NEUROMUSCULAR BLOCKING AGENTS

PART IX. SOME SHORT-ACTING LINEAR *NNN*-TRIS-ONIUM ESTERS

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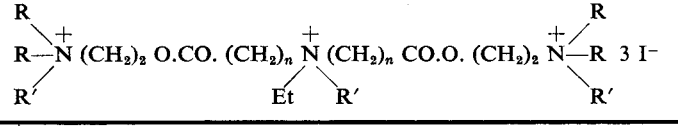
SUXAMETHONIUM (Fusco, Palazzo, Chiaverelli and Bovet, 1949), is the short-acting muscle relaxant most widely used in current clinical practice. This drug, however, has disadvantages; being a depolarising agent there is no satisfactory antidote and, owing to its initial stimulant action, it may cause post-operative muscular soreness (Churchill-Davidson, 1954; Foster, 1960; Morris and Dunn, 1957). More serious is the possibility of prolonged apnoea in patients deficient in pseudocholinesterase (Churchill-Davidson, 1959; Ottolenghi, 1959). For these reasons, attempts have been made to introduce short-acting non-depolarising muscle relaxants. Examples are 2,2′-dodecamethylene-bis-(*N*-dimethylpiperidinium), (Mantegazza, 1955), diohexadecanium bromide [Prodeconium; Prestonal; 3,14-dioxohexadecane-1,16-bis-(dimethylpropoxycarbonylmethylammonium) dibromide] (Frey, 1955; Griffith, Cullen and Welt, 1956), *p*-phenylene-bis-acetylcholine (Rosnati, 1957); 1,4-bis(4′-dimethylaminobutoxy)benzene dimethiodide (Bovet-Nitti, 1959), 2-diethylaminoethoxyethyl α-phenyl-α-1′-piperidylacetate dimethiodide (Cheymol, Guidicelli, Chabrier and Najer, 1959), γ-oxalolaudexium bromide (Brittain, Collier and D'Arcy, 1961) and the bis-onium tropeïne derivatives of Haining, Johnston and Smith (1960). None of the compounds introduced has yet succeeded in supplanting suxamethonium and there remains a need for a short-acting non-depolarising muscle relaxant (Foldes, 1957).

TABLE I

LINEAR TRIS-ONIUM ESTERS



Compound	*n*	R	R′	m.p.	Molecular formula	Found					Requires				
						C	H	I	N	Eq. (sap.)	C	H	I	N	Eq. (sap.)
201	2	Et	Et	174–176°	$C_{28}H_{56}I_3N_3O_4$	35·6	6·8	44·8	4·9	429	36·5	6·6	44·5	4·9	427·7
202	2	Et	Me	164–165°	$C_{25}H_{50}I_3N_3O_4$	33·8	6·5	46·5	5·1	414	33·95	6·2	46·8	5·2	406·7
203	2	Me	Me	166–167°	$C_{19}H_{42}I_3N_3O_4$	29·9	5·6	49·9	5·55	380	30·1	5·6	50·3	5·55	378·6
205	1	Et	Me	169–170°	$C_{21}H_{44}I_3N_3O_4$	32·4	6·3	48·6	5·3	397	32·1	5·9	48·5	5·35	392·7

In general, aliphatic linear ethonium esters are non-depolarising drugs of low potency. Potency may be increased by stepwise replacement of ethyl groups by methyl, although depolarising activity with its attendant

TABLE II

A QUALITATIVE COMPARISON OF THE NEUROMUSCULAR BLOCKING PROPERTIES OF COMPOUNDS 201, 202, 203 AND 205 WITH THOSE OF TUBOCURARINE AND SUXAMETHONIUM

	Effects upon blockade of the cat gastrocnemius-sciatic preparation of				Average duration of action at doses causing 40 to 60 per cent block (in min.)	
Compound	Neostigmine	Edrophonium	Ether	Tetanus	Cat	Hen
201	Antagonises	Antagonises	Prolongs	Transient decurarization	10	5
202	Antagonises	Antagonises	Prolongs		14	5
203	Potentiates	———	Antagonises	None	†	4
205			Prolongs		8	4
Tubocurarine	Antagonises	Antagonises	Prolongs	Transient decurarization	20	18
Suxamethonium	Potentiates	Potentiates		None	5	5

During block by 203 or suxamethonium, a tetanus was sustained and a contracture producing action was present in the frog and hen. The other compounds did not sustain tetanus and did not produce contracture.

† Block could only be produced in the neostigmine-treated cat by intra-arterial injection of the drug.

TABLE III

POTENCY AND TOXICITY

				Rabbit‡		Mouse			
Compound	Molecular weight	Cat* mg./kg.	Hen* mg./kg.	Single dose HD50 mg./kg.	LD50/HD50	i.p. PD50 mg./kg.	i.v. PD50 mg./kg.	LD50/PD50 i.v.	Frog† µg./ml.
201	855·4	1·7	2·3	14	>2·8	54	33	2·1	65
202	813·3	5·9	7·8	4·9	1·3	15	6·6	1·9	26
203	757·2	—	1·7	—	—	¶	¶	¶	—
205	785·3	>50	>50	—	—	—	—	—	—
Suxamethonium chloride	361·0	0·05	0·013	0·14	3·6	1·2	0·33	2·4	—
Tubocurarine chloride	785·7	0·12	0·35	—	—	0·38	0·07	3·0	1·6

* Dose causing 50 per cent inhibition of the gastrocnemius/sciatic preparation.
† Dose causing 50 per cent inhibition of acetylcholine contractions on rectus abdominis muscle.
‡ 202, slow injection gave a head drop dose in the rabbit of 8·6 mg./kg. while tubocurarine gave 0·31.
¶ Muscarine-like side effects prevented assay.

disadvantages then appears (Bovet, Bovet-Nitti, Guarino, Longo and Fusco, 1951; Ginzel, Klupp and Werner, 1952). Low potency, however, does not necessarily rule out the clinical trial of a muscle relaxant, provided that it is non-depolarising, has the required duration of effect, and has a satisfactory therapeutic index.

In Parts I–VIII of this series we have shown that linear polyethonium compounds, in which the onium groups are separated by five or six methylene groups or their equivalent, are tubocurarine-like. We have now synthesised the short series of linear tris-onium esters described in Table I.

The methods used for the pharmacological testing have been described previously by Edwards, Lewis, Stenlake and Zoha (1957; 1958). In Table II some qualitative actions of the four compounds are shown. Compounds 201, 202 and 205 are tubocurarine-like whilst the methonium derivative, compound 203, is a depolarising agent. Its contracture-producing action upon the hen gastrocnemius muscle is shown in Fig. 1.

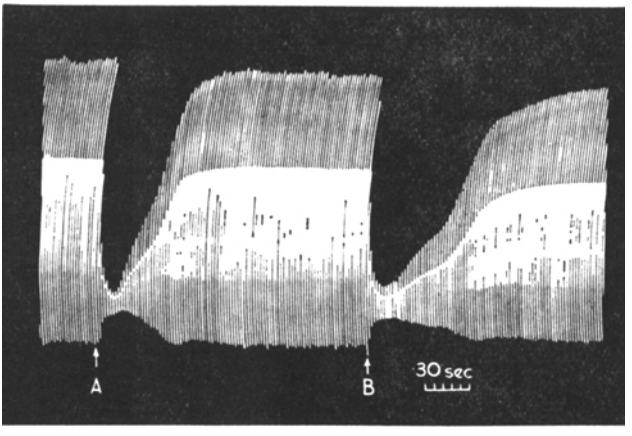


FIG. 1. Effects of 203 and suxamethonium on the gastrocnemius muscle-sciatic nerve preparation of the pentobarbitone-anaesthetised hen (2 kg.). A, 3·0 mg./kg. 203, i.v. causes an inhibition of contractions and the development of contracture.
Similar effects are seen with (B), 0·05 mg./kg. suxamethonium chloride, i.v.

In Table III provisional figures for the potencies and toxicities of compounds 201, 202, 203 and 205 are compared with those for tubocurarine and suxamethonium on the hen, cat, mouse, rabbit and frog.

Compounds 201 and 202 were much less potent than suxamethonium and tubocurarine, while the time of onset and their duration of effect was similar to that of suxamethonium (Table II). 205 was very weak indeed. In the hen, 203 had suxamethonium-like activity which was weaker and shorter in duration. It caused severe muscarine-like effects in the cat and mouse, produced a contracture of the frog rectus muscle and in the anaesthetised cat, induced a weak block. Equipotent muscle relaxant doses of 201, 202 and tubocurarine reduced the response of the nictitating membrane of the cat to electrical stimulation to about the same extent and both new compounds caused a brief depression of the arterial blood pressure of the anaesthetised cat. Some variations in potency between batches of compounds 201 and 202 have been observed, and the extent to which the rate of hydrolysis affects potency and duration of action of these esters is at present under investigation.

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