236. *Synthetic Neuromuscular Blocking Agents. Part III.* Miscellaneous Quaternary Ammonium Salts.*

By E. P. Taylor.

Two series of heterocyclic polymethylene- and 5-oxanonamethylene-bis-(quaternary ammonium salts) have been prepared, none of the members of which possesses greater neuromuscular blocking activity in the rabbit than does the corresponding decamethylene derivative. Some compounds related to succinoylcholine (the dicholine ester of succinic acid) and a sulphur analogue of decamethonium iodide have been prepared, but none is as active as the corresponding parent substance.

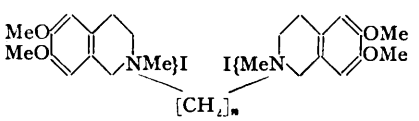
It was shown (Part I, *J.*, 1951, 1150) that certain heterocyclic decamethylenebis(quaternary ammonium salts) possess strong neuromuscular blocking activity. In Part II * a further series of bis(quaternary ammonium salts) derived from the alkaloid laudanosine was described in which the two quaternary groups were separated by polymethylene and oxapolymethylene chains of various lengths. In this series, the maximum neuromuscular blocking activity in rabbits was found to be associated with a nonamethylene or decamethylene chain, the former being slightly the more active. It was therefore decided to prepare some polymethylene and oxapolymethylene analogues of the two most active compounds described in Part I to ascertain whether the optimal chain length for neuromuscular blocking activity in these two series was the same as in the laudanosinium salts. These compounds (I—IX) were prepared by the two general methods described in Part I. The pharmacological properties were determined by Dr. H. O. J. Collier, and will be described in full elsewhere. In those salts derived from 1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethoxy-2-methyl*iso*quinoline (I—V), the optimal chain length for neuromuscular blocking activity in rabbits appeared to be 10—11, the decamethylene derivative being slightly the more active. The maximum neuromuscular blocking activity in the 1 : 2 : 3 : 4-tetrahydro-6 : 7 : 8-trimethoxy-2-methyl*iso*quinolinium series (VI—IX) was associated with the decamethylene chain. In both of these series, as in the laudanosinium series, introduction of oxygen into the polymethylene chain lowered the pharmacological activity, (V and IX) being considerably less active than (II) and (VI).

At one stage, it appeared possible that bisquaternary salts derived from hydrocotarnine might be of pharmacological interest. For various reasons, however, these compounds were abandoned, and therefore only the octamethylene (X) and nonamethylene (XI) derivatives are described in this paper.

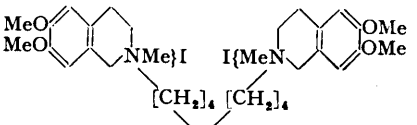
Considerable interest has recently been shown in the neuromuscular blocking activity of certain bischoline esters, in particular succinoylcholine [the dimethiodide of bis-2-dimethylaminoethyl succinate] (XII) and related compounds (see Bovet and his collaborators, *Rend. Ist. Sup. Sanità*, 1949, **12**, Parts I—III; Phillips, *J. Amer. Chem. Soc.*, 1949, **71**, 3264; Walker, *J.*, 1950, 193; Vanderhaeghe, *Nature*, 1951, **167**, 527). It appeared possible therefore that quaternary salts derived from heterocyclic esters of succinic acid might be worth investigation, and accordingly di-8-hydroxyquinolyl succinate dimethosulphate (XIII) was prepared. In this, as in the choline ester, the two quaternary groups are separated by a chain of 10 atoms. This compound, however, had no paralysing activity in rabbits in doses up to 4 mg./kg. (the M.E.D. of the choline ester in rabbits is of the order of 0·15 mg./kg.). It was originally intended to prepare the corresponding 1 : 2 : 3 : 4-tetrahydroquinolyl derivative, since it has been shown in Part I that reduction

* Part II, *J.*, 1952, 142.

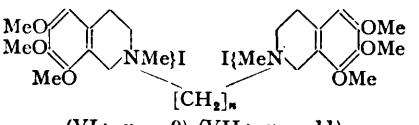
of the heterocyclic nucleus considerably increased the neuromuscular blocking activity. However, in an attempt to prepare the succinate of 1 : 2 : 3 : 4-tetrahydro-8-hydroxy-1-methylquinoline, the bulk of the original base was recovered, and in view of the apparent



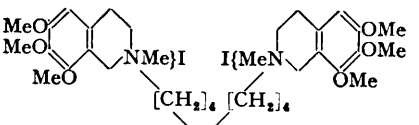
(I; n = 8) (III; n = 11)
(II; n = 9) (IV; n = 12)



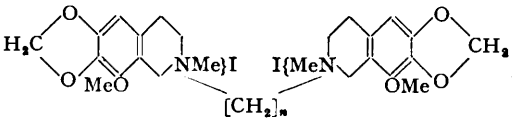
(V)



(VI; n = 9) (VII; n = 11)
(VIII; n = 12)



(IX)

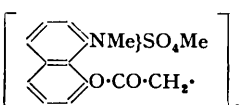


(X; n = 8)
(XI; n = 9)

lack of activity of (XIII), this route was abandoned. Dr. Collier suggested examination of quaternary salts derived from 2-dimethylaminoethyl esters of citric and tricarballylic acids, since these possess three quaternary groups separated by chains of 10 atoms. Accordingly, tris-2-dimethylaminoethyl tricarballylate was prepared from tricarballyloyl chloride and 2-dimethylaminoethanol, and converted into the trimethiodide (XIV). However, in mice, this compound possessed only approximately 1/70th of the paralysing activity of the choline ester. The method of preparing (XIV) could not be used for the citric acid derivative (XV) since the chloride of citric acid is unobtainable. Attempts to convert either 2-chloroethyl citrate or the corresponding 2-bromoethyl ester into tris-2-dimethylaminoethyl citrate by treatment with dimethylamine were unsuccessful. Further, an attempt to transesterify ethyl citrate with dimethylaminoethanol failed.

$[I\{Me_3N{\cdot}CH_2{\cdot}CH_2{\cdot}O{\cdot}CO{\cdot}CH_2{\cdot}\}_2$

(XII)



(XIII)

$I\{Me_3N{\cdot}CH_2{\cdot}CH_2{\cdot}O{\cdot}CO{\cdot}CR(CH_2{\cdot}CO{\cdot}O{\cdot}CH_2{\cdot}CH_2{\cdot}NMe_3\}I)_2$
(XIV; R = H) (XV; R = OH)

$I\{Me_3N{\cdot}[CH_2]_2{\cdot}S{\cdot}[CH_2]_4{\cdot}S{\cdot}[CH_2]_2{\cdot}NMe_3\}I$
(XVI)

Finally, the effect of replacing methylene groups in decamethonium iodide $I\{Me_3N{\cdot}[CH_2]_{10}{\cdot}NMe_3\}I$ by sulphur atoms was investigated. Butane-1 : 4-dithiol, on treatment with 2-dimethylaminoethyl chloride hydrochloride and sodium, gave 1 : 4-bis-2′-dimethylaminoethylthiobutane. The derived dimethiodide (XVI) had approximately 75% of the paralysing activity of decamethonium iodide in mice.

Experimental

(M. p.s and b. p.s are uncorrected. Microanalyses are by Drs. Weiler and Strauss, Oxford. The microanalyses of all quaternary salts were carried out on material dried *in vacuo* at 100°.)

Heterocyclic Bis(quaternary Ammonium Salts).—The following intermediates are new :

1 : 2 : 3 : 4-*Tetrahydro*-6 : 7 : 8-*trimethoxyisoquinoline*, rhombs, m. p. 60—61°, from benzene–light petroleum (b. p. 40—60°), had b. p. 144—145°/0·1 mm. (Found : C, 64·8; H, 7·25; N, 6·1. $C_{12}H_{17}O_3N$ requires C, 64·6; H, 7·7; N, 6·3%). The hydrochloride (Spath, *Monatsh.*, 1921, **42**, 112) became brown at 230° and melted at 242—243° as recorded.

1 : 11-*Bis*-(1 : 2 : 3 : 4-*tetrahydro*-6 : 7 : 8-*trimethoxy*isoquinolino)*undecane dihydrochloride* (from alcohol–ether), m. p. 170—172° (Found: N, 4·4; Cl, 10·3. $C_{35}H_{56}O_6N_2Cl_2$ requires N, 4·2; Cl, 10·6%).

1 : 11-*Bis*-(1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy*isoquinolino)*undecane* (from aqueous alcohol), m. p. 89—91° (Found: C, 73·4; H, 9·4; N, 5·2. $C_{33}H_{50}O_4N_2$ requires C, 73·6; H, 9·4; N, 5·2%).

The following bisquaternary salts were prepared by the general methods previously described (*J.*, 1951, 1151):

Octamethylenebis-(1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy*-2-*methyl*isoquinolinium *iodide*) (I), from methanol–ethanol, microcrystalline, m. p. 225—226° (Found: C, 48·8; H, 6·45; N, 3·4; I, 32·35. $C_{32}H_{50}O_4N_2I_2$ requires C, 49·2; H, 6·5; N, 3·6; I, 32·6%); and the following analogues: *nonamethylene* (II), m. p. 190—192°, from alcohol (Found: C, 49·45; H, 6·3; N, 3·4; I, 31·8. $C_{33}H_{52}O_4N_2I_2$ requires C, 49·9; H, 6·6; N, 3·5; I, 32·0%); *undecamethylene* (III), nodules, m. p. 188—189°, from alcohol (Found: C, 51·15; H, 6·7; N, 3·4; I, 30·4. $C_{35}H_{56}O_4N_2I_2$ requires C, 51·1; H, 6·9; N, 3·4; I, 30·9%); *dodecamethylene* (IV), nodules (from alcohol), containing 3·8% of solvent of crystallisation, which sintered at 55—60° and slowly melted, becoming homogeneous at 173—175° (Found: C, 51·7; H, 7·3; N, 3·3; I, 30·1. $C_{36}H_{58}O_4N_2I_2$ requires C, 51·7; H, 7·0; N, 3·35; I, 30·4%). 5-*Oxanonamethylene* (V), from alcohol, granules, m. p. 201—203° (Found: C, 47·7; H, 6·3; N, 3·6; I, 31·4. $C_{32}H_{50}O_5N_2I_2$ requires C, 48·2; H, 6·3; N, 3·5; I, 31·9%)

Nonamethylenebis-(1 : 2 : 3 : 4-*tetrahydro*-6 : 7 : 8-*trimethoxy*-2-*methyl*isoquinolinium *iodide*) (VI) (from alcohol–ether), m. p. 159—161° (Found: C, 48·8; H, 6·4; N, 3·15; I, 29·9. $C_{35}H_{56}O_6N_2I_2$ requires C, 49·2; H, 6·6; N, 3·3; I, 29·7%); and the following analogues: *undecamethylene* (VII), nodules, m. p. 117—119°, from alcohol–ether (Found: C, 49·9; H, 7·1; N, 3·2; I, 28·3. $C_{37}H_{60}O_6N_2I_2$ requires C, 50·3; H, 6·9; N, 3·2; I, 28·8%); *dodecamethylene* (VIII), granules, m. p. 130—132°, from alcohol–ether (Found: C, 50·6; H, 7·1; N, 2·9; I, 28·1. $C_{38}H_{62}O_6N_2I_2$ requires C, 50·9; H, 7·0; N, 3·1; I, 28·35%). 5-*Oxanonamethylene* (IX), from alcohol, granules, m. p. 191—193° after slight preliminary shrinking (Found: C, 47·5; H, 6·2; N, 3·2; I, 29·4. $C_{34}H_{54}O_7N_2I_2$ requires C, 47·7; H, 6·4; N, 3·3; I, 29·7%).

Octamethylenebis-(1 :2 : 3 : 4-*tetrahydro*-8-*methoxy*-2-*methyl*-6 : 7-*methylenedioxy*isoquinolinium *iodide*) (X), from methyl alcohol, small needles, m. p. 244—246° (decomp.) (Found: C, 47·1; H, 5·6; N, 3·3; I, 31·0. $C_{32}H_{46}O_6N_2I_2$ requires C, 47·5; H, 5·7; N, 3·5; I, 31·4%); and the *nonamethylene* analogue (XI), from methanol–ethanol, m. p. 230—232° (decomp.) (Found: C, 47·9; H, 5·6; N, 3·4; I, 30·7. $C_{33}H_{48}O_6N_2I_2$ requires C, 48·2; H, 5·9; N, 3·4; I, 30·9%).

Substances related to Succinoylcholine.—8-*Hydroxyquinolyl succinate.* Succinoyl chloride (15·5 g., 1 mol.) in dry benzene (50 ml.) was added drop by drop during 20 minutes to a stirred solution of 8-hydroxyquinoline (58 g., 4 mols.) in dry benzene (200 ml.). The mixture became warm, but did not require cooling. After refluxing for 2 hours on the steam-bath and being then left over-night, the mixture was heated and filtered hot, and the residue washed with hot benzene and dried (this residue, dissolved in water and made alkaline with sodium carbonate, gave 28 g. of crude 8-hydroxyquinoline, m. p. 70°). The combined benzene filtrate and washings were evaporated to dryness, giving a white residue (31 g.), m. p. 138—140°, which after recrystallisation from benzene yielded *di*-8-*hydroxyquinolyl succinate* as hard prisms (26 g.), m. p. 141° (Found: C, 70·4; H, 4·4; N, 7·75. $C_{22}H_{16}O_4N_2$ requires C, 71·0; H, 4·3; N, 7·5%). This ester reacted exceedingly slowly with methyl iodide in acetone, benzene, or alcohol. On being heated under reflux in benzene with a 50% excess of methyl sulphate for 24 hours, it gave the *dimethosulphate* (XIII) as colourless needles, m. p. 199—201° (decomp.) (Found: N, 4·45; S, 10·3. $C_{26}H_{28}O_{12}N_2S_2$ requires N, 4·5; S, 10·3%).

Tris-2-*dimethylaminoethyl tricarballylate.* Tricarballyloyl chloride (Emery, *Ber.*, 1889, **22**, 2920) (3·4 g., 1 mol.) in dry ether (15 ml.) was added drop by drop with cooling and shaking to 2-dimethylaminoethanol (4·8 g., *ca.* 3·7 mols.). After 2 hours' gentle refluxing the mixture was set aside overnight; water (20 ml.) was then added, and the mixture thoroughly shaken. The aqueous layer was then separated, treated with an equal volume of saturated potassium carbonate solution, and extracted three times with ether, and the extract dried (Na_2SO_4). The ether was then removed and the residue distilled *in vacuo*, giving the *ester* (2·5 g.), b. p. 178—180°/0·5 mm. (Found: C, 55·8; H, 8·7; N, 10·0. $C_{18}H_{35}O_6N_3$ requires C, 55·5; H, 9·1; N, 10·8%). The *trimethiodide* (XIV) separated from methanol–ethanol as a microcrystalline powder, m. p. 207° (decomp.) (Found: C, 30·95; H, 5·45; N, 5·25; I, 46·2. $C_{21}H_{44}O_6N_3I_3$ requires C, 30·9; H, 5·4; N, 5·15; I, 46·75%).

1 : 2 : 3 : 4-Tetrahydro-8-hydroxy-1-methylquinoline (Fischer, *Ber.*, 1883, **16**, 714) gave a

methiodide, large sheaves of flat needles (from alcohol), m. p. 220—221° (decomp.) (Found: C, 43·3; H, 5·4; N, 4·6; I, 41·5. Calc. for $C_{11}H_{16}ONI$: C, 43·3; H, 5·3; N, 4·6; I, 41·6%). Fischer and Kohn (*ibid.*, 1886, **19**, 1041) describe it as prisms, m. p. 215—216°.

1 : 4-*Bis*-2'-*dimethylaminoethylthiobutane*.—Butane-1 : 4-dithiol (von Braun, *Ber.*, 1909, **42**, 4572) (9 g., 1 mol.) and 2-dimethylaminoethyl chloride hydrochloride (27 g., *ca.* 2·5 mol.) were dissolved in methanol (200 ml.), and the solution was treated at −10° with a solution of sodium (7·64 g., 4·5 mols.) in methyl alcohol (130 ml.). The reaction mixture was then worked up as described by Clinton, Salvador, Laskowski, and Suter [*J. Amer. Chem. Soc.*, 1948, **70**, 951; method A for the preparation of 2-(2-diethylaminoethylthio)ethylamine]. The *dithio*-derivative (5 g.), b. p. 124—126°/0·2 mm., was obtained (Found: C, 54·3; H, 10·7; N, 10·35; S, 24·1. $C_{12}H_{28}N_2S_2$ requires C, 54·55; H, 10·7; N, 10·6; S, 24·2%).

The *dimethiodide* (XVI) crystallised from methanol–ethanol as needles, m. p. 221° (decomp.) (Found: C, 30·9; H, 6·3; N, 5·2; S, 11·3; I, 46·3. $C_{14}H_{34}N_2S_2I_2$ requires C, 30·7; H, 6·25; N, 5·1; S, 11·7; I, 46·35%)

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