\nu_{max.}$ 1700, 1720, and 1735 cm.$^{-1}$) $C_{22}H_{30}O_3$ (M^+ 342). This compound showed no strong u.v. absorption although the spectrum contained a broad band (ε 150) at 275 nm. The n.m.r. spectrum showed no olefinic proton signals. Thus acetone has been added across ring A to give the novel bridged structure (II). This was confirmed by the incorporation of eight atoms of deuterium (*m/e* 350 ion) on treatment with methan[^{2}H]ol containing a trace of sodium methoxide.

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus and are corrected. Rotations were determined for solutions in chloroform. N.m.r. spectra were determined for solutions in deuteriochloroform with Varian A60A and HA100 spectrometers. Alumina refers to Spence type H; light petroleum refers to the fraction of b.p. 60—80°.

17β-*Hydroxy*-5α-*androst*-1-*en*-3-*one*.— 17β-Hydroxy-5α-androstan-3-one (4·35 g.) in dry pyridine (100 ml.) containing methanol-free sodium methoxide [from sodium (0·66 g.)] was treated overnight with ethyl formate (8·0 ml.) (freshly distilled from phosphorous pentoxide). The suspension was poured into an ice-cold solution of glacial acetic acid (75 ml.) in water (700 ml.) and the product was filtered off. It was dissolved in ether and extracted into 0·05N-sodium hydroxide (450 ml.). Bromine (2·4 g.) in aqueous potassium bromide (100 ml.) was added, followed by 0·05N-sodium hydroxide (150 ml.). After 24 hr. stirring at room temperature the solution was acidified with dilute hydrochloric acid and the 2-bromo-compound was recovered in chloroform. The chloroform was evaporated off and the residue was dissolved in dimethylformamide (45 ml.) containing lithium chloride (2·3 g.) and lithium carbonate (1·2 g.) and heated under reflux under nitrogen for 4 hr. The solution was diluted with chloroform, rinsed with dilute hydrochloric acid and water, dried, and evaporated. The residue was chromatographed on alumina (Woelm grade I) to give 17β-hydroxy-5α-androst-1-en-3-one (4 g.), m.p. 157—159°, identical with material prepared by the literature procedure.[2]

4α-*Bromo*-5α-*androst*-2-*ene*-1,17-dione.— 5α-Androst-2-ene-1,17-dione [5] (500 mg.) in benzene (20 ml.) was treated with *N*-bromosuccinimide (374 mg.) and a trace of benzoyl peroxide and then heated under reflux for 10 min. The solution was cooled, filtered, and adsorbed on alumina. Elution with 15% ethyl acetate–light petroleum gave 4α-*bromo*-5α-*androst*-2-*ene*-1,17-*dione* (493 mg.), which afforded needles, m.p. 193—196° (from acetone–light petroleum), $[\alpha]_D^{20}$ −37° (*c* 0·9) (Found: C, 62·5; H, 6·9. $C_{19}H_{25}BrO_2$ requires C, 62·5; H, 6·85%), $\lambda_{max.}$ 227 nm. (ε 6800).

Androsta-2,4-*diene*-1,17-*dione*.— 4α-Bromo-5α-androst-2-ene-1,17-dione (640 mg.) and lithium carbonate (1·3 g.) in dimethylformamide (20 ml.) were heated under reflux under nitrogen for 48 hr. The solution was cooled, filtered, and diluted with chloroform. It was then washed with dilute hydrochloric acid, aqueous sodium carbonate, and water, and dried. Evaporation and chromatography of the residue on alumina gave *androsta*-2,4-*diene*-1,17-*dione* (450 mg.), which yielded needles, m.p. 150—151° (from acetone–light petroleum), $[\alpha]_D^{20}$ −420° (*c* 0·8) (Found: C, 80·4; H, 8·6. $C_{19}H_{24}O_2$ requires C, 80·2; H, 8·5%), τ 9·12 (3H), 8·76 (3H), 4·01, 3·98, and 3·02, $\lambda_{max.}$ 321 nm. (ε 2000).

Dehydrobromination of 4α-bromo-5α-androst-2-ene-1,17-dione with collidine under reflux for 18 hr. also gave the required diene, in 30% yield.

3α,5α-*Epoxyandrostane*-1,17-*dione*.— Androsta-2,4-diene-1,17-dione (100 mg.) dissolved in methanol (1·5 ml.) was cooled to −5°. 10% Methanolic potassium hydroxide (0·3 ml.) was added. After 16 hr. the solution was concentrated and the product was recovered by preparative t.l.c. on silica, with ethyl acetate–light petroleum (2 : 3) as developer to give 3α,5α-*epoxyandrostane*-1,17-*dione* (35 mg.) as needles, m.p. 122—124° (from acetone–light petroleum), $[\alpha]_D^{20}$ +136° (*c* 0·9) (Found: C, 75·6; H, 8·55. $C_{19}H_{21}O_3$ requires C, 75·5; H, 8·7%), τ 9·10 (3H), 8·95 (3H), and 6·43 (m).

Androstane-3β,5α-*diol* 3-*Toluene*-p-*sulphonate*.—Androstane-3β-5α-diol (4·5 g.) in pyridine (25 ml.) was treated with toluene-*p*-sulphonyl chloride (3·1 g.) at room temperature for 48 hr. The solution was taken up in ether, thoroughly extracted with hydrochloric acid, and dried (Na_2CO_3). The extract was evaporated to dryness and the *toluene*-p-*sulphonate* (6·7 g.) gave needles, m.p. 133—134° (from acetone–light petroleum), $[\alpha]_D^{20}$ −26° (*c* 0·8) (Found: C, 69·8; H, 8·5. $C_{28}H_{38}O_4S$ requires C, 69·9; H, 8·6%), τ 9·30 (3H), 9·02 (3H), 7·54 (3H), 5·05br, 2·78 (d), and 2·18 (d, *J* 7 Hz).

3α,5α-*Epoxyandrostane*.—(i) 3α,5α-Epoxyandrostane-1,17-dione (20 mg.) was heated at 50° in hydrazine hydrate (1 ml.) for 10 min. and then set aside overnight. Diethylene glycol (5 ml.) was added and the solution was heated for 6 hr. at 190—200° in the presence of potassium hydroxide (15 mg.). The product was extracted with petroleum and filtered through alumina (Woelm grade IV) to yield 3α,5α-*epoxyandrostane* as a colourless oil (17·5 mg.) which crystallized from methanol at −20°, $[\alpha]_D^{20}$ +44° (*c* 1·0) (Found: C, 82·8; H, 10·8. $C_{19}H_{30}O$ requires C, 83·15; H, 11·0%), τ 9·12 (3H), 9·28 (3H), and 5·54br (d, *J* 8 Hz).

(ii) Androstane-3β,5α-diol 3β-toluene-*p*-sulphonate (2 g.) in sodium-dry-t-butyl alcohol (180 ml.) containing potassium t-butoxide [from potassium (345 mg.)] was kept at 50° for 2 hr. The mixture was poured into water and recovered in ether. The ether solution was treated with lithium aluminium hydride (1·3 g.) for 30 min. at room temperature. The excess of lithium aluminium hydride was destroyed, the solution was washed with dilute hydrochloric acid, and the ether was evaporated off. Chromatography on alumina gave, in the fraction eluted with light petroleum 3α,5α-epoxyandrostane (500 mg.) as a colourless oil, $[\alpha]_D^{20}$, +40° (*c* 1·0) (Found: C, 83·5; H, 10·9. Calc. for $C_{19}H_{30}O$: C, 83·15; H, 11·0%), with n.m.r. and i.r. identical with those of the compound obtained in (i).

Elution with 6% ethyl acetate–light petroleum afforded 4,5-*secoandrost*-3-*en*-5β-*ol* (400 mg.) which yielded plates, m.p. 100—104° (from acetone), $[\alpha]_D^{20}$ +2° (*c* 0·8) (Found: C, 82·7; H, 11·6. $C_{19}H_{32}O$ requires C, 82·5; H, 11·7%), $\nu_{max.}$ 3275br, 1640, 1076, 1038, 980, and 908 cm.$^{-1}$, τ 9·31 (3H), 9·17 (3H), 6·52br, 5·20, 4·98 (d, *J* 7 Hz), and 4·30 (m).

3α,5α-*Epoxyandrostane*-1,17β-*diol*.—(i) Androsta-2,4-

diene-1,17-dione (100 mg.) in (wet) methanol (5 ml.) was heated under reflux with sodium borohydride (150 mg.) for 10 min. and then left overnight. The product was poured into water, filtered, and recrystallized from acetone to give 3α,5α-*epoxyandrostan*-1ξ,17β-*diol* (80 mg.), m.p. 106—108°, $[\alpha]_D^{20}$ +16° (*c* 0·6) (Found: C, 74·75; H, 10·1%; *M*(mass spec.), 306. $C_{19}H_{30}O_3$ requires C, 74·5; H, 9·9%; *M*, 306 τ 9·29, 9·21, and 6·70—6·22 (m).

(ii) 3α,5α-Epoxyandrostane-1,17-dione (30 mg.) in methanol (2 ml.) was treated with sodium borohydride (30 mg.) overnight. The product was poured into water; the product was filtered off and recrystallized from acetone to yield 3α,5α-epoxyandrostane-1ξ,17β-diol (25 mg.) as plates, m.p. 104—107°, $[\alpha]_D^{20}$ +17° (*c* 0·7) (Found: C, 74·9; H, 10·1. Calc. for $C_{19}H_{30}O_3$: C, 74·5; H, 9·9%), with i.r. and n.m.r. spectra identical with those of the product from (i).

Reaction of Androsta-2,4-diene-1,17-dione with Acetone.—Androsta-2,4-diene-1,17-dione (100 mg.) in acetone (5 ml.) containing concentrated hydrochloric acid (0·4 ml.) was heated under reflux for 3 hr. The solution was poured into water and extracted with ether, and the extract was washed with aqueous sodium hydrogen carbonate, dried, and evaporated to give a gum which was purified by preparative layer chromatography in 40% ethyl acetate–light petroleum. 3α,5α-(2-*Oxopropane*-1,3-*diyl*)*androstane*-1,17-*dione* (38 mg.) crystallized from acetone–light petroleum as plates, m.p. 143—144°, $[\alpha]_D$ +105° (*c* 0·5) (Found: C, 77·6; H, 9·0%; *M* (mass spec.) 342. $C_{22}H_{30}O_3$ requires C, 77·15; H, 8·8%; *M*, 342), τ 9·16 and 8·98. After treatment for 48 hr. with methan[^{2}H]ol (0·5 ml.) containing a trace of sodium methoxide the adduct (3 mg.) showed a peak at *m/e* 350 in its mass spectrum.

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