NEUROMUSCULAR BLOCKING AGENTS

PART VIII. LINEAR BIS- AND TRIS-ONIUM ETHERS

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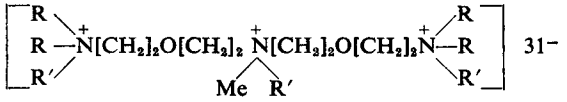
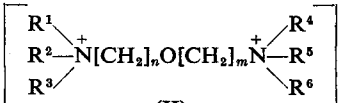
Linear bis- and tris-onium ethers (I and II) have weak tubocurarine-like properties. In both series, potency increased with increase in alkyl group size. No evidence was found for a one point receptor attachment in bis-onium ethers.

IN Part VII (Edwards, Lewis, McPhail, Muir and Stenlake, 1960), we drew attention to changes in neuromuscular blocking potency seen in some linear polyonium ethers in which one of the methylene groups was replaced by an ether oxygen. In the cat, rabbit, chick and mouse, the potency fell sharply, but in the frog it was increased. We have now synthesised and tested a further series of linear poly-onium ethers of the general formula (I), to obtain additional information on the influence of



(I)

the ether oxygen and *N*-alkyl substituents on neuromuscular block in compounds of this type. The influence of the position of the ether-oxygen atom in the chain has not been investigated. Fakstorp and Pedersen (1954, 1957, 1958), however, have studied the ganglion blocking activity of a series of bis-onium ethers of the general formula (II) in which this factor has been considered. Their studies showed that the ether function increased ganglion blocking potency, supported the concept of a one-point receptor attachment at the post synaptic membrane, and indicated that the inter-O-N distance is an important factor in determining potency. They did not, however, investigate the neuromuscular blocking properties of these compounds. We are much indebted to Dr. Pedersen for supplies of the compounds listed in Table II which we have now tested for neuromuscular blocking activity in the cat.



(II)

CHEMICAL

The quaternary compounds (I) were prepared by quaternisation with the appropriate alkyl halides of either *NN*-bis[2-(2-dimethylamino-ethoxy)ethyl]methylamine or *NN*-bis[2-(2-diethylaminoethoxy)ethyl]-methylamine. The latter bases were obtained by the method of Protiva and Pliml (1953) by condensation of di(2-hydroxyethyl)methylamine (*N*-methyldiethanolamine) (Maxwell, 1939) with 2-dimethylaminoethyl chloride and 2-diethylaminoethyl chloride respectively.

EXPERIMENTAL

Di(2-hydroxyethyl)methylamine was prepared as described by Maxwell (1939) and obtained in 81 per cent yield b.p. 130–133°/9 mm. Maxwell gives b.p. 131–133°/9 mm. It was characterised by treatment with ethyl iodide to yield *ethyldi(2-hydroxyethyl)methylammonium iodide*, m.p. 188–190° (from ethanol-ether). Found: N, 5·1; I, 46·0. $C_7H_{18}I\,NO_2$ requires N, 5·1; I, 46·1 per cent.

NN-*Di*[2-(2-*dimethylaminoethoxy*)*ethyl*]*methylamine*. Di(2-hydroxyethyl) methylamine (25·4 g.) in dry toluene (300 ml.) and sodamide (25 g. finely powdered under 50 ml. of toluene) were heated under reflux (oil bath 120–130°) with constant stirring for 2 hr. Heating was interrupted and freshly distilled 2-dimethylaminoethyl chloride (45·67 g.) in dry toluene (50 ml.) was added (20 min.) to the reaction mixture. Refluxing was then continued for a further 6 hr. When cold, the reaction mixture was decomposed by the cautious addition of water. The toluene solution was washed with water (10 ml.), dried (anhydrous K_2CO_3) and removed under reduced pressure. Fractionation of the oily residue gave a forerun of impure starting materials (6·5 g.), b.p. 106–112°/0·07 mm. and then NN-*di*[2-(2-*dimethylaminoethoxy*)*ethyl*]*methylamine* (17·15 g.; 31 per cent) as a pale yellow oil, b.p. 121–123°/0·08 mm. n_D^{23} 1·4520. Found: N, 16·15; equiv. 87·1. $C_{13}H_{31}N_3O_2$ requires N, 16·1 per cent; equiv 87·1.

NN-*Di*[2-(2-*diethylaminoethoxy*)*ethyl*]*methylamine* was prepared from di(2-hydroxyethyl)methylamine (11·9 g.) in dry toluene (150 ml.), sodamide (12 g. finely powdered under 50 ml. of toluene) and freshly distilled 2-diethylaminoethyl chloride (27·1 g.) by the method described for the preparation of *NN*-di[2-(2-dimethylaminoethoxy)ethyl]methylamine, the final reaction mixture being heated for 1 hr. only. Distillation of the crude product gave a forerun of impure starting materials (1·2 g.) b.p. 100–130°/0·05 mm. followed by NN-*di*[2-(2-*diethylaminoethoxy*)*ethyl*]-*methylamine* (9·85 g.; 31 per cent) as a pale yellow oil, b.p. 137–138°/0·06 mm., n_D^{21} 1·4540. Protiva and Pliml (1953) gave b.p. 152°/0·5 mm. Found: N, 13·1; equiv. 105·8. Calc. for $C_{17}H_{39}N_3O_2$, N, 13·2 per cent; equiv. 105·8.

NNN-*Tris-onium Compounds* were prepared by mixing either *NN*-di[2-(2-dimethylaminoethoxy)ethyl]methylamine (1 part) or *NN*-di[2-(2-diethylaminoethoxy)ethyl]methylamine (1 part) with the appropriate alkyl halide (3 parts) and dry ethanol (5 parts), and maintaining the mixture at room temperature. Reaction time, crystallisation solvent and yields are indicated for each compound in that order, in parenthesis.

6 - *Ethyl* - 6 - *methyl* - 3,9 - *dioxa* - 6 - *azoniaundecamethylenebis*(*triethylammonium*) *tri-iodide* (7 days; water-ethanol 4:1; 97 per cent) m.p. 263°. Protiva and Pliml (1953) gave m.p. 263°. Found: N, 5·2; I, 48·4. Calc. for $C_{23}H_{54}I_3N_3O_2$ requires N, 5·35, I, 48·5 per cent.

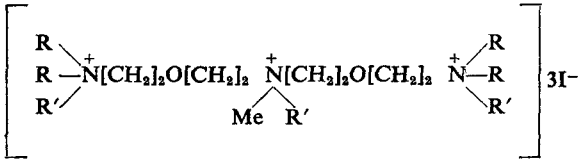
6,6 - *Dimethyl* - 3,9 - *dioxa* - 6 - *azoniaundecamethylenebis*(*trimethylammonium*) *tri-iodide* (3 days; water-ethanol 4:1; 95·0 per cent), m.p. 306–8° (decomp.). Found: N, 6·1; I, 55·1. $C_{16}H_{40}I_3N_3O_2$ requires N, 6·1; I, 55·4 per cent.

6-*Ethyl*-6-*methyl*-3,9-*dioxa*-6-*azoniaundecamethylenebis*(*ethyldimethylammonium*) *tri-iodide* (5 days; water-ethanol 1:9; 97 per cent), m.p. 278° (decomp.). Found: N, 5·7; I, 51·95. $C_{19}H_{46}I_3N_2O_2$ requires N, 5·8; I, 52·2 per cent.

6-*Methyl*-6-*propyl*-3,9-*dioxa*-6-*azoniaundecamethylenebis* (*dimethylpropylammonium*) *tri-iodide* (16 days; ethanol-acetone; 93 per cent),

TABLE I

NEUROMUSCULAR BLOCKING ACTIVITY IN A SERIES OF LINEAR TRIS-ONIUM ETHERS OF STRUCTURE



Compound	Substituents		Relative molar potencies (TC = 100)				Type of activity
	R	R'	Cat	Hen	Frog	Rabbit	
IA	Me	Me	†	*	1·0	*	TC-like
IB	Me	Et	0·4	5·0	2·0	*	TC-like
IC	Me	Pr	1·0	5·2	2·5	*	TC-like
ID	Et	Me	0·7	15·0	4·0	*	TC-like
IE	Et	Et	3·0	20·0	7·0	0·36	TC-like
IF	Et	Pr	14·5	46·0	10·5	*	TC-like

* Insufficient material. † No block at 30 mg./kg. TC = Tubocurarine.

m.p. 196–198° (decomp., after softening at 169–170°). Found, after drying for 5 hr. over P_2O_5 at 56° under high vacuum, N, 5·4; I, 49·1. $C_{22}H_{52}I_3N_3O_2$ requires N, 5·45; I, 49·4 per cent.

6,6-*Dimethyl*-3,9-*dioxa*-6-*azoniaundecamethylenebis*(*diethyl-methylammonium*) *tri-iodide* (7 days; water-ethanol, 4:1; 98 per cent), m.p. 275° (decomp.). Found: N, 5·7; I, 50·95. $C_{20}H_{48}I_3N_3O_2$ requires N, 5·65, I; 51·2 per cent.

6-*Methyl*-6-*propyl*-3,9-*dioxa*-6-*azoniaundecamethylenebis*(*diethylpropylammonium*) *tri-iodide* (70 days; propanol; 79 per cent), m.p. 194° (decomp. after softening at 174°). Found, after drying for 5 hr. over P_2O_5 at 56° under high vacuum: N, 5·0; I, 45·95. $C_{26}H_{60}I_3N_3O_2$ requires N, 5·1; I, 46·0 per cent.

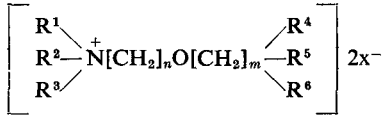
Pharmacological Methods and Results

The methods have been described elsewhere (Edwards and others, 1957, 1958, 1961) and Tables I and II show the comparative molar potencies of the compounds. All possessed muscle-relaxant properties, qualitatively similar to tubocurarine and without depolarising activity. This was true even of the methonium compound IA which caused no contracture of the hen gastrocnemius muscle at doses of 20 mg./kg. which caused an approximately 50 per cent neuromuscular block. In addition, this compound caused no contracture of the isolated frog rectus abdominis muscle. No evidence of sympathetic ganglion-blocking activity was

found in compounds IA to IF when these were tested on the nictitating membrane of the cat and when injected intravenously into the cat anaesthetised with pentobarbitone, doses sufficient to produce an approximately 50 per cent neuromuscular block, caused no significant alteration in the arterial blood pressure level. Compounds IIA to IIH are all ganglion blocking agents (Fakstorp and Pedersen, 1954, 1957, 1958).

TABLE II

NEUROMUSCULAR BLOCKING ACTIVITY IN A SERIES OF LINEAR BIS-ONIUM ETHERS OF STRUCTURE



Compound	Structure					Relative molar potencies Cat (TC = 100)	Type of activity
	$R^1R^2R^3$	n	m	$R^4R^5R^6$	X^-		
IIA (F. & P. 16575) ..	Me_3	2	3	Me_3	I	0·08	TC-like
IIB (F. & P. 16677) ..	$MeEt_2$	2	3	Me_3	I	0·16	TC-like
IIC (F. & P. 8302) ..	$MeEt_2$	2	3	$MeEt_2$	I	0·13	TC-like
IID (F. & P. 16678) ..	Et_3	2	3	Me_2Et	Br	0·30	TC-like
IIE (F. & P. 8303) ..	Et_3	2	3	Et_3	Br	0·45	TC-like
IIF (F. & P. 16701) ..	Me_3	3	3	Me_3	I	No block at 25 mg./kg.	—
IIG (F. & P. 17843) ..	Me_2Et	3	3	Et_3	Br	0·17	TC-like
IIH (F. & P. 8212) ..	Et_3	3	3	Et_3	Br	2·0	TC-like
IIJ	Et_2Pr	3	3	Et_2Pr	I	1·86*	?
Hexamethonium	Me_3			Me_3	I	0·44†	TC-like

* Calculated from the figures of Pradhan and his colleagues (1954).
† Calculated from the figures of Paton and Zaimis (1949).

DISCUSSION

The results confirm those of our earlier work which showed that linear poly-onium ethers of general formula (I) have weak tubocurarine-like neuromuscular blocking activity. In particular, they also confirm that compound IE, which was tested by Vaněček and Protiva (1955) on the rat masseter muscle and phrenic-nerve diaphragm preparation, has only a low potency, although it was one of the more potent of the compounds examined. Our results show this compound to be less potent in the cat than the analogous compound XIIIA $\{[(Et_3\overset{+}{N}[CH_2]_2O[CH_2]_2)_2\overset{+}{N}\ Et_2]3I^-\}$ described in Part VII (Edwards, Lewis and others, 1960), and that it is significantly less potent than the latter in the rabbit. These two substances differ only in the alkyl substituents on the central nitrogen atom, and the observed decline in potency on replacement of an ethyl by a methyl substituent is in agreement with our previous observation on related compounds.

The neuromuscular blocking potency of Fakstorp and Pedersen's compounds is also extremely low and again demonstrates, when IIA is

considered in comparison with hexamethonium, the sharp reduction in potency which is apparently due to replacement of a methylene group by an ether oxygen. As with most of the other groups of linear poly-onium compounds examined, the methonium compounds are weaker than the corresponding ethonium analogues with potency increasing roughly in parallel with the bulk of the onium group. The position of the ether-oxygen atom in the chain appears not to influence neuromuscular block significantly. Thus, although the range of compounds is not fully representative of the series, the observed potencies do not show the marked structural relations which are a feature of the activity of these same compounds as ganglion-blocking agents. This in itself is perhaps not surprising, but it none the less clearly demonstrates that the theory of a one-point receptor attachment at the ganglion postulated by Fakstorp and Pedersen for these and similar compounds does not hold for neuromuscular blockade.

The lowering of potency which is observed with the substitution of an ether-linked oxygen atom in the polymethylene chain of bis- and poly-onium compounds is also in marked contrast to the influence of aromatic ether links on the potency of the tubocurarine and isoquinoline derivatives discussed in Part VII. The potentiating effects of aromatic ether links in these and similar compounds suggests that the real significance of the ether functions may lie in their ability to donate electrons into the aromatic rings. The redistribution of these electrons over the ring would yield a larger charge-bearing structure potentially capable of receptor interaction and hence of reinforcing van der Waal's bonding in a way which is not possible in aliphatic ether derivatives. The reason for the fall in potency when ether links are substituted into aliphatic onium compounds is still not clear, and is being examined further.

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