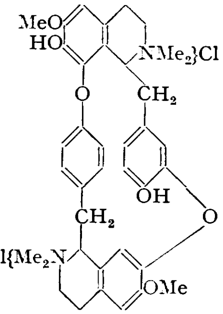
44. *Some New Curarising Agents.*

By JAMES WALKER.

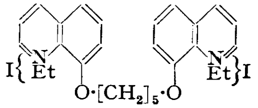
As all of the more potent of the newer curarising agents contain at least two quaternary ammonium groups separated by a chain of about ten atoms, *decamethylene*-1 : 10-*bisdimethylsulphonium di-iodide* (VI) and *decamethylene*-1-*dimethylsulphonium*-10-*trimethylammonium di-iodide* (VIII) have been prepared and examined. Both were found to be powerful curarising agents but to be less active than decamethylene-1 : 10-bistrimethylammonium di-iodide (IV). Succinoylcholine dibromide has also been studied.

ALTHOUGH the curariform activity of 'onium cations has been known for many years, none has, until recently, been known to exert an effect comparable in magnitude with that of the active constituents of native curare. The elucidation of the structure of (+)-tubocurarine chloride (I) by King (*J.*, 1935, 1381; 1939, 1157; 1948, 265) and its introduction as an adjuvant in anæsthesia (Griffith and Johnson, *Anesthesiology*, 1942, **3**, 418; Cullen, *Surgery*, 1943, **14**, 261) have, however, provided a stimulus to further search for other compounds with similar properties.

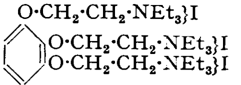
This work has been recently reviewed by Bovet and Bovet-Nitti (*Experientia*, 1948, **4**, 325; *Rend. Ist. Superiore di Sanita*, 1949, **12**, Parte I—III, *Numero speciale sui curari di sintesi*) and by Paton (*J. Pharm. Pharmacol.*, 1949, **1**, 273), and, as the earlier work relating curariform activity with chemical constitution has been reviewed by Ing (*Physiol. Rev.*, 1936, **16**, 527) and by Craig (*Chem. Reviews*, 1948, **42**, 285), it is only necessary to indicate here the trends which recent work has taken. Bisbenzyl*iso*quinoline quaternary salts closely related to, and structurally reminiscent of, (+)-tubocurarine chloride (I) have been shown to have paralysant properties similar to those of (I) (Marsh *et al.*, *J. Pharmacol.*, 1948, **92**, 454; 1948, **93**, 109; 1949, **95**, 100; *Feder. Proc.*, 1949, **8**, 318; Collier *et al.*, *Nature*, 1948, **161**, 817; Stoelting *et al.*, *Anesthesia and Analgesia*, 1949, **28**, 130) but to possess no marked advantages over the latter. Bovet and his collaborators (*Compt. rend.*, 1946, **223**, 597) attempted to analyse the structure of (+)-tubocurarine chloride (I) and observed marked activity in 1 : 5-bis-(8-quinolyloxy)-pentane diethiodide (3381 R.P.) (II). In subsequent phases of this work, Bovet's group has examined substituted ethers, including choline ethers, of phenols and polyhydric phenols (*ibid.*, 1947, **225**, 74), among which pyrogallol trisdiethylaminoethyl ether triethiodide (" Flaxedil "), (3697 R.P.) (III) has received clinical application (Mushin *et al.*, *Lancet*, 1949, I, 726). Choline esters of dibasic aromatic acids were moderately active but their action was more transient (Bovet *et al.*, *Helv. physiol. Acta*, 1948, **6**, C52).



(I.)



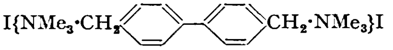
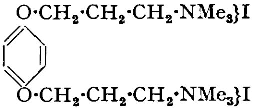
(II.)



(III.)

The most potent synthetic compound hitherto obtained was discovered independently by Barlow and Ing (*Nature*, 1948, **161**, 718; *Brit. J. Pharmacol.*, 1948, **3**, 298) and, in this Institute, by Paton and Zaimis (*Nature*, 1948, **161**, 718) in decamethylene-1 : 10-bistrimethylammonium di-iodide (C10, " Decamethonium iodide ") (IV), which has already proved satisfactory in clinical use (Organe, Paton, and Zaimis, *Lancet*, 1949, I, 21; Organe, *ibid.*, p. 773; Davies and Lewis, *ibid.*, p. 775; Hewer *et al.*, *ibid.*, p. 817; Hobson and Prescott, *ibid.*, p. 819). Furthermore, higher and lower homologues were less active than (IV) and pentamethylene-1 : 5-bistrimethylammonium di-iodide (V) actually antagonises the relaxation produced by (IV) (Paton and Zaimis, *Nature*, 1948, **162**, 810; Organe, Paton, and Zaimis, *loc. cit.*). The feature common to all the more active compounds, despite certain differences in their pharmacological action, is that two quaternary ammonium groups are separated by a chain of between 8 and 12 atoms, indicating that the essential structural requirement for high activity may be that two such groups should occupy positions optimally separated in the same molecule (Barlow and Ing, *loc. cit.*; cf. also Kimura *et al.*, *J. Pharmacol.*, 1949, **95**, 149). The present communication describes several extensions of this thesis and includes sulphonium types.

Decamethylene-1 : 10- (VI) and *pentamethylene*-1 : 5-*bisdimethylsulphonium di-iodide* (VII), the sulphonium analogues of (IV) and (V), were obtained by the addition of methyl iodide to 1 : 10-*bismethylthio*-n-*decane* and 1 : 5-*bismethylthio*-n-*pentane* respectively. *Decamethylene*-1-*dimethylsulphonium*-10-*trimethylammonium di-iodide* (VIII), a hybrid of (IV) and (VI), was obtained by converting ethyl ω-bromoundecoate into *ethyl* ω-*methylthioundecoate* and then methylating the 10-*methylthio*-n-*decylamine hydrochloride* obtained by Curtius degradation As the two quaternary ammonium groups in the succinic ester of choline are separated by a chain of 10 atoms, thereby complying with the above postulate, choline succinate dibromide (IX) was prepared and examined. Shortly afterwards it was learned that Bovet and his collaborators had also examined this ester (*Gazzetta*, 1949, **79**, 129; *Rend. Ist. Superiore di Sanita*, 1949, **12**, 106), and the appearance of a note by Phillips (*J. Amer. Chem. Soc.*, 1949, **71**, 3264) on aliphatic dicarboxylic acid aminoethyl ester alkyl iodides is a further indication of the interest aroused in purely aliphatic compounds by the work of Paton and Zaimis (*locc. cit.*). It should be noted in passing that (IX) may be considered as being derived by linking two molecules of acetylcholine through the acetyl groups by the removal of two hydrogen atoms. Although the distance between the two quaternary ammonium groups in (I) is fixed by stereochemical considerations, the separation of the two charged groups in the aliphatic and mixed aromatic–aliphatic types is not uniquely determined, apart from the fact that the two charged groups will be mutually repulsive. As an example of a rigid structure, 4 : 4′-*bis*(*dimethylaminomethyl*)*diphenyl dimethiodide* (X) was prepared, since, in this substance, the fourteen carbon atoms forming the " backbone " of the molecule are coplanar; the compound, however, was found to be less active than (I), (IV), or (IX). 1 : 4-*Bis*-(3-*dimethylaminopropoxy*)*benzene dimethiodide* (XI), obtained by methylation of the corresponding *diprimary amine hydrochloride*, is a higher homologue of the choline ethers of quinol studied by Bovet and his colleagues (*Compt. rend.*, 1947, **225**, 74). The compounds described in the present communication were kindly tested by Dr. W. D. M. Paton and Dr. E. J. Zaimis using the rabbit " head-drop " technique, and the results are recorded above. It is noteworthy that the decline in activity in passing from (IV) to (VIII) and (VI) closely parallels the observations of Ing and Wright (*Proc. Roy. Soc.*, 1933, *B*, **114**, 48) on the relative activities of the tetramethylammonium and trimethylsulphonium ions.

	Compound.	Rabbit " head-drop " dose (mg./kg.).	Mean relative molecular activities.*
(VI.)	$I\{SMe_2{\cdot}[CH_2]_{10}{\cdot}SMe_2\}I$	1·7	6·5
(VII.)	$I\{SMe_2{\cdot}[CH_2]_5{\cdot}SMe_2\}I$	>38	—
(VIII)	$I\{SMe_2{\cdot}[CH_2]_{10}{\cdot}NMe_3\}I$	0·35	31·6
(IX.)	$CH_2{\cdot}CO{\cdot}O{\cdot}CH_2{\cdot}CH_2{\cdot}NMe_3\}Br$ $CH_2{\cdot}CO{\cdot}O{\cdot}CH_2{\cdot}CH_2{\cdot}NMe_3\}Br$	0·15—0·25	48·3
(X.)		1·53	7·8
(XI.)		0·47	27·0
(IV.)	$I\{NMe_3{\cdot}[CH_2]_{10}{\cdot}NMe_3\}I$	0·10—0·12	100
(I.)	(+)-Tubocurarine chloride	0·22—0·23	74·0
(III.)	" Flaxedil "	0·5	38·3

* Expressed as percentage of the activity of (IV).

EXPERIMENTAL.

Decamethylene-1 : 10-*di*iso*thiourea Dihydrobromide*.—A solution of decamethylene dibromide (15 g.) and thiourea (7·6 g.) in alcohol (150 c.c.) was refluxed until a test drop of the solution no longer gave a dark precipitate with ammoniacal silver nitrate, about 5 hours being required. The *dihydrobromide* separated from alcohol in clusters of colourless, rectangular plates, m. p. 160—161° (Found : N, 12·7. $C_{12}H_{26}N_4S_2,2HBr$ requires N, 12·4%). The yield was quantitative.

1 : 10-*Bismethylthio*-n-*decane*.—The foregoing dihydrobromide (20 g.) was dissolved in N-sodium hydroxide solution (180 c.c.) with gentle warming on the water-bath, and the small amount of oil which separated was taken into solution by addition of a further small volume of alkali. The cold, filtered, alkaline solution was shaken with methyl iodide (5·6 c.c., 2 mols.) for 3 hours and the resulting oil was extracted with ether, washed with aqueous sodium hydroxide, dried, and recovered (9·64 g.). Distillation afforded the *bismethylthio*-compound as a colourless, mobile oil (8·3 g.), b. p. 195—196°/16 mm., n_D^{20} 1·4946 (Found : C, 61·3; H, 11·1. $C_{12}H_{26}S_2$ requires C, 61·5; H, 11·1%).

Decamethylene-1 : 10-*bisdimethylsulphonium Di-iodide* (VI).—The preceding bisthioether (7·1 g.) was treated with methyl iodide (4 c.c.) and methyl alcohol (2 c.c.) was added. The mixture gradually became viscous when kept at room temperature and solidified on scratching after 2½ days. The *di-iodide* separated from methyl alcohol–ethyl acetate (1 : 1·5) in small, stout, colourless prisms (12·3 g.), m. p. 119—120° (effervescence) (Found : C, 32·7; H, 6·2. $C_{14}H_{32}S_2I_2$ requires C, 32·4; H, 6·2%).

1 : 5-*Bismethylthio*-n-*pentane*.—A solution of pentamethylene dibromide (11·2 g.) and thiourea (7·6 g.) in alcohol (100 c.c.) was refluxed until all the thiourea had reacted; on removal of the solvent the residue crystallised. The crude bisthiuronium bromide was decomposed with 10% aqueous sodium hydroxide solution (120 c.c.) in the manner described above, and the filtrate was shaken for 3 hours with methyl iodide (6·6 c.c.). The *bismethylthio*-compound was a colourless oil (4·8 g.), b. p. 128°/22 mm., $n_D^{18·5}$ 1·5103 (Found : C, 51·4; H, 10·3. $C_7H_{16}S_2$ requires C, 51·2; H, 9·8%).

Pentamethylene-1 : 5-*bisdimethylsulphonium Di-iodide* (VII).—The preceding bisthioether (3·5 g.), methyl iodide (3 c.c.), and methyl alcohol (3 c.c.) were mixed and kept at 37° for 48 hours, the product crystallising out. The *di-iodide* separated from alcohol in colourless, fern-like masses, m. p. 182—183° (effervescence) (Found : C, 24·3; H, 5·0. $C_9H_{22}S_2I_2$ requires C, 24·1; H, 4·9%).

Ethyl ω-Methylthioundecoate.—ω-Bromoundecoic acid (Ashton and Smith, *J.*, 1934, 1308) is conveniently esterified with only one-fifth of the proportions of alcohol and concentrated sulphuric acid recommended by Walker and Lumsden (*J.*, 1901, **79**, 1196). ω-Carbethoxyundecyl*iso*thiourea hydrobromide (26·1 g.), prepared from equimolecular amounts of ethyl ω-bromoundecoate and thiourea in the usual manner, was dissolved in alcohol (50 c.c.) and treated with alcoholic sodium ethoxide (from 1·63 g. of sodium and 25 c.c. of alcohol). After 2 hours at room temperature a further equivalent of alcoholic sodium ethoxide was added. The filtered solution was then treated with methyl iodide (4·7 c.c.); heat was evolved, and the mixture was left at room temperature overnight. The alcohol was removed by distillation, and the *ethyl* ester, recovered in ether, washed, dried, and distilled, was a colourless oil (17·8 g.), b. p. 199—200°/18 mm., n_D^{23} 1·4608 (Found : C, 64·8; H, 10·7. $C_{14}H_{28}O_2S$ requires C, 64·6; H, 10·8%).

Free ω-methylthioundecoic acid, obtained by alkaline hydrolysis of the ester, was a waxy solid and could not be recrystallised easily. The *benzamidine* salt separated from 25% alcohol in colourless, microscopic plates, m. p. 191—192° (Found : C, 65·1; H, 9·0; N, 7·9. $C_{12}H_{24}O_2S,C_7H_8N_2$ requires C, 64·8; H, 9·1; N, 8·0%).

The *hydrazide*, obtained by refluxing the ester with a slight excess of 90% hydrazine hydrate in *n*-propyl alcohol for 5 hours, separated from that solvent in fine, colourless needles, m. p. 88—89° (Found : C, 58·9; H, 10·4; N, 11·7. $C_{12}H_{26}ON_2S$ requires C, 58·5; H, 10·6; N, 11·4%).

10-*Methylthio*-n-*decylamine Hydrochloride.*—The preceding hydrazide (10·5 g., crude) in alcohol (200 c.c.) was treated in a freezing mixture with a concentrated aqueous solution of sodium nitrite (2·6 g.), and concentrated hydrochloric acid (6 c.c.) was added dropwise during about 40 minutes. The mixture was then diluted with ice-water (800 c.c.) and extracted with benzene. The washed benzene extract was dried and warmed slowly on the water-bath and finally boiled for 15 minutes. Most of the benzene was then distilled off and the residue was treated with concentrated hydrochloric acid (25 c.c.) and warmed on the water-bath for a short time. The acid solution was diluted with water, extracted with ether, made strongly alkaline with sodium hydroxide, and again extracted with ether. The resulting oily base (4·9 g.) was treated with excess of alcoholic hydrogen chloride and the alcohol was distilled off. The *hydrochloride* separated from ethyl acetate, or from a small volume of water, in rosettes of small, colourless plates, m. p. 160—161° (Found : C, 55·1; H, 10·8; N, 5·9. $C_{11}H_{25}NS,HCl$ requires C, 55·1; H, 10·9; N, 5·8%).

Decamethylene-1-*dimethylsulphonium*-10-*trimethylammonium Di-iodide* (VIII).—A solution of the preceding hydrochloride (1·2 g.) and sodium hydroxide (1·32 g.) in methyl alcohol (20 c.c.) was refluxed with methyl iodide (3 c.c.) for 7 hours. The neutral solution was filtered from sodium chloride and exhaustively evaporated to dryness with absolute alcohol. The residue was treated with warm acetone to dissolve the sodium iodide and the insoluble product (2·53 g.) was collected and washed with cold acetone. The *di-iodide* separated from absolute alcohol in clusters of colourless plates, m. p. 136—137° (effervescence) (Found : C, 34·7; H, 7·0; N, 2·6. $C_{15}H_{35}NSI_2$ requires C, 34·9; H, 6·9; N, 2·7%).

Di-2-bromoethyl Succinate.—A mixture of ethylene bromohydrin (35·2 c.c.), succinic acid (23·6 g.), benzene (80 c.c.), and concentrated sulphuric acid (1 c.c.) was refluxed for 12 hours on the water-bath. The mixture was diluted with ether and water, and the upper layer was thoroughly washed with sodium hydrogen carbonate solution, dried, and fractionated. The compound was obtained as a pale yellow oil (37 g.), b. p. 169°/3 mm., n_D^{20} 1·5023, crystallising on immersion in a freezing mixture (Found : C, 28·9; H, 3·9. Calc. for $C_8H_{12}O_4Br_2$: C, 28·9; H, 3·6%). Glick (*J. Biol. Chem.*, 1941, **137**, 357) records b. p. 216—217°/26 mm., and Fusco *et al.* (*Gazzetta*, 1949, **79**, 139) record b. p. 150°/1—2 mm.

Succinoylcholine Dibromide (IX).—A mixture of the above ester (25 g.), benzene (18 c.c.), and trimethylamine (9 g.) was heated in a sealed tube at 90° for 8 hours. After cooling, the upper layer of benzene was decanted and the residual gum was triturated with alcohol. The resulting white powder (17·3 g.) was collected, washed with alcohol and dried. The substance separated from absolute alcohol as a colourless, microcrystalline powder, m. p. 211° (Found : C, 37·1; H, 6·4; N, 6·4. Calc. for $C_{14}H_{30}O_4N_2Br_2$: C, 37·4; H, 6·7; N, 6·2%). Fusco *et al.* (*loc. cit.*) record m. p. 219° but no analytical data for this salt, and Glick (*loc. cit.*) records a bromine determination but no m. p.

4 : 4′-*Bis*(*aminomethyl*)*diphenyl Dihydrochloride.*—4 : 4′-Dicyanodiphenyl (23·5 g.) was reduced in methyl-alcoholic ammonia (630 c.c.; 12%) in the presence of Raney nickel (5 g.) with hydrogen at 60 atm. The mixture was warmed to about 65° and reduction was complete in about 2 hours. The catalyst was filtered off, and the solvent removed by distillation, leaving a brown syrup. The crude base was dissolved in excess of 2N-hydrochloric acid, and the solution, treated with charcoal, was concentrated to saturation at the b. p. On cooling, the dihydrochloride crystallised in colourless thin, transparent, rectangular plates (21·3 g.), m. p. above 350° (Found : C, 59·2; H, 6·5; N, 9·9. Calc. for $C_{14}H_{16}N_2,2HCl$: C, 59·0; H, 6·3; N, 9·8%). The observation by Albert *et al.* (*J.*, 1947, 1454) that the crystals of this salt acquire a blue tint on exposure to light was confirmed.

4 : 4′-*Bis*(*dimethylaminomethyl*)*diphenyl Dimethiodide* (X).—The preceding dihydrochloride (2·85 g.) was treated with sodium hydroxide (3·6 g.) and methyl iodide (7 c.c.) in methyl alcohol (60 c.c.) under reflux for 6 hours. The alcohol was distilled off and the residue was crystallised from water, the *dimethiodide* separating in fine colourless needles (4·8 g.), m. p. above 350° (Found : C, 43·4; H, 5·6; N, 4·8. $C_{20}H_{30}N_2I_2$ requires C, 43·5; H, 5·4; N, 5·1%). The crystals of this salt also acquired a blue tint on exposure to light.

1 : 4-*Di*-(3-*aminopropoxy*)*benzene Dihydrochloride.*—1 : 4-Di-(2-cyanoethoxy)benzene (22 g.) (Cook and Reed, *J.*, 1945, 920) was reduced in alcoholic ammonia (500 c.c.; 10%) in the presence of Raney nickel (7 g.) with hydrogen at 20 atm. The catalyst was removed, and the solvent and ammonia were distilled off. The residue was taken up in excess of 2N-hydrochloric acid (charcoal) and the solution was concentrated, affording a crystalline solid (21·1 g.). The *dihydrochloride* separated from 70% alcohol in clusters of colourless, irregular plates, m. p. 313—314° (Found : C, 48·6; H, 7·5; N, 9·2. $C_{12}H_{20}O_2N_2,2HCl$ requires C, 48·5; H, 7·4; N, 9·4%).

1 : 4-*Bis*-(3-*dimethylaminopropoxy*)*benzene Dimethiodide* (XI).—A solution of the preceding dihydrochloride (3 g.) and sodium hydroxide (3·6 g.) in methyl alcohol (50 c.c.) was refluxed with methyl iodide

(6·2 c.c.) for 6 hours. The solid (6·8 g.) which separated from the reaction mixture consisted of the product mixed with sodium chloride. Recrystallisation from alcohol afforded the pure *dimethiodide* in the form of sheaves of colourless needles (5·3 g.), which effloresced on drying, m. p. 267° (Found : C, 36·8; H, 6·5; loss at 100°/vac., 4·5, 4·8. Found, on material dried at 100°/vac. : C, 38·1; H, 6·3; N, 4·8. $C_{18}H_{34}O_2N_2I_2,1\frac{1}{2}H_2O$ requires C, 36·5; H, 6·3; H_2O, 4·6%. $C_{18}H_{34}O_2N_2I_2$ requires C, 38·3; H, 6·0; N, 5·0%).

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