NEUROMUSCULAR BLOCKING AGENTS

PART V. LINEAR *NNNN*-TETRA-ONIUM, *NNSNN*-PENTA-ONIUM AND *NNNNNN*-HEXA-ONIUM COMPOUNDS

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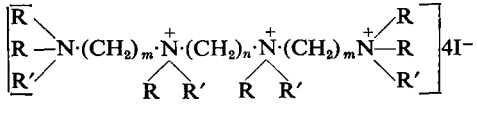
Preliminary observations upon a series of *NNNN*-tetra-onium compounds (IA to IH), an *NNSNN*-penta-onium compound (II) and an *NNNNNN*-hexa-onium compound (III) have so far indicated that inter-onium distance is more important in determining the type of activity than the overall length of the molecule or the number of onium centres it contains.

IN Part III of this series[1] we made a preliminary report on the neuromuscular blocking activity of the linear *NNNN*-tetra-ethonium compounds, trihexatetrazonium (IA; $m = n = 6$; R = R′ = Et) and tridecatetrazonium (IG; $m = n = 10$; R = R′ = Et), chemically related to the tris-ethonium salts described previously[2,3]. We have now prepared



(I)

the further series of tetra-onium compounds (I), described in Table I, the *NNSNN*-penta-ethonium compound, 7,7,14,21,21-penta-ethyl-7,21-diazonia-14-thioniaheptacosylenebis (triethylammonium) penta-iodide (II), and the *NNNNNN*-hexa-ethonium compound, 7,7,14,14,21,21,28,28-octaethyl-7,14,21,28-tetra-azoniatetratriacontylenebis (triethylammonium)

TABLE I

THE CHEMICAL CHARACTERISTICS OF THE LINEAR *NNNN*-TETRA-ONIUM COMPOUNDS, IB TO IH OF THE *NNSNN*-PENTA-ONIUM COMBOUND (II) AND OF THE *NNNNNN*-HEXA-ONIUM COMPOUND (III)

Compound					Formula	Melting point (° C.)	Nitrogen (per cent)		Iodine (per cent)	
	m	*n*	R	R′			Found	Required	Found	Required
IB	6	8	Et	Et	$C_{40}H_{90}N_4I_4$	235–235·5°	4·8	4·9	45·2	44·7
IC	8	6	Et	Et	$C_{42}H_{94}N_4I_4$	246·5–247°	4·8	4·8	43·7	43·6
ID	8	8	Et	Et	$C_{44}H_{98}N_4I_4$	253·5–254°	4·7	4·7	42·5	42·6
IE	6	10	Et	Et	$C_{42}H_{94}N_4I_4$	167·5–168·5°	4·7	4·8	43·2	43·6
IF	10	6	Et	Et	$C_{46}H_{102}N_4I_4$	221–222°	4·7	4·6	41·6	41·6
IH	6	6	Et	*n*-Pr	$C_{42}H_{94}N_4I_4$	197·5–198·5°	4·9	4·8	43·7	43·6
II					$C_{46}H_{103}N_4SI_5$	165·5–166·5°	4·2	4·1	46·2	46·0
III					$C_{58}H_{130}N_6I_6$	248°	5·0	5·0	45·6	45·5

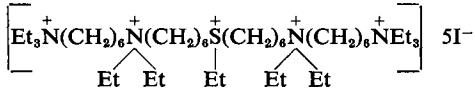
TABLE II

A COMPARISON OF SOME OF THE QUALITATIVE PROPERTIES OF COMPOUNDS IA, IB, IC, ID, IE, IF, IG, IH, II AND III ON THE CAT, CHICK, AND FROG RECTUS ABDOMINIS MUSCLE

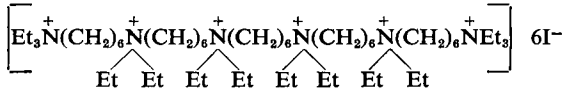
Compound	Effect on block of						Nature of tetanus during block	Effect of tetanus on block	Chick paralysis	Frog rectus	General characteristics
	Neo-stigmine	Edro-phonium	Ether	Adrenaline	TC	C 10					
IA	−	−	+	−	+	−	Poorly held	Decurarisation	Flaccid	No. Stimuln. Antag. Ach	TC-like
IB	−	−	+	±	+	−	,,	,,	,,	,,	,,
IC	−	−	+	±	+	−	,,	,,	,,	,,	,,
ID	±	±	+	±	+	−	,,	,,	,,	,,	,,
IE	±	−	+	±	+	±	,,	Slight decurarisation	,,	,,	,,
IF	0	+	0	±	+	+	Poorly held in most expts	None	Spastic-flaccid	,,	Transitional (?)
IG	0	+			−	+	Fairly well maintained	,,	,,	,,	C 10
IH	−	−	+	±	+	−	Poorly held	,,	Flaccid	,,	TC-like
II	±	±	+	±	+	−	,,	Decurarisation	,,	,,	,,
III	±	−	+	±	+	±	,,	,,	,,	,,	,,

+ = potentiation, addition or prolongation − = antagonism ± = partial antagonism 0 = no effect

hexa-iodide (III). Preliminary pharmacological observations on these compounds are recorded below.



(II)



(III)

The experimental methods and materials have been described in detail elsewhere[2,3]. Table II summarises some of the properties of the new compounds and includes for comparison trihexatetrazonium tetra-ethiodide (IA) and tridecatetrazonium tetra-ethiodide (IG)[1]. Our preliminary observations indicate that the neuromuscular blocking actions of compounds IB, IC, ID, IE, IH, II and III qualitatively resemble those of tubocurarine (TC) rather than those of decamethonium (C 10). These compounds all caused a flaccid paralysis in chicks, had no direct stimulant actions on the isolated frog rectus abdominis muscle and on this tissue antagonised the action of acetylcholine. Most of their other properties were TC-like but we noted that ID, IE, II and III were incompletely antagonised by neostigmine and in addition ID and II incompletely antagonised by edrophonium. These observations may be significant should these compounds be considered for clinical trial in anaesthesia. Of the compounds tested IF was in some ways the most interesting. In some experiments it caused twitching of the limbs, had a very prolonged action and block was intensified by edrophonium and unaffected by neostigmine. Block was not potentiated by ether and in the chick, IF caused an initial spastic paralysis which changed to flaccid. It had no direct stimulant action on the frog rectus abdominis muscle.

Although our observations on the compounds described are incomplete, certain interesting trends are shown. It appears that inter-onium distance is more important in determining the type of activity than the overall length of the molecule and the number of onium centres which it contains. Compounds in which n and $m = 6$ or 8 are essentially TC-like in their qualitative effects but when $n = 6$ and $m = 10$, C 10-like activity appears and is increased when $n = m = 10$.

Acknowledgements. We wish to acknowledge the technical assistance of Miss Gladys Marren.

REFERENCES

1. Edwards, Lewis, Stenlake and Zoha, *J. Pharm. Pharmacol.*, 1958, **10**, Suppl., *122 T.*
2. Edwards, Lewis, Stenlake and Zoha, *ibid.*, 1957, **9**, 1004.
3. Edwards, Lewis, Stenlake and Zoha, *ibid.*, 1958, **10**, Suppl., *106T.*

DISCUSSION

After Mrs. Stothers presented the papers there was a DISCUSSION. The following points were made.

The introduction of an *iso*propyl group into the study had been considered but serious interactions might arise as the grouping was bulky. The metabolism of the compounds had not been studied, but the rapidity of action of most of the compounds suggested that this did not occur. The *NSN* compounds were excreted unchanged.