Amino-steroids. Part 7.[1] The Synthesis of 3α-Amino-2β-hydroxy- and 2β-Amino-3α-hydroxy-androst-5-en-17-one

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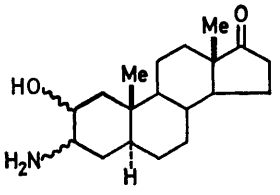
Stereospecific transformations of 5α,6β-dichloroandrost-2-en-17-one into 3α-amino-2β-hydroxyandrost-5-en-17-one and 2β-amino-3α-hydroxyandrost-5-en-17-one have been achieved *via* the Δ^5-2β,3β- and 2α,3α-epoxides. Direct treatment of the 5α,6β-dichloro-2β,3β-epoxide with sodium azide gave 3α,6α-bisazido-2β-hydroxyandrost-4-en-17-one, while the 5α,6β-dichloro-2α,3α-epoxide gave 2β,6α-bisazido-3α-hydroxyandrost-4-en-17-one.

As part of a synthetic programme involving the preparation of steroidal *vicinal* aminoalcohols of potential pharmacological importance the four epimeric 2-hydroxy-3-amino-5α-androstan-17-ones (1) and the four epimeric 2-amino-3-hydroxy-5α-androstan-17-ones (2) have been prepared.[1] We now report the synthesis of two representative members of the androst-5-en-17-one series,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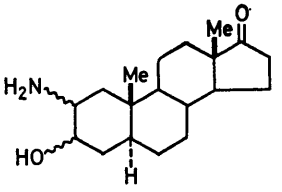
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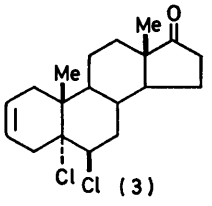
in which it was anticipated that conformational ring changes, variations in inductive effects, and alternative metabolic pathways due to the 5,6-double bond would be reflected in changes in pharmacological activity relative to the epimers of (1) and (2).

RESULTS AND DISCUSSION

The required starting material, the 5α,6β-dichloroandrost-2-en-17-one (3) was prepared by a variation of the literature procedure,[2a] involving chlorination[2b] of 3β-hydroxyandrost-5-en-17-one acetate (4), hydrolysis of the acetate (5) to the 3β-hydroxy-compound (6), then tosylation and elimination of toluene-*p*-sulphonic acid by refluxing in dimethyl sulphoxide. It was noted that if the chlorination temperature was allowed to rise above 35 °C, or if an excess of chlorine was used in a large volume of solvent, the 5,6,16,16-tetrachloride[3] (9) was obtained. The structure of (9) was established from elemental analysis and the n.m.r. spectrum, which indicated two chlorine atoms replacing the 16-C protons and showed 6-H as a 'sharp' multiplet corresponding to an equatorial proton. Additionally, the i.r. spectrum showed the cyclopentanone carbonyl at 1 765 cm^{-1}, in accord with α-dichlorination. Mesylation was also investigated as an alternative to tosylation, and although a higher yield of methanesulphonate (8) was obtained, the elimination of methanesulphonate in dimethyl sulphoxide gave rise to more by-products. Alternative elimination reactions which were investigated included refluxing in collidine which led very slowly to the required material (3) from either the methanesulphonate or toluene-*p*-sulphonate, and also lithium bromide–lithium carbonate treatment of the 5,6-dichloro-3β-methanesulphonate which afforded the triene (10), readily identified by its u.v. spectrum.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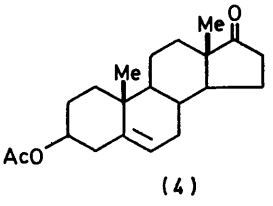
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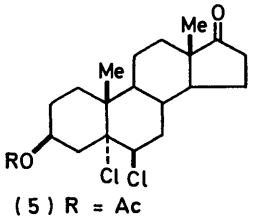
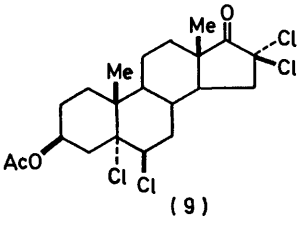

(5) R = Ac
(6) R = H
(7) R = $OSO_2C_6H_4Me$-*p*
(8) R = OSO_2Me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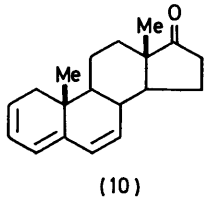
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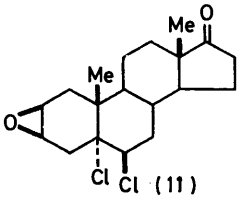
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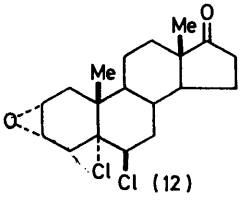
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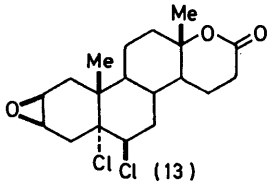
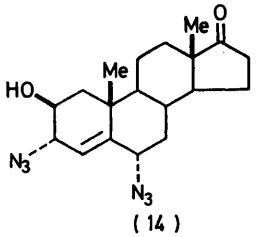

(13)

Epoxidation of (3) with *m*-chloroperbenzoic acid gave as the major product the 2β,3β-epoxide (11) (70%) together with the 2α,3α-oxide (12) (13%) and the 2β,3β-epoxide ring-D lactone (13) (10%). The formation of the β-epoxide as the major product contrasts with the α-stereochemistry of the single epoxide formed under identical conditions from 5α-androst-2-en-17-one,[1,4] and reflects the stereochemical bulk of the 5α-chloro-group. The stereochemistries assigned to (11) and (12) were suggested by the characteristic coupling patterns of 2-H and 3-H,[4,*] and confirmation was obtained at a later stage in the subsequent transformation of (11) into a known saturated amino-alcohol.

Attempted *trans*-diaxial ring-opening of (11) and (12) by sodium azide led to complications. For example, (11) when treated with sodium azide in dimethyl sulphoxide gave in good yield the 3α,6α-bisazido-2β-hydroxyandrost-4-en-17-one (14), the stereochemistry of which is tentatively assigned. The 3,6-bisazido-2-hydroxyandrost-4-ene structure was supported by the appearance of the vinylic proton 4-H as a 'narrow' singlet. (An alternative 3,4-bisazido-2-hydroxyandrost-5-ene structure, which could not be precluded on mechanistic grounds, and which arises from allylic rearrangement of a 4,5-unsaturated intermediate, was discounted since most examples of androst-5-enes in this investigation showed the vinylic 6-H proton as a doublet, J 4—6 Hz). Although Julia *et al.*[5] have demonstrated for a series of cholest-4-enes that a 6α-azido group has little effect on the chemical shift of 10-Me, and that a 6β-azide causes a downfield shift, in our case this analysis could not safely be applied because the double bond and possible conformational changes in ring A could affect the 10-Me resonance. On mechanistic grounds, however, the most direct routes would lead to (14) with stereochemistry as depicted. The hydroxy-bisazide (14) could be converted into the allylic diamine (15) by formation of the 17-ethylene acetal, reduction with lithium aluminium hydride, and deprotection.



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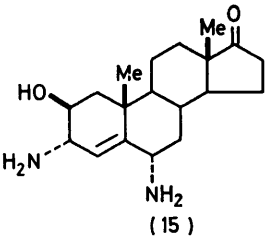
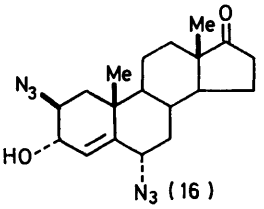


(15)

Similarly the α-epoxide (12) when treated with sodium azide in dimethyl sulphoxide gave 2β,6α-hydroxyandrost-4-en-17-one (16) in high yield. Again, the 4-ene structure was assigned on the basis of 4-H appearing as a singlet. The stereochemistry of 2-H, 3-H, and 6-H was inferred mainly on mechanistic grounds, and could not rigorously be assigned on the basis of coupling constants because of uncertainty about the conformation of ring A. (The 2β-substituent may force A into pseudo-boat or flattened-chair form.)

Since azide ring-opening of (11) and (12) had given unexpected products, it was decided to regenerate the 5,6-double bond at this stage. Sodium iodide–acetone failed to dechlorinate (11) or (12), and zinc–anhydrous methanol (without aqueous work-up) led to complex mixtures. Zinc–methanol–water,[6] however, smoothly transformed (11) and (12) into 2β,3β-epoxyandrost-5-en-17-one (17) (86%) and 2α,3α-epoxyandrost-5-en-17-one (18) (82%). The spectroscopic data were in accord with the structures depicted.[4]



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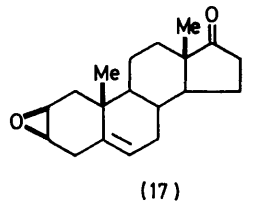

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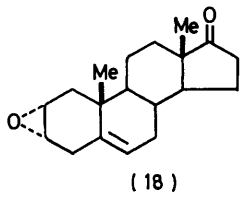

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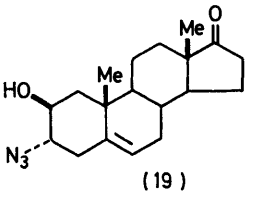

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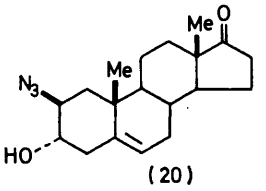


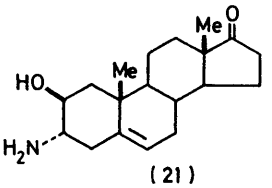
(20)

Ring-opening of (17) and (18) by sodium azide–dimethylacetamide–water proceeded in good yield to give 3α-azido-2β-hydroxyandrost-5-en-17-one (19) and 2β-azido-3α-hydroxyandrost-5-en-17-one (20). In each case 2-H and 3-H, being equatorial, appeared as 'sharp' multiplets.[1]

Protection of the 17-ketone as the ethylene acetal by a standard method (ethylene glycol–triethyl orthoformate–6% toluene-*p*-sulphonic acid, reflux) led to mixtures, but was achieved with 3% toluene-*p*-sulphonic acid at room temperature. Reduction with lithium aluminium hydride and deprotection led to the target amino-alcohols (21) and (22) in good yield. Again, the equatorial 2-H and 3-H protons appeared as 'sharp' multiplets. In the mass spectra of (21) and (22) diagnostically-useful major fragments appeared at *m/e* 72, and are assigned structures (23) and (24) respectively.[7] Correlation of the stereochemistry at C-2 and C-3 in (21) was achieved by catalytic hydrogenation, giving as the major product

* Comparison of our chemical-shift data for 18- and 19-Me, and the coupling patterns exhibited by 2-H and 3-H, with the data quoted by Tori *et al.*,[4] and with similar data from our earlier studies (ref. 1), supported our structure assignments. Conclusive proof was not obtained until the subsequent chemical transformation of (11) into a known compound.

2β-hydroxy-3α-amino-5α-androstan-17-one,[1] identified spectroscopically and also by t.l.c. comparison with an authentic sample. An inseparable by-product was not characterized. The pharmacological properties of (21) and (22) will be reported elsewhere.



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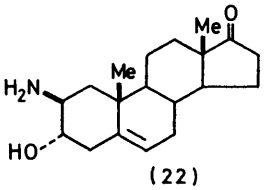

(22)

(23)

(24)

EXPERIMENTAL

M.p.s were determined using an Electrothermal Mk II melting point apparatus and a Kofler micro-hot-stage apparatus. I.r. spectra were recorded with Perkin-Elmer 457 and 257 grating spectrophotometers. Optical rotations were determined for solutions in chloroform at room temperature unless otherwise stated. ^{1}H N.m.r. spectra were recorded at 60 MHz with Perkin-Elmer R12 and R12B, and at 100 MHz with JEOL JNM-MH-100 spectrometers (tetramethylsilane as internal standard). Light petroleum refers to the fraction of b.p. 40—60 °C and ether refers to diethyl ether. Other solvents used were reagent grade unless otherwise stated.

5α,6β-Dichloro-3β-hydroxyandrostan-17-one Acetate (5).—Chlorine gas was bubbled into a stirred solution of pyridine (40 ml) and benzene (600 ml) until a pale yellow colour was obtained. A small portion of a solution of steroid (4) (110 g, 0.33 mol) in pyridine (40 ml) and benzene (600 ml) was added, keeping the temperature at 20—30 °C. When the yellow colour was discharged another portion of chlorine was bubbled in followed by more steroidal solution. The cycles were repeated until all the steroid had been added and the chlorine was in slight excess. The solution was washed successively with dilute sodium metabisulphite solution, dilute hydrochloric acid, and water. The organic layer was then dried (Na_2SO_4) and the solvent was evaporated under reduced pressure to yield a white solid. Crystallisation from dichloromethane–ether gave 5α,6β-dichloro-3β-hydroxyandrostan-17-one acetate (5) (119.8 g, 89.6%), m.p. 216—218 °C [lit.,[3] m.p. 217—218 °C].

5α,6β-Dichloro-3β-hydroxyandrostan-17-one (6).—A solution of acetate (5) (119 g, 0.30 mol) in methanol (600 ml) was refluxed with potassium hydroxide (40 ml; 10M) for 40 min and then allowed to cool. The solution was reduced to half volume *in vacuo* and water (1 l) was added. The precipitated solid was filtered off, dissolved in dichloromethane and the organic solution was washed with water and dried (Na_2SO_4). The solvent was removed under reduced pressure, affording a yellow oil (105 g). Crystallisation of a portion of this from methanol gave 5α,6β-dichloro-3β-hydroxy-androstan-17-one (6), m.p. 170—174 °C (lit.,[3] m.p. 171—172 °C).

5α,6β-Dichloro-3β-hydroxyandrostan-17-one Toluene-p-sulphonate (7).—Toluene-*p*-sulphonyl chloride (1.0 g, 5.81 mmol) was added to a cooled (0 °C) solution of the steroid alcohol (6) (1.0 g, 2.79 mmol) in pyridine (20 ml) and the mixture was allowed to stand at 4 °C for 2 d. The precipitate which formed on addition of water was filtered off and dissolved in dichloromethane. This solution was successively washed with water, dilute copper sulphate solution, and water, and dried ($MgSO_4$). Removal of the solvent *in vacuo* gave 5α,6β-dichloro-3β-hydroxyandrostan-17-one toluene-*p*-sulphonate (7) (1.17 g, 82%), m.p. 166—168 °C (lit.,[2a] m.p. 174—177 °C).

Reaction of 5α,6β-Dichloro-3β-hydroxyandrostan-17-one Toluene-p-sulphonate (7) *with Dimethyl Sulphoxide.*—A solution of toluene-*p*-sulphonate (7) (300 mg, 0.59 mmol) in dimethyl sulphoxide was heated at 90 °C for 18 h. Water was added to give a brown precipitate, which was filtered off and dissolved in ether. The ethereal solution was washed with water, dried, and the solvent was removed to yield a yellow oil. Chromatography on silica gel afforded 5α,6β-dichloroandrost-2-en-17-one (3) (105 mg, 53%), m.p. 156—157 °C (lit.,[2a] m.p. 154—156 °C).

3β-Hydroxy-5α,6β,16α,16β-tetrachloroandrostan-17-one Acetate (9).[3]—Chlorine gas was bubbled into a stirred solution of pyridine (40 ml) and benzene (1 600 ml) until a saturated solution was obtained. A portion of a solution of steroid (4) (100 g) in pyridine (40 ml) and benzene (600 ml) was added dropwise. Another portion of chlorine was bubbled in to definite excess, followed by another portion of steroid. The cycles were repeated until all the steroid had been added and the chlorine was in excess. The solution was washed successively with dilute sodium metabisulphite solution, dilute hydrochloric acid and water, dried (Na_2SO_4) and the solvent removed under reduced pressure. Crystallisation of a sample from dichloromethane–ether afforded 3β-hydroxy-5α,6β,16α,16β-tetrachloroandrostan-17-one acetate (9), m.p. 230—234 °C (lit.,[3] m.p. 229—232 °C); $[\alpha]_D$ 0° (*c* 1.0); $\nu_{max.}$ (KBr) 1 765, 1 727, 1 238, 1 022, and 642 cm^{-1}; δ($CDCl_3$) 1.12 and 1.38 (each 3 H, s, 13- and 10-Me), 2.03 (3 H, s, OCOMe), 4.38 (1 H, sharp m, 6α-H), and 5.34 (1 H, br m, 3α-H) (Found: C, 53.2; H, 5.8; Cl, 30.3. Calc. for $C_{21}H_{28}Cl_4O_3$: C, 53.6; H, 6.0; Cl, 30.2%).

5α,6β-Dichloro-3β-hydroxyandrostan-17-one Methanesulphonate (8).—To a solution of steroid alcohol (6) (1.0 g, 2.79 mmol) in pyridine (20 ml), methanesulphonyl chloride (1 ml) was added dropwise and the resulting mixture was left at 0 °C for 18 h. The mixture was poured into ice–water and the solid which precipitated was filtered off. The solid was dissolved in dichloromethane and the organic solution was washed with dilute copper sulphate solution and water, dried ($MgSO_4$), and the solvent removed under reduced pressure to yield a white solid (1.3 g). Crystallisation from dichloromethane–ether afforded 5α,6β-*dichloro*-3β-*hydroxyandrostan*-17-*one methanesulphonate* (8) (1.08 g, 89%), m.p. 177—178 °C (decomp.); $[\alpha]_D$ −9° (*c* 0.96); $\nu_{max.}$ (KBr) 1 730, 1 340, 1 130, 935, and 655 cm^{-1}; δ ($CDCl_3$) 0.92 and 1.43 (each 3 H, s, 13- and 10-Me), 3.04 (3 H, s, $MeSO_2$), 4.42 (1 H, sharp m, 6α-H), and 5.25 (1 H, br m, 3α-H) (Found: C, 55.0; H, 6.8; Cl, 16.2; S, 7.3%. $C_{20}H_{30}Cl_2O_4S$ requires C, 54.9; H, 6.9; Cl, 16.2; S, 7.3%).

The Reaction of 5α,6β-Dichloro-3β-hydroxyandrostan-17-one Methanesulphonate (8) *with Dimethyl Sulphoxide.*—A solution of the steroid methanesulphonate (8) (150 mg, 0.344 mmol) in dimethyl sulphoxide (5 ml) was heated under reflux. Water was added and the product was

extracted into ether. The ethereal solution was washed with water, dried ($MgSO_4$), and the solvent was evaporated to yield a brown oil. Column chromatography on silica (3 g) eluting with light petroleum–ethyl acetate, afforded 5α,6β-dichloroandrost-2-en-17-one (3) (45 mg, 38%), m.p. 155—156.5 °C (lit.,[2a] m.p. 154—156 °C), the spectroscopic characteristics of which were identical to those in the literature.

Treatment of 5α,6β-*Dichloro*-3β-*hydroxyandrostan*-17-*one Methanesulphonate* (8) *with Collidine*.—A solution of the methanesulphonate (8) (230 mg, 0.52 mmol) in xylene (4 ml) was refluxed with collidine (0.72 ml, 5.45 mmol) for 8 h. T.l.c. analysis indicated mostly starting material with a trace of 5α,6β-dichloroandrost-2-en-17-one (3).

Reaction of 5α,6β-*Dichloro*-3β-*hydroxyandrostan*-17-*one Methanesulphonate* (8) *with Lithium Bromide and Lithium Carbonate in* NN-*Dimethylacetamide*.—Lithium carbonate (300 mg) was added to a suspension of the steroidal methanesulphonate (8) (300 mg, 0.688 mmol) in *NN*-dimethylacetamide (3 ml) followed by lithium bromide (60 mg) and the resultant mixture was refluxed for 1 h. Water was added and the product was extracted into ether. The ethereal solution was washed with water, dried ($MgSO_4$), and the solvent removed *in vacuo*. Column chromatography of the residue on silica (5 g) eluting with light petroleum–ethyl acetate afforded *androsta*-2,4,6-*trien*-17-*one* (10) (155 mg, 84%), m.p. 125—130 °C; $[\alpha]_D$ +60° (*c* 0.8); $\lambda_{max.}$ 297, 308, and 322 nm (log ε 4.16, 4.23, and 4.08); $\nu_{max.}$ (KBr) 3 010, 1 735, 1 450, and 760 cm^{-1}; δ($CDCl_3$) 0.92 and 0.98 (each 3 H, s, 13- and 10-Me) and 5.8 (5 H, m, 2-, 3-, 4-, 6-, and 7-H) (Found: M^+, 268.182 1. $C_{19}H_{24}O$ requires *M*, 268.182 7).

Reaction of 5α,6β-*Dichloroandrost*-2-*en*-17-*one* (3) *with* 3-*Chloroperbenzoic Acid*.—To a stirred solution of the steroidal alkene (3) (9.0 g, 26.5 mmol) in chloroform (150 ml) at 0 °C was added a pre-cooled solution of 3-chloroperbenzoic acid (6.0 g, 34.9 mmol) in chloroform (50 ml) and the resultant solution was stirred at ambient temperature for 2 d. After the addition of more 3-chloroperbenzoic acid (0.5 g, 2.9 mmol) the reaction mixture was left overnight. The mixture was then diluted with chloroform (300 ml) and washed in sequence with 10% sodium metabisulphite solution, dilute sodium bicarbonate solution, and water. The final extracts were dried ($MgSO_4$) and the solvent was removed *in vacuo* to yield a white solid (10.5 g). Column chromatography on silica (100 g), eluting with light petroleum–ethyl acetate, afforded starting material (3) (520 mg). Further elution afforded 5α,6β-*dichloro*-2β,3β-*epoxyandrostan*-17-*one* (11) (6.2 g, 70%) as white crystals, m.p. 170—171 °C (from methanol or dichloromethane–ether); $[\alpha]_D$ +13° (*c* 0.94); $\nu_{max.}$ (KBr) 1 734, 800, and 625 cm^{-1}, δ($CDCl_3$) 0.91 and 1.35 (each 3 H, s, 13- and 10-Me), 3.30 (2 H, m, 2α- and 3α-H), and 4.46 (1 H, m, $W_{\frac{1}{2}}$ 5 Hz, 6α-H) (Found: C, 63.7; H, 7.3; Cl, 19.6. $C_{19}H_{26}Cl_2O_2$ requires C, 63.4; H, 7.3; Cl, 19.8%).

Further elution afforded white crystals of the isomeric epoxide, 5α,6β-*dichloro*-2α,3α-*epoxyandrostan*-17-*one* (12) (1.12 g, 13%), m.p. 166—168 °C; $[\alpha]_D$ +28° (*c* 0.86); $\nu_{max.}$ (KBr) 1 732, 1 006, 802, and 627 cm^{-1}; δ($CDCl_3$) 0.92 and 1.33 (each 3 H, s, 13- and 10-Me), 3.3 (2 H, m, 2β- and 3β-H), and 4.46 (1 H, $W_{\frac{1}{2}}$ 5 Hz, 6α-H) (Found: C, 63.2; H, 7.3; Cl, 19.5. $C_{19}H_{26}Cl_2O_2$ requires C, 63.4; H, 7.3; Cl, 19.8%).

Also obtained from the column was the most polar reaction product, 5α,6β-*dichloro*-2β,3β-*epoxy*-17-*oxo*-17a-*oxa*-D-*homoandrostane* (13) (0.98 g, 10.5%), m.p. 197—199 °C; $[\alpha]_D$ −75° (*c* 3.52); $\nu_{max.}$ (KBr) 1 725, 1 085, 992, 798, and 635 cm^{-1}; δ($CDCl_3$) 1.28 and 1.36 (each 3 H, s, 13- and 10-Me), 3.32 (2 H, m, 2α- and 3α-H), and 4.47 (1 H, m, $W_{\frac{1}{2}}$ 5 Hz, 6α-H) (Found: C, 61.4; H, 7.2; Cl, 19.1. $C_{19}H_{26}Cl_2O_3$ requires C, 61.1; H, 7.0; Cl, 19.0%).

3α,6α-*Bisazido*-2β-*hydroxyandrost*-4-*en*-17-*one* (14).—A solution of the β-epoxide dichloride (11) (675 mg, 1.89 mmol) and sodium azide (620 mg, 9.53 mmol) in dimethyl sulphoxide (20 ml) was heated on a water bath at 90 °C for 18 h. The solution was allowed to cool to room temperature, water was added, and the pale brown precipitate was filtered off. The solid was dissolved in dichloromethane and the solution was washed with water, dried ($MgSO_4$), and the solvent removed *in vacuo* to give a pale brown solid (570 mg). Crystallisation from ether–light petroleum afforded 3α,6α-*bisazido*-2β-*hydroxyandrost*-4-*en*-17-*one* (14) (422 mg, 60%), m.p. 177—179 °C (decomp.); $[\alpha]_D$ +227° (*c* 1.03); $\nu_{max.}$ (KBr) 3 498, 2 100, 1 735, 1 657, 1 250, and 822 cm^{-1}; δ($CDCl_3$) 0.94 and 1.15 (each 3 H, s, 13- and 10-Me), 2.64 (1 H, m, OH, exchangeable), 3.5—4.5 (3 H, m, 2α-, 3β-, and 6β-H), and 5.65 (1 H, s, $W_{\frac{1}{2}}$ 4 Hz, 4-H) (Found: M^+, 370.211 2. $C_{18}H_{26}N_6O_2$ requires *M*, 370.211 7).

3α,6α-*Bisazido*-2β-*hydroxyandrost*-4-*en*-17-*one Ethylene Acetal*.—A solution of the bisazido-ketone (14) (600 mg, 1.62 mmol) in triethyl orthoformate (1.2 ml, 2 vol) and ethylene glycol (0.6 ml, 1 vol) with toluene-*p*-sulphonic acid (36 mg, 6% catalytic amount) was refluxed for 1 h. The reaction mixture was poured into dilute sodium bicarbonate solution and the solid which precipitated was filtered off and dissolved in dichloromethane. The solution was washed with water, dried ($MgSO_4$), and the solvent removed *in vacuo* to give a pale yellow solid (660 mg). Crystallisation from ether–light petroleum afforded 3α,6α-*bisazido*-2β-*hydroxyandrost*-4-*en*-17-*one ethylene acetal* (543 mg, 81%), m.p. 161—163 °C; $[\alpha]_D$ +133° (*c* 0.69); $\nu_{max.}$ (KBr) 3 500, 2 082, 1 652, and 1 170 cm^{-1}; δ($CDCl_3$) 0.88 and 1.10 (each 3 H, s, 13- and 10-Me), 2.22 (1 H, m, OH exchangeable), 3.2—4.4 (7 H, m, 17-acetal, 2α-H, 3β-H, and 6β-H), and 5.60 (1 H, s, 4-H) (Found: M^+, 414.238 5. $C_{21}H_{30}N_6O_3$ requires *M*, 414.237 9).

3α,6α-*Bisamino*-2β-*hydroxyandrost*-4-*en*-17-*one* (15).—Lithium aluminium hydride (605 mg) was added slowly with stirring to a cooled solution (0 °C) of the bisazido-ethylene acetal (600 mg, 1.45 mmol) in diethyl ether (40 ml). The mixture was then stirred at ambient temperature for 6 h. The excess of lithium aluminium hydride was destroyed by successive addition of water (0.66 ml), 15% sodium hydroxide solution (0.6 ml), and water (1.8 ml). The inorganic salts were filtered through Celite and washed with hot tetrahydrofuran. The ethereal solution and washings were evaporated *in vacuo* to give a creamy white solid (530 mg). The solid residue was dissolved in 10% aqueous acid and left on a steam-bath for 1 h. The solution was allowed to cool to room temperature, basified (4M NaOH), sodium chloride was added, and the product was extracted into dichloromethane. The organic solution was washed with saturated brine, dried ($MgSO_4$), and the solvent was removed under reduced pressure to yield a cream foam (400 mg). Crystallisation from dichloromethane–ether afforded 3α,6α-*bisamino*-2β-*hydroxyandrost*-4-*en*-17-*one* (15) (215 mg, 47%), m.p. *ca.* 150 °C (decomp.); $\nu_{max.}$ (KBr) 3 300br and 1 730 cm^{-1}; δ([$^2H_6$]DMSO) 0.83 and 1.07 (each 3 H, s, 13- and 10-Me), 3.3—4.2 (4 H, m, 2α-H, 3β-H, 6β-H,

and 2β-OH exchangeable), 5.32 (1 H, s, 4-H), and 8.2—9.0 (4 H, 3α-NH_2 exchangeable and 6α-NH_2 exchangeable) (Found: M^+, 318.230 5. $C_{19}H_{30}N_2O_2$ requires M, 318.230 7).

2β,6α-*Bisazido*-3α-*hydroxyandrost*-4-*en*-17-*one* (16).—A solution of the α-epoxide dichloride (12) (700 mg, 1.96 mmol) and sodium azide (700 mg, 10.8 mmol) in dimethyl sulphoxide (20 ml) was heated on a water-bath at 90 °C for 48 h. The mixture was poured into dilute sodium carbonate solution, extracted with ether, and the ethereal solution was washed with water, dried ($MgSO_4$), and the solvent was removed *in vacuo* to yield a brown oil. Crystallisation from ether–light petroleum gave 2β,6α-*bisazido*-3α-*hydroxyandrost*-4-*en*-17-*one* (16) (490 mg, 68%), m.p. 158—164 °C; $[\alpha]_D$ +59° (*c* 1.0); $\nu_{max.}$ (KBr) 3 470, 2 090, 2 065, 1 728, 1 265, and 860 cm^{-1}; δ($CDCl_3$) 0.88 and 1.14 (each 3 H, s, 13- and 10-Me), 2.70 (1 H, m, 3α-OH exchangeable), 3.5—4.2 (3 H, m, 2α-, 3β-, and 6β-H), and 5.54 (1 H, s, $W_{\frac{1}{2}}$ 5 Hz, 4-H) (Found: M^+, 370.212 2. $C_{19}H_{26}N_6O_2$ requires M, 370.211 7).

2β,3β-*Epoxyandrost*-5-*en*-17-*one* (17).—To a methanolic solution (50 ml) of 5α,6β-dichloride 2β,3β-epoxide (11) (800 mg, 2.25 mmol) was added zinc dust (1.6 g, 2 equiv.) and several drops of water, and the mixture was heated on a steam-bath for 0.5—1.5 h. The zinc was filtered off, the solution was poured into water, and the precipitated white solid was filtered off and dissolved in dichloromethane. The organic solution was washed with water, dried ($MgSO_4$), and the solvent was removed under reduced pressure to yield a white solid (600 mg). Crystallisation from methanol yielded 2β,3β-*epoxyandrost*-5-*en*-17-*one* (17) (553 mg, 86%), m.p. 162—163.5 °C; $[\alpha]_D$ +17° (*c* 1.18); $\nu_{max.}$ (KBr) 1 735, 1 365, 1 010, and 790 cm^{-1}; δ($CDCl_3$) 0.88 and 1.10 (each 3 H, s, 13- and 10-Me), 3.20 (2 H, m, 2α- and 3α-H), and 5.38 (1 H, d, *J* 5 Hz, 6-H) (Found: C, 79.4; H, 9.0. $C_{19}H_{26}O_2$ requires C, 79.7; H, 9.15%).

3α-*Azido*-2β-*hydroxyandrost*-5-*en*-17-*one* (19).—To a solution of the steroidal β-epoxide (17) (1.1 g, 3.86 mmol) in *NN*-dimethylacetamide (12 ml) was added sodium azide (0.36 g, 5.54 mmol) in water (1.2 ml). The solution was refluxed for 4 h, then allowed to cool. The precipitated solid which formed on addition of water was washed with water, dissolved in ethyl acetate, dried ($MgSO_4$), and the solvent removed *in vacuo* to give a pale brown solid (1.3 g). Column chromatography on silica gel (40 g), eluting with toluene–ether, afforded 3α-*azido*-2β-*hydroxyandrost*-5-*en*-17-*one* (19) (855 mg, 68%) as white prisms, m.p. 144—145 °C (from ether–light petroleum); $[\alpha]_D$ +176° (*c* 0.46); $\nu_{max.}$ (KBr) 3 450, 2 028, 1 728, 1 260, 1 080, and 789 cm^{-1}; δ($CDCl_3$) 0.90 and 1.20 (each 3 H, s, 13- and 10-Me), 2.05 (1 H, s, OH, exchangeable), 3.71 and 3.94 (2 H, m, 2α-H and 3β-H), and 5.50 (1 H, d, *J* 5 Hz, 6-H) (Found: C, 69.0; H, 8.3; N, 12.6. $C_{19}H_{27}N_3O_2$ requires C, 69.3; H, 8.3; N, 12.8%).

3α-*Azido*-2β-*hydroxyandrost*-5-*en*-17-*one Ethylene Acetal*.—A solution of steroid (19) (600 mg, 1.83 mmol) in triethyl orthoformate (2 ml) and ethylene glycol (1 ml) with toluene-*p*-sulphonic acid (25 mg) was allowed to stand at ambient temperature for 4 h. Water was added and the product was extracted into ether. The ethereal layer was washed with water, dried ($MgSO_4$), and the solvent removed under reduced pressure to yield a pale yellow foam (707 mg). Column chromatography on silica gel (20 g), eluting with toluene–ether, afforded 3α-*azido*-2β-*hydroxyandrost*-5-*en*-17-*one ethylene acetal* (413 mg, 61%) as white needles, m.p. 53—56 °C (from methanol); $[\alpha]_D$ +25° (*c* 1.86); $\nu_{max.}$ (KBr) 3 460, 2 081, 1 168, 1 037, and 783 cm^{-1}; δ($CDCl_3$) 0.86 and 1.19 (each 3 H, s, 13- and 10-Me), 2.03 (1 H, s, OH, exchangeable), 3.4—4.1 (6 H, m, 17-acetal, 2α- and 3β-H), and 5.50 (1 H, d, *J* 4 Hz, 6-H) (Found: C, 67.4; H, 8.6; N, 11.3. $C_{21}H_{31}N_3O_3$ requires C, 67.5; H, 8.4; N, 11.3%).

3α-*Amino*-2β-*hydroxyandrost*-5-*en*-17-*one* (21).—Lithium aluminium hydride (300 mg) was added slowly with constant stirring to a cooled solution (0 °C) of the ethylene acetal from (19) (305 mg, 0.817 mmol) in ether (10 ml). The mixture was allowed to warm to room temperature and stirred for 2 h. The excess of lithium aluminium hydride was destroyed by the addition of wet ether, and the inorganic salts were removed by filtration through Celite and washed with hot tetrahydrofuran. The combined, ethereal solution and washings were concentrated *in vacuo* yielding a cream solid (270 mg, 96%). The solid residue was taken up in 10% aqueous acetic acid and heated on a steam-bath for 2 h. The solution was allowed to cool, basified (4M NaOH), and the product was extracted into dichloromethane. The organic layer was washed with water, dried ($MgSO_4$), and the solvent was removed *in vacuo* to give a yellow solid. Crystallisation from methanol–ether gave pure 3α-*amino*-2β-*hydroxyandrost*-5-*en*-17-*one* (21) (155 mg, 62%), m.p. *ca.* 240 °C (decomp.); $[\alpha]_D$ not obtainable because of insolubility; $\nu_{max.}$ (KBr) 3 440, 3 270, 1 730, and 790 cm^{-1}; δ(CF_3CO_2D) 1.05 and 1.25 (each 3 H, s, 13- and 10-Me), 3.2 (2 H, m, 4α- and 4β-H), 3.82 (1 H, m, $W_{\frac{1}{2}}$ 10 Hz, 3β-H), 4.18 (1 H, m, $W_{\frac{1}{2}}$ 11 Hz, 2α-H), 5.66 (1 H, m, $W_{\frac{1}{2}}$ 10 Hz, 6-H), and 6.84 (2 H, br m, NH_2, exchangeable) (Found: C, 75.1; H, 9.7; N, 4.5. $C_{19}H_{29}NO_2$ requires C, 75.2; H, 9.6; N, 4.6%).

2α,3α-*Epoxyandrost*-5-*en*-17-*one* (18).—To a solution of the 2α,3α-epoxy-5α,6β-dichloro-steroid (12) (170 mg, 0.477 mmol) in methanol containing several drops of water, was added zinc dust (680 mg) and the mixture was heated on a steam-bath for 1 h. The zinc was filtered off and the methanolic solution was poured into water. The precipitated white solid was filtered off and dissolved in dichloromethane. The organic solution was washed with water, dried ($MgSO_4$), and the solvent removed under reduced pressure. Crystallisation from methanol afforded 2α,3α-*epoxyandrost*-5-*en*-17-*one* (18) (112 mg, 82%), m.p. 153—154 °C; $[\alpha]_D$ −28° (*c* 1.37); $\nu_{max.}$ (KBr) 1 735, 1 415, and 805 cm^{-1}; δ($CDCl_3$) 0.88 and 1.04 (each 3 H, s, 13- and 10-Me), 2.66 (2 H, m, 4α- and 4β-H), 3.21 (2 H, m, 2β- and 3β-H), and 5.50 (1 H, d, *J* 5 Hz, 6-H) (Found: C, 79.4; H, 9.1. $C_{19}H_{26}O_2$ requires C, 79.7; H, 9.15%).

2β-*Azido*-3α-*hydroxyandrost*-5-*en*-17-*one* (20).—A solution of the steroidal α-epoxide (18) (200 mg, 0.70 mmol) in *NN*-dimethylacetamide (3 ml) and water (0.3 ml) was refluxed for 3 h with sodium azide (70 mg, 1.07 mmol). After the usual work-up procedure, the solvent was removed to yield a white solid (221 mg). Crystallisation from methanol afforded 2β-*azido*-3α-*hydroxyandrost*-5-*en*-17-*one* (20) (195 mg, 85%), m.p. 177—178 °C; $[\alpha]_D$ +24° (*c* 0.41); $\nu_{max.}$ (KBr) 3 450, 2 095, 1 715, 1 258, 1 040, and 780 cm^{-1}; δ($CDCl_3$) 0.90 and 1.20 (each 3 H, s, 13- and 10-Me), 1.91 (1 H, m, OH exchangeable), 3.84 (2 H, m, $W_{\frac{1}{2}}$ 7 Hz, 2α- and 3β-H), and 5.54 (1 H, d, *J* 5 Hz, 6-H) (Found: C, 69.2; H, 8.2; N, 13.0. $C_{19}H_{27}N_3O_2$ requires C, 69.3; H, 8.3; N, 12.8%).

2β-*Azido*-3α-*hydroxyandrost*-5-*en*-17-*one Ethylene Acetal*.—A solution of the ketone (20) (380 mg, 1.16 mmol) in triethyl orthoformate (1 ml) and ethylene glycol (0.4 ml) with

toluene-*p*-sulphonic acid (10 mg) was allowed to stand at room temperature for 2 h. The reaction mixture was poured into dilute sodium bicarbonate solution, and the precipitate was filtered off and dissolved in dichloromethane. The solution was washed with water, dried ($MgSO_4$), and the solvent was removed under reduced pressure to give 2β-*azido*-3α-*hydroxyandrost*-5-*en*-17-*one ethylene acetal* (365 mg, 84.5%), m.p. 131—132 °C (from methanol); $[\alpha]_D$ −60° (*c* 1.08); $\nu_{max.}$ (KBr) 3 450, 3 355, 2 082, 1 037, and 778 cm^{-1}; δ($CDCl_3$) 0.87 and 1.18 (each 3 H, s, 13- and 10-Me), 2.07 (1 H, s, OH, exchangeable), 3.81 (2 H, m, $W_{\frac{1}{2}}$ 7 Hz, sharp, 2α- and 3β-H), 3.88 (4 H, s, 17-acetal), and 5.49 (1 H, d, *J* 5 Hz, 6-H) (Found: C, 67.6; H, 8.5; N, 11.4. $C_{21}H_{31}N_3O_3$ requires C, 67.5; H, 8.4; N, 11.3%).

2β-*Amino*-3α-*hydroxyandrost*-5-*en*-17-*one* (22).—Lithium aluminium hydride (340 mg) was added slowly with stirring to a cooled solution (0 °C) of the acetal from (20) (340 mg, 0.917 mmol) in dry tetrahydrofuran (30 ml). The mixture was allowed to warm up to room temperature and stirred for 2 h. After the usual work-up procedure, the product was obtained as a cream solid (295 mg), which was dissolved in aqueous acetic acid (10%). The solution was heated on a steam-bath for 2 h, then allowed to cool, basified (4M NaOH) and the product was extracted into dichloromethane. The organic solution was washed with water, dried ($MgSO_4$), and the solvent removed *in vacuo*. Crystallisation from dichloromethane–ether gave 2β-*amino*-3α-*hydroxyandrost*-5-*en*-17-*one* (22) (168 mg, 60%), m.p. *ca.* 160 °C (decomp.); $[\alpha]_D$ not obtainable because of insolubility; $\nu_{max.}$ (KBr) 3 485, 3 378, 3 305, 1 730, 1 610, 1 050, and 773 cm^{-1}; δ(CF_3CO_2H) 1.05 and 1.15 (each 3 H, s, 13- and 10-Me), 2.6—3.8 (3 H, m, 2α-H, 4α-H, and 4β-H), 4.30 (1 H, m, $W_{\frac{1}{2}}$ 11 Hz, 3β-H), 5.61 (1 H, m, $W_{\frac{1}{2}}$ 9 Hz, 6-H), and 6.94 (2 H, br m, NH_2, exchangeable) (Found: C, 74.9; H, 9.6; N, 4.6. $C_{19}H_{29}NO_2$ requires C, 75.2; H, 9.6; N, 4.6%).

Reduction of 3α-*Amino*-2β-*hydroxyandrost*-5-*en*-17-*one* (21).—Treatment of an acetic acid solution (15 ml) of (21) (100 mg, 0.33 mmol) with hydrogen over palladium–charcoal (5%) for 12 h gave, as the major product, 3α-amino-2β-hydroxy-5α-androstan-17-one,[1] identified by comparison with an authentic sample (i.r., t.l.c., mass-spectrometry). The reduction product contained an unidentified component which could not be separated.

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