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OBSERVATIONS ON Ω-AMINO-POLYMETHYLENE TRIMETHYLAMMONIUM COMPOUNDS

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The series of bis-onium compounds which includes hexamethonium and decamethonium (Barlow and Ing, 1948; Paton and Zaimis, 1949) has been extensively studied. The high biological activity of the members of this series is closely linked with the presence, in one molecule, of the two onium groups. If these groups are replaced by amino groups, as in hexamethylene diamine or decamethylene diamine, compounds result which are without the characteristic biological action of the onium compound.

As far as is known the bis-onium compounds are not metabolized in the animal body. Zaimis (1950) has shown that hexamethonium is excreted as such in the urine. On the other hand, the diamines are broken down. This was first shown for tetramethylene diamine and pentamethylene diamine by Udranszky and Baumann (1891). More recently, the oxidation of the members of the homologous series $H_3\overset{+}{N}(CH_2)_n\overset{+}{N}H_3$ by the enzymes amine oxidase and histaminase has been studied (Blaschko and Hawkins, 1950). It was found, in agreement with Zeller (1938), that the short-chain members of this series were oxidized by histaminase; an optimum rate of oxidation was attained with a 4-carbon chain (putrescine), and the rate of oxidation decreased with increasing chain length. Amine oxidase catalysed the oxidation of long-chain diamines but not that of short-chain diamines.

The present paper contains an account of a study of the homologous series

$$Me_3\overset{+}{N}(CH_2)_n\overset{+}{N}H_3,$$

the series which is intermediate between the bis-onium and bis-amino series. Observations on the oxidation of these compounds as well as on their biological activity are reported.

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MATERIAL AND METHODS

Compounds and Nomenclature.—In the following, the members of the homologous series studied are briefly referred to as the *hybrids*, e.g., the C5-hybrid or the C11-hybrid; in the figures, they are shown as

The members of the bis-onium series are shown thus: C6 stands for hexamethonium and C10 for decamethonium.

We are grateful to Dr. R. Wien, of Messrs. May & Baker Ltd., for the C6-hybrid, hexane-1-ammonium-6-trimethylammonium bishydrogen tartrate; the synthesis of all the other compounds studied is described below.

Enzyme Preparations.—Two preparations with amine oxidase activity were made; one was a homogenate of guinea-pig's liver, the other of rabbit's liver. One gramme of fresh tissue was homogenized and made up to a total volume of 2 ml. with 0.067 M-sodium phosphate buffer of *p*H 7.4. These homogenates were dialysed overnight against tap water; at the end of the dialysis 0.1 ml. of 0.2 M-sodium phosphate buffer of *p*H 7.4 was added to each ml. of dialysate. One ml. of this preparation was usually added to each manometer flask. The compounds were used in an initial concentration of 0.005 M; (−)-*p*-sympatol served as a typical substrate of amine oxidase.

As a source of spermine oxidase, each flask contained 1.6 ml. of ox serum, fully dialysed against the 0.067 M phosphate buffer. As a typical substrate, 0.005 M-spermine tetrahydrochloride was added.

The preparation of histaminase from pig's kidney was as described before (Blaschko and Hawkins, 1950); 0.005 M-cadaverine was the reference substrate.

Cat's Gastrocnemius.—This muscle was prepared as described by Bülbring and Burn (1942). Anaesthesia was induced with ether and maintained by an intravenous injection of 80 mg./kg. chloralose. Stimulation of the left sciatic nerve by supramaximal stimuli was by shocks of 0.7 msec. duration at a rate of 8–10 min.

Preganglionic Stimulation of the Cat's Superior Cervical Ganglion.—The animals were under chloralose anaesthesia. The contractions of the right nictitating membrane were recorded by a frontal writing lever; magnification of movements was 7.5 times. Electrical stimulation of the cervical sympathetic chain, divided and placed on shielded electrodes and covered with paraffin, was at a rate of 15/sec.; duration of each stimulus was 0.7 msec.

The rat's phrenic nerve-diaphragm preparation was set up as described by Bülbring (1946). The diaphragms were suspended in a bath of 75 ml. capacity in Tyrode's solution; oxygenation was by bubbling through a mixture of 95% O_2 and 5% CO_2; the temperature was 37.5° C.

The decerebrate pigeon's gastrocnemius was prepared as described by Ginzel, Klupp, and Werner (1951).

Chemical Section

Preparation of ω-amino-*n*-pentyl,ω-amino-*n*-heptyl, and ω-amino-*n*-decyl trimethylammonium bromide hydrobromides. — Pentamethylene, heptamethylene, and decamethylene dibromides were converted into the corresponding ω-bromoalkyl phthalimides by heating with potassium phthalimide. These were refluxed for 8–12 hr. with a large excess of a 33% w/v solution of trimethylamine in ethanol; the reaction mixture was then concentrated under reduced pressure. The oily residues were redissolved in ethanol, treated with a slight excess of hydrazine hydrate, and made acid to Congo red with dilute (approximately 10%) hydrobromic acid. The phthalyl hydrazide formed was filtered off and the filtrates were concentrated. The resultant gums were dissolved in ethanol and either crystallized from this solvent or were induced to crystallize by addition of methyl ethyl ketone and ether. The yields of pure material were from 20–40%, based on the amounts of bromoalkyl phthalimide.

ω-*Amino*-n-*pentyltrimethylammonium bromide hydrobromide,* recrystallized from ethanol, melted at 221°. Found*: C, 31.2; H, 7.56; N, 9.33. $C_8H_{22}N_2Br_2$ requires C, 31.4; H, 7.26; N, 9.15%.

ω-*Amino*-n-*heptyltrimethylammonium bromide hydrobromide,* recrystallized from ethanol, melted at 224–5°. Found: C, 36.2; H, 7.69; N, 8.30. $C_{10}H_{26}N_2Br_2$ requires C, 35.9; H, 7.79; N, 8.38%.

ω-*Amino*-n-*decyltrimethylammonium bromide hydrobromide,* recrystallized from a mixture of ethanol, methyl ethyl ketone, and ether, sintered at 162° and melted at 164°. Found: C, 41.3; H, 8.24; N, 7.55. $C_{13}H_{32}N_2Br_2$ requires C, 41.5; H, 8.52; N, 7.45%.

Preparation of ω-amino-*n*-undecyltrimethylammonium bromide hydrobromide. — ω-Bromoundecylic nitrile (Barlow, 1951) was refluxed for 12 hr. with a large excess of a 33% w/v solution of trimethylamine in ethanol. The reaction mixture was concentrated under reduced pressure and the oily residue dissolved in ethanol saturated with ammonia. This solution was reduced with hydrogen and Raney nickel catalyst at 90 atmospheres and 160°. The catalyst was filtered off, the filtrate concentrated and made acid to Congo red with 50% hydrobromic acid, and then concentrated once more. The residue was dissolved in a mixture of ethanol and methyl ethyl ketone from which the ω-*amino*-n-*undecyltrimethylammonium bromide hydrobromide* crystallized. Recrystallized material sintered at 182° and melted at 185°. Found: C, 43.3; H, 8.69; N, 7.35. $C_{14}H_{34}N_2Br_2$ requires C, 43.1; H, 8.80; N, 7.18%. The yield of pure material was 30%, based on the amount of ω-bromoundecylic nitrile.

Preparation of ω-amino-*n*-dodecyltrimethylammonium bromide hydrobromide (with N. A. Dobson).—Ethyl ω-cyanoundecylic ester, obtained in 80% yield from the ω-bromo ester, was reduced with lithium aluminium hydride (1 g./2 g. ester) dissolved in dry ether. When the reaction was over the excess of lithium aluminium hydride was decomposed with water. The mixture was filtered and the ethereal filtrate was used to extract the solid in a Soxhlet apparatus. The ether extract was dried with solid caustic potash and concentrated. The residue was moderately pure ω-amino-*n*-dodecanol and was recrystallized from ether. It melted at 79–80°. Found: C, 71.5; H, 13.4; N, 6.85. $C_{12}H_{27}NO$ requires C, 71.6; H, 13.5; N, 6.97%. The yield was 83%. The substance appears to be a histamine liberator and should be handled with some care.

The amino-alcohol (1 mol.) and phthalic anhydride (1 mol.), dissolved in glacial acetic acid, were heated for 30 min. on a steam-bath. The acetic acid was distilled off under reduced pressure, but the oily residue, presumed to be ω-hydroxy-*n*-dodecyl phthalimide, could not be induced to crystallize. It was heated on a steam-bath for 1 hr. with a slight excess of phosphorus tribromide and a few drops of pyridine. The product was poured into water and the mixture extracted with chloroform. The chloroform extract was dried with anhydrous sodium sulphate and concentrated. The solid residue was recrystallized from petrol (b.p. 60–80°). It melted at 56–58°. Found: C, 61.2; H, 6.85. $C_{20}H_{28}NO_2Br$ requires C, 60.9; H, 7.16%. The yield was 80%.

The ω-bromo-*n*-dodecyl phthalimide was converted into ω-*amino*-n-*dodecyltrimethylammonium bromide hydrobromide* by the method described for the synthesis of the ω-aminopentyl, -heptyl, and -decyl compounds. This was crystallized from a mixture of ethanol and methyl ethyl ketone. It sintered at 200° and melted at 212°. Found: C, 44.4; H, 9.01; N, 6.84. $C_{15}H_{36}N_2Br_2$ requires C, 44.5; H, 8.98; N, 6.93%. The yield of recrystallized material was 30%.

* All analyses are by Mr. J. M. Cameron and and Miss M. M. Christie; M.p.s are uncorrected.

RESULTS

Amine Oxidase.—The compounds of the hybrid series were tested as substrates of amine oxidase. The result of these experiments is shown in Table I.

TABLE I

OXIDATION OF MEMBERS OF THE "HYBRID" SERIES $Me_3\overset{+}{N}(CH_2)_n\overset{+}{N}H_3$ BY AMINE OXIDASE OF GUINEA-PIG AND RABBIT LIVER

The figures are percentages of the rate of oxidation of (−)-*p*-sympatol; they are means of several experiments. Gas: O_2; t=37·5° C.

No. of Methylene Groups *n*	Rate of Oxidation of "Hybrid" Compound as % of Rate of Oxidation of (−)-*p*-sympatol	
	Guinea-pig Liver	Rabbit Liver
5	8	8
6	20	26
7	12	26
10	24	55
11	18	94
12	41	211

No significant oxidation of the pentamethylene hybrid was seen, but with increasing chain length the rate of oxygen consumption increased; with both guinea-pig and rabbit liver it was the C12-hybrid that was most rapidly oxidized. That amine oxidase was responsible for the oxidation is supported by the observation that in mixed substrate experiments with (−)-*p*-sympatol the rates of oxidation were not additive, but always intermediate between the rate with the hybrid alone and with (−)-*p*-sympatol alone. This is illustrated by the experiment shown in Fig. 1, where the C11-hybrid was used as substrate and a homogenate of guinea-pig liver as source of enzyme.

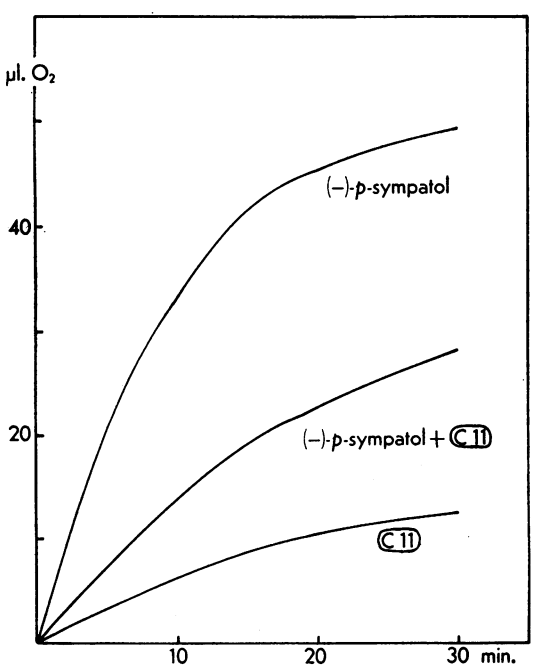


FIG. 1.—Oxidation of the C11-hybrid by a guinea-pig's liver homogenate. The rate of oxidation in the presence of both (−)-*p*-sympatol and C11-hybrid is intermediate between the rates with either substrate alone. Substrate concentrations 0.005M. Gas phase: O_2; t=37.5° C.

In an experiment with rabbit liver homogenate, the rates of oxidation of the C10- and C12-hybrids were compared with those of the corresponding members of the bis-onium group. The amounts of oxygen consumed in the first 15 min. in this experiment were:

with (−)-*p*-sympatol	23 µl.
„ the C10-hybrid	20 µl.
„ decamethylene diamine ..	43 µl.
„ the C12-hybrid	53 µl.
„ dodecamethylene diamine	80 µl.

In other words, the diamine was oxidized at a faster rate than the hybrid compound of the same chain length.

Spermine Oxidase.—This enzyme, which has recently been found in the serum of ruminants (Hirsch, 1953), acts not only on spermine but also on other amines. Tabor, Tabor, and Rosenthal (1954) have shown that spermine oxidase also oxidizes decamethylene diamine.

We have found that the enzyme also acts on the C12-hybrid. In an experiment with bovine serum, the amounts of oxygen used in 1 hr. were:

with 0.005 M-spermine ..	128 µl.
„ „ -C-12-hybrid ..	19 µl.
„ both amines	26 µl.

This result shows that the hybrid compound, although only slowly oxidized, had a marked effect upon the rate of oxidation of spermine, indicating a high affinity for spermine oxidase.

Histaminase.—None of the hybrid compounds was oxidized at a significant rate. When cadaverine was used as a reference substrate, with equimolecular concentrations of either the C5- or the C6-hybrids, the rate of oxidation of cadaverine was not affected, but in the presence of the C7-hybrid cadaverine was not oxidized. With the C10-, C11-, or the C12-hybrids present, the rate of oxidation of cadaverine was about halved.

Cholinesterases.—It is known that the bis-onium compounds inhibit acetylcholinesterase (Paton and Zaimis, 1949; Bergmann, Wilson, and Nachmansohn, 1950). The lower members of the hybrid

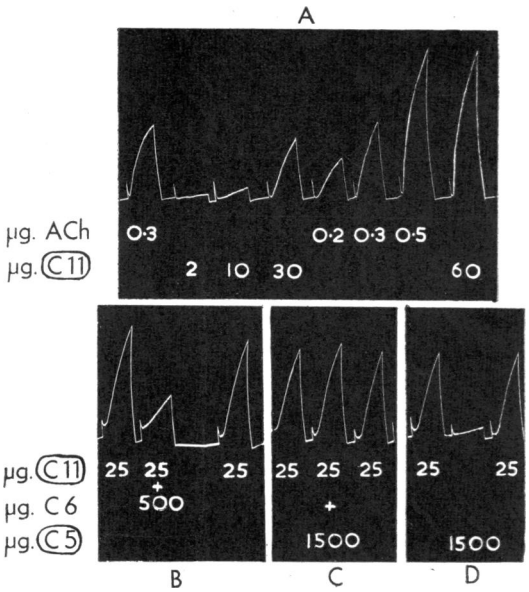


FIG. 2.—Frog's rectus; 1: 100,000 eserine. (A) Comparison of contractures caused by acetylcholine and the C11-hybrid. (B) Effect of hexamethonium on the contracture caused by the C11-hybrid. (C) Effect of the C5-hybrid on the contracture caused by the C11-hybrid. (D) Effect of the C5-hybrid on the muscle.

series had little effect on the hydrolysis of acetyl-β-methylcholine (initial concentration 0.03M) by a preparation of dog's caudate nucleus, but with the C11-hybrid in 10^{-3}M the rate of hydrolysis was 50% of that without the compound; with the C12-hybrid in the same concentration it was 45% of the uninhibited rate.

With horse serum, the lower members of the hybrid series did not affect the rate of hydrolysis of 0.06M-benzoylcholine; with the C11-hybrid the inhibition was 20%; with the C12-hybrid the inhibition was 90%.

Frog's Rectus.—From the work of Paton and Zaimis (1949) it is known that the long-chain members of the bis-onium series (n=10, 11, or 12) cause an acetylcholine-like contracture of this muscle; the short-chain members (n=5 or 6) are very inactive, but they antagonize the contractions induced by either acetylcholine or decamethonium.

The eserinized frog's rectus muscle was stimulated also by the C11-hybrid. This is shown in Fig. 2a, where the contracture caused by 30 μg. of C11-hybrid was intermediate between that caused by 0.2 μg. and 0.3 μg. respectively of acetylcholine, and the shortening after a dose of 60 μg. of the C11-hybrid equivalent to that after 0.5 μg. of acetylcholine. In this experiment, therefore, acetylcholine was about 120 times as active as the C11-hybrid.

(+)-Tubocurarine, given in a dose of 10 μg., depressed the contracture caused by C11-hybrid, as it depressed the response to acetylcholine. Return of the contracture after tubocurarine occurred slowly.

Whereas there was no qualitative difference in the action of the long-chain members of the hybrid and bis-onium series on the frog's rectus, the C5-hybrid differed from the corresponding bis-onium compound and from hexamethonium in that it had no blocking action on the shortening induced by either acetylcholine or the C11-hybrid (Fig. 2c). Hexamethonium, however, depressed the contracture caused by the C11-hybrid (Fig. 2b). The C5-hybrid, by itself, caused practically no stimulation of the rectus muscle (Fig. 2d).

Decerebrate Pigeon's Gastrocnemius.—We are indebted to Dr. K. H. Ginzel for performing the experiment shown in Fig. 3, where an intravenous injection of 10 μg. of decamethonium was given between two injections of 30 μg. each of the C11-hybrid and the C10-hybrid. It can be seen that, like decamethonium, the two compounds of the hybrid series caused a contracture of the pigeon's gastrocnemius muscle. The height of the contractures was of about the same magnitude as that caused by decamethonium, but the shortening with the two hybrids set in very rapidly, and the muscle relaxed again after a shorter interval than after a dose of decamethonium. In a second similar experiment, 1 mg. of the C7-hybrid, given intravenously, caused about the same depression as

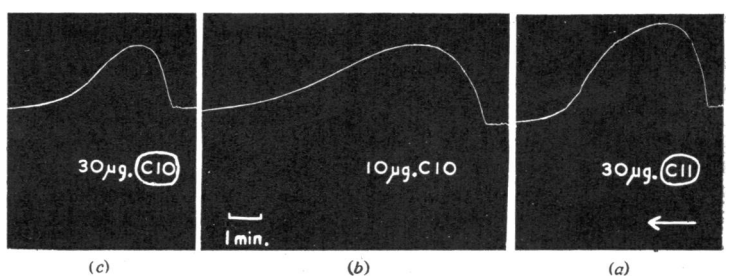


FIG. 3.—Decerebrate pigeon. M. gastrocnemius. Reading from right to left, the figure shows the contractures after intravenous injection of: (*a*) 30 μg. C11-hybrid, (*b*) 10 μg. decamethonium, (*c*) 30 μg. C10-hybrid.

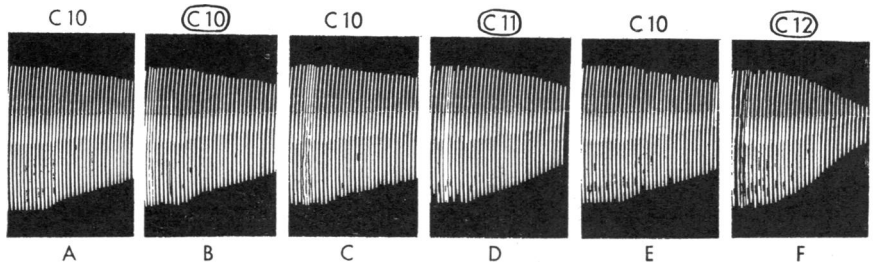
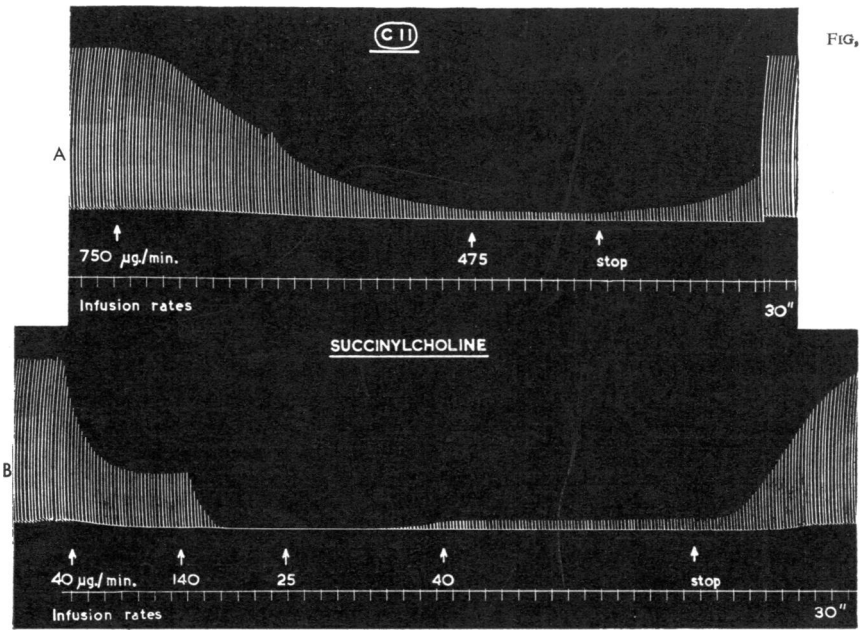


FIG. 4



FIG, 5 A and B

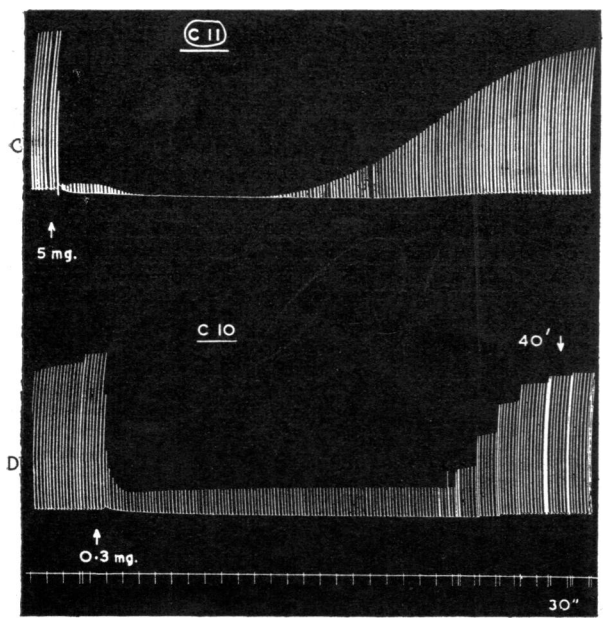


FIG. 5 C and D

FIG. 4.—Rat's phrenic nerve-diaphragm. Each dose was kept in the bath for 3 min.; interval between successive doses 15 min. (A) 1 mg. decamethonium: C10. (B) 1 mg. C10-hybrid: C 10. (C) 1 mg. decamethonium: C10. (D) 1 mg. C11-hybrid: C 11. (E) 1 mg. decamethonium: C10. (F) 1 mg. C12-hybrid: C 12.

FIG. 5.—Cat's gastrocnemius. All tracings were obtained from the same preparation. (A) Intravenous infusion of C11-hybrid was started with 750 µg./min. and later reduced to 475 µg./min. (B) I.v. infusion of succinylcholine; after several changes in the rate of infusion, a depression of contractions similar to that in 5 (A) was obtained with 40 µg./min. (C) Single intravenous dose of 5 mg. C11-hybrid. Note relatively fast recovery. (D) Single i.v. dose of 0.3 mg. decamethonium. Note slow rate of recovery.

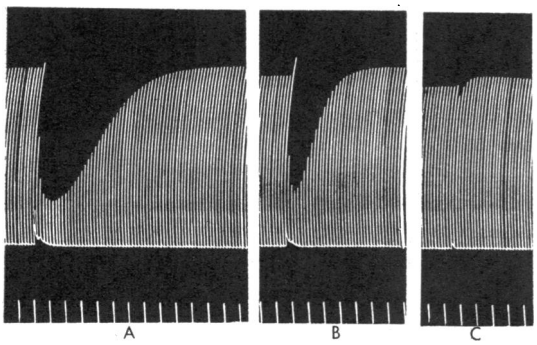


FIG. 6.—Cat's gastrocnemius. Intra-arterial injection of: (A) 200 μg. C10-hybrid, (B) 200 μg. C11-hybrid, and (C) 200 μg. C12-hybrid.

133 μg. of the C10-hybrid; however, the depression came on more gradually and passed off more slowly. An intravenous injection of 20 μg. of decamethonium caused a slightly less pronounced depression, but one which had a time course closely similar to that of the C7-hybrid and very different from the effects of the C10-, C11-, and C12-hybrids with their characteristic rapid onset and rapid recovery.

Rat's Phrenic Nerve-Diaphragm Preparation.—Three of the hybrid compounds were tested, those with 10, 11, and 12 methylene groups respectively. All three compounds depressed the response of the muscle to indirect stimulation. The relative potency of the hybrid compounds, in comparison with decamethonium, varied a little from experiment to experiment; in that illustrated in Fig. 4 the C10-hybrid appeared just a little more effective than decamethonium; the blocking activity increased with increasing chain length; the C12-hybrid was the most active compound tested.

The blocking action of the C11-hybrid, like that of decamethonium, was not affected in the presence of neostigmine.

Cat's Gastrocnemius Muscle.—In this preparation the long-chain members of the hybrid series also depressed the response to indirect stimulation, but, in contrast to the rat's diaphragm, they were less active than decamethonium.

In one preparation the inhibition of the contractions of the gastrocnemius muscle upon intravenous infusion of the C11-hybrid was compared with that after an infusion of succinylcholine. It was found that the slow infusion of 475 μg./min. of C11-hybrid depressed the response of the muscle to indirect stimulation as strongly as an infusion of 40 μg./min. of succinylcholine. The onset of recovery was slower than after succinylcholine (Fig. 5a and b).

In the same preparation the effects of a single intravenous dose of 300 μg. decamethonium and of 5 mg. of C11-hybrid were also compared; the latter caused an immediate and deep block; however, the effect was transient and the block was complete for only 6 min., and full recovery

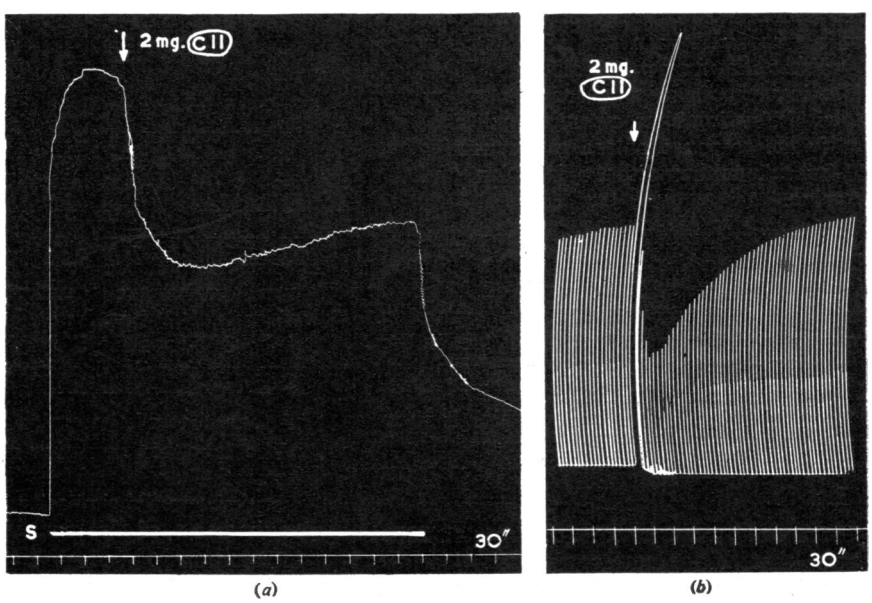


FIG. 7.—Cat; chloralose. Ganglionic blocking action of C11-hybrid. (*a*) Record of contraction of nictitating membrane stimulated preganglionically at *S*. (*b*) Simultaneous record of gastrocnemius muscle stimulated indirectly.

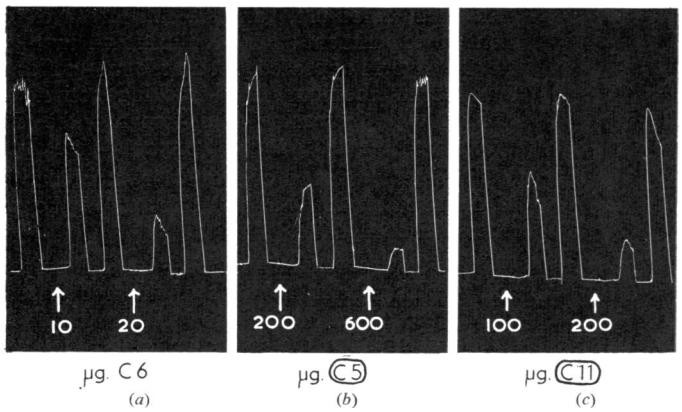


FIG. 8.—Guinea-pig ileum. Capacity of bath, 10 ml. Each contraction is induced by 20 μg. nicotine bitartrate. The following substances were added 30 sec. before the nicotine: at (*a*) hexamethonium, (*b*) C5-hybrid, (*c*) C11-hybrid.

occurred within 15 min. (Fig. 5c). After decamethonium, the block was not complete, but recovery was slower and complete only after 45 min. (Fig. 5d).

The blocking actions of the three long-chain hybrids were compared by intra-arterial injection (Fig. 6). The compounds were given in a dose of 200 μg. The C10-hybrid proved more active than the C11-hybrid, and the C12-hybrid had scarcely any effect in this dose. Given in larger doses, the action of the C12-hybrid was found to be qualitatively similar to that of the deca- and hendecamethylene compounds. Fig. 6 also shows close qualitative similarity between the type of action of the hybrids and those of decamethonium: the depression of the response to indirect stimulation is preceded by a potentiation of the response to indirect stimulation (see also Fig. 7b).

The intravenous injection of 500 mg. iproniazid (Marsilid), an inhibitor of amine oxidase, did not modify the response of the gastrocnemius to the C11-hybrid, neither did the injection of 2.5 mg. tyramine.

Ganglionic-blocking Action of the C11-hybrid.—Fig. 7a shows the response, to an intravenous injection of 2 mg. of C11-hybrid, of the preganglionically stimulated nictitating membrane; Fig. 7b shows a simultaneous record of the indirectly stimulated gastrocnemius. It can be seen that the C11-hybrid differs from decamethonium in that it has a ganglionic blocking action which is about as strong as its action upon the neuromuscular junction. The initial excitatory action is clearly shown in Fig. 7b.

Guinea-pig's Intestine.—Feldberg (1951) has shown that bis-onium compounds like hexamethonium depress the nicotine-induced contraction of the guinea-pig's intestine. The short-chain members of the hybrid series have only a very feeble activity of this kind. From the experiment shown in Fig. 8, it appears that the C5-hybrid has about one-fifteenth of the activity of hexamethonium; in this preparation the C11-hybrid had a stronger depressor action than the pentamethylene compound.

DISCUSSION

The members of the series of hybrid compounds were prepared in the first instance in order to test them as possible substrates of amine oxidase. The results of these experiments are in agreement with a picture of amine oxidase as an enzyme with a single receptor for amino groups, whereas histaminase has two. Amine oxidase has no affinity for the short-chain diamines, and this has been explained by the disturbing effect that the second basic group has on the attachment of the first. It is therefore not surprising that the strongly basic onium groups exert a similar disturbing effect. This effect, like that of the amino group in the polymethylene diamines, decreases as the intramolecular distance between the two basic groups increases, and the long-chain members of the hybrid series are therefore oxidized by amine oxidase. A comparison of the rates of oxidation of the C10- and the C12-hybrids with those of the corresponding diamines suggests that the disturbing effect of the onium group is a little more powerful than that of the amino group.

The fact that spermine oxidase, which acts on decamethylene diamine, also oxidizes the C12-hybrid shows the similarity between the specificity requirements of this enzyme and amine oxidase.

Histaminase, which will act on penta- and hexamethylene diamines, does not oxidize the corresponding members of the hybrid series. This is of

interest, because it shows that this enzyme, which requires two basic groups for successful attachment, does not have a significant affinity for compounds in which one of the two amino groups is replaced by an onium group.

The biological activity of the C5-hybrid was compared with that of hexamethonium on the frog's rectus and on the guinea-pig's intestine. On the frog's rectus the compound was without the characteristic depressor action of hexamethonium, and on the guinea-pig's intestine, where the action of hexamethonium is interpreted as a ganglionic-blocking action (Feldberg, 1951), the C5-hybrid is only feebly active. In fact, the long-chain member of the series, the C11-hybrid, was more active upon the intestine than the corresponding pentamethylene derivative, and it is in keeping with this finding that C11-hybrid was also active as blocking agent on the superior cervical ganglion.

On the other hand, the long-chain members of the hybrid series had the characteristic activity of decamethonium on the neuromuscular junction. In most preparations the activity of the hybrids was less, but in the pigeon muscle the ratio was only about one to three, and on the rat's diaphragm the hybrids appeared to be more active than decamethonium.

The responses of striped muscle to the hybrid series were always of much shorter duration than those to decamethonium. On the cat's gastrocnemius the type of response resembled that to succinylcholine. The short duration of the response might be considered as due to destruction of the hybrids by amine oxidase, but this is unlikely. It seems more likely to assume that the amino group, although able to react with the receptor, is less firmly held than the onium group and therefore more easily removed. This is supported by the observation that in the diaphragm, which remains immersed in the fluid containing the hybrid, the potencies of the three hybrids relative to decamethonium were high.

The observations reported show that for the typical activity on the neuromuscular junction one of the two fully methylated onium groups is essential, but the second can be replaced by the primary amino group.

Summary

1. The synthesis of some members of the "hybrid" series of ω-aminopolymethylene trimethylammonium, $Me_3\overset{+}{N}(CH_2)_n\overset{+}{N}H_3$, is described.

2. The long-chain members of the series are substrates of both amine oxidase and spermine oxidase; the short-chain members are not oxidized by histaminase.

3. The short-chain members of the hybrid series are without the biological activity of the corresponding members of the bis-onium series.

4. The long-chain members of the hybrid series have an action upon the neuromuscular junction which qualitatively is similar to the action of decamethonium; in addition they have some ganglionic blocking action.

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