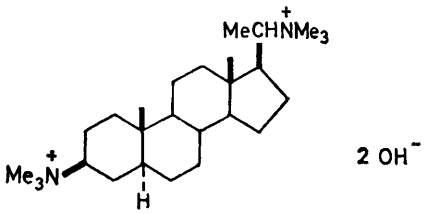
Steroids and Related Studies. Part XX.[1] 4,17a-Diaza-D-homo-steroids

By **Harkishan Singh,* Dharam Paul,** and **Veerendra V. Parashar,** Department of Pharmaceutical Sciences, Panjab University, Chandigarh 160014, India

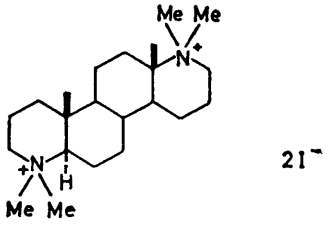
Oxidation of 17a-aza-D-homoandrost-4-ene-3,17-dione with sodium periodate–potassium permanganate yields 5,17-dioxo-17a-aza-D-homo-A-nor-3,5-secoandrostan-3-oic acid which has been used to prepare some 4,17a-diaza-D-homo-steroids. We report the synthesis of 4,17a-dimethyl-4,17a-diaza-D-homo-5α-androstane dimethiodide (HS-342), which possesses neuromuscular-blocking activity.

THE discovery of neuromuscular-blocking potency in the steroidal alkaloid malouetine [2] (1) and its synthetic stereoisomers [3,4] prompted the synthesis of several



(1)

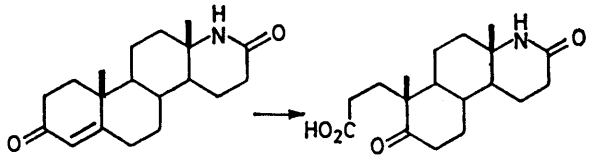
quaternary ammonium analogues with the steroid nucleus as the supporting system. Malouetine and its stereoisomers possess similar potency to tubocurarine but produce hypotension when injected. Alauddin *et al.*[5] and Bamford *et al.*[6] synthesized and tested stereoisomers of dialkylamino- and cyclic amino-steroids substituted at positions 3 and 17; they all possessed lower potency than tubocurarine in cat or in monkey. Recently, pancuronium bromide (2β,16β-dipiperidino-5α-androstane-3α,17β-diyl diacetate dimethobromide) was prepared and found to be a potent neuromuscular-blocking agent [7] with a duration of action comparable with that of tubocurarine.



(2)

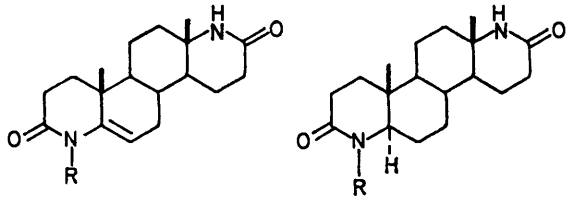
We have initiated a programme of synthesis of bis-'onium steroids as potential neuromuscular-blocking agents, with one or both of the cationic systems present as part of the steroid ring skeleton at different inter-'onium distances. We first developed the 4,17a-diaza-D-homo-steroid system,[8] and now report the synthesis of 4,17a-dimethyl-4,17a-diaza-D-homo-5α-androstane dimethiodide (HS-342) (2).[9]

17a-Aza-D-homoandrost-4-ene-3,17-dione (3) [10] was oxidized with the periodate–permanganate reagent [11,12] to give 5,17-dioxo-17a-aza-D-homo-A-nor-3,5-seco-androstan-3-oic acid (4). This was refluxed with



(3) (4)

benzylamine to give the enamine lactam (5), $\lambda_{max.}$ 234 nm. Similarly ethanolamine gave the lactam (6). The oxime of the seco-keto-acid (4) could be readily prepared by heating with hydroxylamine hydrochloride



(5) R = $C_6H_5CH_2$ (7) R = OH
(6) R = CH_2CH_2OH (8) R = H

and potassium hydroxide in ethanol. Reduction of the oxime with zinc and acetic acid yielded the hydroxamic acid (7). Leuckart reaction with (4) yielded the key compound 4,17a-diaza-D-homo-5α-androstane-3,17-dione (8).

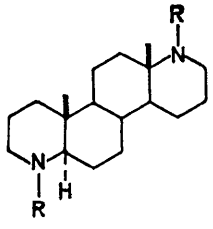
Structures (7) and (8) are assigned by analogy with

[1] Part XIX, H. Singh, S. Padmanabhan, A. K. Bose, and I. Kugajevsky, *J.C.S. Perkin I*, 1972, 993.
[2] A. Quevauviller and F. Laini, *Ann. pharm. franç*, 1960, **18**, 678 (*Chem. Abs.*, 1961, **55**, 9665).
[3] R. Goutarel, *Tetrahedron*, 1961, **14**, 126.
[4] F. Khoung Huu-Laine and W. Pinto-Scognamiglio, *Arch. Int. Pharmacodyn. Ther.*, 1964, **147**, 209.
[5] M. Alauddin, B. Caddy, J. J. Lewis, M. Martin-Smith, and M. F. Sugrue, *J. Pharm. Pharmacol.*, 1965, **17**, 55.
[6] D. G. Bamford, D. F. Biggs, M. Davis, and E. W. Parnell, *Brit. J. Pharmacol.*, 1967, **30**, 194.
[7] W. R. Buckett, C. E. B. Marjoribanks, F. A. Marwick, and M. B. Morton, *Brit. J. Pharmacol.*, 1968, **32**, 671.
[8] H. Singh and V. V. Parashar, *Chem. Comm.*, 1970, 522.
[9] H. Singh, D. Paul, and V. V. Parashar, IUPAC Symposium on the Chemistry of Natural Products, New Delhi, February 1972, Abstracts, p. 247.
[10] B. M. Regan and F. N. Hayes, *J. Amer. Chem. Soc.*, 1956, **78**, 639.
[11] R. U. Lemieux and E. von Rudloff, *Canad. J. Chem.*, 1955, **33**, 1701, 1710.
[12] E. von Rudloff, *Canad. J. Chem.*, 1955, **33**, 1714; 1956, **34**, 1413.

work of Edward and Morand.[13] They prepared 4-aza-5α-cholestan-3-one by a Leuckart reaction with 5-oxo-A-nor-3,5-secocholestan-3-oic acid, and also converted the oxime of the latter into 4-hydroxy-4-aza-5α-cholestan-3-one with zinc and acetic acid. The configuration at position 5 was shown to be alpha. The Leuckart reaction is known to be sensitive to steric effects[14,15] since it generates the 3β-amino-derivative from 5α-cholestan-3-one.[16]

The lactam (8) was reduced by refluxing with sodium in pentanol. The product lacked lactam carbonyl vibrations and was characterized as 4,17-diaza-D-homo-5α-androstane (9). This was also obtained by direct reduction of the oxime of the seco-keto-acid (4) with sodium–pentanol. The i.r. spectra of the products obtained by both the procedures were identical. The tertiary amine (10) was prepared by refluxing (9) with formaldehyde and formic acid. The n.m.r. spectrum of (10) (in $CDCl_3$) showed singlets at δ 2·14 and 2·18 (each 3H, NMe), and there was no NH stretching in the i.r. spectrum. The bis-'onium derivative (2) was prepared by treating (10) with methyl iodide in ethanol.

In anaesthetized cat HS-342 (2) exhibited non-depolarising neuromuscular-blocking activity approximately equal to that of tubocurarine, but of shorter



(9) R = H
(10) R = Me

duration and with rapid onset of action; it also showed ganglion blockade.[17] This combination of blocking actions is probably related to the inter-'onium distance, 8 Å (derived from Dreiding models), which falls between the optima for these two activities. The details of biological testing of HS-342 are being published elsewhere.[18,19]

EXPERIMENTAL

Optical rotations were measured for solutions in chloroform. U.v. and i.r. spectra were obtained for solutions in methanol and for potassium bromide discs, respectively. T.l.c. was carried out on silica gel G (Merck) and plates were developed by exposure to iodine vapour. The usual procedures of work-up of the reaction mixtures were followed.

5,17-Dioxo-17a-aza-D-homo-A-nor-3,5-secoandrostan-3-oic Acid (4).—A solution of potassium carbonate (3·38 g) in water (96 ml) was added to a vigorously stirred solution of 17a-aza-D-homoandrost-4-ene-3,17-dione (3) (4·7 g) in 90% aqueous t-butyl alcohol (360 ml), and immediately sodium periodate solution (60 ml; 24 g in 300 ml water) and then potassium permanganate solution (6 ml; 0·8%) were added. Stirring was continued and the periodate solution was added at 13 ml min^{-1} during the first 10 min and at 3·5 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, treated with sodium disulphite to remove the permanganate colour, acidified with ice-cold 50% sulphuric acid, diluted with water (150 ml), and extracted with chloroform and worked up. The solid residue was dissolved in potassium hydroxide solution (50 ml; 10%), extracted with ether, and acidified. The precipitated fine needles crystallized from methanol to give the *azasteroid* (4) (3·8 g, 79·5%), m.p. 266—268°; $\nu_{max.}$ 3258, 1710, 1692, 1687, and 1605 cm^{-1} (Found: C, 67·15; H, 8·7; N, 4·65. $C_{18}H_{27}NO_4$ requires C, 67·25; H, 8·45; N, 4·35%).

5-Hydroxyimino-17-oxo-17a-aza-D-homo-A-nor-3,5-seco-androstan-3-oic Acid.—A mixture of the acid (4) (1·0 g), hydroxylamine hydrochloride (0·45 g), and potassium hydroxide (1·4 g) in ethanol (45 ml) and water (30 ml), was refluxed for 2 h, and worked up in the usual way. The solid crystallized from methanol to give the *oxime* (0·85 g, 80·7%), m.p. 245—247°; $\nu_{max.}$ 3460, 3208, 1700, and 1640 cm^{-1} (Found: C, 64·05; H, 7·9; N, 8·7. $C_{18}H_{28}N_2O_4$ requires C, 64·25; H, 8·40; N, 8·35%).

4-Benzyl-4,17a-diaza-D-homoandrost-5-ene-3,17-dione (5).—A solution of the acid (4) (0·6 g) in freshly distilled benzylamine was refluxed for 6 h and kept overnight at room temperature. After dilution with water, the mixture was extracted with chloroform and worked up. The residue was crystallized from acetone to give the *lactam* (5) (0·44 g, 62%), m.p. 278—280°, $[\alpha]_D^{20}$ −127·2° (*c* 1·05); $\lambda_{max.}$ 234 nm (log ε 4·004), $\nu_{max.}$ 1655 and 1625 cm^{-1} (Found: C, 76·8; H, 7·85; N, 7·0. $C_{25}H_{32}N_2O_2$ requires C, 76·5; H, 8·2; N, 7·15%).

4-(2-Hydroxyethyl)-4,17a-diaza-D-homoandrost-5-ene-3,17-dione (6).—A solution of the acid (4) (0·7 g) in freshly distilled ethanolamine (2·8 ml) was gently refluxed for 6 h, cooled, diluted with water (*ca.* 70 ml), and extracted with chloroform and worked up. Repeated crystallizations of the residue from acetone afforded the *lactam* (6) (0·15 g, 21%), m.p. 238—240°, $[\alpha]_D^{20}$ −109·3° (*c* 1·16); $\lambda_{max.}$ 235 nm (log ε 4·009); $\nu_{max.}$ 3335 and 1645 cm^{-1} (Found: C, 69·65; H, 8·8; N, 8·45. $C_{20}H_{30}N_2O_3$ requires C, 69·35; H, 8·75; N, 8·1%).

4-Hydroxy-4,17a-diaza-D-homo-5α-androstane-3,17-dione (7).—A solution of 5-hydroxyimino-17-oxo-17a-aza-D-homo-A-nor-3,5-secoandrostan-3-oic acid (0·6 g) in glacial acetic acid (15 ml) was heated on a steam-bath and treated with zinc dust (1·5 g). The mixture was cooled after 2 h and filtered, and the residue was washed with glacial acetic acid (15 ml). The combined filtrate and washings were diluted with water (450 ml), extracted with chloroform, and worked up to give a pink residue (0·4 g, 70%),

[13] J. T. Edward and P. F. Morand, *Canad. J. Chem.*, 1960, **38**, 1316.
[14] D. S. Noyce and F. W. Batchelor, *J. Amer. Chem. Soc.*, 1952, **74**, 4577.
[15] M. Mousseron, R. Jacquier, and R. Zagdoun, *Bull. Soc. chim. France*, 1953, 974.
[16] R. R. Sauers, *J. Amer. Chem. Soc.*, 1958, **80**, 4721.
[17] I. G. Marshall, H. Singh, and D. Paul, Abstracts of the British Pharmaceutical Conference, Keele, 1972; *J. Pharm. Pharmacol.*, 1972, **24**, 146P.
[18] I. G. Marshall, D. Paul, and H. Singh, *J. Pharm. Pharmacol.*, in the press.
[19] I. G. Marshall, D. Paul, and H. Singh, *European J. Pharmacol.*, in the press.

m.p. >300°. An analytical sample was obtained by crystallization from chloroform–methanol–acetone, m.p. >300°, $\nu_{max.}$ 3175 and 1640 cm^{-1} (Found: N, 8·35. $C_{18}H_{28}N_2O_3$ requires N, 8·75%).

4,17a-*Diaza*-D-*homo*-5α-*androstane*-3,17-*dione* (8).—Concentrated aqueous ammonia was added dropwise to formic acid (98%; 3·0 ml) until the mixture was just alkaline. A suspension of the acid (4) (2·0 g) in nitrobenzene (10 ml) was then added to the ammonium formate, previously brought to 165° in an oil-bath. The mixture was occasionally stirred during 20 h at 180—200°, cooled, washed with water, refluxed with ethanol (20 ml) and concentrated hydrochloric acid (5·0 ml) for 2 h, and steam-distilled to remove nitrobenzene. The residue was extracted with chloroform and worked up. The amorphous residue was crystallized from chloroform–acetone to give the *dione* (8) (0·3 g, 31%), m.p. >330°; $\nu_{max.}$ 3175 and 1655 cm^{-1} (Found: C, 71·1; H, 9·4; N, 9·1. $C_{18}H_{28}N_2O_2$ requires C, 71·0; H, 9·25; N, 9·2%).

4,17a-*Diaza*-D-*homo*-5α-*androstane* (9).—*Procedure A*. Sodium metal (1·2 g) was added in small portions to a refluxing solution of the dilactam (8) (0·15 g) in n-pentanol (24 ml). The mixture was refluxed until the sodium metal had reacted, then cooled to room temperature, and water (20 ml) was added. The solvent was removed by steam-distillation. The residue was then extracted with chloroform and worked up, and the solid residue was crystallized from acetone to yield the *product* (9) (0·07 g, 51%), m.p. 174—175°, $[\alpha]_D^{20}$ +10·13° (*c* 1·225); $\nu_{max.}$ 3285 cm^{-1} (Found: C, 78·0; H, 11·8; N, 10·2. $C_{18}H_{32}N_2$ requires C, 78·2; H, 11·65; N, 10·15%).

Procedure B. Sodium metal (12·0 g) was added slowly to a refluxing solution of 5-hydroxyimino-17-oxo-17a-aza-D-homo-A-nor-3,5-secoandrostan-3-oic acid (1·2 g) in n-pentanol (300 ml). The refluxing was continued until sodium metal had completely reacted and the mixture was worked up as before. Recrystallization from acetone gave the product (9) as characterized above.

4,17a-*Dimethyl*-4,17a-*diaza*-D-*homo*-5α-*androstane* (10).—A mixture of formic acid (6 ml), formaldehyde (6 ml), and 4,17a-diaza-D-homo-5α-androstane (9) (0·1 g) was refluxed for 8 h. The mixture was worked up and the residue was crystallized from acetone to yield the *product* (10) (0·09 g, 81·7%), m.p. 162—163°, $[\alpha]_D^{23}$ −1·1° (*c* 0·35); $\nu_{max.}$ 2850 cm^{-1} (Found: C, 79·1; H, 12·05; N, 9·55. $C_{20}H_{36}N_2$ requires C, 78·9; H, 11·9; N, 9·2%).

4,17a-*Dimethyl*-4,17a-*diaza*-D-*homo*-5α-*androstane Dimethiodide* (2).—Methyl iodide (0·4 ml) was added to the refluxing solution of 4,17a-dimethyl-4,17a-diaza-D-homo-5α-androstane (10) (0·1 g) in absolute ethanol (2 ml). The mixture was refluxed for 1 h, cooled, and poured into dry ether (50 ml). The precipitated yellow material was filtered off, and crystallized from methanol–acetone to give the *dimethiodide* (2) (0·16 g, 82·7%), m.p. 293—295° (Found: I, 42·7; N, 4·7. $C_{22}H_{42}I_2N_2$ requires I, 43·2; N, 4·75%).

We acknowledge financial support from the Council of Scientific and Industrial Research, New Delhi, and a supply of the starting material from G. D. Searle & Co. We thank Professor W. B. Whalley, University of London, for help in obtaining the spectra.

[2/2484 *Received*, 2*nd November*, 1972]