Steroids and Related Studies. Part 44.[1] 17a-Methyl-3β-(*N*-pyrrolidinyl)-17a-aza-D-homo-5α-androstane Bis(methiodide) (Dihydrochandonium Iodide) and Certain Other Analogues of Chandonium Iodide

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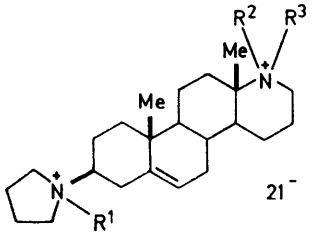
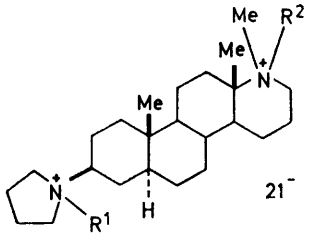
The bisquaternary analogues 17a-methyl-3β-(*N*-pyrrolidinyl)-17a-aza-D-homo-5α-androstane bismethiodide (dihydrochandonium iodide) (4), 17a-methyl-3β-(*N*-pyrrolidinyl)-17a-aza-D-homo-5α-androstane bisethiodide (5), 17a-methyl-3β-(*N*-pyrrolidinyl)-17a-aza-D-homoandrost-5-ene bisethiodide (2), and 17a-ethyl-3β-(*N*-pyrrolidinyl)-17a-aza-D-homoandrost-5-ene bisethiodide (3) related to chandonium iodide (1) have been prepared. 5,6-Saturation and increase in 'onium bulk decrease the neuromuscular blocking potency: however, dihydrochandonium iodide (4) appears to be a promising compound for further study.

OUR work on bis('onium) azasteroids [2,3] led to the discovery of chandonium iodide (1),[3] which is a potent



(1) $R^1 = R^2 = R^3 = Me$
(2) $R^1 = R^2 = Et, R^3 = Me$
(3) $R^1 = R^2 = R^3 = Et$



(4) $R^1 = R^2 = Me$
(5) $R^1 = R^2 = Et$

neuromuscular blocking agent, with virtually no ganglion blocking action, and appears to be the most potent short-acting non-depolarising agent reported so far.[4,5] Further biological studies on chandonium iodide are in progress and it seems to have clinical potential.

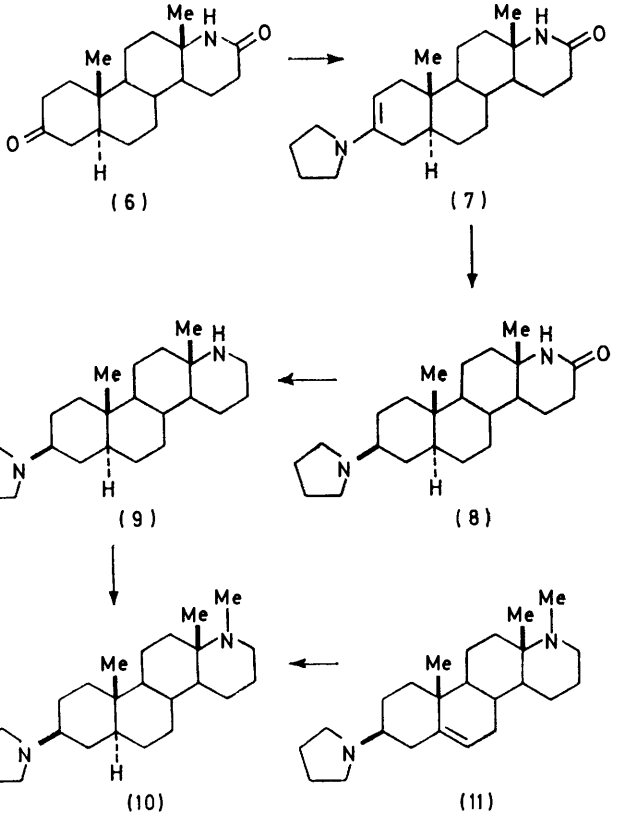
Using chandonium as a prototype, further chemical modifications have been carried out. One obvious change of interest was to design a 5,6-saturated congener and as such dihydrochandonium iodide (4) has been synthesised.

RESULTS AND DISCUSSION

Starting with epiandrosterone, 3β-hydroxy-17a-aza-D-homo-5α-androstan-17-one was prepared,[6] and its oxidation with Jones' reagent yielded the 3-oxo-analogue (6). Treatment with pyrrolidine in methanol gave the enamine (7), and the latter on sodium borohydride reduction yielded (8). The 2-ene structure in (7) and 3β-(*N*-pyrrolidinyl) configuration in (8) are assigned on the basis of similar reported reactions.[7] Sodium–pentanol reduction of (8) led to the diamine (9), from which the methyl derivative (10) was prepared. Catalytic reduction of the 5-ene (11) [3] gave only one product in 75% yield, which was identical to (10). Dihydrochandonium iodide (4) was prepared from (10).

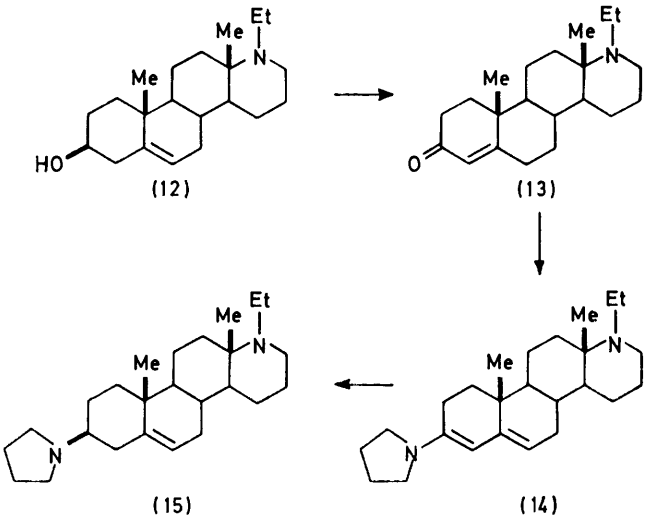
The other modification considered was the change of bulk of the 'onium functions in (1) and (4). The bis(ethiodides) (2) and (5) were prepared from the respective tertiary amines (11) and (10) by treatment with ethyl iodide in ethanol. To prepare the bis('onium) (3) the respective tertiary amine (15) was prepared as follows. 17a-Aza-D-homoandrost-5-en-3β-ol [8] on treatment with ethyl iodide in the presence of potassium carbonate gave the *N*-ethyl derivative (12), which on Oppenauer oxidation yielded (13). This αβ-unsaturated ketone was treated with pyrrolidine in methanol. The product showed $\lambda_{max.}$ 275 nm, which indicates it to be the enamine (14). The latter on sodium borohydride reduction yielded (15), the 3β-configuration being assigned in analogy with similar reductions reported earlier.[9,10]

In anaesthetised cats, all the new bisquaternary compounds (4), (5), (3), and (2) exhibited non-depolarising



neuromuscular blocking activity of rapid onset and short duration,[11] these characteristics being indistinguishable

from those of chandonium iodide (1). The order of potency relative to chandonium (1.0) was (4) (0.5) > (5)



(0.25) > (3) (0.1) = (2) (0.1). Evidently, the saturation of the 5,6-double bond in chandonium iodide (1) and increase in the 'onium bulk compared to (1) or (4) diminishes the potency. Nevertheless, dihydrochandonium iodide (4) is a compound worthy of further study. It causes powerful but short-acting neuromuscular block, no ganglion block, and little vagolytic action.

EXPERIMENTAL

Optical rotations were measured for solutions in chloroform. U. v. and i.r. spectra were obtained in methanol solution and potassium bromide discs, respectively. N.m.r. spectra (60 MHz) were recorded in deuteriochloroform containing tetramethylsilane as internal reference. T.l.c. was carried out on silica gel G (E. Merck) and plates were developed by exposure to iodine vapour, and cerium(IV) sulphate solution (2 g in 100 ml of 10% v/v sulphuric acid), followed by heating at 150 °C. Anhydrous sodium sulphate was employed as the drying agent.

17a-*Aza*-D-*homo*-5α-*androstane*-3,17-*dione* (6).—Jones reagent [12] (0.3 ml) was added dropwise with stirring to a cool solution (10—15 °C) of 3β-hydroxy-17a-aza-D-homo-5α-androstan-17-one (0.3 g) in acetone (40 ml, distilled from permanganate). After 2—5 min the reaction mixture was diluted with water (250 ml) and extracted with chloroform (3 × 50 ml). The chloroform extract was washed with water, dried, and solvent removed under reduced pressure. The residue was taken up in chloroform and passed through a column of alumina. The product so obtained was crystallised from ethyl acetate to give (6) (0.24 g, 80.5%), m.p. 300—301 °C; $\nu_{max.}$ 3 226, 3 125, 3 030, 1 715, 1 685, and 1 620 cm^{-1}; δ 1.01 (3 H, s), 1.18 (3 H, s), and 6.76 (1 H, disappearing on deuterium exchange) (Found: C, 75.0; H, 9.60; N, 4.75. $C_{19}H_{29}NO_2$ requires C, 75.20; H, 9.63; N, 4.62%).

3-(N-*Pyrrolidinyl*)-17a-*aza*-D-*homo*-5α-*androst*-2-*en*-17-*one* (7).—Freshly distilled pyrrolidine (1 ml) was added to a boiling solution of 17a-aza-D-homo-5α-androstane-3,17-dione (6) (1.5 g) in pure methanol (20 ml). The yellow needles which crystallised out on cooling were filtered, washed with methanol, and dried in a vacuum desiccator to give 3-(*N*-pyrrolidinyl)-17a-aza-D-homo-5α-androst-2-en-17-one (7) (1.5 g, 85.1%), m.p. 280—283 °C (decomp.); $\nu_{max.}$ 3 125, 3 030, 1 675, and 1 650 cm^{-1}; δ 0.77 (3 H, s), 1.16 (3 H, s), 2.85—3.13 (4 H, m), 4.16 (1 H, m), and 6.32 (1 H, disappearing on deuterium exchange) (Found: C, 77.15; H, 10.55; N, 7.85. $C_{23}H_{36}N_2O$ requires C, 77.48; H, 10.18; N, 7.86%).

3β-(N-*Pyrrolidinyl*)-17a-*aza*-D-*homo*-5α-*androstan*-17-*one* (8).—Sodium borohydride (1.0 g) was added to a stirred suspension of 3-(*N*-pyrrolidinyl)-17a-aza-D-homo-5α-androst-2-en-17-one (7) (1.5 g) in methanol (30 ml) during 4 h. The reaction mixture was stirred for a further 2 h, poured into ice-cold water (250 ml), extracted with chloroform (5 × 25 ml), and processed. The residue was crystallised from acetone to give 3β-(*N*-pyrrolidinyl)-17a-aza-D-homo-5α-androstan-17-one (8) (1.25 g, 82.85%), m.p. 292—295 °C (decomp.); $\nu_{max.}$ 3 125, 3 030, and 1 672 cm^{-1}; δ 0.77 (3 H, s), 1.13 (3 H, s), 2.25—2.85 (5 H, m), and 6.23 (1 H, disappearing on deuterium exchange) (Found: C, 77.40; H, 11.10; N, 7.95. $C_{23}H_{38}N_2O$ requires C, 77.04; H, 10.68; N, 7.81%).

3β-(N-*Pyrrolidinyl*)-17a-*aza*-D-*homo*-5α-*androstane* (9).—Sodium metal (5.0 g) was added slowly to a refluxing solution of 3β-(*N*-pyrrolidinyl)-17a-aza-D-homo-5α-androstan-17-one (8) (1.25 g) in n-pentanol (100 ml). Refluxing was continued until the sodium metal had reacted. The reaction mixture was cooled, steam-distilled to remove n-pentanol, and processed. Crystallisation from acetone gave 3β-(*N*-pyrrolidinyl)-17a-aza-D-homo-5α-androstane (9) (0.9 g, 74.9%), m.p. 203—205 °C; $\nu_{max.}$ 3 226 cm^{-1}; δ 0.78 (3 H, s), 1.03 (3 H, s), 1.40 (1 H, disappearing on deuterium exchange), 2.18—2.70 (5 H, m), and 2.70—3.07 (2 H, m) (Found: C, 79.90; H, 12.05; N, 8.45. $C_{23}H_{40}N_2$ requires C, 80.17; H, 11.70; N, 8.13%).

17a-*Methyl*-3β-(N-*pyrrolidinyl*)-17a-*aza*-D-*homo*-5α-*androstane* (10).—Sodium borohydride (0.4 g) was added in small portions during 0.5 h to a stirred solution of the *amine* (9) (0.85 g) and formalin (2 ml) in methanol (50 ml). The mixture was poured into water (200 ml), extracted with chloroform (4 × 25 ml) and worked up as usual. The solid residue was crystallised from acetone to give 17a-methyl-3β-(*N*-pyrrolidinyl)-17a-aza-D-homo-5α-androstane (10) (0.6 g, 67.85%), m.p. 155—157 °C; $[\alpha]_D^{25}$ +11.9° (*c* 0.9); $\nu_{max.}$ 2 915, 2 825, and 2 762 cm^{-1}; δ 0.77 (3 H, s), 0.82 (3 H, s), 2.21 (3 H, s), and 2.38—2.85 (5 H, m) (Found: C, 79.75; H, 11.75; N, 7.85. $C_{24}H_{42}N_2$ requires C, 80.38; H, 11.81; N, 7.81%).

Catalytic Reduction of 17a-*Methyl*-3β-(N-*pyrrolidinyl*)-17a-*aza*-D-*homoandrost*-5-*ene* (11).—A solution of (11) (0.6 g) in glacial acetic acid (25 ml) was hydrogenated over platinum oxide (0.3 g) at 50 lb in^{-2} for 20 h. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure. The reaction mixture was made alkaline with potassium hydroxide solution (10%) and extracted with chloroform (4 × 50 ml). The chloroform extract was processed and the residue was crystallised from acetone to give 17a-methyl-3β-(*N*-pyrrolidinyl)-17a-aza-D-homo-5α-androstane (10) (0.45 g, 74.7%), m.p. 156—157 °C; $[\alpha]_D^{25}$ +11.4° (*c* 1.01); $\nu_{max.}$ 2 915, 2 825, and 2 762 cm^{-1}; δ 0.77 (3 H, s), 0.82 (3 H, s), 2.21 (3 H, s), and 2.38—2.85 (5 H, m) (Found: C, 80.50; H, 11.95; N, 7.85. $C_{24}H_{42}N_2$ requires C, 80.38; H, 11.81; N, 7.81%).

17a-*Methyl*-3β-(N-*pyrrolidinyl*)-17a-*aza*-D-*homo*-5α-*androstane Bis*(*methiodide*) (4).—Methyl iodide (0.5 ml) was

added to a boiling solution of the amine (10) (0.35 g) in absolute ethanol (5 ml), and the mixture was refluxed for 10 min. The separated material was filtered, washed with dry ether (50 ml), and dried. Crystallisation from absolute ethanol gave the *bis(methiodide)* (4) (0.4 g, 63.8%), m.p. 300—301 °C (Found: C, 48.20; H, 7.50; I, 40.05; N, 4.35. $C_{26}H_{48}I_2N_2$ requires C, 48.61; H, 7.53; I, 39.50; N, 4.36%).

17a-*Methyl*-3β-(N-*pyrrolidinyl*)-17a-*aza*-D-*homo*-5α-*androstane Bis(ethiodide)* (5).—Ethyl iodide (0.8 ml) was added to a boiling solution of the *amine* (10) (0.4 g) in absolute ethanol (4 ml). Refluxing was continued for 4 h; the reaction mixture was then concentrated, cooled, and then poured into dry ether. The precipitated material was filtered off and crystallised from ethanol to give the *bis-(ethiodide)* (5) (0.4 g, 53.7%), m.p. 277—278 °C (Found: I, 37.70; N, 4.15. $C_{28}H_{52}I_2N_2$ requires I, 37.85; N, 4.18%).

17a-*Ethyl*-17a-*aza*-D-*homoandrost*-5-*en*-3β-*ol* (12).—Ethyl iodide (1.0 ml) was added to a refluxing solution of 17a-aza-D-homoandrost-5-en-3β-ol (0.5 g) in absolute ethanol (10 ml) containing anhydrous potassium carbonate (3.0 g), and refluxing was continued for 12 h. The reaction mixture was cooled, filtered, and the filtrate evaporated to dryness. Water (25 ml) was added to the residue, extracted with chloroform (5 × 20 ml), and processed. The residue so obtained was crystallised from acetone to give 17a-ethyl-17a-aza-D-homoandrost-5-en-3β-ol (12) (0.38 g, 68.2%), m.p. 162—164 °C; $\nu_{max.}$ 3 356, 3 226, 1 685, and 1 055 cm^{-1}; δ 0.86 (3 H, s), 0.97 (3 H, s), 2.62—3.14 (2 H, m), 3.50 (1 H, m), and 5.33 (1 H, m) (Found: N, 4.55. $C_{21}H_{35}NO$ requires N, 4.41%).

17a-*Ethyl*-17a-*aza*-D-*homoandrost*-4-*en*-3-*one* (13).—A solution of 17a-ethyl-17a-aza-D-homoandrost-5-en-3β-ol (12) (0.5 g) in cyclohexanone (5 ml), dioxan (21 ml), and toluene (15 ml) was slowly distilled as aluminium isopropoxide (0.5 g) in toluene (6 ml) was added. Distillation was continued for 40 min as more toluene (12 ml) was added and 33 ml of distillate was collected. The mixture was refluxed for 5 h and then set aside overnight. It was then filtered, and the filtrate steam-distilled and then extracted with chloroform (4 × 50 ml). The combined chloroform extract was washed with water, dried, and solvent removed under reduced pressure to give a residue which was crystallised from acetone to yield the *enone* (13) (0.3 g, 60.4%), m.p. 166—168 °C; $\lambda_{max.}$ 240 nm (log ε 4.29); $\nu_{max.}$ 1 689 and 1 626 cm^{-1}; δ 0.88 (3 H, s), 1.16 (3 H, s), 2.62—3.10 (2 H, m), and 5.72 (1 H, br s) (Found: C, 80.10; H, 10.60; N, 4.65. $C_{21}H_{33}NO$ requires C, 79.94; H, 10.54; N, 4.44%).

17a-*Ethyl*-3-(N-*pyrrolidinyl*)-17a-*aza*-D-*homoandrosta*-3,5-*diene* (14).—Freshly distilled pyrrolidine (0.5 ml) was added to a boiling solution of 17a-ethyl-17a-aza-D-homoandrost-4-en-3-one (13) (0.5 g) in 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 17a-ethyl-3-(*N*-pyrrolidinyl)-17a-aza-D-homoandrosta-3,5-diene (14) (0.55 g, 94.8%), m.p. 194—196 °C; $\lambda_{max.}$ 275 nm (log ε 4.36); $\nu_{max.}$ 1 650 and 1 608 cm^{-1}; δ 0.88 (3 H, s), 0.96 (3 H, s), 2.62—3.30 (6 H, m), 4.80 (1 H, s), and 5.10 (1 H, m) (Found: C, 81.20; H, 10.90; N, 7.85. $C_{25}H_{40}N_2$ requires C, 81.46; H, 10.94; N, 7.60%).

17a-*Ethyl*-3β-*pyrrolidinyl*-17a-*aza*-D-*homoandrost*-5-*ene* (15).—Sodium borohydride (0.44 g) was added to a stirred suspension of 17a-ethyl-3-(*N*-pyrrolidinyl)-17a-aza-D-homoandrosta-3,5-diene (14) (0.55 g) in methanol (12 ml) during 4 h. The reaction mixture was filtered, poured into ice-cold water (85 ml), and extracted with chloroform (4 × 25 ml). The chloroform extract was processed and the residue crystallised from methanol to give 17a-ethyl-3β-(*N*-pyrrolidinyl)-17a-aza-D-homoandrost-5-ene (15) (0.3 g, 60.0%), m.p. 184—186 °C; $\nu_{max.}$ 1 681 cm^{-1}; δ 0.86 (3 H, s), 0.98 (3 H, s), 2.50—3.40 (7 H, m), and 5.33 (1 H, m) (Found: C, 80.85; H, 11.45; N, 7.80. $C_{25}H_{42}N_2$ requires C, 81.02; H, 11.62; N, 7.56%).

17a-*Ethyl*-3β-(N-*pyrrolidinyl*)-17a-*aza*-D-*homoandrost*-5-*ene Bis(ethiodide)* (3).—Ethyl iodide (0.4 ml) was added to a boiling solution of the amine (15) (0.2 g) in absolute ethanol (2 ml). Refluxing was continued for 4 h; the reaction mixture was then concentrated, cooled, and poured into dry ether. The precipitated material was filtered off and crystallised from ethanol to give the *bis(ethiodide)* (3) (0.28 g, 76.03%), m.p. 277—278 °C (Found: I, 39.2; N, 4.15. $C_{29}H_{52}I_2N_2$ requires I, 37.18; N, 4.10%).

17a-*Methyl*-3β-(N-*pyrrolidinyl*)-17a-*aza*-D-*homoandrost*-5-*ene Bis(ethiodide)* (2).—Ethyl iodide (0.6 ml) was added to a boiling solution of the amine (11) (0.3 g) in absolute ethanol (3 ml). The mixture was refluxed for 4 h, concentrated, cooled, and poured into dry solvent ether. The precipitated material was filtered off and crystallised from ethanol to give the *bis(ethiodide)* (2) (0.35 g, 62.2%), m.p. 295—296 °C (Found: I, 38.70; N, 4.20. $C_{28}H_{50}I_2N_2$ requires I, 37.96; N, 4.19%).

We thank the Council of Scientific and Industrial Research and the University Grants Commission, New Delhi, for financial support, and Professor W. B. Whalley, University of London, for many of the spectra and elemental analyses.

[7/1947 *Received*, 7th *November*, 1977]

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