THE NEUROMUSCULAR BLOCKING ACTIVITY OF ETHYL ANALOGUES OF DECAMETHONIUM

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The properties of the ethyl analogues (VI, VII and VIII below) of acetylcholine (V) have been reviewed by Ing.[1] Similar analogues (X, XI and XII) of the ganglionic blocking agent hexamethonium (IX) have been studied by Wien and Mason.[2] Replacement of methyl groups by ethyl produces in the nicotine-like and muscarine-like properties of acetylcholine quite different changes from those produced in ganglionic blocking activity by similar replacement in hexamethonium. This has led us to examine the effects of substitution of methyl groups by ethyl in the neuromuscular blocking agent decamethonium (I).

This paper describes the synthesis of decamethylene bisethyldimethyl, bismethyldiethyl and bistriethyl ammonium iodides (II, III and IV respectively) and contains a preliminary comparison of their neuromuscular blocking activity with that of decamethonium using the isolated diaphragm of the rat and the quadriceps in spinal rabbits. A more comprehensive investigation has been undertaken by Dr. Zaimis of the Department of Pharmacology, the School of Pharmacy, London.

The formulæ of the compounds mentioned are listed below:—

Decamethonium and analogues.		Acetylcholine and analogues.	
$Me_3\overset{+}{N}(CH_2)_{10}\overset{+}{N}Me_3$	I	$CH_3COOCH_2CH_2\overset{+}{N}Me_3$	V
$Me_2EtN(CH_2)_{10}NEtMe_2$	II	$CH_3COOCH_2CH_2NMe_2Et$	VI
$MeEt_2N(CH_2)_{10}NEt_2Me$	III	$CH_3COOCH_2CH_2NMeEt_2$	VII
$Et_3N(CH_2)_{10}NEt_3$	IV	$CH_3COOCH_2CH_2NEt_3$	VIII

Hexamethonium and analogues.

$Me_3N(CH_2)_6NMe_3$	IX
$Me_2EtN(CH_2)_6NEtMe_2$	X
$MeEt_2N(CH_2)_6NEt_2Me$	XI
$Et_3N(CH_2)_6NEt_3$	XII

Substance IV, prepared as dibromide, was briefly investigated by Barlow and Ing[3] and found to have about 1/9th of the activity of decamethonium in blocking conduction from the phrenic nerve in the isolated rat diaphragm preparation.

METHODS

1. The rat diaphragm preparation was set up as described by Bülbring[4] and Chou.[5] The phrenic nerve was stimulated with a single shock from an induction coil every 10 seconds at a strength well above threshold. The drugs were allowed to act for 3 minutes.

2. Rabbits were anæsthetised with ether, the spinal cord was cut across through the atlanto-occipital membrane and the brain was destroyed. Artificial respiration was then given from a Starling pump. The femur was pinned at each end and the patellar tendon was freed and arranged for isometric recording on a kymograph. The femoral nerve was stimulated with a single 0·1 m.sec. square-wave shock every 10 seconds at a strength well above threshold. The drugs were injected through a cannula in the external jugular vein and the response, when obtained, showed as a decrease in the amplitude of the twitch. This passed through a minimum within 1 or 2 minutes and then gradually returned to the original size. The maximum response always took place within 3 minutes of the administration of the drug. Recovery was rarely complete in less than 20 minutes so that at least this interval was allowed between doses even if the first had not produced a noticeable response. Where a dose caused complete block it was often necessary to wait up to an hour or more. In some experiments a particular dose produced at a later time a larger response than it had given earlier but we do not think there is evidence that the substances accumulate in the animal.

In both types of preparation it was possible to achieve a steady state between doses of the drugs. The effect of each dose was assessed as the percentage reduction in the amplitude of the twitches. The reduction produced in 3 minutes after the addition of the drug was measured in experiments on the rat diaphragm: in those on the rabbit, the percentage reduction was calculated at the period of maximum effect.

In earlier experiments the effect produced by a dose of one drug was estimated as being greater or less than that of a dose of another and, if possible, was bracketed between the effects of two doses of the second compound, one more effective and the other less effective than the dose of the first drug. Later, however, it was possible to compare directly doses of the drugs which produced approximately the same effect. For this purpose pairs of responses which did not differ by more than 15 (i.e., were not further apart than 60 per cent. and 75 per cent. or than 20 per cent. and 35 per cent.) in the rabbit experiments, or by 10 in the rat experiments, were regarded as equivalent.

RESULTS

In all, 32 comparisons were obtained from 4 rat diaphragm preparations and 18 comparisons from 7 rabbit preparations. Of these, 16 on the rat and 10 on the rabbit were between doses which produced equivalent effects. The drugs were given in different sequences to eliminate any interaction. In spite of individual variation between rabbits (they were of various strains and some required up to 10 times the dose per kg.

required by others) the relative activities of the compounds amongst themselves were remarkably constant. For instance, direct comparisons between II and III, III and IV etc., gave the same results as those derived from comparison of each drug with I. The relative activities of the compounds may be expressed as the ratio of the number of molecules required to produce equivalent effects. When all the comparisons on the rat diaphragm preparations are considered this ratio is

$$I : II : III : IV = 1 : 8 : 8 : 7.$$

The extreme values of individual comparisons give ratios of

$$1 : 6{\cdot}7 : 6{\cdot}7 : 6{\cdot}7 \text{ and } 1 : 12{\cdot}5 : 12{\cdot}5 : 10.$$

Previous estimates of the relative activity of I and IV (9 : 1)[3] agree with these figures.

On the rabbit quadriceps the compound ratio is

$$I : II : III : IV = 1 : 15 : 10 : 4,$$

extreme values giving ratios of

$$1 : 20 : 10 : 2{\cdot}5 \text{ and } 1 : 12{\cdot}5 : 10 : 5.$$

Discussion

These ratios are quite different from those obtained by replacing the methyl groups of acetylcholine by ethyl groups. Both nicotine-like and muscarine-like activity are only slightly reduced (to between one half and one fifth) when one methyl group is substituted (VI) but thereafter fall sharply (to between 1/300th and 1/1500th in VII).[1]

The results are also different from those obtained by replacing the methyl groups of hexamethonium by ethyl groups. The ganglionic blocking power of X is about twice that of IX or XI, the two latter being approximately equal. XII, which has negligible ganglionic blocking activity, has greater neuromuscular blocking activity than IX.[2]

These results suggest that the structure of the cationic head has quite different roles in decamethonium, acetylcholine and hexamethonium.

Chemical Section

(With D. A. Reid)

Experimental.—(Analyses are by Mr. Cameron and Miss Christie; m.pts. uncorrected.)

Decamethylene dibromide dissolved in ethanol was refluxed for 5 hours with an excess of either dimethylamine or diethylamine. The mixtures were evaporated down on a steam bath and the residues made strongly alkaline with potassium hydroxide and extracted with ether. The extracts were dried and distilled.

1 : 10-Bisdimethylaminodecane had b.pt. 115° to 120° C./5 mm., yield 60 per cent. Von Braun[6] recorded b.pt. 157° to 158° C./17 mm.

1 : 10-Bisdiethylaminodecane had b.pt. 186° to 188° C./16 mm., $N_D^{16° C.}$, 1·4537, yield 70 per cent.

The bases, dissolved in ethanol, were refluxed with methyl or ethyl iodide. The crude quaternary salts, which were obtained in almost theoretical yield, were recrystallised from ethanol. Decamethylene bisethyldimethylammonium iodide had m.pt. 251° to 252° C. Found: C, 40·2; H, 7·45; N, 5·34; $C_{18}H_{42}N_2I_2$ requires: C, 40·0; H, 7·80; N, 5·19 per cent.

Decamethylene bismethyldiethylammonium iodide had m.pt. 236° to 237° C.; Found: C, 42·5; H, 8·19; N, 5·07; $C_{20}H_{46}N_2I_2$ requires: C, 42·3; H, 8·10; N, 4·93 per cent.

Decamethylene bistriethylammonium iodide had m.pt. 213° to 214° C.; Found: C, 44·2; H, 8·52; N, 4·96; $C_{22}H_{50}N_2I_2$ requires: C, 44·3; H, 8·39; N, 4·69 per cent.

Summary

1. Replacement of one methyl group by ethyl at each end of the decamethonium molecule reduces neuromuscular blocking activity to about 1/8th for the isolated diaphragm preparation of the rat and to about 1/15th for the quadriceps of the spinal rabbit.

2. Further substitution of methyl groups by ethyl does not affect the activity on the rat diaphragm but increases that on the rabbit quadriceps.

3. The fully ethylated compound, decamethylene bistriethylammonium, is about 1/4th as active as decamethonium on the rabbit quadriceps but only 1/7th as active as decamethonium on the rat diaphragm.

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References

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4. Bülbring, *ibid.*, 1946, **1**, 38.
5. Chou, *ibid.*, 1947, **2**, 1.
6. Von Braun, *Liebigs Ann.*, 1912, **386**, 280.