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THE PHARMACOLOGICAL ACTIONS OF A SERIES OF PHENYL ALKANE *p*-ω-BIS(TRIALKYLAMMONIUM) COMPOUNDS*

BY

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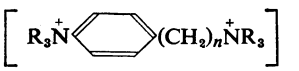
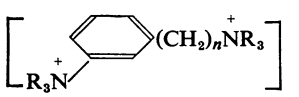
A collaborative programme of research undertaken for the development of a better drug than hexamethonium, which has certain clinical disadvantages, has led to the pharmacological examination of a large number of compounds in several homologous series with a view to obtaining a substance possessing greater duration of action and a more selective effect on ganglia. For the compounds in the present series we are indebted to Dr. J. N. Ashley. They constitute an aromatic series of bis-quaternary compounds,



where $n=0$, 1, 2, 3, 4, 5 or 6, and $R_3=Me_3$, Me_2Et, $MeEt_2$ or Et_3, and of the *meta* isomers,



where $n=1$, 2, 3 or 4, and $R_3=Me_3$. Several compounds were found to have outstanding pharmacological actions, but special attention was paid to one compound in the *para* series where $n=2$ and $R_3=Me_3$ which was examined in more detail; this compound was several times more potent than hexamethonium, and it had a similar type of action. The actions of compounds examined in other series will be described in another paper.

METHODS

The methods employed were those previously described (Wien and Mason, 1951) except that the rate of stimulation of the superior cervical ganglion varied from 12 to 20 instead of 20 per sec. The results shown in Table I were obtained by matching submaximal effects of the test compounds with the standard drugs, hexamethonium bromide and *d*-tubocurarine chloride; each result was the mean value derived from several experiments, but these figures are only approximate because compounds may differ in their slopes of response. Details of other procedures are given in the Results section.

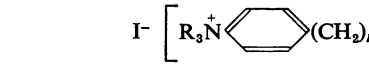
The compounds were all stable substances, soluble in water to give neutral solutions.

RESULTS

A summary of our results is given in Table I. In the *para* series, where $R_3=Me_3$, there was a peak of activity for ganglionic paralysis at the ethane member (M & B 1950); neuromuscular-paralysing activity increased up to the hexane

TABLE I

SUMMARY OF THE ACTIONS OF A SERIES OF PHENYL ALKANE *p*-ω-BIS(TRIALKYLAMMONIUM) COMPOUNDS



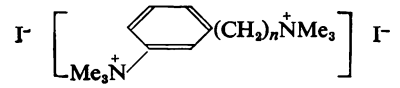
M & B No.	*n*	R_3	Toxicity LD50 mg./kg. i.v. (Mice)	Relative Potencies: Superior Cervical Ganglion (Cat)	Peristaltic Reflex of Ileum (Guinea-pig)	Sciatic-gastrocnemius (Cat)	Phrenic Nerve-diaphragm (Rabbit)
Hexamethonium bromide			50	100	100	—	0·3
d-Tubocurarine chloride			0·2	—	—	100	100
1878	0	Me_3	83	<2	<5	<2	0·1
1899	1	Me_3	34	0·5	<5	<2	0·2
1950	2	Me_3	22	300	250	<2	0·2
2072	2	Me_2Et	9	330	250	<2	0·6
2175	2	$MeEt_2$	36	180	100	7	2·5
2132	2	Et_3	1·8	<2	10*	6	3·0
2034	3	Me_3	20	25	50	<10	0·2
2056	3	Me_2Et	5	50	100	<10	1·0
2278	3	$MeEt_2$	3·2	15	50	—	4·0
2184	3	Et_3	2·2	<4	15*	25	6·0
2071	4	Me_3	1	<5	33*	30*d*	3·0
2082	4	Me_2Et	5	10	25*	5	1·5
2297	4	$MeEt_2$	2·7	5	25*	8	5·0
2272	4	Et_3	1·4	<3	<5*	15	20·0
2268	5	Me_3	1·7	<5	<2	50	6·0
2363	5	Et_3	1·5	<5	<2	50	10·0
2357	6	Me_3	3·1	20*a*	100*b*	100*e*	5·0
2362	6	Et_3	0·6	<12	12·5*c*	100*f*	25·0

* Stimulant effect. *a* Influence of neuromuscular block. *b* Eserine-like effect on rabbit ileum. *c* Acetylcholine-like effect on rabbit ileum. *d* In small doses potentiates the muscle twitch. *e* Not reversed by eserine. *f* Reversed by eserine.

*The results recorded in this paper were communicated to the British Pharmacological Society at Edinburgh in July, 1952.

TABLE II

SUMMARY OF THE ACTIONS OF THE *META* COMPOUNDS



M & B No.	*n*	Toxicity LD50 mg./kg. i.v. (Mice)	Relative Potencies: Superior Cervical Ganglion (Cat)	Peristaltic Reflex of Ileum (Guinea-pig)	Sciatic-gastro-cnemius (Cat)	Phrenic Nerve-diaphragm (Rabbit)
Hexamethonium bromide		50	100	100	—	0·3
d-Tubocurarine chloride		0·2	—	—	100	100
2030	1	6	<5	<5	<10	0·1
2064	2	20	150	125	<10	0·2
2090	3	12	100	50	<10	0·3
2139	4	2	100	100	<10	0·5

member (M & B 2357), which was as far as the series was examined. The influence of chain length was illustrated in a striking manner in the sharp increase in ganglion-blocking activity (600 times) in passing from the methane member (M & B 1899) to the next higher homologue. For this latter compound the potency was much the same on both sympathetic and parasympathetic ganglia, but we would emphasize that these results were based on only two types of ganglia in two different species (the superior cervical ganglion of the cat, and the ganglia mediating the peristaltic reflex of the guinea-pig intestine).

The results in Table I and Fig. 9 (see below) bring out the interdependence between activity and chain length in the *para* series, which followed a similar pattern to that in the methonium series (Paton and Zaimis, 1951). The results for the four compounds of the *meta* series are given in Table II. Since the ethane member (M & B 2064) was only one half as active as its *para* isomer (M & B 1950) the *meta* series was not examined in greater detail.

Just as replacement of methyl by ethyl groups in the methonium series exerts a profound effect on the intensity and type of action of various members (Wien, Mason, Edge, and Langston, 1952), so in this series the complete substitution of methyl by ethyl groups caused generally an increase in toxicity, a reduction or complete suppression of ganglion-blocking activity, and an increase in neuromuscular-blocking properties.

Of particular interest were the two hexane members which were both as active as *d*-tubocurarine in producing neuromuscular paralysis in the cat under chloralose. But one (M & B 2357, where $R_3=Me_3$ and $n=6$) had an action similar to that of decamethonium, whereas the other (M & B 2362, where $R_3=Et_3$ and $n=6$) had an action like *d*-tubocurarine in the cat. This is in sharp contrast to the complete replacement of methyl by ethyl groups in decamethonium, which considerably reduces activity (Paton and Zaimis, 1952).

Actions of M & B 1950 : Phenyl Ethane p-ω-*bis(trimethylammonium Iodide)*

Paralysis of Autonomic Ganglia.—On the superior cervical ganglion of the cat M & B 1950 was three times as potent as hexamethonium bromide, and in equipotent doses the duration of action was somewhat longer (Fig. 1).

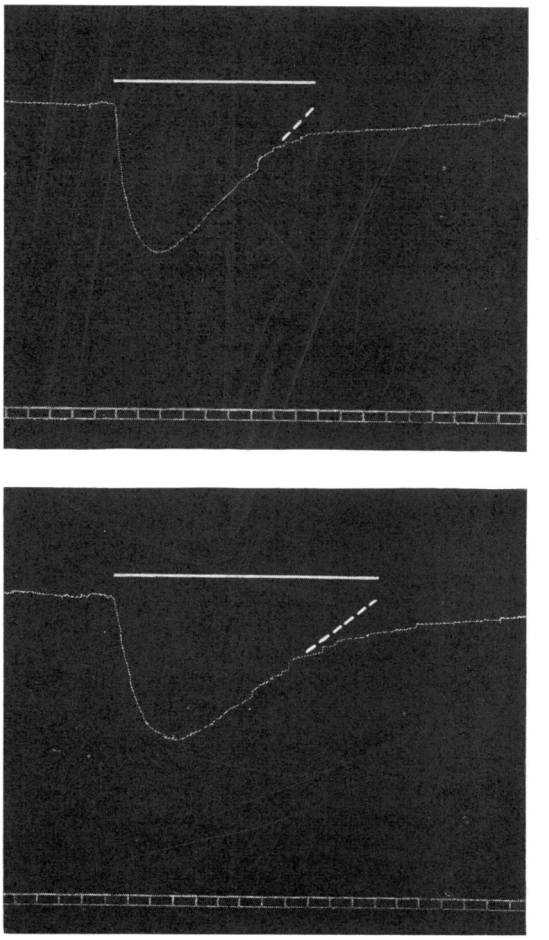


FIG. 1.—Cat, chloralose. Record of contractions of nictitating membrane on sustained preganglionic excitation of cervical sympathetic at 12 stimuli per sec. Upper record shows effect of 0.8 mg. intravenously of hexamethonium bromide, and lower record of 0.25 mg. intravenously of M & B 1950. (Time= 30 sec.) Note slightly prolonged duration of latter compound.

The onset of action was similar, though slightly slower and more gradual in reaching a maximum; the recovery phase was correspondingly slower. The doses required for these effects on the nictitating membrane (ranging from 0.05 to 0.4 mg. depending on the rate of stimulation) had little depressor effect on the arterial blood pressure. When the rate of stimulation was decreased from 20 to 5 per sec. the sensitivity of the ganglion to paralysis by both the phenethyl compound and hexamethonium was decreased considerably, about five times, the ratio of their potencies remaining the same. The stimulant action of nicotine on the blood pressure of the dog under chloralose was inhibited, and the intensity and duration of the pressor effect of adrenaline were slightly enhanced (Fig. 2).

The compound was two and a half times as potent as hexamethonium in preventing the peristaltic reflex of the guinea-pig intestine. The preparation readily differentiated between two-fold increases in the dose, and doses of 150 to 300 μg. in a 50 ml. bath caused partial to complete inhibition of the reflex; recovery occurred quickly after washing out once or twice.

The slowing of the pulse and the fall in blood pressure in the cat on vagal excitation were abolished with doses of 0.25 mg./kg., but the depressor action of acetylcholine was unmodified. It was difficult to obtain reliable comparative figures by this method because of the long duration of the effects, sometimes for several hours.

The mydriatic effect in the mouse, due to paralysis of the ciliary ganglion, was four times greater than that of hexamethonium. On intraperitoneal injection, after 10 minutes, the potency figure was assayed as 4.19, with fiducial limits of 3.5 to 5.1 for P=0.95 (experiment by Mr. N. D. Edge).

Mode of Action.—In several ways we have shown that the compound M & B 1950 has a mode of action similar to that of hexamethonium. The stimulant effect of nicotine on the intestine was abolished, leaving unaltered the effects of acetylcholine, histamine, and of pilocarpine, exactly similar to a result previously described for a homologue of hexamethonium (Wien and Mason, 1951). Freedom from an atropine-like action was confirmed in the cat by the absence of any inhibitory effect with an intravenous dose of 2 mg. on salivary flow induced by carbamylcholine, compared with the effect of 5 μg. atropine which markedly inhibited the flow. The paralysis of transmission occurred most probably at the gang-

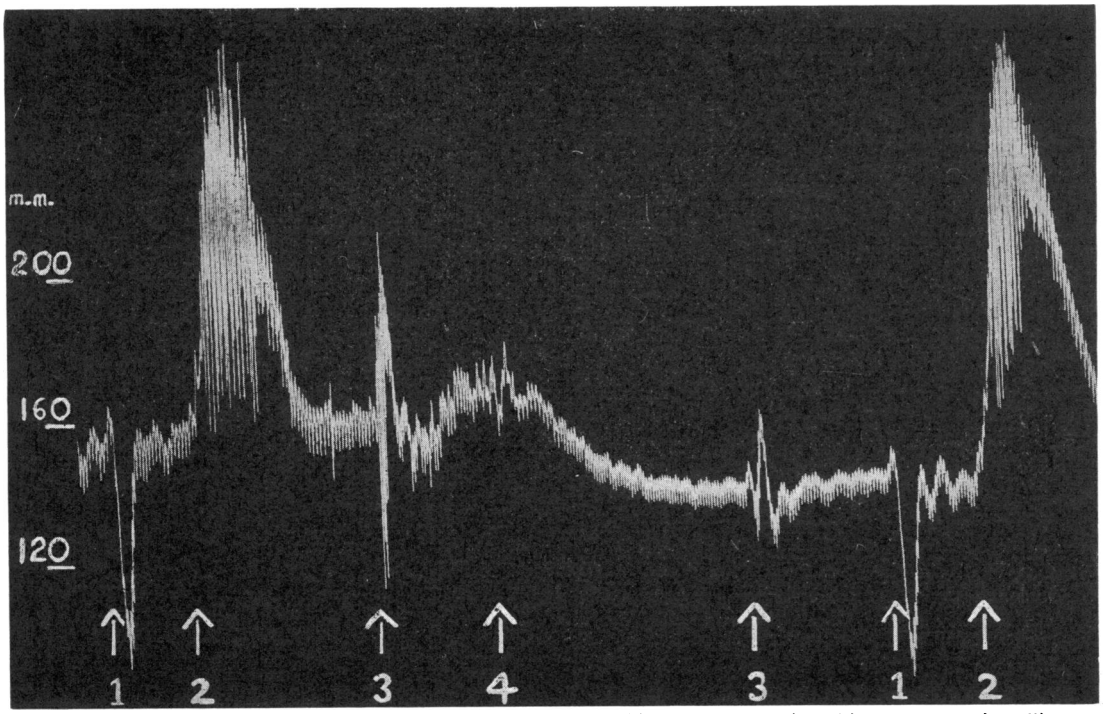


FIG. 2.—Dog, chloralose. Blood-pressure record. Injections intravenously. At (1), 50 μg. acetylcholine; (2), 50 μg. adrenaline; (3), 0.5 mg. nicotine acid tartrate; (4), 0.05 mg./kg. M & B 1950.

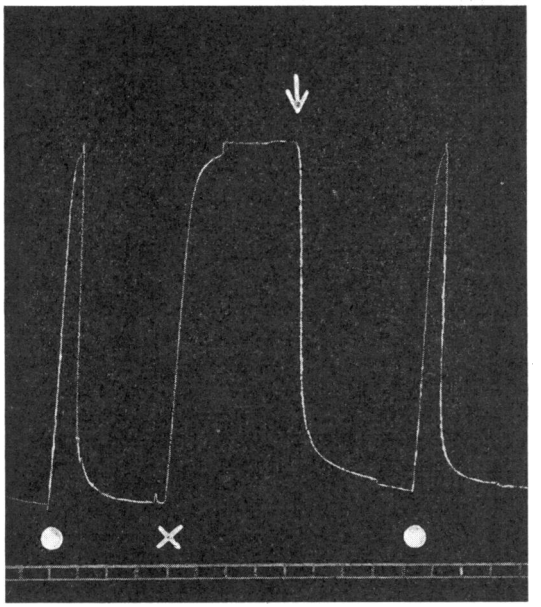


FIG. 3.—Cat, chloralose. Contractions of nictitating membrane. At dots, postganglionic stimulation of cervical sympathetic for 15 sec.; at cross, sustained preganglionic stimulation. At arrow, intravenous injection of 0.5 mg. M & B 1950. (Time=30 sec.)

lion synapse, since the block was confined to preganglionic, not extending to postganglionic, excitation of the cervical sympathetic (Fig. 3); furthermore, the nictitating membrane reacted normally to adrenaline during a complete paralysis.

Though it has not been proven that acetylcholine is normally released during paralysis of the superior cervical ganglion or that the ganglion is not depolarized, the preceding evidence taken collectively strongly suggests a competitive type of action like hexamethonium. And in all experiments no actions have been encountered which could be explained in any other way. There was no evidence of any anticholinesterase activity, determined manometrically, at a concentration as great as 3×10^{-3} M.

Toxicity

(i) *Acute Toxicity*

Mice.—The intravenous, subcutaneous, and oral LD50 figures were 22 ± 2.3, 83 ± 8.5, and 575 ± 73 mg./kg. respectively, the ratios being 1:4:26. These figures show this compound to be about two and a half times as toxic as hexamethonium bromide. Death resulted from respiratory failure.

Rabbits.—Each dose was tested by injection into six adult rabbits and the injections were made into the marginal ear vein. Doses up to 3 mg./kg. caused flushing of the ears, but no other obvious symptoms. Much larger doses (30 mg./kg.) caused depression of the respiratory rate and head-drop, typical of neuromuscular paralysis; a dose of 40 mg./kg. was fatal.

Cats.—Injections were made into the saphena vein, three cats being used for each dose. Doses of 0.5 to 2.0 mg./kg. of M & B 1950 caused immediate dilatation of the pupil, the heart rate was slowed, and in some animals there was ataxia. Recovery occurred within thirty minutes. A dose of 10 mg./kg. was fatal to two of three cats, owing to respiratory failure; the heart continued to beat strongly for several minutes after respiration had ceased.

(ii) *Chronic Toxicity*

Rats.—Daily subcutaneous injections to young albino rats (Wistar strain) caused no retardation in the growth rate over a period of two weeks. Six rats, 40 to 50 g. body weight, were in each group, and the treated animals received a daily dose of 16 mg./kg., which is far in excess of the pharmacologically effective dose. Litter-mate controls showed a mean increase in weight of 16 ± 1.6 g. compared with 15 ± 2.6 g. for the treated group.

Rabbits.—During daily intravenous injections of 3 mg./kg. to four rabbits for a period of one month no ill effects were observed in the health of the animals, as shown by urine analysis (absence of glucose, protein, and blood) and blood analysis (normal values for glucose and urea). Flushing of the ears was observed, but no local damage was caused to the veins. Dr. R. Williamson, of the Department of Pathology, Cambridge, has kindly allowed us to quote from his report on the examination of tissues from these animals after they were killed. "In each animal kidney, liver, heart muscle, spleen, bone marrow, and lungs were examined. In some animals the spinal cord, pancreas, portion of intestine, suprarenal and lymph nodes were examined. In all animals the condition of blood vessels, nerves, or other common structures was noted. In one rabbit in the kidney section there was a small area of inflammation due to an ascending pyelitis. In the heart there was evidence of slight scarring, probably due to intracardiac puncture (which had been carried out to obtain samples of blood). In the trachea there was some infiltration of the mucous membrane with polymorphs; a tracheitis. No other pathological changes were found in any of the sections, and there is nothing to suggest that the compound was responsible for these changes."

Guinea-pigs.—Each animal in a group of six guinea-pigs received a daily subcutaneous injection of 8 mg./kg. for one month. During this period, and for another three weeks after stopping the injections, a complete blood-picture examination was made twice weekly of each animal. No abnormalities were observed except a slight increase in large lymphocytes which fell to normal when treatment was discontinued (we are indebted to Mr. W. A. Freeman for the results of this experiment).

Cardiovascular System

Blood Pressure.—In the dog under chloralose the fall of arterial blood pressure after an intravenous injection of 0.05 to 0.25 mg./kg. (see Fig. 2) depended not only on the size of the dose but on the initial level of the blood pressure. The fall appeared slowly and reached a maximum within a few minutes. Its duration depended on the dose and often there was not complete recovery to the initial level. This effect, resulting most probably from the release of sympathetic tone in the vessels, is characteristic of ganglion-blocking drugs, and once the tone in the vessels has been released no further fall can be produced. Though the first few doses produced a fall, subsequent injections had little effect even after several hours. There was hardly any effect on the respiration in the cat (chloralose) with an intravenous dose of 5 mg./kg., which produced a fall in blood pressure of 65 mm.; 10 mg./kg. depressed the respiration but did not completely inhibit it.

Heart.—No direct action was observed on the perfused heart of the rabbit or cat (Langendorff's preparation). In the dog the effect was variable, but a decrease in coronary flow was never observed. Two experiments typify our findings; in one the coronary outflow was increased from 74 to 90 ml./min. with 20 μg. of adrenaline, and from 84 to 120 ml./min. with 0.5 mg./kg. intravenously of M & B 1950; in the other, though adrenaline in the same dose increased the flow from 76 to 100 ml./min., 0.5 or 1.0 mg./kg. of the compound left the flow unaltered.

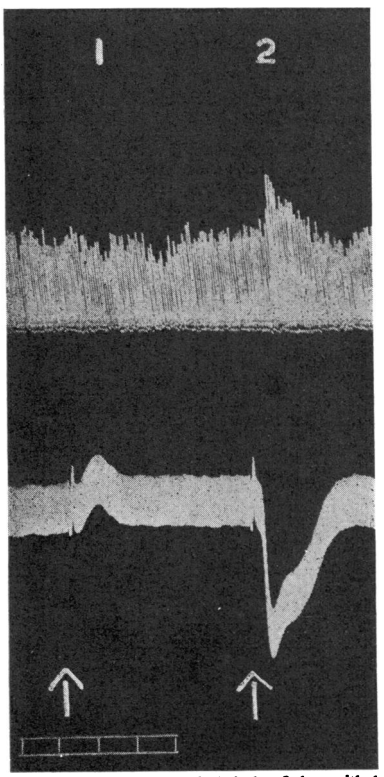


FIG. 4.—Perfusion of vessels of hind-limb of dog with heparinized blood. Upper record, venous outflow; lower record, arterial pressure. Intra-arterial injections of (1) 3 mg. M & B 1950; (2) 3 mg. hexamethonium bromide. (Time=30 sec.)

Vessels.—The vessels of the hind-limb of the dog (severed from the trunk) were perfused by means of a Dale-Schuster pump with heparinized blood which was oxygenated through the lungs. In several experiments in which the compound was injected into the arterial supply in a dose of 3 mg. no effect on the vessels was demonstrable, though hexamethonium in the same dose caused a perceptible vasodilatation (Fig. 4).

Gastric Secretion.—In the dog under chloralose in which a secretion of acid gastric juice is promoted by vagal excitation, as previously described, the intravenous injection of M & B 1950 was very effective in reducing the volume, acidity and, to a lesser extent, the peptic activity of the juice. Seven experiments were performed and the results are summarized in Fig. 5. The dose range was from 0.05 to 0.40 mg./kg.; the highest dose caused achlorhydria for at least three hours, the maximum period of observation. On intravenous injection of the compound, when a steady state of acid secretion was established, the inhibitory effect reached a maximum within about 30 minutes, and it was noticeable that inhibition of gastric secretion outlasted the vagal blocking action on the heart. When the compound was given via the small intestine (introduced by catheter through the abdominal incision), in a dose of 1 to 5 mg./kg., the effect was slower in starting, but achlorhydria was obtained, indicating that it is absorbed from the intestine.

Other Actions.—The knee-jerk reflex in the cat (chloralose) was unmodified with doses as large as 10 mg./kg. intravenously. There was no evidence of the release of histamine, since after atropine and nicotine there was no effect on the blood pressure in a dose of 5 mg./kg. Injection into the cisterna magna in the conscious rabbit produced slight depression but no convulsive movements. The compound had no anticholinesterase activity even in a concentration of 1,000 μg./ml.

Urinary Excretion in Rabbits.—Estimations were made by the reineckate method of Zaimis (1950), and groups of four rabbits were used to

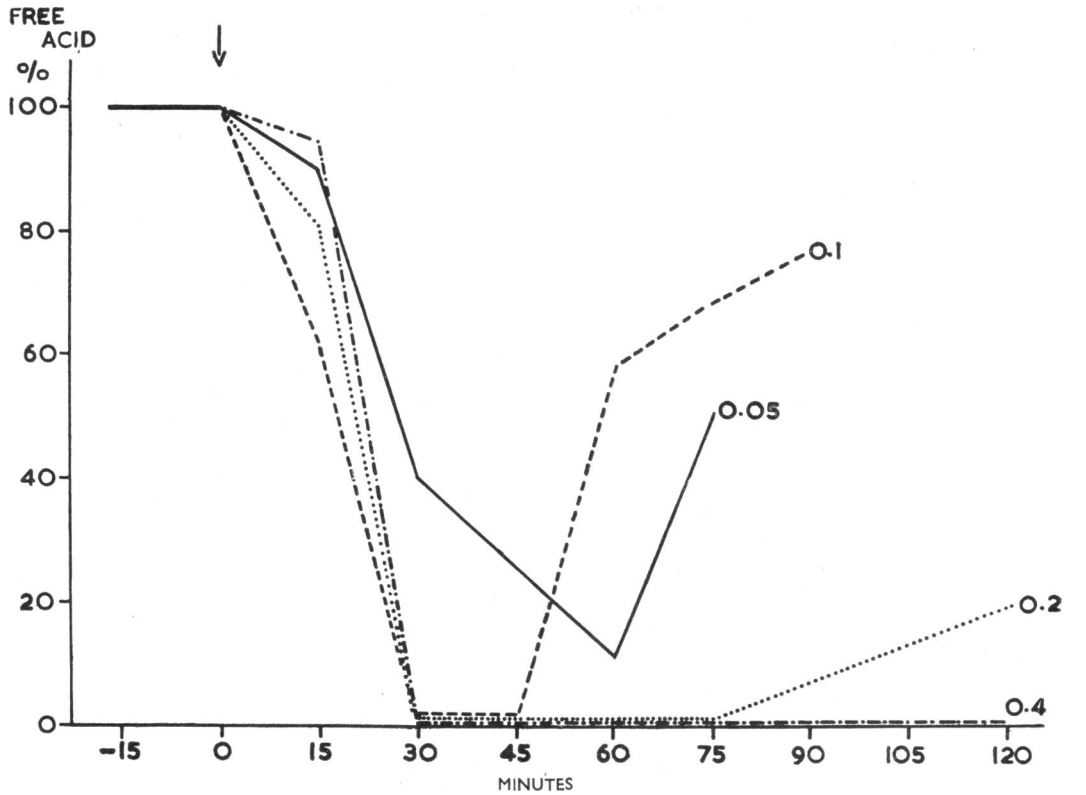


FIG. 5.—The effect of M & B 1950 on gastric secretion in dogs, induced by vagal stimulation (Babkin's method as used by Wien and Mason, 1951). Curves showing the effects of varying doses, 0.05 to 0.4 mg./kg. intravenously, on the secretion of free acid (ml. 0.1N-HCl), expressed as a percentage of the pre-injection level (ordinate) against time in minutes (abscissa). The drug was not injected until a steady level had been attained for at least 1 hour, although only a 15-minute control period is shown.

test each dose. After a single intravenous injection of 15 mg./kg., from 68% to 89% of the dose was excreted within 24 hours. From 54% to 86% was found in the urine within 48 hours after 20 mg./kg. subcutaneously; from 55% to 76% after 20 mg./kg. intramuscularly; but only 9% to 21% was recovered in the urine within five days after 300 mg./kg. given by stomach tube.

Neuromuscular Paralysis (Para Series of Compounds)

Influence of Length of Alkane Chain

(i) *Where* $R_3=Me_3$.—Neuromuscular-blocking properties first appeared in the butane member (one-third as active as *d*-tubocurarine), and increased to the hexane member which was approximately as active, superficially, as *d*-tubocurarine in the sciatic-gastrocnemius preparation of the cat (Table I). Though injections were spaced sufficiently far apart, the effect of one compound might have influenced the other and further study, using other species and preparations, is required to obtain a more precise evaluation.

(ii) *Where* $R_3=Et_3$.—Activity first appeared in the ethane member (6% of *d*-tubocurarine), and increased to the hexane member, which was also as active as *d*-tubocurarine in the cat. Higher homologues have not as yet been examined to see whether the peak of activity occurs beyond the hexane members.

Results on the phrenic nerve-diaphragm preparation showed the same general trend of events in relative activities, though the absolute values were lower, which may be due to species or muscle differences, or to some other factor. The two hexane members were exceptional; they were equally active in the cat, but the bis-Et_3 compound was five times as active as the bis-Me_3 compound by the phrenic nerve-diaphragm method.

Type of Action.—The well-known distinction between depolarizing and competitive block at the neuromuscular junction can be readily tested, on

the frog rectus muscle, by intravenous injection in the chick, by the ability of neostigmine to reverse the paralysis, and by the response to a tetanus; these methods have been applied to the present compounds.

The compounds with $R_3=Me_3$, and with $R_3=Et_3$, had different modes of action. When $R_3=Me_3$, the pentane and hexane members produced contractions of the frog's rectus, which were inhibited by *d*-tubocurarine; and subthreshold concentrations potentiated the action of acetylcholine. In the chick these compounds produced

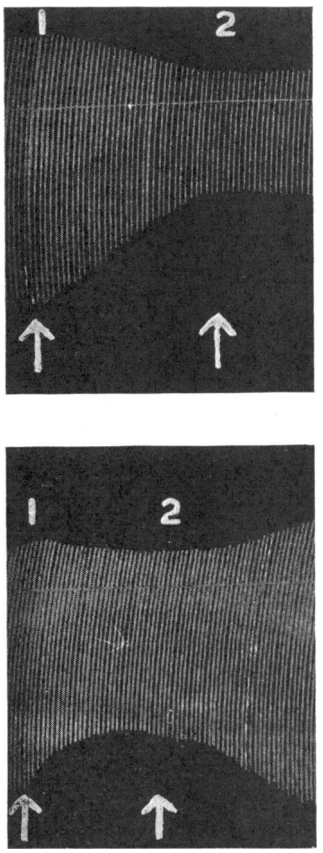


FIG. 6.—Phrenic nerve-diaphragm (rabbit). Contractions of diaphragm on stimulation of nerve (6 stimuli per min.). Upper record, (1) 1.5 mg. M & B 2357 and (2) 125 μg. neostigmine. Lower record, (1) 0.4 mg. M & B 2362 and (2) 150 μg. neostigmine.

a spastic paralysis in intravenous doses of 0.25 to 1.0 μg./g. compared with 1.0 to 5.0 μg./g. for decamethonium iodide. Neuromuscular block of the phrenic nerve-diaphragm preparation by the hexane member was not reversed by neostigmine (Fig. 6). A tetanus of cat's gastrocnemius muscle, partially paralysed by the hexane member, was well sustained (Fig. 7).

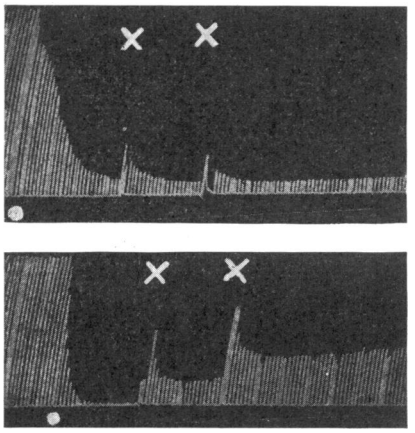


FIG. 7.—Cat, chloralose. Gastrocnemius twitch tensions on stimulation of sciatic nerve (12 stimuli per min., 0.5 msec. duration). Upper tracing, 0.5 mg. M & B 2357 intravenously at dot; at crosses, tetanus of 50 stimuli per sec. for 2 to 5 sec. Lower tracing, 0.5 mg. M & B 2362 intravenously at dot; at crosses, tetanus as before.

With the $R_3=Et_3$ compounds, the pentane and hexane members did not produce contracture of the frog rectus, but they did block the response to acetylcholine. Intravenous injections (0.5 to 1.5 μg./g.) in the chick produced a flaccid paralysis comparable with that of *d*-tubocurarine chloride (0.5 μg./g.). On the phrenic nerve-diaphragm preparation, neuromuscular block produced by the hexane member was reversed by neostigmine; in the cat (under chloralose) a tetanus of the gastrocnemius muscle, almost completely blocked by this compound, was not well sustained, and after the tetanus there was a partial reversal of the block.

The two hexane compounds consequently had contrasting actions: the compound in which $R_3=Me_3$ resembles decamethonium, and the compound in which $R_3=Et_3$ resembles *d*-tubocurarine. This was borne out by the observation that the bis-Me_3 compound was able to reverse the paralysis produced by the bis-Et_3 compound (Fig. 8), just as decamethonium can reverse a *d*-tubocurarine paralysis. The paralysis caused by the bis-Me_3 compound was also reversed by the ethane member, $R_3=Me_3$, just as a decamethonium paralysis is reversed by hexamethonium.

DISCUSSION

In the present aromatic series of bis-quaternary compounds there were several members of outstanding pharmacological interest. M & B 1950, phenyl ethane *p*-ω-bis(trimethylammonium iodide),

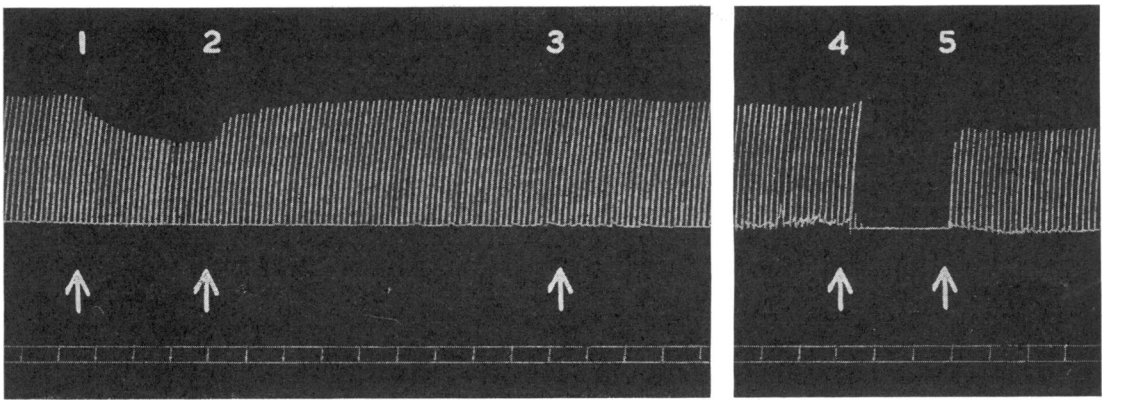


FIG. 8.—Cat, chloralose; same preparation as Fig. 7. Intravenous injections of (1) 0.75 mg. M & B 2362 which caused a partial block, reversed by (2) 0.5 mg. M & B 2357. A subsequent injection (3) of 1.0 mg. M & B 2362 was ineffective. Later, (4) 5 mg. of M & B 2362 caused complete paralysis which was immediately reversed by (5) 5 mg. of M & B 2357. (Time=30 sec.)

was three times as potent as, and slightly longer in its duration than, hexamethonium on the cat's superior cervical ganglion, with a similar type of action in specifically paralysing transmission at the ganglion synapse. It did not possess any greater selectivity on the ganglia studied. The compound M & B 2072 was slightly more active, but the difference was not sufficiently great to warrant further study.

Two higher members, phenyl hexane *p*-ω-bis-(trimethylammonium iodide), M & B 2357, and the bis-triethyl analogue, M & B 2362, possessed superficially about the same activity as *d*-tubocurarine in the cat under chloralose. But their types of action were quite different; the actions of the former compound resembled a block by depolarization, whereas those of the latter were like a competitive block. These two compounds have not been studied in the same detail as M & B 1950, but the compound M & B 2362 in particular offers promise as a useful neuromuscular-blocking drug.

By ascending the series and increasing the inter-quaternary distance it was found that there were two active compounds of similar neuromuscular-blocking potency, but of different types of action. In this way this aromatic series differed from the methonium series.

The sharp definition of the peak of ganglion-blocking activity (Fig. 9) can be considered of some significance. This might be due to the aromatic nucleus conferring greater rigidity in the molecule, thus reducing the number of possible configurations which the molecule can take up in which a fit with the receptor groups is not obtained. From measurements on molecular models the compound M & B 1950 has a chain length of 8.5 Å between the polar groups in the fully extended state, intermediate between that of penta-methonium and hexamethonium, indicating possibly a better fit on the receptors. But we would agree with the very apt comment of Paton and Zaimis (1952) that "the literature is full of shipwrecks in the quicksands of 'structure-action-relationship,' and it is obvious that our biophysical knowledge is inadequate to the pharmacological strains placed on it."

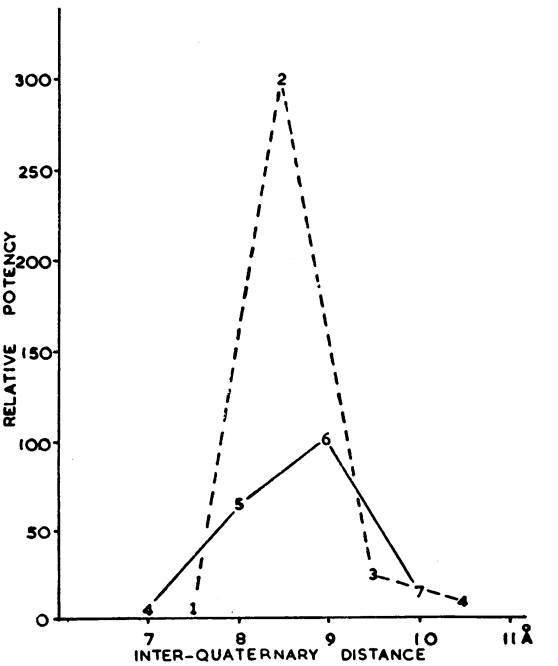


FIG. 9.—Graph relating potency (paralysis $_{\circ}$ of superior cervical ganglion) and interquaternary distance in Å units in two homologous series. Solid line, $(CH_3)_3N^+(CH_2)_nN^+(CH_3)_3$. Broken line, $(CH_3)_3N^+C_6H_4(CH_2)_nN^+(CH_3)_3$. Figures in the curves show the values for *n*.

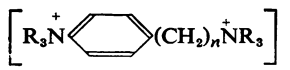
If ganglion-blocking activity depended simply on the distance separating the two polar groups, then the propane member of the *meta* series and the ethane compound of the *para* series, with equivalent interquaternary distances, might be expected to be equipotent. That this was not so demonstrates the fallacy of this supposition, even when two isomers are compared. The successive replacement of methyl by ethyl groups on both nitrogen atoms did generally produce throughout the series, by previous analogy (Wien *et al.*, 1952), a decrease in ganglion-blocking activity and an increase in neuromuscular-blocking properties.

The contrasting actions of the two hexane compounds, M & B 2357 and M & B 2362, have been referred to, and their pharmacological interest and potential value as neuromuscular-blocking substances invite more detailed investigation. It is intriguing that the transition from one type of action to another, in the same species (cat), is brought about by a relatively small change in chemical structure. It is also interesting that the injection of one compound should reverse the effect of the other (Fig. 8).

The relative activities on the superior cervical ganglion and on the peristaltic reflex of the intestine were compared, and one member, M & B 2175, where $n=2$ and $R_3=MeEt_2$, had a more selective effect on sympathetic ganglia. But, apart from the appearance of mixed actions in this compound, such a comparison was likely to be misleading, because of the species differences and the totally different types of preparation employed (whole animal and isolated tissue). A far better comparison would have been the simultaneous examination on different ganglia in the same animal, and experiments in this direction have been performed on the ciliary and pelvic ganglia and chorda tympani in the cat, the results of which will form the subject of another communication.

Summary

1. The series of phenyl alkane *p*-ω-bis(trimethylammonium) salts,



showed a sharp peak of activity for ganglionic paralysis where $R_3=Me_3$ at $n=2$. As far as the series was examined maximal neuromuscular-blocking activity was observed at $n=6$. This roughly corresponded to the two peaks in the methonium series (on the assumption that the phenyl group is equivalent to 3 to 4 methylene groups). These maxima occurred at chain lengths of approximately 8.5 Å and 12.5 Å in the fully extended state.

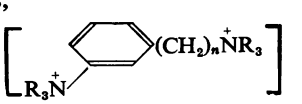
2. The ethane compound ($R_3=Me_3$) was three times as potent as hexamethonium (with a slightly longer duration of action). Two hexane compounds ($R_3=Me_3$ and Et_3 respectively) were approximately as active as *d*-tubocurarine in the cat (sciatic-gastrocnemius preparation).

3. The influence of chain length in this series was illustrated by the remarkably sharp peak of ganglion-blocking activity, since there was a 600-fold increase in passing from the methane to the ethane member.

4. In all the experiments performed the properties of the ethane compound were essentially similar to those of hexamethonium.

5. The complete substitution of methyl by ethyl groups at $n=6$ led to an alteration in the type of neuromuscular-block from one which resembled decamethonium to one like *d*-tubocurarine, without loss of activity. But the modes of action of these two compounds have not been investigated in detail. The neuromuscular paralysis in the cat caused by the hexane compound, where $R_3=Me_3$, was reversed by the ethane compound, where $R_3=Me_3$; the former compound also reversed the block due to the hexane compound, where $R_3=Et_3$.

6. Only four compounds were examined in the *meta* series,



The second member was only one half as active as its corresponding isomer in the *para* series.

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