Steroids and Related Studies. Part 48.[1] A Chandonium Iodide Analogue possessing an Acetylcholine-like Moiety

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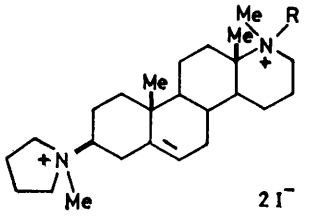
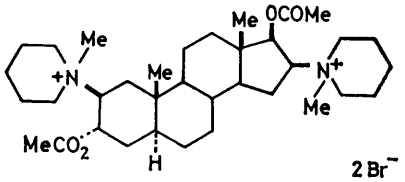
A chandonium iodide analogue containing anacetylcholine-like moiety, 17a-(2-acetoxyethyl)-3β-pyrrolidino-17a-aza-D-homoandrost-5-ene dimethiodide (1), 17a-(2-hydroxyethyl)-3β-pyrrolidino-17a-aza-D-homoandrost-5-ene dimethiodide (22), and some monoquaternary derivatives have been prepared. Both (1) and (22) possess a marked neuromuscular blocking activity.

It was considered of interest to design an analogue (1) of chandonium iodide (2) [2] having a moiety corresponding to the neurotransmitter acetylcholine. Notwithstanding the observation [3] that there is a decrease in potency with increase in the 'onium bulk in (2), preparation of (1) was considered to be a worthwhile project since pancuronium bromide (3),[4] an effective neuromuscular blocker, has bulky quaternary groups and contains



(1) R = CH_2CH_2OCOMe
(2) R = Me

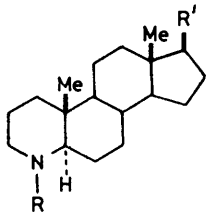


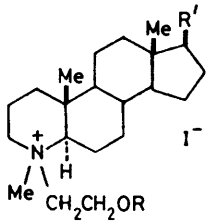
(3)

acetylcholine-like fragments. The high potency and specificity of action of the agent at a neuromuscular receptor site may be associated with the particular molecular geometries and electronic structures of the acetylcholine-like moieties in the molecule.

RESULTS AND DISCUSSION

First, exploratory work was carried out with 4-aza- and 17a-aza-D-homo-steroids and the respective nitrogens made into part of the acetylcholine-like fragments.





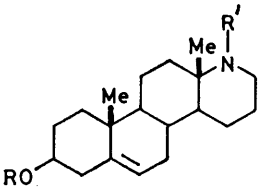
(4) R = H, R′ = C_8H_{17}
(5) R = CH_2CH_2OH, R′ = C_8H_{17}
(6) R = CH_2CH_2OCOMe, R′ = C_8H_{17}
(9) R = H, R′ = OH
(10) R = CH_2CH_2OH, R′ = OH

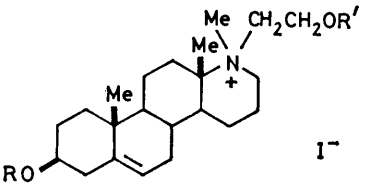
(7) R = H, R′ = C_8H_{17}
(8) R = COMe, R′ = C_8H_{17}
(11) R = H, R′ = OH
(12) R = COMe, R′ = OCOMe

4-Aza-5α-cholestane (4),[5] when refluxed with ethylene chlorohydrin in ethanol in the presence of potassium carbonate, furnished 4-(2-hydroxyethyl)-4-aza-5α-cholestane (5). The OH function was discernible from the stretching band at 3 365 cm^{-1}. In the n.m.r. spectrum there was a broad multiplet in the range δ 2.45—3.35 (4 H, collapsing to 3 H on deuterium exchange). The multiplet appears to arise from C*H* (5α) and NCH_2CH_2OH. Another multiplet at δ 3.50 is assigned to NCH_2CH_2OH. The alcohol (5) was acetylated and the product (6) characterised as the hydrochloride.

Difficulty was experienced in quaternisation of (6) with methyl iodide. However, (5) could be converted to the 'onium derivative (7), which on heating with acetic anhydride gave (8).

The other 4-aza-quaternary compound prepared was (12), starting from 4-aza-5α-androstan-17β-ol (9) [5] and





(13) R = R′ = H
(14) R = H, R′ = CH_2CH_2OH
(17) R = COMe, R′ = CH_2CH_2OCOMe

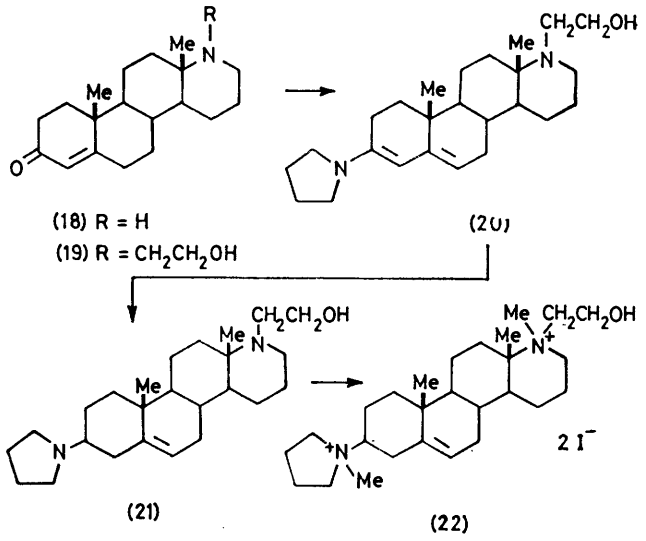
(15) R = R′ = H
(16) R = R′ = COMe

following the sequence: treatment with ethylene chlorohydrin, quaternisation of (10) to (11), and acetylation of the latter to yield (12).

Likewise, starting with 17a-aza-D-homoandrost-5-en-3β-ol (13) [6] the analogue (16) was prepared through (14) and (15). Again difficulty was experienced in quaternising the acetylation product (17), and so quaternisation to (15) was carried out before acetylation to obtain (16) from (14).

The synthesis of the chandonium iodide analogue (1) was then commenced. Compound (13) on Oppenauer oxidation using the cyclohexanone–toluene system gave the α,β-unsaturated ketone (18),[6] $\lambda_{max.}$ 239 nm. Treat-

ment of (18) with ethylene chlorohydrin gave the *N*-(2-hydroxyethyl)-derivative (19). Reaction with pyrrolidine in methanol yielded the enamine (20), $\lambda_{max.}$ 275 nm. Sodium borohydride reduction of (20) gave (21), the



3β-configuration being assigned by analogy with similar reductions reported earlier.[7,8] The quaternary compound (22) was prepared by treating (21) with methyl iodide. Acetylation of (22) yielded the desired product (1).

In anaesthetised cat (1) and (22) were twice as active as chandonium iodide (2) as neuromuscular blockers and produced less vagolytic action than chandonium iodide at neuromuscular blocking doses.[9]

EXPERIMENTAL

U.v. and i.r. spectra were obtained in methanol and for 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, and then ceric 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 drying agent.

4-(2-*Hydroxyethyl*)-4-*aza*-5α-*cholestane* (5).—Ethylene chlorohydrin (0.5 ml) was added to a refluxing solution of 4-aza-5α-cholestane (4) [5] (0.25 g) in absolute ethanol (15 ml) containing anhydrous potassium carbonate (0.6 g), and refluxing was continued for 16 h. The reaction mixture was cooled, filtered, and the solvent removed under reduced pressure. The residue was taken up in acetone, filtered, and crystallised to obtain 4-(2-hydroxyethyl)-4-aza-5α-cholestane (5) (0.22 g, 78.7%), m.p. 118—120 °C; $\nu_{max.}$ 3 365 cm^{-1}, δ 0.66 (3 H, s), 0.83 (3 H, s), 0.94 (9 H, m), 2.45—3.35 (4 H, m, collapsing to 3 H on deuterium exchange), and 3.50 (2 H, m) (Found: C, 80.65; H, 12.25; N, 3.35. $C_{28}H_{51}NO$ requires C, 80.51; H, 12.31; N, 3.35%).

The Hydrochloride of 4-(2-*Acetoxyethyl*)-4-*aza*-5α-*cholestane* (6).—A mixture of 4-(2-hydroxyethyl)-4-aza-5α-cholestane (5) (0.25 g) and acetic anhydride (0.5 ml) was heated on a steam-bath for 2 h. The reaction mixture was cooled, poured into ice-cold water, and made alkaline with 10% potassium hydroxide solution. The precipitated material was extracted with ether (3 × 15 ml) and processed to give a residue (0.22 g). This was taken up in dry ether and alcoholic hydrochloric acid was added to it to acidity. The precipitated material was filtered off and crystallised from acetone to yield 4-(2-acetoxyethyl)-4-aza-5α-cholestane hydrochloride (0.23 g, 77.5%), m.p. 255—257 °C; $\nu_{max.}$ 1 753 and 1 263 cm^{-1} (Found: C, 72.05; H, 10.5; Cl, 7.3; N, 3.0. $C_{30}H_{54}ClNO_2$ requires C, 72.58; H, 10.88; Cl, 7.15; N, 2.82%).

4-(2-*Hydroxyethyl*)-4-*aza*-5α-*cholestane Methiodide* (7).—Methyl iodide (0.1 ml) was added to a boiling solution of 4-(2-hydroxyethyl)-4-aza-5α-cholestane (5) (0.25 g) in absolute ethanol (2 ml). The mixture was refluxed for 1 h, cooled, and poured into dry ether. The precipitated material was filtered off and crystallised from acetone to afford 4-(2-hydroxyethyl)-4-aza-5α-cholestane methiodide (7) (0.15 g, 45.0%), m.p. 271—273 °C; $\nu_{max.}$ 3 320 cm^{-1} (Found: C, 61.7; H, 9.6; I, 22.5; N, 2.45. $C_{29}H_{54}INO$ requires C, 62.25; H, 9.66; I, 22.71; N, 2.50%).

4-(2-*Acetoxyethyl*)-4-*aza*-5α-*cholestane Methiodide* (8).—A mixture of 4-(2-hydroxyethyl)-4-aza-5α-cholestane methiodide (7) (0.18 g) and acetic anhydride (0.3 ml) was heated on a steam-bath for 6 h. The reaction mixture was cooled and poured into dry ether. The precipitated material was filtered off and crystallised from acetone to give 4-(2-acetoxyethyl)-4-aza-5α-cholestane methiodide (8) (0.07 g, 36.8%), m.p. 242—243 °C; $\nu_{max.}$ 1 742 and 1 259 cm^{-1} (Found: C, 61.4; H, 9.35; I, 20.85; N, 2.3. $C_{31}H_{56}INO_2$ requires C, 61.89; H, 9.31; I, 21.13; N, 2.35%).

4-(2-*Hydroxyethyl*)-4-*aza*-5α-*androstan*-17β-*ol* (10).—Ethylene chlorohydrin (0.5 ml) was added to a refluxing solution of 4-aza-5α-androstan-17β-ol (9) [5] (0.5 g) in absolute ethanol (25 ml). Anhydrous potassium carbonate (0.66 g) was added to the reaction mixture and it was refluxed for 12 h. The reaction mixture was cooled, filtered, and the solvent removed under reduced pressure. The residue so obtained was crystallised from acetone to give 4-(2-hydroxyethyl)-4-aza-5α-androstan-17β-ol (10) (0.46 g, 79.3%), m.p. 178—179 °C; $\nu_{max.}$ 3 300 cm^{-1}; δ 0.73 (3 H, s), 0.95 (3 H, s), 2.50—3.35 (4 H, m, collapsing to 3 H on deuterium exchange), and 3.35—3.75 (3 H, m) (Found: C, 75.0; H, 11.15; N, 4.35. $C_{20}H_{35}NO_2$ requires C, 74.71; H, 10.97; N, 4.36%).

4-(2-*Hydroxyethyl*)-4-*aza*-5α-*androstan*-17β-*ol Methiodide* (11).—Methyl iodide (0.5 ml) was added to a refluxing solution of 4-(2-hydroxyethyl)-4-aza-5α-androstan-17β-ol (10) (0.5 g) in absolute ethanol (10 ml). The reaction mixture was refluxed for 2 h, concentrated, and cooled. It was poured into dry ether, and the precipitated material filtered off and crystallised from methanol–acetone to yield 4-(2-hydroxyethyl)-4-aza-5α-androstan-17β-ol methiodide (11) (0.55 g, 76.3%), m.p. 232—234 °C; $\nu_{max.}$ 3 390 and 3 295 cm^{-1} (Found: C, 54.25; H, 8.7; I, 27.4; N, 2.9. $C_{21}H_{38}INO_2$ requires C, 54.42; H, 8.27; I, 27.38; N, 3.02%).

4-(2-*Acetoxyethyl*)-4-*aza*-5α-*androstan*-17β-*yl Acetate Methiodide* (12).—A mixture of 4-(2-hydroxyethyl)-4-aza-5α-androstan-17β-ol methiodide (11) (0.4 g) and acetic anhydride (1.0 ml) was heated on a steam-bath for 2 h. The reaction mixture was cooled and poured into dry ether. The precipitated material was filtered off and crystallised from acetone to give 4-(2-acetoxyethyl)-4-aza-5α-androstan-17β-yl acetate methiodide (12) (0.34 g, 71.9%), m.p. 230—232 °C; $\nu_{max.}$ 1 730 and 1 235 cm^{-1} (Found: C, 55.1; H,

7.65; I, 23.6; N, 2.45. $C_{25}H_{42}INO_4$ requires C, 54.84; H, 7.73; I, 23.18; N, 2.56%).

17a-(2-*Hydroxyethyl*)-17a-*aza*-D-*homoandrost*-5-*en*-3β-*ol* (14).—Ethylene chlorohydrin (0.8 ml) was added to a refluxing solution of 17a-aza-D-homoandrost-5-en-3β-ol (13)[6] (0.8 g) in absolute ethanol (25 ml) containing anhydrous potassium carbonate (0.9 g). The reaction mixture was refluxed for 16 h, cooled, filtered, and the solvent removed under reduced pressure. The residue so obtained was crystallised from acetone to give 17a-(2-hydroxyethyl)-17a-aza-D-homoandrost-5-en-3β-ol (14) (0.71 g, 68.0%), m.p. 221—223 °C; $\nu_{max.}$ 3 333 cm^{-1}; δ 0.89 (3 H, s), 0.98 (3 H, s), 2.52—3.35 (4 H, m, collapsing to 2 H on deuterium exchange), 3.35—3.70 (3 H, m), and 5.35 (1 H, m) (Found: C, 75.65; H, 10.65; N, 4.15. $C_{21}H_{35}NO_2$ requires C, 75.63; H, 10.58; N, 4.20%).

17a-(2-*Hydroxyethyl*)-17a-*aza*-D-*homoandrost*-5-*en*-3β-*ol Methiodide* (15).—Methyl iodide (0.1 ml) was added to a refluxing solution of 17a-(2-hydroxyethyl)-17a-aza-D-homoandrost-5-en-3β-ol (14) (0.1 g) in absolute ethanol (1 ml). The reaction mixture was refluxed for 1 h, cooled, and poured into dry ether. The precipitated material was collected and crystallised from acetone to give 17a-(2-hydroxyethyl)-17a-aza-D-homoandrost-5-en-3β-ol methiodide (15) (0.07 g, 49.0%), m.p. 240—241 °C; $\nu_{max.}$ 3 540 and 3 360 cm^{-1} (Found: C, 55.25; H, 7.75; I, 26.2; N, 3.2. $C_{22}H_{38}INO_2$ requires C, 55.58; H, 8.0; I, 26.73; N, 2.94%).

17a-(2-*Acetoxyethyl*)-17a-*aza*-D-*homoandrost*-5-*en*-3β-*yl Acetate Methiodide* (16).—A mixture of 17a-(2-hydroxyethyl)-17a-aza-D-homoandrost-5-en-3β-ol methiodide (15) (0.15 g) and acetic anhydride (0.3 ml) was heated on a steam-bath for 8 h. The reaction mixture was cooled and poured into dry ether. The precipitated material was filtered off and crystallised from acetone to give 17a-(2-acetoxyethyl)-17a-aza-D-homoandrost-5-en-3β-yl acetate methiodide (16) (0.1 g, 56.6%), m.p. 254—255 °C; $\nu_{max.}$ 1 740 and 1 243 cm^{-1} (Found: C, 55.4; H, 7.2; I, 22.6; N, 2.7. $C_{26}H_{42}INO_4$ requires C, 55.81; H, 7.51; I, 22.72; N, 2.50%).

17a-(2-*Acetoxyethyl*)-17a-*aza*-D-*homoandrost*-5-*en*-3β-*yl Acetate* (17).—A mixture of 17a-(2-hydroxyethyl)-17a-aza-D-homoandrost-5-en-3β-ol (14) (0.1 g), pyridine (0.5 ml), and acetic anhydride (0.2 ml) was heated on a steam-bath for 1 h, cooled, and poured into ice-cold water. The resulting solution was made alkaline with 10% potassium hydroxide solution, and the precipitated material was filtered off and washed with water. The residue obtained was crystallised from acetone to afford 17a-(2-acetoxyethyl)-17a-aza-D-homoandrost-5-en-3β-yl acetate (17) (0.06 g, 48%), m.p. 124—125 °C; $\nu_{max.}$ 1 740, 1 728, and 1 245 cm^{-1}; δ 0.85 (3 H, s), 0.98 (3 H, s), 2.04 (6 H, s), and 5.38 (1 H, m) (Found: C, 71.95; H, 9.3; N, 3.3. $C_{25}H_{39}NO_4$ requires C, 71.89; H, 9.41; N, 3.36%).

17a-(2-*Hydroxyethyl*)-17a-*aza*-D-*homoandrost*-4-*en*-3-*one* (19).—Ethylene chlorohydrin (3.0 ml) was added to a refluxing solution of 17a-aza-D-homoandrost-4-en-3-one(18)[6] (2.9 g) in absolute ethanol (80 ml) containing anhydrous potassium carbonate (4.0 g), and the refluxing continued for 16 h. The reaction mixture was cooled, filtered, and the filtrate evaporated to dryness. The residue so obtained was crystallised from acetone to afford 17a-(2-hydroxyethyl)-17a-aza-D-homoandrost-4-en-3-one (19) (2.3 g, 68.8%), m.p. 188—189 °C; $\lambda_{max.}$ 241 nm (log ε 4.19); $\nu_{max.}$ 3 390, 1 675, and 1 626 cm^{-1}; δ 0.94 (3 H, s), 1.17 (3 H, s), 2.52—3.35 (3 H, m, collapsing to 2 H on deuterium exchange), 3.35—3.70 (2 H, m), and 5.74 (1 H, s) (Found: C, 76.7; H, 10.25; N, 4.15. $C_{21}H_{33}NO_2$ requires C, 76.09; H, 10.03; N, 4.23%).

17a-(2-*Hydroxyethyl*)-3-*pyrrolidino*-17a-*aza*-D-*homoandrosta*-3,5-*diene* (20).—Freshly distilled pyrrolidine (1.0 ml) was added to a boiling solution of 17a-(2-hydroxyethyl)-17a-aza-D-homoandrost-4-en-3-one (19) (1.2 g) in methanol (20 ml). The reaction mixture was refluxed for 30 min, and the yellow needles which crystallised out on cooling were filtered off, washed with methanol, and dried in a vacuum desiccator to yield 17a-(2-hydroxyethyl)-3-pyrrolidino-17a-aza-D-homoandrosta-3,5-diene (20) (1.0 g, 71.8%), m.p. 162—165 °C; $\lambda_{max.}$ 275 nm (log ε 4.39); $\nu_{max.}$ 3 356, 3 175, 1 653, and 1 626 cm^{-1}; δ 0.92 (3 H, s), 0.97 (3 H, s), 2.55—2.97 (3 H, m; collapsing to 2 H on deuterium exchange), 2.97—3.35 (4 H, m), 3.35—3.70 (2 H, m), 4.81 (1 H, br s), and 5.10 (1 H, m) (Found: C, 77.6; H, 10.65; N, 7.25. $C_{25}H_{40}N_2O$ requires C, 78.03; H, 10.47; N, 7.29%).

17a-(2-*Hydroxyethyl*)-3β-*pyrrolidino*-17a-*aza*-D-*homoandrost*-5-*ene* (21).—Sodium borohydride (1.0 g) was added to a stirred solution of 17a-(2-hydroxyethyl)-3-pyrrolidino-17a-aza-D-homoandrosta-3,5-diene (20) (1.0 g) in methanol (25 ml) during 4 h. The reaction mixture was stirred for a further 2 h, poured into ice-cold water, and the precipitated material was extracted with chloroform (3 × 25 ml), and processed. The residue was crystallised from acetone to give 17a-(2-hydroxyethyl)-3β-pyrrolidino-17a-aza-D-homoandrost-5-ene (21) (0.7 g, 69.6%), m.p. 152—155 °C; $\nu_{max.}$ 3 333 cm^{-1}; δ 0.90 (3 H, s), 0.98 (3 H, s), 2.75—3.35 (3 H, m, collapsing to 2 H on deuterium exchange), 3.35—3.70 (2 H, m), and 5.30 (1 H, m) (Found: C, 77.2; H, 10.95; N, 7.15. $C_{25}H_{42}N_2O$ requires C, 77.66; H, 10.95; N, 7.25%).

17a-(2-*Hydroxyethyl*)-3β-*pyrrolidino*-17a-*aza*-D-*homoandrost*-5-*ene Dimethiodide* (22).—Methyl iodide (0.3 ml) was added to a boiling solution of 17a-(2-hydroxyethyl)-3β-pyrrolidino-17a-aza-D-homoandrost-5-ene (21) (0.2 g) in absolute ethanol (0.5 ml). The mixture was refluxed for 1 h, cooled, poured into dry ether, and the precipitated material was filtered off and crystallised from methanol to yield 17a-(2-hydroxyethyl)-3β-pyrrolidino-17a-aza-D-homoandrost-5-ene dimethiodide (22) (0.2 g, 57.7%), m.p. 280—282 °C; $\nu_{max.}$ 3 226 cm^{-1} (Found: C, 48.8; H, 7.3; I, 37.5; N, 4.15. $C_{27}H_{48}I_2N_2O$ requires C, 48.37; H, 7.12; I, 37.84; N, 4.18%).

17a-(2-*Acetoxyethyl*)-3β-*pyrrolidino*-17a-*aza*-D-*homoandrost*-5-*ene Dimethiodide* (1).—A mixture of 17a-(2-hydroxyethyl)-3β-pyrrolidino-17a-aza-D-homoandrost-5-ene dimethiodide (22) (0.5 g) and acetic anhydride (2.0 ml) was heated on a steam-bath for 8 h, and the reaction mixture was then cooled and poured into dry ether. The precipitated material was filtered off and crystallised from methanol–acetone to give 17a-(2-acetoxyethyl)-3β-pyrrolidino-17a-aza-D-homoandrost-5-ene dimethiodide (1) (0.25 g, 47.1%), m.p. 245—250 °C, $\nu_{max.}$ 1 742 and 1 247 cm^{-1} (Found: C, 48.8; H, 7.3; I, 36.0; N, 4.0. $C_{29}H_{50}I_2N_2O_2$ requires C, 48.88; H, 7.07; I, 35.61; N, 3.93%).

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

[9/027 *Received, 8th January,* 1979]

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