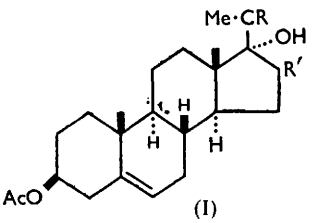
155. *Modified Steroid Hormones. Part VIII.* Some 16-Bromo- and 16-Chloro-derivatives of Testosterone.*

By B. Ellis, D. Patel, and V. Petrow.

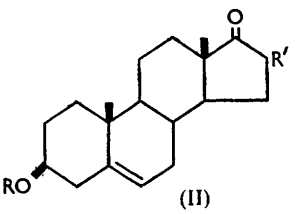
Methods are described for the preparation of 16α- and 16β-bromo- and 16-chloro-androstenediones and their conversion, with the exception of the 16α-bromo-isomer, into the corresponding 16-halogenotestosterones.

The compounds named in the title were required for biological study.

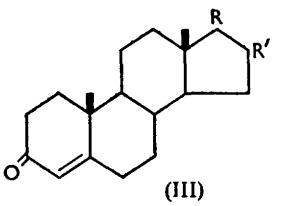
When the oxime (I; R = :N·OH, R′ = Br) derived from 3β-acetoxy-16β-bromo-17α-hydroxypregn-5-en-20-one [1] (I; R = :O, R′ = Br) was treated with phosphorus oxychloride in pyridine, Beckmann rearrangement followed by degradation to 3β-acetoxy-16β-bromoandrost-5-en-17-one (II; R = Ac, R′ = β-Br) occurred [cf. the conversion of 3β-acetoxy-17α-hydroxypregn-5-en-30-one oxime (I; R = :N·OH, R′ = H) into dehydro*epi*androsterone acetate (II; R = Ac, R′ = H) under similar experimental conditions [2]]. Debromination of the 16-bromo-ketone (II; R = Ac, R′ = β-Br) with chromous chloride [3] gave dehydro*epi*androsterone acetate. Hydrolysis with methanolic hydrochloric acid



(I)



(II)



(III)

afforded the corresponding alcohol (II; R = H, R′ = β-Br) which passed into 16β-bromoandrost-4-ene-3 : 17-dione (III; R = :O, R′ = β-Br) on brief Oppenauer oxidation. The last compound was reduced with sodium borohydride under conditions favouring the conversion of both oxo-functions into hydroxyl groups to give material which was oxidised selectively at $C_{(3)}$. The resulting 16 : 17-bromohydrin passed smoothly into androst-4-ene-3 : 17-dione (III; R = :O, R′ = H) when warmed with methanolic alkali, an observation establishing its constitution as 16β-bromo-17β-hydroxyandrost-4-en-3-one (16β-bromotestosterone) (III; R = β-OH, R′ = β-Br).

Treatment of 3β : 17-diacetoxyandrosta-5 : 16-diene [4] with two equivalents of bromine, followed by brief reaction of the product with sodium iodide in acetone, led to a monobromo-ketone, which passed into dehydro*epi*androsterone acetate on reduction with chromous chloride. This compound differed from the 16β-bromo-ketone (II; R = Ac, R′ = β-Br), and is therefore formulated as the isomeric 3β-acetoxy-16α-bromoandrost-5-en-17-one (II; R = Ac, R′ = α-Br). Its hydrolysis with methanolic hydrochloric acid gave 16α-bromo-3β-hydroxyandrost-5-en-17-one (II; R = H, R′ = α-Br) in excellent yield, no evidence for inversion at $C_{(16)}$ being obtained. This is a somewhat surprising result as Fajkoš has shown [5] that in the saturated androstane series the 16α-bromo-17-ketones are thermodynamically less stable than their 16β-isomers into which they are converted by alkaline or acidic reagents. Treatment of the 16α-bromo-17-ketone (II; R = Ac, R′ = α-Br) with hydrogen bromide in acetic acid afforded only an intractable gum (cf. Fajkoš [5]). Brief Oppenauer oxidation of the alcohol (II; R = H, R′ = α-Br

* Part VII, *J.*, 1957, 4112.

[1] Romo and De Vivar, *J. Org. Chem.*, 1956, **21**, 902; Patel, Petrow, and Stuart-Webb, *J.*, 1957 665.

[2] B.P. 747,793; Schmidt-Thomé, *Annalen*, 1957, **603**, 43.

[3] Rosenkranz, Mancera, Gatica, and Djerassi, *J. Amer. Chem. Soc.*, 1950, **72**, 4077.

[4] Moffet and Weisblat, *ibid.*, 1952, **74**, 2183.

[5] Fajkoš, *Coll. Czech. Chem. Comm.*, 1955, **20**, 312.

gave 16α-bromoandrost-4-ene-3 : 17-dione (III; R = :O, R′ = α-Br), no evidence for the concomitant formation of the 16β-epimer (III; R = :O, R′ = β-Br) being obtained. Attempts to convert the 16α-isomer (III; R = :O, R′ = α-Br) into 16α-bromotestosterone proved disappointing, however, as reduction with sodium borohydride under conditions similar to those employed by Norymberski and Woods [6] for the preparation of testosterone from androst-4-ene-3 : 17-dione, or with excess of sodium borohydride or lithium aluminium hydride followed by selective oxidation at $C_{(3)}$, furnished in each case a complex mixture from which a pure species could not be isolated.

Epoxide ring fission of 3β-acetoxy-16α : 17α-epoxypregn-5-en-20-one with hydrogen chloride gave 3β-acetoxy-16β-chloro-17α-hydroxypregn-5-en-20-one (I; R = :O, R′ = β-Cl), which was converted *via* the oxime into 3β-acetoxy-16β-chloroandrost-5-en-17-one (II; R = Ac, R′ = β-Cl). The last compound proved inert to chromous chloride (cf. the similar stability of 2α-chlorocholestan-3-one [7]), but was readily reduced to dehydro*epi*-androsterone acetate by zinc dust in acetic acid. Acid hydrolysis furnished the alcohol (II; R = H, R′ = β-Cl), converted by Oppenauer oxidation into 16β-chloroandrost-4-ene-3 : 17-dione (III; R = :O, R′ = β-Cl). When the latter compound was treated with a limited quantity of sodium borohydride under carefully controlled conditions, selective reduction of the 17-oxo-group occurred with formation of a 16 : 17-chlorohydrin, also obtained by reduction of both oxo-groups present in the ketone (III; R = :O, R′ = β-Cl) followed by preferential oxidation at $C_{(3)}$. The product passed into androst-4-ene-3 : 17-dione on being warmed with alkali, and is hence regarded as 16β-chloro-17β-hydroxyandrost-4-en-3-one (16β-chlorotestosterone) (III; R = β-OH, R′ = β-Cl).

3β-Acetoxy-5 : 6-dibromoandrostan-17-one in carbon tetrachloride was treated with one equivalent of chlorine to give a mixture from which a dibromomonochloro-ketone was isolated in *ca.* 40% yield. Debromination of the last compound with sodium iodide in acetone gave an unsaturated 16-chloro-ketone which differed from the 16β-chloro-derivative (II; R = Ac, R′ = β-Cl) and is therefore regarded as the isomeric 3β-acetoxy-16α-chloroandrost-5-en-17-one (II; R = Ac, R′ = α-Cl). Acid hydrolysis gave the alcohol (II; R = OH, R′ = α-Cl), converted by brief Oppenauer oxidation into 16α-chloroandrost-4-ene-3 : 17-dione (III; R = :O, R′ = α-Cl). Prolonged Oppenauer oxidation, in contrast, was accompanied by epimerisation of the 16-halogen atom with the formation of the thermodynamically more stable 16β-chloroandrost-4-ene-3 : 17-dione (see above). Transformation of the 16α-epimer (III; R = :O, R′ = α-Cl) into the required 16α-chloro-17β-hydroxyandrost-4-en-3-one (16α-chlorotestosterone) (III; R = β-OH, R′ = α-Cl) was effected by reduction with an excess of sodium borohydride and subsequent preferential oxidation of the $C_{(3)}$-allylic alcohol group.

3β-Acetoxy-16α : 17α-epoxypregn-5-en-20-one proved resistant to anhydrous hydrogen fluoride under the conditions employed by Fried and Sabo [8] for the preparation of 9α-fluorohydrocortisone acetate from 21-acetoxy-9α : 11α-epoxy-17α-hydroxypregn-4-ene-3 : 20-dione. A similar failure to effect epoxide ring fission of 11-oxo-16α : 17α-epoxypregnanes with hydrogen fluoride has been reported.[9]

Experimental

Optical rotations were measured for $CHCl_3$ solutions in a 1 dm. tube. Ultraviolet absorption spectra were kindly determined (for EtOH solutions) by Mr. M. T. Davies, B.Sc.

3β-*Acetoxy*-16β-*bromo*-17α-*hydroxypregn*-5-*en*-20-*one Oxime*.—Hydroxylamine hydrochloride (2·1 g.) and anhydrous sodium acetate (2·4 g.) in water (10 ml.) were added to 3β-acetoxy-16β-bromo-17α-hydroxypregn-5-en-20-one [1] (4·5 g.) in ethanol (75 ml.) and the mixture kept at

[6] Norymberski and Woods, *J.*, 1955, 3426.
[7] Ellis and Petrow, *J.*, 1953, 3869.
[8] Fried and Sabo, *J. Amer. Chem. Soc.*, 1957, **79**, 1130.
[9] Beyler and Hoffmann, *J. Org. Chem.*, 1956, **21**, 572.

room temperature for 2 days. Careful addition of water gave crystals (2·8 g.) which were purified from aqueous methanol. The *oxime* separated in flat needles, m. p. 175° (decomp.), $[\alpha]_D^{23}$ −3° (*c* 0·76) (Found: C, 59·2; H, 7·4. $C_{23}H_{34}O_4NBr$ requires C, 59·0; H, 7·3%). The compound was not obtained by employing brief reaction periods at the b. p.

3β-*Acetoxy*-16β-*bromoandrost*-5*e*-*n*-17-*one*.—The foregoing oxime (5·8 g.) in pyridine (30 ml.) was treated at 0° with phosphorus oxychloride (5 g.) in pyridine. After 2 hr. at 0°, the mixture was poured into water and the solids were crystallised from aqueous methanol. The *bromoketone* (4·2 g.) formed needles, m. p. 175—176°, $[\alpha]_D^{20}$ +39° (*c* 1·1) (Found: C, 61·8; H, 7·2. $C_{21}H_{29}O_3Br$ requires C, 61·6; H, 7·1%).

It (0·5 g.) in acetone (30 ml.) under carbon dioxide was treated for 15 min. with chromous chloride solution [3] (10 ml.). The product was purified from aqueous methanol, to give dehydro-*epi*androsterone acetate, m. p. and mixed m. p. 169—170°.

16β-*Bromo*-3β-*hydroxyandrost*-5-*en*-17-*one*.—The foregoing bromo-ketone (5 g.) in methanol (100 ml.) and concentrated hydrochloric acid (5 ml.) was heated under reflux for 1 hr. Addition of water gave the *alcohol* (4·1 g.), blades (from aqueous methanol), m. p. 176—177°, $[\alpha]_D^{20}$ +61° (*c* 0·92) (Found: C, 62·2; H, 7·6. $C_{19}H_{27}O_2Br$ requires C, 62·1; H, 7·4%).

16β-*Bromoandrost*-4-*ene*-3 : 17-*dione*.—A solution of the foregoing alcohol (4 g.) in toluene (180 ml.) and *cyclo*hexanone (40 ml.) was distilled until 40 ml. of distillate had collected. After the addition of aluminium *iso*propoxide (2·5 g.) in toluene (10 ml.), the mixture was refluxed for 10 min., cooled, and washed with dilute sulphuric acid. Organic solvents were removed by steam-distillation and the product was extracted into methylene dichloride. Addition of ether to the dried and concentrated extract gave a solid (2·6 g.; m. p. 174—175°) which was purified from acetone–hexane. 16β-*Bromoandrost*-4-*ene*-3 : 17-*dione* formed prisms, m. p. 182°, $[\alpha]_D^{22}$ +184° (*c* 0·98), $\lambda_{max.}$ 239·5 mμ (log ε 4·23) (Found: C, 62·6; H, 6·5. $C_{19}H_{25}O_2Br$ requires C, 62·5; H, 6·9%).

16β-*Bromotestosterone*.—The foregoing compound (1 g.) in methanol (200 ml.) was treated with sodium borohydride (250 mg.) and set aside overnight. After addition of a few drops of acetic acid, most of the solvent was removed *in vacuo* and the product isolated with ether. Crystallisation from acetone–hexane gave material (0·9 g.), m. p. 142—143°, which was oxidised (Oppenauer) at room temperature to 16β-*bromotestosterone* (0·41 g.), prisms (from methanol), m. p. 191—193°, $[\alpha]_D^{25}$ +73° (*c* 1·03), $\lambda_{max.}$ 240 mμ (log ε 4·22) (Found: C, 62·0; H, 7·1. $C_{19}H_{27}O_2Br$ requires C, 62·1; H, 7·4%).

Brief warming with 5% methanolic potassium hydroxide gave androst-4-ene-3 : 17-dione, identified by direct comparison with an authentic specimen.

3β-*Acetoxy*-16α-*bromoandrost*-5-*en*-17-*one*.—Bromine (11·5 g.) in methylene dichloride (100 ml.) was added dropwise during 30 min. to a stirred solution of 3β : 17-diacetoxyandrosta-5 : 16-diene [4] (13·1 g.) in methylene dichloride (200 ml.) at 0°. After being washed successively with aqueous sodium thiosulphate, aqueous sodium hydrogen carbonate, and water, the mixture was dried and the solvent removed *in vacuo*. A suspension of the solid residue in acetone (200 ml.) was treated with sodium iodide (25 g.), and the mixture stirred for 5 min., and then poured into an excess of aqueous sodium thiosulphate. The precipitate was washed, air-dried, and crystallised from acetone–methanol. 3β-*Acetoxy*-16α-*bromoandrost*-5-*en*-17-*one* (10·9 g.) formed plates or needles, m. p. 186°, $[\alpha]_D^{20}$ −27° (*c* 1·02) (Found: C, 61·5; H, 7·4. $C_{21}H_{29}O_3Br$ requires C, 61·6; H, 7·1%).

Treatment with chromous chloride gave dehydro*epi*androsterone acetate, identified by m. p. and mixed m. p.

16α-*Bromo*-3β-*hydroxyandrost*-5-*en*-17-*one*.—The foregoing bromo-ketone (10·5 g.) in chloroform (50 ml.) was treated with methanol (500 ml.) and concentrated hydrochloric acid (10 ml.). The mixture was agitated for 2 days, the solvents were removed *in vacuo*, and the residue was purified from aqueous methanol. 16α-*Bromo*-3β-*hydroxyandrost*-5-*en*-17-*one* separated in fluffy needles (8·4 g.), m. p. 179—180°, $[\alpha]_D^{20}$ −20° (*c* 0·79) (Found: C, 61·7; H, 7·5. $C_{19}H_{27}OBr$ requires C, 62·1; H, 7·4%).

16α-*Bromoandrost*-4-*ene*-3 : 17-*dione*.—A solution of the foregoing alcohol (8·4 g.) in toluene (360 ml.) and *cyclo*hexanone (80 ml.) was distilled until 80 ml. of distillate had collected. After the addition of aluminium *iso*propoxide (5 g.) in toluene (20 ml.), the mixture was refluxed for 10 min., cooled rapidly, and washed with dilute sulphuric acid and then with water. Solvents were removed by steam-distillation and the product was extracted into methylene dichloride. Addition of ether to the dried and concentrated extract gave a solid (5·9 g.; m. p. 161—162°).

16α-*Bromoandrost-4-ene-3 : 17-dione* crystallised from acetone–hexane in prisms, m. p. 165—166°, $[\alpha]_D^{20}$ +112° (*c* 0·97), $\lambda_{max.}$ 239·5 mμ (log ε 4·21) (Found: C, 62·6; H, 7·1. $C_{19}H_{25}O_2Br$ requires C, 62·5; H, 6·9%).

3β-*Acetoxy*-16β-*chloro*-17α-*hydroxypregn-5-en*-20-*one*.—Concentrated hydrochloric acid (10 ml.) was added to 3β-acetoxy-16α : 17α-epoxypregn-5-en-20-one (10 g.) in acetic acid (120 ml.). After 1 hr. at room temperature, the mixture was poured into water and the precipitated solid crystallised from aqueous ethanol, to give the *chlorohydrin* (9·1 g.), plates, m. p. 167—168°, $[\alpha]_D^{22}$ −36° (*c* 1·04) (Found: C, 68·0; H, 8·0. $C_{23}H_{33}O_4Cl$ requires C, 67·5; H, 8·1%).

The *oxime*, prepared by heating the chlorohydrin (3·7 g.) in ethanol (50 ml.) under reflux for 30 min. with hydroxylamine hydrochloride (2·1 g.) and anhydrous sodium acetate (2·4 g.) in water (5 ml.), crystallised from aqueous ethanol in needles, m. p. 207—208° (decomp.), $[\alpha]_D^{22}$ −17° (*c* 0·98) (Found: C, 65·0; H, 8·1. $C_{23}H_{34}O_4NCl$ requires C, 65·2; H, 8·1%).

3β-*Acetoxy*-16β-*chloroandrost-5-en*-17-*one*.—Phosphorus oxychloride (5 ml.) in pyridine (15 ml.) was added dropwise during 10 min. to the foregoing oxime (7 g.) in pyridine (30 ml.). After 2 hr. at 0°, the mixture was poured into water and the solids were purified from aqueous methanol. 3β-*Acetoxy*-16β-*chloroandrost-5-en*-17-*one* (5 g.) formed needles, m. p. 174—175°, $[\alpha]_D^{20}$ +25° (*c* 0·67) (Found: C, 69·5; H, 7·9; Cl, 9·6. $C_{21}H_{29}O_3Cl$ requires C, 69·1; H, 8·0; Cl, 9·7%). The compound was recovered unchanged after treatment with the chromous chloride reagent. The compound (200 mg.) was heated for 10 min. at 100° with zinc dust (2 g.) and acetic acid (7 ml.). The product (120 mg.) was crystallised from aqueous methanol and identified as dehydro*epi*androsterone acetate.

16β-*Chloro*-3β-*hydroxyandrost-5-en*-17-*one*.—The foregoing chloro-ketone (5 g.) in methanol (100 ml.) and concentrated hydrochloric acid (5 ml.) was heated under reflux for 1 hr. Purification of the product from aqueous methanol gave the *alcohol* (4 g.), needles or plates, m. p. 158—160°, $[\alpha]_D^{25}$ + 38° (*c* 0·74) (Found: C, 70·0; H, 8·3. $C_{19}H_{27}O_2Cl$ requires C, 70·7; H, 8·4%).

16β-*Chloroandrost-4-ene-3 : 17-dione*.—The foregoing alcohol (4 g.) was oxidised under the same conditions as those employed for the preparation of 16β-bromoandrost-4-ene-3 : 17-dione (above). The product was crystallised from acetone–hexane, to give 16β-*chloroandrost-4-ene-3 : 17-dione* (2·4 g.), prisms, m. p. 173—174°, $[\alpha]_D^{20}$ +190° (*c* 1·02), $\lambda_{max.}$ 239·5 mμ (log ε 4·22) (Found: C, 70·7; H, 7·8; Cl, 11·2. $C_{19}H_{25}O_2Cl$ requires C, 71·1; H, 7·8; Cl, 11·1%).

16β-*Chlorotestosterone*.—(*a*) Sodium borohydride (100 mg.) was added to a solution of the foregoing compound (436 mg.) in methanol (100 ml.) at 5°. After 45 min. at this temperature, the mixture was treated with a few drops of acetic acid, most of the solvent was removed *in vacuo*, and the product was isolated with ether. Crystallisation from acetone–hexane gave 16β-*chlorotestosterone* (295 mg.), needles, m. p. 194—196°, $[\alpha]_D^{22}$ +89° (*c* 1·01), $\lambda_{max.}$ 240 mμ (log ε 4·20) (Found: C, 70·6; H, 8·6; Cl, 10·9. $C_{19}H_{27}O_2Cl$ requires C, 70·7; H, 8·4; Cl, 11·0%).

(*b*) 16β-Chloroandrost-4-ene-3 : 17-dione (1·3 g.) in methanol (300 ml.) was treated with sodium borohydride (500 mg.) for 18 hr. at room temperature. The product was isolated with ether and oxidised at room temperature (Oppenauer). Crystallisation gave 16β-chlorotestosterone (0·98 g.), identical with a specimen prepared by method (*a*) above.

The 17β-*propionate* separated from acetone–hexane in needles, m. p. 126—128°, $[\alpha]_D^{23}$ +136° (*c* 1·02) (Found: C, 69·9; H, 8·2; Cl, 9·7. $C_{22}H_{31}O_3Cl$ requires C, 69·7; H, 8·2; Cl, 9·4%).

When the foregoing compound (300 mg.) in methanolic potassium hydroxide (5 ml. of 4%) was heated under reflux for 10 min., and water added to turbidity, there was obtained androst-4-ene-3 : 17-dione (150 mg.), m. p. 170—172°, not depressed in admixture with an authentic specimen.

3β-*Acetoxy*-5 : 6-*dibromo*-16α-*chloroandrostan*-17-*one*.—3β-Acetoxy-5 : 6-dibromoandrostan-17-one [10] (49 g.) in carbon tetrachloride (1170 ml.) was treated at room temperature with chlorine (6·8 g.) in acetic acid (100 ml.). Absorption of chlorine was complete after 3 days. The mixture was washed with aqueous sodium hydrogen carbonate, then with water, and kept for several hours at 0°. The crystalline precipitate (22 g., m. p. 164—165°) was collected and purified from acetone, to give 3β-*acetoxy*-5 : 6-*dibromo*-16α-*chloroandrostan*-17-*one*, needles, m. p. 168—170° (decomp.), $[\alpha]_D^{20}$ −11° (*c* 0·96) (Found: C, 48·3; H, 5·5. $C_{21}H_{29}O_3Br_2Cl$ requires C, 48·1; H, 5·5%).

Examination of the carbon tetrachloride mother-liquor led to the isolation of a dichloro-derivative (6 g.), dense prisms (from methylene dichloride–methanol), m. p. 175—176° (decomp.), $[\alpha]_D^{20}$ −4°, which consistently failed to give satisfactory analytical data.

[10] Levy and Jacobsen, *J. Biol. Chem.*, 1947, **171**, 71.

3β-*Acetoxy*-16α-*chloroandrost*-5-*en*-17-*one*.—Sodium iodide (30 g.) was added to the foregoing 16α-chloro-5 : 6-dibromide (15·7 g.) in acetone (250 ml.). The mixture was stirred for 30 min., then poured into an excess of aqueous sodium thiosulphate, and the precipitated solids (9·3 g., m. p. 178—180°) were crystallised from methylene dichloride–methanol. 3β-*Acetoxy*-16α-*chloroandrost*-5-*en*-17-*one* formed dense prisms, m. p. 188—190°, $[\alpha]_D^{25}$ −5° (*c* 0·71) (Found: C, 69·2; H, 8·0; Cl, 9·6. $C_{21}H_{29}O_3Cl$ requires C, 69·1; H, 8·3; Cl, 9·8%). The compound was unaffected by the chromous chloride reagent. Reduction with zinc and acetic acid gave dehydro*epi*androsterone acetate.

16α-*Chloro*-3β-*hydroxyandrost*-5-*en*-17-*one*.—Methanol (1200 ml.) and concentrated hydrochloric acid (15 ml.) were added to the foregoing compound (15 g.) in methylene dichloride (40 ml.), and the mixture set aside for 2 days. Solvents were removed *in vacuo* and the residue was purified from aqueous methanol, to give the *alcohol* (11·5 g.), needles, m. p. 179—180°, $[\alpha]_D^{25}$ +1° (*c* 0·98) (Found: C, 68·3; H, 8·7; Cl, 9·7. $C_{19}H_{27}O_2Cl,CH_3{\cdot}OH$ requires C, 67·7; H, 8·7; Cl, 10·0%).

16α-*Chloroandrost*-4-*ene*-3 : 17-*dione*.—The foregoing alcohol (11·5 g.) was oxidised for 10 min. under conditions similar to those employed for the preparation of 16α-bromoandrost-4-ene-3 : 17-dione (above). Crystallisation of the product from acetone–hexane gave 16α-*chloroandrost*-4-*ene*-3 : 17-*dione* (6·1 g.), m. p. 179—180°, $[\alpha]_D^{23}$ +159° (*c* 0·57), $\lambda_{max.}$ 239·5 mμ (log ε 4·19) (Found: C, 70·7; H, 8·0. $C_{19}H_{25}O_2Cl$ requires C, 71·1; H, 7·8%). In admixture with 16β-chloroandrost-4-ene-3 : 17-dione a m. p. depression of 25° was obtained.

When the reaction time was extended to 3 hr. the product was only 16β-chloroandrost-4-ene-3 : 17-dione (30%), m. p. and mixed m. p. 171—173°.

16α-*Chlorotestosterone*.—16α-Chloroandrost-4-ene-3 : 17-dione (6 g.) in methanol (1 l.) was treated with sodium borohydride (2·5 g.) and set aside overnight. After addition of acetic acid (3 ml.), most of the solvent was removed *in vacuo*, and the product isolated with ether. Treatment with acetone (50 ml.) gave an insoluble fraction (1·4 g.; m. p. 202—204°; no ultraviolet absorption; positive Rosenheim reaction) which was discarded. The acetone-soluble fraction was oxidised at room temperature (Oppenauer). 16α-*Chlorotestosterone* (2·7 g.) separated from acetone–hexane in prisms, m. p. 198—199°, $[\alpha]_D^{22}$ +60° (*c* 0·92), $\lambda_{max.}$ 240 mμ (log ε 4·20) (Found: C, 70·4; H, 8·8. $C_{19}H_{27}O_2Cl$ requires C, 70·7; H, 8·4%).

The compound was recovered mostly unchanged after being heated under reflux for 30 min. with 2·5% methanolic potassium hydroxide.

The 17β-*propionate* crystallised from aqueous ethanol in needles, m. p. 223—225°, $[\alpha]_D^{23}$ +27° (*c* 1·01) (Found: C, 69·5; H, 8·1. $C_{22}H_{31}O_3Cl$ requires C, 69·7; H, 8·2%).

The authors thank the Directors of The British Drug Houses Ltd. for permission to publish this work.

Chemical Research Laboratories,
The British Drug Houses Ltd., London, N.1. [*Received, October 11th*, 1957.]