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THE ANTICHOLINESTERASE ACTIVITY OF POLYMETHYLENE BIS-QUINOLINIUM SALTS

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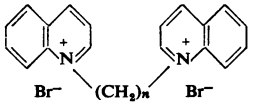
It is known that decamethylene bis-quinolinium (Barlow and Ing, 1948) is a moderately powerful anticholinesterase: Blaschko and Holton (1949), using a preparation of dog caudate nucleus and acetylcholine (ACh) as substrate, recorded a *p*I 50 of 7.0. The hexa, hepta, octa, and nonamethylene members of the series have now been prepared and tested on the enzyme.

METHODS

The substances were tested for their ability to inhibit the hydrolysis of acetylcholine (10^{-3}M) by the cholinesterase of dog caudate nucleus (10 mg. tissue/flask) suspended in Krebs bicarbonate Ringer (*p*H 7.2). The gas phase was 95% N_2 and 5% CO_2; the temperature was 37°. The volume of CO_2 produced during the period from 3 to 9 min. after the start of the experiment was recorded. The amounts produced in flasks containing enzyme, substrate, and inhibitor were compared with those containing enzyme and substrate only. The percentage inhibition of the production of CO_2 was plotted against the logarithm of the concentration of inhibitor and the *p*I 50 calculated from the graph. Results (Table I) are the mean of two experiments.

TABLE I

ANTICHOLINESTERASE ACTIVITY OF POLYMETHYLENE BIS-QUINOLINIUM BROMIDES



On preparation from dog's caudate nucleus:

n ..	6	7	8	9	10
*p*I 50 ..	5·3	6·2	6·5	6·7	7·2

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RESULTS

The members of the bis-quinolinium series examined all proved to be inhibitors of the cholinesterase of dog caudate nucleus. There is a steady rise in the *p*I 50 values up the series, without any maximum or even any sudden change from one compound to the next in the series. This absence of a maximum may be considered as support for the idea, previously discussed (Barlow, 1955), that only those bis-onium compounds which are able to become attached to the esteratic sites of the enzyme will show a maximum—or large rise—in affinity at the octamethylene member of the series.

CHEMICAL SECTION

Analyses are by Mr. J. M. L. Cameron and Miss M. W. Christie; m.p.s are uncorrected.

The compounds were prepared by heating the polymethylene dibromides, dissolved in ethanol, with freshly distilled quinoline in an atmosphere of nitrogen in a sealed tube at 100° for 6 to 12 hours. These precautions were necessary to reduce the formation of bright red products. Some of the compounds crystallized with water of crystallization which was extremely difficult to remove.

Hexamethylene bis-quinolinium bromide, recrystallized from ethanol, had m.p. 241–2° (dec.); Found: C, 53.6; H, 5.60; N, 5.36; Br^-, 29.8; $C_{24}H_{26}N_2Br_2$, $2H_2O$ requires: C, 53.6; H, 5.63; N, 5.21; Br^-, 29.8%.

Heptamethylene bis-quinolinium bromide, recrystallized from a mixture of ethanol and ether, had m.p. 150–1° (dec.); Found: C, 56.0; H, 5.62; Br^-, 30.3; $C_{25}H_{28}N_2Br_2$, $1H_2O$ requires: C, 56.1; H, 5.67; Br^-, 30.0%.

Octamethylene bis-quinolinium bromide, recrystallized from a mixture of ethanol and ether, had m.p. 231–2° (dec.); Found: C, 57.1; H, 5.70; N, 5.17;

Br^-, 29.0; $C_{26}H_{30}N_2Br_2$, $1H_2O$ requires: C, 56.9; H, 5.90; N, 5.11; Br^-, 29.2%.

Nonamethylene bis-quinolinium bromide, recrystallized from a mixture of ethanol, methyl ethyl ketone and ether, had m.p. 186° (dec.); Found: C, 57.6; H, 6.00; Br^-, 28.6; $C_{27}H_{32}N_2Br_2$, $1H_2O$ requires: C, 57.7; H, 6.11; Br^-, 28.5%.

SUMMARY

The ability of polymethylene bis-quinolinium bromides to inhibit the hydrolysis of acetylcholine by the cholinesterase of dog caudate nucleus increases as the length of the polymethylene chain is increased from 6 to 10 methylene groups.

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