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THE GANGLION-BLOCKING PROPERTIES OF HEXAMETHYLENE BISDIALKYLSULPHONIUM SALTS

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The pharmacological properties of tertiary sulphonium salts appear to be similar to those of quaternary ammonium salts. The trimethylsulphonium ion, $Me_3\overset{+}{S}$, resembles the tetramethylammonioum ion, $Me_4\overset{+}{N}$, in its ability to paralyse the frog sartorius preparation (Ing and Wright, 1933): decamethylene bisdimethylsulphonium $Me_2\overset{+}{S}-(CH_2)_{10}-\overset{+}{S}Me_2$, resembles decamethonium, $Me_3\overset{+}{N}-(CH_2)_{10}-\overset{+}{N}Me_3$, in its neuromuscular blocking properties (Walker, 1950): acetoxyethyldimethylsulphonium, $CH_3COOCH_2CH_2\overset{+}{S}Me_2$, resembles acetylcholine, $CH_3COOCH_2CH_2\overset{+}{N}Me_3$, in its effects on cat's blood pressure, rabbit's intestine, frog's heart and frog's rectus (Ing, Kordik, and Tudor Williams, 1952). The resemblance, however, is only qualitative; decamethylene bisdimethylsulphonium has only about 6% of the neuromuscular blocking activity of decamethonium by the rabbit head-drop test: acetoxyethyldimethylsulphonium has only between 2% and 6% of the activity of acetylcholine on the preparations listed above.

Ing, Kordik, and Tudor Williams suggested that there might be some connexion between the activity of onium analogues of acetylcholine and the size of their cationic head—a molecule with a large head, such as sulphonium or arsonium, might be less able to fit the receptor group normally holding the quaternary ammonium group in acetylcholine.

Another possibility is that the low activity of the tertiary sulphonium salts may be because they have only two methyl groups attached to the onium atom: the other compounds examined have three methyl groups attached to the onium atom. We noted that, in the results obtained by Ing *et al.*, the phosphonium analogue of acetylcholine ($CH_3COOCH_2CH_2\overset{+}{P}Me_3$; C–P bond, 1.87Å) was appreciably more active than the sulphonium analogue ($CH_3COOCH_2CH_2\overset{+}{S}Me_2$; C–S bond, 1.82Å; the C–S–C bond angle in sulphonium salts does not seem to be known.) Further, the activity of the sulphonium analogue of acetylcholine was about the same as that of acetoxyethyldimethylamine,

$$CH_3COOCH_2CH_2\overset{+}{N}Me_2H.$$

It seemed to us, therefore, that tertiary sulphonium salts should be compared with salts of tertiary amines (provided these are in the ionized form in the conditions of the tests) rather than with quaternary salts.

To test this idea, we have compared the ganglion-blocking properties of hexamethonium, hexamethylene bisdimethylsulphonium, and of salts of hexamethylene bisdimethylamine. We have also examined the effects of replacing methyl groups in these compounds by ethyl groups. The variation of activity with the number of groups thus substituted in the hexamethonium molecule is already known (Wien and Mason, 1951). We were interested to see if there was a similar variation in activity in the analogous series of bistertiary amine dihydrobromides:

$Me_2\overset{+}{H}N.(CH_2)_6.\overset{+}{N}HMe_2$, $2Br^-$, hexamethylene bisdimethylamine dihydrobromide,

$MeEt\overset{+}{H}N.(CH_2)_6.\overset{+}{N}HEtMe$, $2Br^-$, hexamethylene bisethylmethylamine dihydrobromide, and

$Et_2\overset{+}{H}N.(CH_2)_6\overset{+}{N}HEt_2$, $2Br^-$, hexamethylene bisdiethylamine dihydrobromide,

and if the variation in the analogous series of sulphonium salts,

$Me_2\overset{+}{S}(CH_2)_6\overset{+}{S}Me_2$, $2I^-$, hexamethylene bisdimethylsulphonium diiodide,

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$MeEt\overset{+}{S}.(CH_2)_6\overset{+}{S}EtMe$, $2I^-$, hexamethylene bisethylmethylsulphonium diiodide, and

$Et_2\overset{+}{S}.(CH_2)_6\overset{+}{S}Et_2$, $2I^-$, hexamethylene bisdiethylsulphonium diiodide,

resembled the variation in the hexamethonium series or that in the series of bistertiary amine dihydrobromides.

METHODS

The ganglion-blocking activity of the compounds relative to hexamethonium was determined in cats anaesthetized with pentobarbitone sodium (30 mg./kg.). The sympathetic trunk in one side of the neck, carefully dissected free from the vagus nerve and other tissues, was tied and cut. The peripheral end was laid across a pair of electrodes connected to the output of a square wave stimulator. The nictitating membrane was attached to a lever (18:1 magnification) by a thread running over a light pulley. Records of the movements of the lever and of the blood pressure (from a mercury manometer attached to a femoral artery) were made simultaneously on a smoked paper. All drugs were injected intravenously through a cannula in a femoral vein and washed into the circulation with 2–3 ml. of saline.

The preganglionic sympathetic trunk was stimulated for 10 sec. by the application of a series of maximal shocks at a rate of 20 shocks/sec. During this stimulation the nictitating membrane contracted at a fast rate for the first few seconds and then more slowly. At the end of ten seconds the rate of contraction was negligible. When the stimulation ceased, the membrane slowly relaxed and returned to its original position within 40–70 sec. The preparation was then ready for further stimulation: usually, therefore, the nerve was stimulated for 10 seconds every minute.

When a series of contractions of similar height had been obtained a dose of hexamethonium was given intravenously to test the sensitivity of the preparation. It was usually found that 200 μg. hexamethonium (as ion) reduced the contraction of the nictitating membrane by about 20–30%. Thereafter, a dose of the test drug was given between doses of hexamethonium which produced smaller and larger effects. Three or four different doses of hexamethonium were used, so that at the end of the experiment a graph could be obtained of the logarithm of the dose plotted against the effect. From this graph it was possible to calculate the dose of hexamethonium which would produce an effect equivalent to that produced by the dose of test drug, and hence the number of molecules of the test drug required to produce the same effect as one molecule of hexamethonium. The relative activities of the test drug and of hexamethonium are thus expressed as an equipotent molar ratio. Graphs of the logarithm of the dose plotted against the effect were also obtained for the most potent drugs in each series, and these were found to be parallel to the graph for hexamethonium.

RESULTS

These are summarized in Table I. The figures indicate the number of molecules of a compound (± the standard error) required to produce the same effect as one molecule of hexamethonium. A high number indicates a low activity.

TABLE I

BLOCKING EFFECTS OF COMPOUNDS ON THE SUPERIOR CERVICAL GANGLION OF THE CAT

Activities are expressed as the number of molecules of the compound (± the standard error) required to produce the same effect as one molecule of hexamethonium—that is, as equipotent molar ratios. The larger the ratio, the lower the activity.

Compound	No. of Expts.	Mean Equipotent Molar Ratio ± Standard Error
Hexamethylene bisdimethylsulphonium iodide	4	20·2±1·8
,, bisethylmethylsulphonium iodide	5	3·5±0·2
,, bisdiethylsulphonium iodide	6	1·9±0·2
,, bisdimethylamine dihydrobromide	16	12·0±1·4
Hexamethylene bisethylmethylamine dihydrobromide	13	8·2±0·6
Hexamethylene bisdiethylamine dihydrobromide	13	7·1±0·5
Hexamethonium		1·0

In doses large enough to abolish completely the response of the nictitating membrane to preganglionic stimulation, none of the compounds reduced the contractions produced either by adrenaline or by postganglionic stimulation. Nor did any of the compounds stimulate the ganglion, when given either in small doses or in doses large enough to cause complete block.

Freshly made solutions in distilled water of the salts of the tertiary amines were slightly acid, but only a very small amount of alkali was needed to bring the solutions to *p*H 7.6. This amount corresponded to less than 5 milliequivalents of the bisdiethyl compound and to less than 25 milliequivalents of the other two compounds. In solution at *p*H 7.6, then, not more than 0.5% hydrolysis of the dihydrobromide of the bisdiethyl compound had occurred, and not more than 2.5% hydrolysis of the other compounds. It would seem reasonable to assume, therefore, that it is the ionized forms of these compounds which are active.

The duration of action of most of the substances was less than that of hexamethonium. The bisdimethyl compounds in both series had the briefest action; after the intravenous injection the effects lasted about half as long as those of an equipotent dose of hexamethonium. The bismethylethyl and

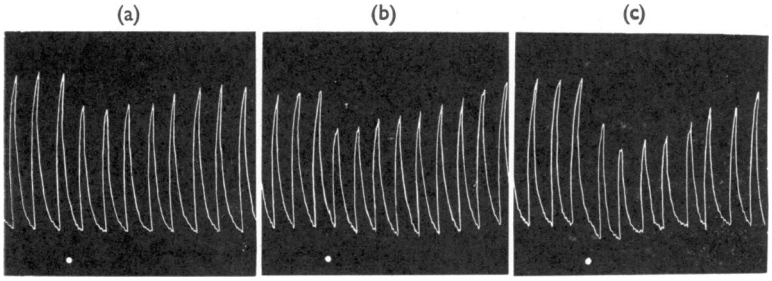

FIG. 1.—Cat, ♀, 2·2 kg., pentobarbitone sodium 30 mg./kg. Contractions of nictitating membrane. Sympathetic trunk stimulated at 20/sec. with supramaximal pulses for 10 sec. every minute. The figure shows the effects of (a), 250 μg. hexamethonium bromide; (b), 2·5 mg. hexamethylene bisdiethylamine dihydrobromide; and (c), 1 mg. hexamethylene bisdiethylsulphonium iodide, all given intravenously. Doses are expressed as base.

bisdiethyl compounds were longer acting (Fig. 1): in fact the duration of action seemed to vary with the potency, the most potent compound, hexamethylene bisdiethylsulphonium, being the longest acting and producing effects which lasted about the same time as those of a comparable dose of hexamethonium.

DISCUSSION

The results confirm our impression that tertiary sulphonium compounds are pharmacologically similar to tertiary ammonium compounds—that is, to the salts of tertiary amines (provided these are not extensively hydrolysed at *p*H 7.6). They also strengthen the argument that the low activity of the sulphur analogue of acetylcholine, acetoxyethyldimethylsulphonium, may be ascribed to its possession of only two methyl groups attached to the onium atom. The beneficial effects on activity of replacing all the methyl groups in the sulphonium and tertiary ammonium compounds by ethyl groups is rather surprising, in view of the effects of these changes in the hexamethonium molecule. However, one is reminded of the fallacy of regarding particular groups in a cationic head as being beneficial to, or detrimental to, activity. This fallacy was thoroughly exposed by the work of Ing and Wright (1931, 1933; review by Ing, 1936) on simple onium salts. They showed that, although many onium compounds containing ethyl groups were much less active blocking agents on the frog sartorius preparation than their methyl analogues, this was not invariably true. The ethyl group was not intrinsically detrimental to activity —the size of the central onium atom and the nature of the other groups attached to it had to be considered. It would seem quite possible, therefore, that further search among sulphonium or tertiary ammonium compounds might be rewarding.

CHEMICAL SECTION

Analyses are by the Huffman Microanalytical Laboratories, Colorado: m.p.s are uncorrected.

Preparation of hexamethylene bisdimethyl, bisethylmethyl, and bisdiethyl sulphonium diiodides.—Hexamethylene diiodide, an equal volume of ethanol and a large excess of the appropriate sulphide were sealed up and left at room temperature (approximately 30° C.). After a few days, crystals of the sulphonium salt began to form, and at the end of from two to six weeks the tube was opened and the salt filtered off. The substances were recrystallized from mixtures of methanol and ethanol, care being taken to avoid heating them above 60° because they decompose rapidly when heated.

Hexamethylene bisdimethylsulphonium diiodide melted at 146–7°(dec.) in a sealed tube. Found: C, 26.0; H., 5.27; I^-, 54.7. $C_{10}H_{24}S_2I_2$ requires C, 26.0; H, 5.25; I^-, 55.0%.

Hexamethylene bisethylmethylsulphonium diiodide melted at 83–4° in a sealed tube. Found: C, 31.2; H, 6.01; I^-, 48.8. $C_{12}H_{28}S_2I_2$ requires C, 29.4; H, 5.77; I^-, 51.9; $C_{12}H_{28}S_2I_2$, 0.75 EtOH, requires C, 30.9; H, 6.25; I^-, 48.4%.

Hexamethylene bisdiethylsulphonium diiodide melted at 151–2° (dec.) in a sealed tube. Found: C, 32.6; H, 6.34; I^-, 48.9. $C_{14}H_{32}S_2I_2$ requires C, 32.4; H, 6.30; I^-, 49.0%.

Hexamethylene bisethylmethylsulphonium diiodide appeared to contain ethanol of crystallization. It was not possible to determine this directly because the compound decomposed when heated. The ultra-violet absorption spectra of the sulphonium compounds in water show a maximum at 226–227 mμ. The absorption is apparently due entirely to the iodide ion present, because the absorption spectrum of sodium iodide in water has a peak at exactly the same wavelength. The values of $\log\varepsilon$ (molar) were 4.38 and 4.39 for the bisdimethyl and bisdiethyl compounds respectively. From the absorption of a solution of the bisethylmethyl compound of known concentration, it was therefore possible to obtain two estimates of the molecular weight of the compound. The values, 526 and 513, agreed more closely with the theoretical value (525) for the formula with 0.75 molecules of ethanol of crystallization than with that (490) for the formula without alcohol.

Preparation of hexamethylene bisdimethyl, bisethylmethyl, and bisdiethylamine dihydrobromides.—Hexamethylene dibromide, dissolved in ethanol, was

refluxed with an excess of the appropriate secondary base. After several hours the ethanol and unreacted base were distilled off under reduced pressure and the solid residue treated with strong sodium hydroxide solution. The free base liberated was extracted with ether and the ether extract dried with solid sodium hydroxide, filtered, and the ether distilled off. The residue was treated with an excess of concentrated hydrobromic acid and the dihydrobromide recrystallized from mixtures of ethanol and methanol.

Hexamethylene bisdimethylamine dihydrobromide melted at 223°. Found : Br^-, 47.8. $C_{10}H_{26}N_2Br_2$ requires Br^-, 47.9%.

Hexamethylene bisethylmethylamine dihydrobromide melted at 213–4°. Found : Br^-, 44.1. $C_{12}H_{30}N_2Br_2$ requires Br^-, 44.2%.

Hexamethylene bisdiethylamine dihydrobromide melted at 267°. Found : Br^-, 41.1. $C_{14}H_{34}N_2Br_2$ requires Br^-, 41.0%.

Summary

1. Hexamethylene bisdimethyl, bisethylmethyl, and bisdiethylsulphonium iodides have been prepared and tested on the superior cervical ganglion of the cat.

2. The ganglion-blocking activity was greatest in the bisdiethyl compound and least in the bisdimethyl compound. On a molecular basis, hexamethylene bisdiethylsulphonium iodide has about half the ganglion-blocking activity of hexamethonium on the preparation.

3. The analogous tertiary amine dihydrobromides, hexamethylene bisdimethyl, bisethylmethyl, and bisdiethyl amine dihydrobromides, also had ganglion-blocking properties. The bisdiethyl compound was again the most active and the bisdimethyl compound the least.

4. The bearing of these results on the difference between the properties of acetylcholine and acetoxyethyldimethylsulphonium is discussed.

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