Steroids and Related Studies. Part XXV.[1] Chandonium Iodide (17a-Methyl-3β-pyrrolidino-17a-aza-D-homoandrost-5-ene Dimethiodide) and Other Quaternary Ammonium Steroid Analogues

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The bisquaternary analogues 17a-methyl-3β-pyrrolidino-17a-aza-D-homoandrost-5-ene dimethiodide (chandonium iodide) (1) (HS-310) and 4-methyl-17β-dimethylamino-4-aza-5α-androstane dimethiodide (2) (HS-467) and some monoquaternary 17a-aza-D-homo- and 4-aza-androstane derivatives have been prepared. Chandonium iodide is a powerful non-depolarising neuromuscular-blocking agent of short duration and rapid onset. and HS-467 also possesses a marked activity.

We have previously synthesised[2] 4,17a-dimethyl-4,17a-diaza-D-homo-5α-androstane dimethiodide (HS-342), a potent neuromuscular-blocking agent.[3,4] Continuing the work towards the synthesis of different bis-'onium azasteroids of potential neuromuscular-blocking activity, we have now prepared two more potent compounds, 17a-methyl-3β-pyrrolidino-17a-aza-D-homo-androst-5-ene dimethiodide (chandonium iodide) (HS-310) (1) and 4-methyl-17β-dimethylamino-4-aza-5α-androstane dimethiodide (HS-467) (2). We now describe the synthesis of (1) and (2), and the concomitant preparation of some 17a-aza-D-homo- and 4-aza-androstane monoquaternary compounds.

Starting with dehydroepiandrosterone acetate (3), the 3β-acetoxy-compound (4) was prepared using the procedure of Regan and Hayes.[5] Sodium–pentanol reduction of (4) yielded the base (5); the secondary amine had

[1] Part XXIV, H. Singh, R. K. Malhotra, and V. V. Parashar, *Tetrahedron Letters*, 1973, 2587.

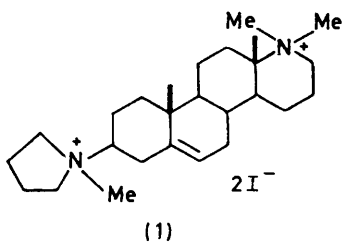
[2] H. Singh, D. Paul, and V. V. Parashar, *J.C.S. Perkin I*, 1973, 1204.

[3] I. G. Marshall, D. Paul, and H. Singh, *J. Pharm. Pharmacol.*, 1973, **25**, 441.

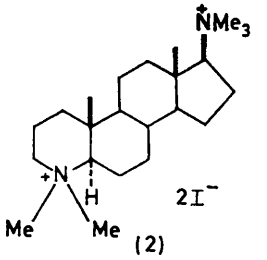
[4] I. G. Marshall, D. Paul, and H. Singh, *European J. Pharmacol.*, 1973, **22**, 129.

[5] B. M. Regan and F. N. Hayes, *J. Amer. Chem. Soc.*, 1956, **78**, 639.

been prepared earlier [5] from (4) by reduction with lithium aluminium hydride. The tertiary amine (6) was prepared and converted into the methiodide (HS-308) (8),



(1)



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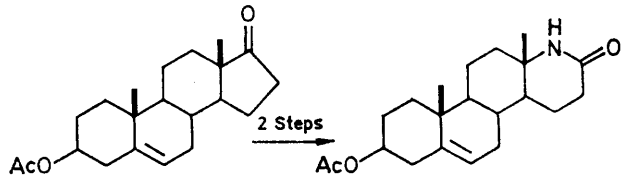
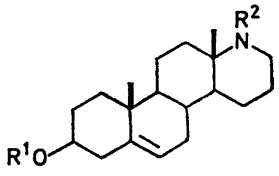
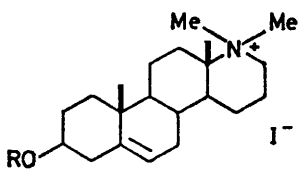


(3) (4)

and from the acetyl derivative (7), the quaternary compound (HS-433) (9) was obtained.

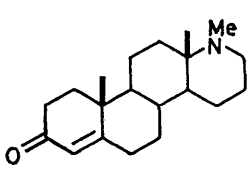


(5) $R^1 = R^2 = H$
(6) $R^1 = H, R^2 = Me$
(7) $R^1 = Ac, R^2 = Me$



(8) R = H
(9) R = Ac

Compound (6) was submitted to Oppenauer oxidation, and the αβ-unsaturated ketone (10) thus obtained was converted into the methiodide (HS-316) (11).



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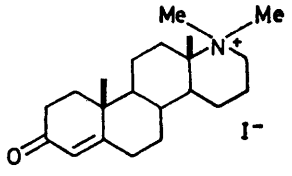
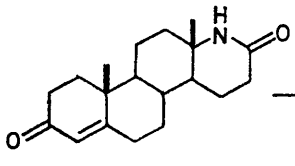


(11)

For the synthesis of (1), the dione (12) [5] was obtained by hydrolysis of the ester (4) followed by Oppenauer oxidation. The intermediate (12) was treated with pyrrolidine in methanol. The product showed $\lambda_{max.}$ 275 nm, which indicates it to be the enamine (13). The latter on sodium borohydride reduction yielded (14), the 3β-configuration being assigned on the basis of similar reductions reported earlier.[6,7] The methiodide (HS-311) (15) was prepared from (14). Sodium–pentanol reduction of (14) led to the diamine (16), the methyl derivative (17) of which was prepared and converted into the dimethiodide (HS-310) (1).

[6] J. Schmitt, J. J. Panouse, A. Hallot, P. J. Cornu, P. Comoy, and H. Pluchet, *Bull. Soc. chim. France*, 1963, 807.
[7] J. A. Marshall and W. S. Johnson, *J. Org. Chem.*, 1963, **28**, 421.
[8] C. C. Bolt, *Rec. Trav. chim.*, 1938, **57**, 905.

The 4-aza-androstane monoquaternary analogues and the bis-'onium derivative (2) were prepared next.



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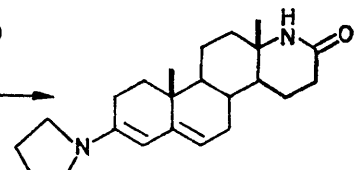

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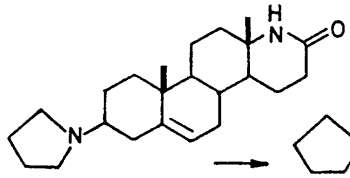
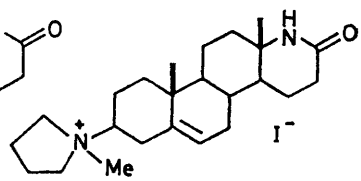


(14)



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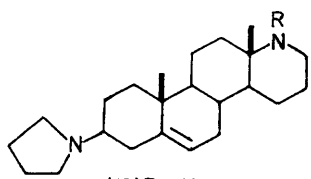
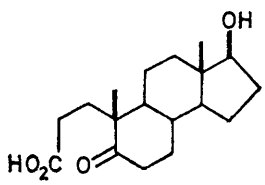
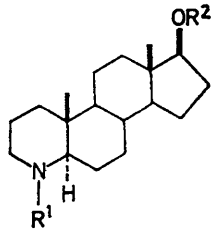


(16) R = H
(17) R = Me

Testosterone acetate was submitted to periodate–permanganate oxidation. In the process the ester function was hydrolysed and the product was the acid (18).

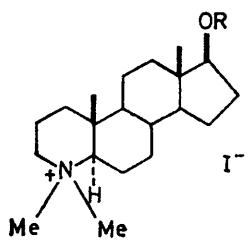


(18)



(19) $R^1 = R^2 = H$
(20) $R^1 = Me, R^2 = H$
(21) $R^1 = Me, R^2 = Ac$

The oxime [8] of (18) on sodium–pentanol reduction directly yielded the 4-azasteroid (19). Bolt [8] had obtained (19) through the lactam obtained by sodium–

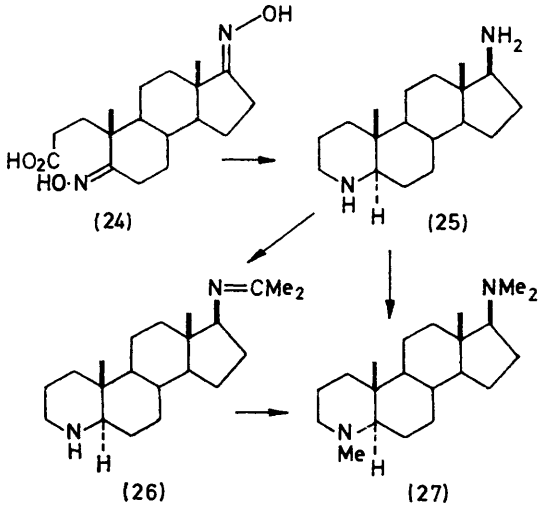


(22) R = H
(23) R = Ac

ethanol reduction of the oxime of (18) followed by sodium–pentanol treatment. Compound (19) was con-

verted into the *N*-methyl derivative (20) and the ester (21) was prepared. These were used to prepare the quaternary compounds HS-419 (22) and HS-435 (23).

For the synthesis of the bis-'onium compound (2), androst-4-ene-3,17-dione was the starting material. Periodate–permanganate oxidation yielded the corresponding seco-keto-acid which was not crystallisable, but it was possible to prepare the crystalline dioxime (24). The latter was reduced with sodium–pentanol to



give 17β-amino-4-aza-5α-androstane (25). The β-configuration for the amino-group assigned by analogy with the reported sodium–alcohol reduction of 17-oximes.[9]

In one of the operations of purification, the material containing (25) was crystallised from acetone. Not unexpectedly the imine (26) was obtained, showing in the n.m.r. spectrum two methyl singlets at δ 1·79 and 1·97. When (26) in methanol was treated with formalin and sodium borohydride, there was obtained the tertiary diamine (27), which was also formed on similar treatment of (25). It appears that the imine (26) is hydrolysed under the reaction conditions to (25), which is then methylated. Treatment of (27) with methyl iodide gave the bis-'onium compound (2).

It is of interest to summarise the n.m.r. data (Table) corresponding to the angular and *N*-methyl groups.

N.m.r. data (δ; 60 MHz)

Compound	18-Me (s)	19-Me (s)	4-Me (*N*-Me) (s)	17a-Me (*N*-Me) (s)
(6)	0·83	0·96		2·20
(7)	0·82	0·97		2·20
(10)	0·87	1·15		2·20
(17)	0·84	0·97		2·20
(20)	0·73	0·96	2·16	
(21)	0·78	0·96	2·15	
(27) *	0·80	0·95	2·16	

* δ 2·21 (6H, s, 17β-NMe_2).

The signal due to 4-methyl (*N*-Me) occurs at δ 2·15 and 2·16, which is slightly upfield as compared with the 17a-methyl (*N*-Me) singlet at δ 2·20 in the 17a-aza methyl derivatives. On the basis of these observations, for 4,17a-dimethyl-4,17a-diaza-D-homo-5α-androstane the reported [2] signals at δ 2·14 and 2·18 may be ascribed to the 4-methyl and 17a-methyl functions, respectively.

In an anaesthetised cat, chandonium iodide (HS-310) (1) possessed a powerful neuromuscular-blocking activity of short duration and rapid onset, being only slightly less active than Pancuronium. It appears to be the most potent short-acting non-depolarising drug so far reported. The ganglion-blocking activity is low. HS-467 (2) was only slightly less active than 4,17a-dimethyl-4,17a-diaza-D-homo-5α-androstane dimethiodide (HS-342) as a non-depolarising neuromuscular-blocking drug and vagolytic agent, but possessed considerably less ganglion-blocking activity than HS-342. The mono-quaternary compounds, HS-308 (8), HS-316 (11), HS-433 (9), HS-419 (22), and HS-435 (23), exhibited extremely weak neuromuscular-blocking action. The biological testing details will be published elsewhere.[10]

EXPERIMENTAL

Optical rotations were measured for solutions in chloroform. U.v. and i.r. spectra were obtained in ethanol and potassium bromide discs, respectively. N.m.r. spectra (60 MHz) were recorded in deuteriochloroform containing tetramethylsilane as internal standard. T.l.c. was carried out on silica gel G (E. Merck) and plates were developed by exposure to iodine vapour. Anhydrous sodium sulphate was employed as a drying agent.

17a-*Methyl*-17a-*aza*-D-*homoandrost*-5-*en*-3β-*ol* (6).—A mixture of formalin (36 ml) and formic acid (36 ml) was added to 17a-aza-D-homoandrost-5-en-3β-ol (5) (1·2 g) and the mixture was refluxed for 6 h. The mixture was cooled and diluted with water (100 ml), and the resulting solution was made alkaline with dilute ammonia, extracted with chloroform (3 × 50 ml), and worked up as usual. Crystallisation of the residue from acetone gave the *alcohol* (6) (0·62 g, 49%), m.p. 172—174°, $[\alpha]_D^{20}$ −64·2° (*c* 1·46), $\nu_{max.}$ 3250, 2900, 2820, and 2730 cm^{-1}, δ 0·83 (3H, s), 0·96 (3H, s), 2·20 (3H, s), and 5·34 (1H), M^+ 303 (Found: C, 79·5; H, 11·1; N, 4·45. $C_{20}H_{33}NO$ requires C, 79·15; H, 10·95; N, 4·6%).

17a-*Methyl*-17a-*aza*-D-*homoandrost*-5-*en*-3β-*yl Acetate* (7).—A mixture of acetic anhydride (0·3 ml) and the alcohol (6) (0·3 g) was heated at 100° for 2 h. Crystallisation of the product from acetone gave the *acetate* (7) (0·25 g, 73%), m.p. 140—143°, $\nu_{max.}$ 2948, 2790, 1736, and 1252 cm^{-1}, δ 0·82 (3H, s), 0·97 (3H, s), 2·01 (3H, s), 2·20 (3H, s), and 5·37 (1H) (Found: N, 4·35. $C_{22}H_{35}NO_2$ requires N, 4·05%).

17a-*Methyl*-17a-*aza*-D-*homoandrost*-5-*en*-3β-*ol Methiodide* (8).—Methyl iodide (0·1 ml) was added to a refluxing solution of the alcohol (6) (0·1 g) in absolute ethanol (2 ml). The mixture was refluxed for 0·5 h, and then cooled, poured into dry ether, and filtered. The material was crystallised from alcohol–ethyl acetate to afford the *methiodide* (8) (0·1 g, 68%), m.p. 238—242° (Found: I, 28·85; N, 3·1. $C_{21}H_{36}INO$ requires I, 28·5; N, 3·15%).

17a-*Methyl*-17a-*aza*-D-*homoandrost*-5-*en*-3β-*yl Acetate Methiodide* (9).—Methyl iodide (0·2 ml) was added to a boiling solution of the acetate (7) (0·15 g) in dry acetone

[9] G. R. Pettit, A. K. Das Gupta, and R. L. Smith, *Canad. J. Chem.*, 1966, **44**, 2023.

[10] A. Gandiha, I. G. Marshall, D. Paul, and H. Singh, *J. Pharm. Pharmacol.*, in the press.

(25 ml), and the mixture was refluxed for 2 h and worked up as above. Crystallisation from acetone gave the *methiodide* (9) (0·2 g, 94%), m.p. 274—276° (Found: C, 56·95; H, 7·85; I, 26·35; N, 2·9. $C_{23}H_{38}INO_2$ requires C, 56·65; H, 7·8; I, 26·1; N, 2·85%).

17a-*Methyl*-17a-*aza*-D-*homoandrost*-4-*en*-3-*one* (10).—A solution of the alcohol (6) (0·5 g) in cyclohexanone (5 ml) and toluene (45 ml) was slowly distilled as aluminium isopropoxide (0·5 g) in toluene (2·5 ml) was added. Distillation was continued for 0·5 h as 10 ml of distillate was collected. The mixture was refluxed for 2·5 h and then allowed to stand for 12 h. It was filtered and the filtrate steam distilled. The residue was worked up and the solid residue crystallised from acetone to give the *enone* (10) (0·35 g, 70%), m.p. 172—173°, $[\alpha]_D^{20}$ +94·2° (*c* 1·43), $\lambda_{max.}$ 240 nm (log ε 4·23), $\nu_{max.}$ 2938, 2858, 2810, 2728, 1670, and 1620 cm^{-1}, δ 0·87 (3H, s), 1·15 (3H, s), 2·20 (3H, s), and 5·70 (1H) (Found: C, 79·8; H, 10·85; N, 4·6. $C_{20}H_{31}NO$ requires C, 79·65; H, 10·35; N, 4·65%).

17a-*Methyl*-17a-*aza*-D-*homoandrost*-4-*en*-3-*one Methiodide* (11).—Methyl iodide (0·1 ml) was added to a refluxing solution of the enone (10) (0·1 g) in absolute ethanol (2 ml). The mixture was refluxed for 0·5 h and worked up as usual. The resulting solid was crystallised from acetone to afford the *methiodide* (11) (0·11 g, 75%), m.p. 264—265° (Found: I, 28·3; N, 2·5. $C_{21}H_{34}INO$ requires I, 28·65; N, 3·15%).

3-*Pyrrolidino*-17a-*aza*-D-*homoandrost*-3,5-*dien*-17-*one* (13) (*with* V. V. PARASHAR).—Freshly distilled pyrrolidine (0·5 ml) was added to a boiling solution of 17a-aza-D-homoandrost-4-ene-3,17-dione (12) (1·2 g) in pure methanol (20 ml). The yellow needles which crystallised out on cooling, were filtered off, washed with methanol, and dried in a vacuum desiccator to give the *dienone* (13) (1·35 g, 94·5%), m.p. 320—325° (decomp.), $\lambda_{max.}$ 275 nm (log ε 4·20) (Found: N, 7·45. $C_{23}H_{34}N_2O$ requires N, 7·9%).

3β-*Pyrrolidino*-17a-*aza*-D-*homoandrost*-5-*en*-17-*one* (14) (*with* V. V. PARASHAR).—Sodium borohydride (2·0 g) was added to a stirred suspension of the dienone (13) (2·5 g) in methanol (50 ml) during 6 h. The mixture was stirred for a further 10 h and allowed to stand overnight. The mixture was filtered, poured into ice-cold water (400 ml), and processed. The residue was crystallised from methanol–acetone to give the *enone* (14) (1·7 g, 67·5%), m.p. 285—290° (decomp.), $[\alpha]_D^{20}$ −78·6° (*c* 1·20), $\nu_{max.}$ 3155, 3050, 2930, 2780, and 1660 cm^{-1}, δ 0·99 (3H, s), 1·16 (3H, s), 5·32 (1H), and 6·61 (1H, disappearing on deuterium exchange) (Found: C, 77·75; H, 10·35; N, 7·65. $C_{23}H_{36}N_2O$ requires C, 77·5; H, 10·1; N, 7·8%).

3β-*Pyrrolidino*-17a-*aza*-D-*homoandrost*-5-*en*-17-*one Methiodide* (15).—Methyl iodide (0·2 ml) was added to a refluxing solution of the enone (14) (0·5 g) in absolute alcohol (5 ml). The mixture was refluxed for 1 h and processed. Crystallisation from ethanol–acetone gave the *methiodide* (15) (0·45 g, 65%), m.p. 317—318° (Found: C, 57·9; H, 8·15; I, 25·1; N, 5·45. $C_{24}H_{39}IN_2O$ requires C, 57·75; H, 7·8; I, 25·45; N, 5·6%).

3β-*Pyrrolidino*-17a-*aza*-D-*homoandrost*-5-*ene* (16).—Sodium metal (4·0 g) was added slowly to a refluxing solution of the enone (14) (1·0 g) in n-pentanol (80 ml). The mixture was refluxed and processed. Crystallisation from acetone yielded the *olefin* (16) (0·6 g, 62%), m.p. 168—172°, $[\alpha]_D^{20}$ −67·6° (*c* 1·68), $\nu_{max.}$ 3250, 2900, and 2775 cm^{-1}, δ 0·96 (3H, s), 1·03 (3H, s), and 5·31 (1H) (Found: C, 80·2; H, 11·25; N, 8·4. $C_{23}H_{38}N_2$ requires C, 80·65; H, 11·2; N, 8·2%).

17a-*Methyl*-3β-*pyrrolidino*-17a-*aza*-D-*homoandrost*-5-*ene* (17).—A mixture of formic acid (15 ml), formalin (15 ml), and the olefin (16) (0·5 g) was refluxed for 8 h and processed. Crystallisation from acetone gave *needles* of (17) (0·3 g, 58%), m.p. 160—164°, $[\alpha]_D^{20}$ −55·1° (*c* 1·34), $\nu_{max.}$ 2900 and 2760 cm^{-1}, δ 0·84 (3H, s), 0·97 (3H, s), 2·20 (3H, s), and 5·31 (1H), M^+ 356 (Found: C, 80·65; H, 11·4; N, 7·55. $C_{24}H_{40}N_2$ requires C, 80·85; H, 11·3; N, 7·85%).

17a-*Methyl*-3β-*pyrrolidino*-17a-*aza*-D-*homoandrost*-5-*ene Dimethiodide* (1).—Methyl iodide (0·2 ml) was added to a boiling solution of the olefin (17) (0·15 g) in absolute ethanol (2 ml). The mixture was refluxed for 10 min. The separated material was filtered off, washed with dry ether (25 ml), and dried. Crystallisation from absolute ethanol gave the *dimethiodide* (1) (0·16 g, 59%), m.p. 306—308° (Found: C, 48·65; H, 7·25; I, 39·3; N, 4·4. $C_{26}H_{46}I_2N_2$ requires C, 48·7; H, 7·2; I, 39·65; N, 4·35%).

17β-*Hydroxy*-5-*oxo*-4-*nor*-3,5-*secoandrostan*-3-*oic Acid* (18).—A solution of potassium carbonate (0·56 g) in water (16 ml) was added to a vigorously stirred solution of 17β-acetoxyandrost-4-en-3-one (1·0 g) in 90% aqueous t-butyl alcohol (60 ml), immediately followed by sodium metaperiodate solution (10 ml; 4 g in 50 ml water) and then potassium permanganate solution (1 ml; 0·8%). Stirring was continued and the periodate solution added at a rate of 2·2 ml min^{-1} during the first 10 min and 0·6 ml min^{-1} during the next 30 min. Permanganate solution was added to maintain the purple colour. The mixture was stirred for another 2 h, and the excess of potassium permanganate was then destroyed with sodium metabisulphite solution. The resulting mixture was concentrated under reduced pressure to about 65 ml, cooled to 4°, made acidic with 50% sulphuric acid, extracted with ether (3 × 50 ml), and worked up in the usual way. Crystallisation of the residue from acetone gave the *acid* (18) (0·25 g, 26·5%), m.p. 206—209°, $\nu_{max.}$ 3380, 1712, and 1700 cm^{-1}, δ 0·81 (3H, s), 1·12 (3H, s), and 4·54 (1H, disappeared on D_2O exchange) (Found: C, 69·75; H, 9·35. $C_{18}H_{28}O_4$ requires C, 70·1; H, 9·15%).

17β-*Hydroxy*-5-*hydroxyimino*-4-*nor*-3,5-*secoandrostan*-3-*oic Acid* [*Oxime of* (18)].—A mixture of the acid (18) (0·2 g), potassium hydroxide (0·4 g), and hydroxylamine hydrochloride (0·12 g) in ethanol (12 ml) and water (8 ml) was refluxed for 2 h. After acidification with glacial acetic acid, the solution was concentrated under reduced pressure, water (20 ml) added, and the mixture was left to crystallise. Recrystallisation from alcohol–water gave the *oxime* (0·12 g, 57%), m.p. 200—204°, $\nu_{max.}$ 3680, 3500, 3250, 1730, 1705, and 1660 cm^{-1} (Found: C, 66·7; H, 8·75; N, 4·15. $C_{18}H_{29}NO_4$ requires C, 66·85; H, 9·05; N, 4·35%).

4-*Aza*-5α-*androstan*-17β-*ol* (19).—Sodium metal (8·0 g) was added slowly to a refluxing solution of the foregoing oxime (1·0 g) in n-pentanol (200 ml). The mixture was refluxed until sodium metal had completely reacted, and was then cooled and steam-distilled to remove the organic solvent. The solid material was crystallised from acetone to afford the *alcohol* (19) (0·65 g, 76%), m.p. 205—207°, $\nu_{max.}$ 3226br cm^{-1}, δ 0·73 (3H, s) and 0·91 (3H, s), M^+, 277 (Found: C, 77·95; H, 11·15; N, 5·2. $C_{18}H_{31}NO$ requires C, 77·9; H, 11·25; N, 5·05%).

4-*Methyl*-4-*aza*-5α-*androstan*-17β-*ol* (20).—Sodium borohydride (0·08 g) was added in small portions over 0·5 h to a stirred solution of the alcohol (19) (0·2 g) and formalin (0·5 ml) in methanol (10 ml). The mixture was poured into water (50 ml) and extracted with chloroform (4 × 25 ml), and the chloroform layer was worked up as usual.

The solid residue was crystallised from acetone to give the *alcohol* (20) (0·19 g, 90%), m.p. 176—177°, $[\alpha]_D^{25}$ +18·58° (*c* 1·88), $\nu_{max.}$ 3226, 2941, 2857, 2809, and 2750 cm^{-1}, δ 0·73 (3H, s), 0·96 (3H, s), and 2·16 (3H, s), M^+ 291 (Found: C, 78·05; H, 11·25; N, 4·95. $C_{19}H_{33}NO$ requires C, 78·3; H, 11·4; N, 4·8%).

4-*Methyl*-4-*aza*-5α-*androstan*-17β-*yl Acetate* (21).—A mixture of the alcohol (20) (0·2 g) and acetic anhydride (0·2 ml) was heated at 100° for 2 h and worked up as usual. Crystallisation from acetone gave the *acetate* (21) (0·19 g, 83%), m.p. 143—145°, $[\alpha]_D^{25}$ −28·28° (*c* 0·88), $\nu_{max.}$ 2940, 2850, 2780, 1732, and 1255 cm^{-1}, δ 0·78 (3H, s), 0·96 (3H, s), 2·02 (3H, s), and 2·15 (3H, s) (Found: C, 76·1; H, 10·3; N, 4·6. $C_{21}H_{35}NO_2$ requires C, 75·65; H, 10·6; N, 4·2%).

4-*Methyl*-4-*aza*-5α-*androstan*-17β-*ol Methiodide* (22).—Methyl iodide (0·1 ml) was added to a refluxing solution of the alcohol (20) (0·2 g) in absolute ethanol (2 ml). The mixture was refluxed for 1 h then cooled and poured into dry ether. The precipitated material was filtered off and crystallised from methanol–acetone to give the *methiodide* (22) (0·23 g, 77%), m.p. 285—286° (Found: C, 55·5; H, 8·15; I, 28·9; N, 3·15. $C_{20}H_{36}INO$ requires C, 55·4; H, 8·4; I, 29·25; N, 3·25%).

4-*Methyl*-4-*aza*-5α-*androstan*-17β-*yl Acetate Methiodide* (23).—Methyl iodide (0·2 ml) was added to the refluxing solution of the acetate (21) (0·15 g) in dry acetone (25 ml), and refluxed for 2 h. The mixture was concentrated to *ca.* 10 ml, cooled, and poured into dry ether. The precipitated material was filtered off and crystallised from acetone to afford the *methiodide* (23) (0·18 g, 84%), m.p. 288—290° (Found: C, 55·65; H, 8·0; I, 26·6; N, 2·9. $C_{22}H_{38}INO_2$ requires C, 55·6; H, 8·0; I, 26·75; N, 2·95%).

5,17-*Dioxo*-4-*nor*-3,5-*secoandrostan*-3-*oic Acid*.—A solution of potassium carbonate (2·2 g) in water (60 ml) was added to a vigorously stirred solution of androst-4-ene-3,17-dione (3·8 g) in 90% aqueous t-butyl alcohol (230 ml), immediately followed by sodium metaperiodate solution (35 ml; 15·2 g in 190 ml) and then potassium permanganate solution (3·8 ml; 0·8%). Stirring was continued and the periodate solution was added at the rate of 8 ml min^{-1} during the first 10 min and 2·5 ml min^{-1} during the next 30 min. The permanganate solution was added when necessary to maintain the purple colour. The mixture was stirred for another 2 h, and processed as for compound (18). The residue obtained was dried in a vacuum desiccator to yield a fluffy material (2·3 g), m.p. 100—105°, which could not be crystallised.

5,17-*Bishydroxyimino*-4-*nor*-3,5-*secoandrostan*-3-*oic Acid* (24).—A mixture of the foregoing acid (2·3 g), hydroxylamine hydrochloride (1·0 g), and potassium hydroxide (3·1 g) in ethanol (100 ml) and water (60 ml), was refluxed for 2 h. The mixture was acidified with glacial acetic acid, diluted with water (100 ml), and concentrated until turbid. The turbidity was removed by adding ethanol (2 ml), and the mixture was allowed to crystallise to obtain the *oxime* (24) (2·05 g, 81%), m.p. 214—216°, $\nu_{max.}$ 3350, 3180, 1690, 1673, and 1650 cm^{-1} (Found: C, 64·0; H, 8·5; N, 8·3. $C_{18}H_{28}N_2O_4$ requires C, 64·25; H, 8·4; N, 8·35%).

17β-*Amino*-4-*aza*-5α-*androstane* (25).—Sodium metal was added slowly to a refluxing solution of the oxime (24) (3·0 g) in n-pentanol (500 ml). Refluxing was continued until the sodium metal had reacted, and the mixture was cooled and water (100 ml) was added. Steam-distillation to remove n-pentanol gave a yellow solid which crystallised from light petroleum to give the *amine* (25) (1·6 g, 65%), m.p. 155—157°, $[\alpha]_D^{25}$ +39·93° (*c* 3·24), $\nu_{max.}$ 3390, 3300, and 1615 cm^{-1}, δ 0·63 (3H, s) and 0·90 (3H s,) (Found: N, 10·3. $C_{18}H_{32}N_2$ requires N, 10·15%).

17β-*Isopropylideneamino*-4-*aza*-5α-*androstane* (26).—Sodium–pentanol reduction as under (25) and crystallisation of the residue from acetone yielded the *imine* (26), m.p. 155—157°, $\nu_{max.}$ 3460, 3280, 1690, and 1583 cm^{-1}, δ 0·82 (3H, s), 0·89 (3H, s), 1·79 (3H, s), and 1·97 (3H, s) (Found: C, 79·25; H, 11·05; N, 9·15. $C_{21}H_{36}N_2$ requires C, 79·7; H, 11·45; N, 8·85%).

17β-*Dimethylamino*-4-*methyl*-4-*aza*-5α-*androstane* (27).—(*a*) Sodium borohydride (0·96 g) was added in small portions, over 0·5 h, to a stirred solution of the amine (25) (0·8 g) and formalin (3·5 g) in methanol (40 ml). The resulting mixture was processed as usual, and crystallisation from acetone gave the *amine* (27) (0·95 g, 100%), m.p. 153—155°, $\nu_{max.}$ 2950, 2780, and 2730 cm^{-1}, δ 0·80 (3H, s), 0·95 (3H, s), 2·16 (3H, s), and 2·21 (6H, s), M^+ 318 (Found: C, 79·4; H, 12·35; N, 8·9. $C_{21}H_{38}N_2$ requires C, 79·2; H, 12·05; N, 8·8%).

(*b*) Sodium borohydride (0·12 g) was added in small portions over 0·5 h to a stirred mixture of the imine (26) (0·1 g) and formalin (0·2 ml) in methanol (10 ml). The mixture was processed as usual. Crystallisation from acetonitrile gave (27) (0·07 g, 70%), m.p. 154—155°, $[\alpha]_D^{25}$ +40·54° (*c* 0·37).

17β-*Dimethylamino*-4-*methyl*-4-*aza*-5α-*androstane Dimethiodide* (2).—Methyl iodide (0·2 ml) was added to a boiling solution of the amine (27) (0·05 g) in absolute ethanol (5 ml). Refluxing was continued for 2 h. Crystallisation of the residue from work-up from acetone–methanol gave the *dimethiodide* (2) (0·03 g, 32%), m.p. 284—285° (Found: I, 42·55; N, 4·65. $C_{23}H_{44}I_2N_2$ requires I, 42·2; N, 4·65%).

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