Brit. J. Pharmacol. (1952), **7**, 392.

THE EFFECT OF CHAIN-LENGTH ON CURARIZING POTENCY IN THREE HOMOLOGOUS SERIES

BY

H. O. J. COLLIER

From the Research Division, Allen and Hanburys Ltd., Ware, Herts

(Received February 28, 1952)

Both Barlow and Ing (1948a and b) and Paton and Zaimis (1948, 1949) have demonstrated a striking relationship between neuromuscular blocking potency and chain-length in a series of polymethylene bis-trimethylammonium salts. Bovet, Bovet-Nitti, Guarino, Longo, and Marotta (1949) have shown that a comparable relationship exists between chain-length and potency in bis-choline esters of aliphatic dicarboxylic acids. Barlow and Ing prepared the methonium compounds as neuromuscular blocking agents by analogy with the structure of *d*-tubocurarine, but it is clear from the analyses by Zaimis (1951) and Burns and Paton (1950) that decamethonium iodide, the most active compound of the series, exerts its blocking effect by a different mechanism from that of curare. Succinylcholine, the most active of the bis-choline ester series, resembles decamethonium in its mode of action. It is therefore of interest to ask how far chain-length influences blocking potency in homologous series of polymethylene bisquaternary ammonium salts that exert true curarizing action.

The three series of compounds that provide the subject of the present paper are homologous with Compounds 14, 15, and 20, which were the most potent members of a group of muscle-relaxant drugs described by Collier and Taylor (1949) and by Taylor and Collier (1950, 1951). Compounds 14, 15, and 20, which were synthesized by Taylor (1951, 1952a), are derivatives of decamethylene bis-1: 2: 3: 4-tetrahydro-2-methyl*iso*quinolinium salts. Their structural formulae are illustrated in Fig. 1; and their pharmacology is described by Collier and Macauley (1952), who give the detailed evidence that these compounds resemble curare in their mode of action.

In the course of these investigations the nonamethylene member of the Compound 20 series proved to be a more active curarizing agent than the decamethylene in the mouse and in the rabbit. Since the decamethylene compound had already been found satisfactory as a curarizing agent in human volunteers (Bodman, 1952) and in clinical trials (Bodman, Morton, and Wylie, 1952), further observations were made on the pharmacology of the nonamethylene member. Experiments on the release of histamine in volunteers, which are reported below, indicated, however, that the nonamethylene compound was a more potent histamine-liberator than the decamethylene, and therefore there appeared to be no call for its clinical trial.

Materials and Methods

The compounds investigated were the hexa-, octa-, nona-, deca-, undeca-, and dodecamethylene members of the Compound 14 and Compound 20 series, and the nona-, deca-

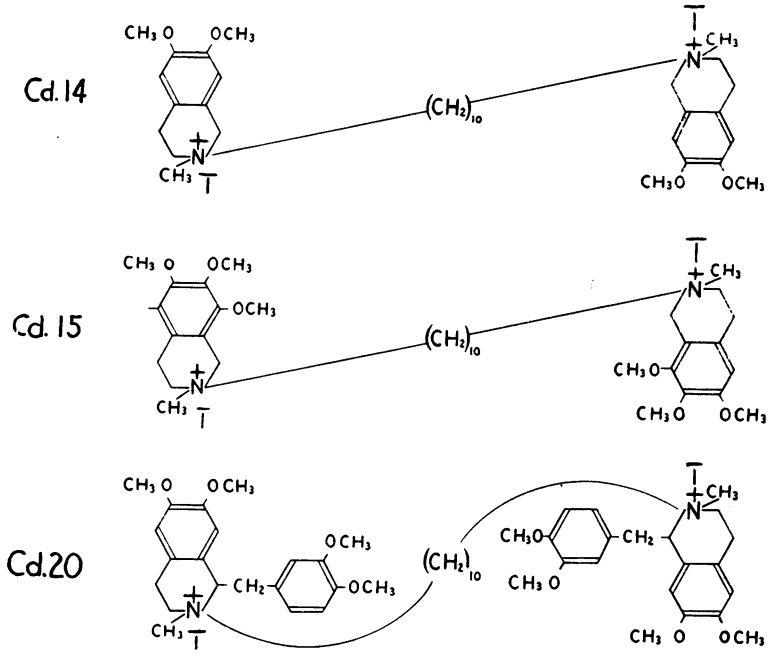

FIG. 1.—Cd. 14. Decamethylenebis [1: 2: 3: 4-tetrahydro-6: 7-dimethoxy-2-methyl*iso*quinolinium iodide]. Cd. 15. Decamethylenebis [1: 2: 3: 4-tetrahydro-6: 7: 8-trimethoxy-2-methyl*iso*-quinolinium iodide]. Cd. 20. Decamethylenebis [1: 2: 3: 4-tetrahydro-6: 7-dimethoxy-1-(3′: 4′-dimethoxybenzyl)-2-methyl*iso*quinolinium iodide].

undeca-, and dodecamethylene members of the Compound 15 series. These compounds were prepared by Taylor, who has described (1952a and b) the synthesis of all but the hexamethylene members. All compounds were crystallized to analytical purity, but possible diastereoisomers were not separated. With the exception of the methosulphates of the deca-, undeca-, and dodecamethylene members of series 20, the iodides of the compounds were used. Values obtained with the methosulphates have been expressed below as those of equivalent iodides.

The curarizing potencies of the compounds were determined in two species by intravenous administration to intact animals. Paralysis after treatment was assessed in the rabbit by the righting response (see Collier, Fieller, and Hall, 1949) and in the mouse with the rotating drum described by Collier, Hall, and Fieller (1949). The curarizing potency of each drug was expressed as the dose paralysing 50 per cent of the animals (ED50). The ED50 of each compound and its standard error were estimated in the first place by the graphical method of Miller and Tainter (1944). In those compounds which were critical in determining the position of the peak of curarizing activity in mice, these values were also computed. There was excellent agreement between the values obtained graphically and by computation.

The potency as histamine-liberators of the nona- and decamethylene members of the Compound 20 series was compared by measuring weal areas in three normal human subjects, who received intradermal injections of the compounds, as described by Collier and Macauley (1952).

RESULTS

Curarizing potencies

The results of estimates of the curarizing potencies of all compounds in the rabbit and mouse are expressed in Table I. The logarithms of the ED50s of each compound are plotted against the number of carbon atoms in the polymethylene chain

TABLE I

POTENCIES OF POLYMETHYLENE BIS*iso*QUINOLINIUM DERIVATIVES IN PARALYSING THE INTACT MOUSE AND RABBIT

Series	No. of C-atoms in chain	Mouse		Rabbit	
		No. of animals	ED50 ± std. error in μg. per kg.	No. of animals	ED50 ± std. error in μg. per kg.
Cd. 14	6	30	3,177.0 ± 287.3	—	—
	8	30	616.6 ± 39.6	11	98.4 ± 1.79
	9	60	382.2 ± 19.1	20	65.6 ± 3.50
	10	60	283.6 ± 19.3	20	41.9 ± 2.15
	11	90	281.7 ± 16.0	16	48.8 ± 4.40
	12	30	371.1 ± 24.1	10	67.6 ± 4.37
Cd. 15	9	60	398.2 ± 21.5	12	50.1 ± 2.29
	10	160	288.4 ± 11.3	123	18.8 ± 1.01
	11	60	421.4 ± 28.2	15	37.4 ± 3.65
	12	30	496.0 ± 20.43	13	77.3 ± 2.97
Cd. 20	6	30	14,620.0 ± 1,959.0	—	—
	8	60	266.5 ± 18.4	10	47.2 ± 3.68
	9	70	156.5 ± 13.0	26	23.7 ± 1.04
	10	540	284.2 ± 8.7	155	29.4 ± 1.61
	11	30	419.2 ± 41.6	20	58.2 ± 7.27
	12	30	786.8 ± 52.6	13	95.0 ± 2.63

in the mouse in Fig. 2 and in the rabbit in Fig. 3. In these figures the results obtained in the same animal species by Paton and Zaimis (1949) with compounds of the methonium series are included for comparison. It will be seen from Fig. 2 that in the mouse the peak in the Compound 14 series occurs at the decamethylene and undecamethylene members, in the Compound 15 series at the decamethylene, and in the Compound 20 series at the nonamethylene member. It will be seen from Fig. 3 that the same trends are shown in the rabbit, though not quite so sharply.

Histamine release in man

The weal areas produced by intradermal injections of the nona- and decamethylene members of the Compound 20 series in three different subjects were compared in a number of experiments, one of which is illustrated in Fig. 4. These experiments showed that the nonamethylene compound was significantly more active as a histamine-liberator in man than the decamethylene.

DISCUSSION

Barlow and Ing (1948) and Paton and Zaimis (1949) have shown that in the methonium series the peak for neuromuscular blocking activity occurs at the decamethylene member. These authors have offered an explanation of this fact in

terms of a " fit " between the drug molecule and drup-receptor groups at its effector site. This explanation supposes that potency is greatest when the distance between the quaternary ammonium groups of the drug molecule corresponds most closely with the commonest distance between recurrent receptor groups.

Bovet *et al.* (1951) and the present author (1951) have expressed the view that neuromuscular blocking drugs of both the decamethonium and curare types become attached to the same receptor groups at the motor end-plate; and that the difference between their modes of action arises after this attachment. This view may be based on the assumption that the receptor groups involved are those of acetylcholine, since, in certain animal species, blockers of the decamethonium type are potentiated, and of the curare type antagonized, by anticholinesterases.

Hitherto the existence of a sharp peak for neuromuscular blocking activity has been demonstrated in homologous series of methonium and like-acting compounds. The fact that in the present series of curarizing compounds the peaks also occur at approximately the same chain-lengths as in the methonium series supports the view that the two types of neuromuscular blockers become attached to the same receptor groups. The observation of Barlow and Ing,

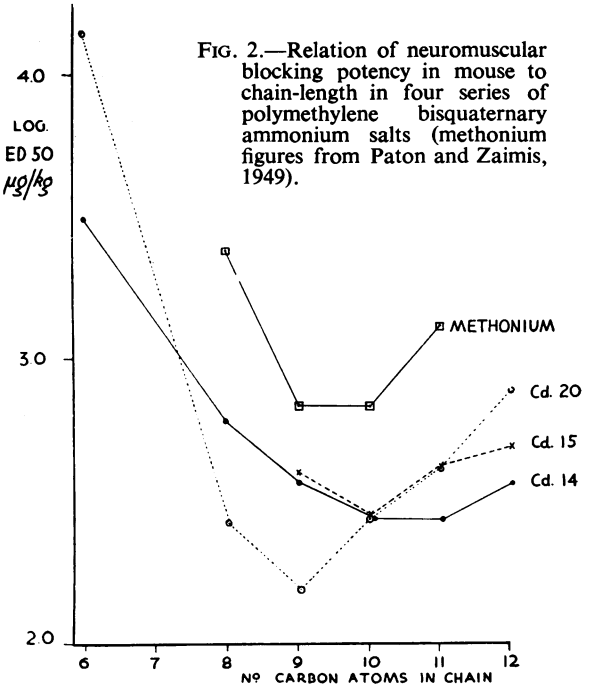

FIG. 2.—Relation of neuromuscular blocking potency in mouse to chain-length in four series of polymethylene bisquaternary ammonium salts (methonium figures from Paton and Zaimis, 1949).

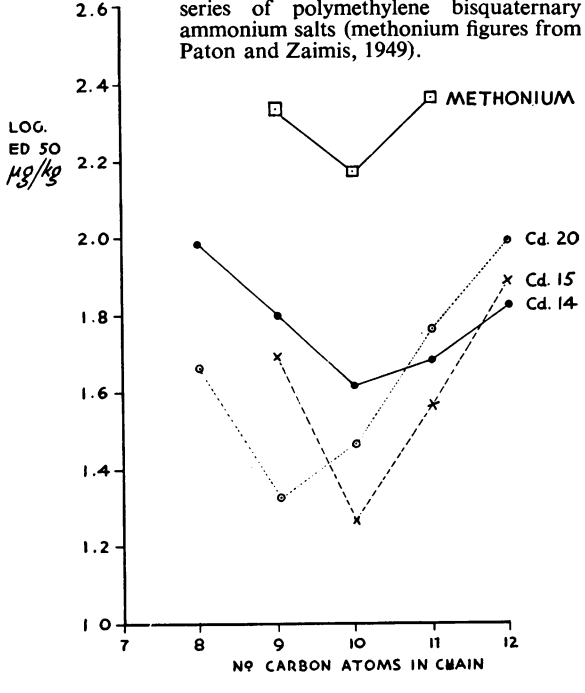

FIG. 3.—Relation of neuromuscular blocking potency in rabbit to chain-length in four series of polymethylene bisquaternary ammonium salts (methonium figures from Paton and Zaimis, 1949).

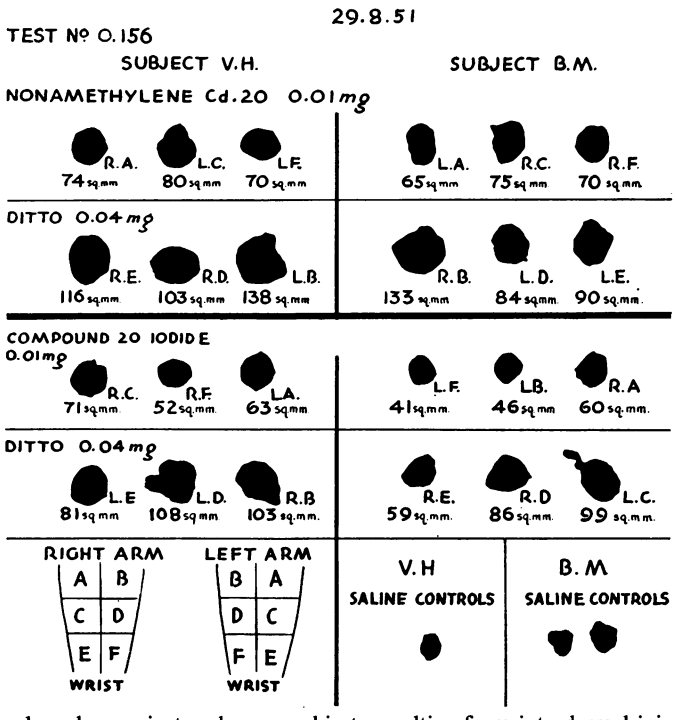

FIG. 4.—Maximal weal areas in two human subjects resulting from intradermal injections of Compound 20 and its nonamethylene homologue.

however, that tridecamethylene bis-triethylammonium bromide is more active than the corresponding decamethylene compound is more difficult to reconcile with the present view.

Although the peak activity for neuromuscular block occurs at or near the decamethylene member, the small but definite differences in the situation of the peak in each series still remain to be explained. Within the framework of the receptor theory, these differences might be accounted for in a number of ways, such as the following.

(1) It is possible that different proportions of diastereoisomers having different curarizing potencies might occur in different members of the same series. An explanation of this sort would, however, have to depend on diastereoisomers based on asymmetric quaternary nitrogen atoms, since the peak falls at a slightly different place in the 14 and 15 series, although neither type contains asymmetric carbon atoms.

(2) A second explanation suggested by Dr. E. P. Taylor is based on the facts that the polymethylene chain is not rigid, and that the side-groups in positions 1 and 8 of the *iso*quinoline nucleus, which are most likely to exert steric effects on the mean chain-length, differ in the three types of compound. In Compound 14, positions 1 and 8 are unsubstituted, in Compond 15 there is a methoxy group in position 8,

while in Compound 20 there is a dimethoxybenzyl group in position 1. These small differences in configuration of the end-groups might cause the mean distance apart of the nitrogen atoms to differ slightly between corresponding members of the three series.

(3) We know that the side-groups on the heterocyclic rings modify potency very strongly. They may be presumed therefore to play a part in attachment to the receptors, and the best " fit " may depend not only on the length of the linking chain, but on the nature of the potentiating side-groups. This explanation seems more applicable if we consider receptor-groups as irregular areas, rather than as points.

SUMMARY

1. In three series of polymethylene bis-*iso*quinolinium salts the peak for curarizing activity occurs between the nonamethylene and undecamethylene members. In the dimethoxy (Compound 14) series, the peak occurs at the deca- and undecamethylene members, in the trimethoxy (Compound 15) series at the decamethylene, and in the dimethoxy-dimethoxybenzyl (Compound 20) series at the nonamethylene member.

2. The nonamethylene member of the 20 series is a more potent histamine-liberator in man than the decamethylene member.

3. The reasons for the slight differences in the position of the peak curarizing activity in the three series are discussed.

I would like to express my thanks to Miss B. Macauley for her co-operation in the experiments on histamine release and to Miss M. P. Hatton and Miss V. Hornshaw for technical assistance. I would like to acknowledge the helpful discussions I have had with Dr. W. D. M. Paton and Dr. E. P. Taylor, and to thank the directors of Allen and Hanburys Ltd. for permission to publish this work.

REFERENCES

Barlow, R. B., and Ing, H. R. (1948a). *Nature, Lond.*, **161**, 718.
Barlow, R. B., and Ing, H. R. (1948b). *Brit. J. Pharmacol.*, **3**, 298.
Bodman, R. I. (1952). *Brit. J. Pharmacol.*, 7, 409.
Bodman, R. I., Morton, H. J. V., and Wylie, W. D. (1952). *Lancet* (in press).
Bovet, D., Bovet-Nitti, F., Guarino, S., Longo, V. G., and Fusco, R. (1951). *Arch. int. Pharmacodyn.*, **88**, 1.
Bovet, D., Bovet-Nitti, F., Guarino, S., Longo, V. G., and Marotta, M. (1949). *Rend. Ist. Sup. di Sanità*, **12**, 106.
Burns, B. D., and Paton, W. D. M. (1951). *J. Physiol.*, **115**, 41.
Collier, H. O. J. (1951). *Proc. roy. Soc. Med.*, **44**, 627.
Collier, H. O. J., and Macauley, B. (1952). *Brit. J. Pharmacol.*, 7, 398.
Collier, H. O. J., and Taylor, E. P. (1949). *Nature, Lond.*, **164**, 491.
Collier, H. O. J., Fieller, E. C., and Hall, R. A. (1949). *Analyst*, **74**, 583.
Collier, H. O. J., Hall, R. A., and Fieller, E. C. (1949). *Analyst*, **74**, 592.
Miller, L. C., and Tainter, M. L. (1944). *Proc. Soc. exp. Biol. N.Y.*, **57**, 261.
Paton, W. D. M., and Zaimis, E. J. (1948). *Nature, Lond.*, **161**, 718.
Paton, W. D. M., and Zaimis, E. J. (1949). *Brit. J. Pharmacol.*, **4**, 381.
Taylor, E. P. (1951). *J. chem. Soc.*, 1150.
Taylor, E. P. (1952a). *J. chem. Soc.*, 142.
Taylor, E. P. (1952b). *J. chem. Soc.*, 1309.
Taylor, E. P., and Collier, H. O. J. (1950). *Nature, Lond.*, **165**, 602.
Taylor, E. P., and Collier, H. O. J. (1951). *Nature, Lond.*, **167**, 692.
Zaimis, E. (1951). *J. Physiol.*, **112**, 176.