glycol had been subjected to sulfuric acid at 0°, then worked up as described in a foregoing section, the product was dissolved in ethanol, and diluted to 100 cc. in a volumetric flask. Exactly 50.0 cc. of the solution was added to a weighed portion of non-radioactive *m*-methylbenzhydryl phenyl ketone (IV), and 50.0 cc. was added to a weighed portion of benzhydryl *m*-tolyl ketone (V). Each mixture was then homogenized, and by successive alternate crystallizations from 95% ethanol and hexane, the ketones were reisolated and assayed for radioactivity. In certain of the experiments "hold-back carrier"[19] was added and the samples were repurified and reassayed. All pertinent data relative to these yield determinations are given in Table VII.

Calculations of m_i of Table III.—From Table I, the average yields of IV and V, respectively, from *threo*-I and *erythro*-I are 70.3 and 29.7%. Thus: $m_a + m_b = 0.703$; $m_c = 0.297$. From Chart I and Table II

$$m_a + \frac{m_b}{2} = 0.596 \times 0.703$$

Thus $m_a = 0.135$; $m_b = 0.568$; and $m_c = 0.297$

$$\frac{k_{Ph}}{k_H} = \frac{m_b + m_c}{m_a} = 6.4 \text{ and } \frac{m_c}{m_b} = 0.523$$

From Table I, the yields of IV and V, respectively, from IIa are 63.2% and 36.8%. Thus

$$m_d + m'_b = 0.632; \quad m_e + m'_c = 0.368$$

From Table II

$$m_d = 0.632 \times 0.042 - 0.026$$
$$m'_b = 0.632 - 0.026 = 0.606$$
$$m'_c = 0.606 \times \frac{m_c}{m_b} = 0.317$$

and $m_e = 0.051$; $\frac{k_{tol}}{k'_H} = 18$; and $\frac{2k_T}{k_P}$ (from equation 1) $= 2.7$

Estimate of Error in Calculation of $2k_T/k_P$.—Assuming all pertinent factors are in error by 0.02 such that $2k_T/k_P$ is a minimum

$$m_e + m'_c = 0.388; \quad m_d + m'_b = 0.612$$
$$m_a + m_b = 0.723; \quad m_c = 0.277$$

and the value (0.596 ± 0.003) for fraction of radioactivity in *m*-benzoylbenzoic acid from rearrangement of Ic (Table II) becomes 0.586, thus

$m_a = 0.121$; $m_b = 0.602$; $m_c = 0.277$; $m'_c = 0.270$; $m'_b = 0.586$

$m_e = 0.118$; and $m_d = 0.026$. Thus:

$\frac{k_H}{k_{Ph}} = 0.14$; $\frac{k_{tol}}{k'_H} = 8.25$; $\frac{m_c}{m_b} = 0.46$; and

$\frac{2k_T}{k_P}$ (from equation 1) $\cong 1.05$

OAK RIDGE, TENN.

(19) See E. J. Dewitt, C. T. Lester and G. A. Ropp, THIS JOURNAL, **78**, 2101 (1956), for a good discussion of the use of "hold back carrier."

[CONTRIBUTION FROM THE RESEARCH DIVISION, CUTTER LABORATORIES]

Hypotensors. 2-Ammonioalkyl 3-Ammonioalkanoate Salts[1]

BY I. F. HALVERSTADT, W. R. HARDIE AND A. R. WILLIAMS[2]

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A series of 2-ammonioalkyl 3-ammonioalkanoate salts has been prepared in which the quaternary ammonium groups have been derived from lower aliphatic amines and heterocycles such as pyrrolidine, piperidine, morpholine and pyridine. Data on these and their intermediate compounds are reported and the methods of synthesis are discussed. A number of these diammonio esters exhibited marked hypotensive activity *via* ganglionic blockade.

Introduction

The use of hexamethylenebis-(trimethylammonium chloride) (hexamethonium chloride) in the treatment of hypertension has led to the synthesis of many related structures. Some of these, such as 1,1′-pentamethylenebis-(1-methylpyrrolidinium hydrogen tartrate) (pentolinium tartrate), have been more potent but have had similar side effects. Prominent among these is intestinal stasis due to parasympathetic blockade.

A more limited use of hexamethonium chloride has been for the lowering of blood pressure during surgical operations in order to reduce hemorrhage. Here its long action has been disadvantageous and shorter acting hypotensors such as *d*-1,3-dibenzyldecahydro-2-oxo-imidazo[*c*]thieno[1,2-*a*]thiolium *d*-camphorsulfonate (trimethaphen camphorsulfonate) have been more useful.

This paper reports the preparation of members of the $R_1R_2R_3\overset{+}{N}CH_2CH_2COOCH_2CH_2\overset{+}{N}R_4R_5R_6 \cdot 2X^-$ series and derivatives in which certain of the CH_2 groups have alkyl substituents. These compounds, which are listed in Tables I and II, may be considered to be derived from the hexamethonium series by replacing two adjacent methylene groups by an ester linkage.

Discussion

Five routes (excluding anion exchange methods used to prepare the salts of Table II) were followed in these syntheses (see formular).

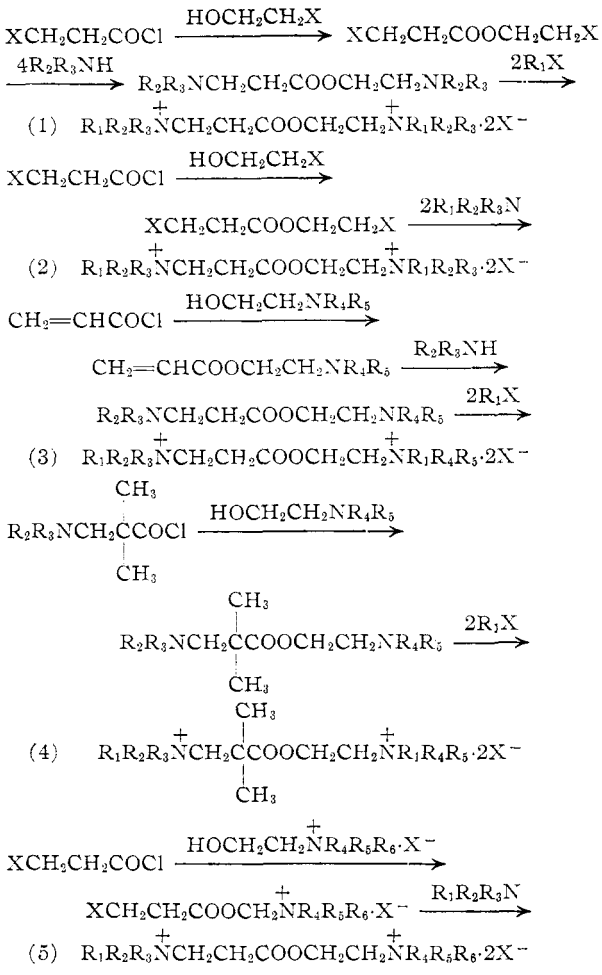
Route 1.—Fusco, *et al.*,[3] used this synthesis to prepare the first member of our ester series, 2-trimethylammonioethyl 3-trimethylammoniopropionate diiodide, I-1 (Table I, compound 1), but did not report any testing of its hypotensive activity. In repeating this work, we have found that the second step of the series may give ditertiary aminoester which is contaminated with unreacted halogen ester in cases where the boiling points do not differ greatly, *e.g.*, compound V-1 by method B of Table V (method V-B). If desired, this can be purified through the dihydrochloride salt.

Route 2.—This procedure, the second step of which appears as method I-B, has been used to prepare compounds I-1, I-2 and I-57 and this last one, 2-pyridinioethyl 3-pyridiniopropionate di-

(1) In agreement with the proposals of H. J. Barber and K. Gaimster, *Chemistry & Industry*, 670 (1952); J. F. Bunnett, *et al.*, THIS JOURNAL, **75**, 642 (1953); A. M. Patterson, *Chem. Eng. News*, **32**, 90 (1954), and A. P. Gray, *et al.*, THIS JOURNAL, **77**, 3534 (1955), we wish to use the term "ammonio" as the prefix form of "ammonium."

(2) Department of Chemistry, Colorado School of Mines, Golden, Colo.

(3) R. Fusco, G. Palazzo, S. Chiavarelli and D. Bovet, *Gazz. chim. ital.*, **79**, 836 (1949).



bromide, could not have been prepared as easily by any of the other routes. Schueler and Keasling[4] presumably prepared the dibromide salt of our I-1 by this method and attempted the preparation of our II-4A (Table II), this attempt being described in a later paper.[5] We have repeated this latter preparation and have obtained a material whose physical properties agree with those of their RACET (presumed by them to be 2-triethylammonioethyl 3-triethylammoniopropionate dibromide, our II-4A). We find this material to be triethylamine hydrobromide, confirmed by analysis and by mixed melting point. The true 2-triethylammonioethyl 3-triethylammoniopropionate dibromide, II-4A, which we have prepared by route 3, is quite different in physical and pharmacological properties from those reported for RACET.

Route 3.—This synthesis, based on the addition of secondary amines to aminoalkyl acrylates, was used for the majority of the compounds. In two cases, IV-1 and IV-9, the intermediate aminoalkyl acrylates (Table IV) were obtained by transesterification of methyl acrylate according to Rehberg and Faucette[6]; in all other cases we used acrylyl chloride and the aminoalcohol in benzene.[7] Traces of methylene blue (for acrylyl chloride) and N-phenyl-2-naphthylamine (for the esters) inhibited polymerization very well but did not retard the addition of amines to the double bond. Many of these addition reactions were rapid and exothermic, but in general the undiluted mixture was let stand one or two weeks at room temperature to give maximum yields. The diamino esters were isolated easily by vacuum distillation.

In one case, the addition of dimethylamine to 2-dimethylaminoethyl senecioate (V-11), the reaction did not go at room temperature but a moderately good yield was obtained when a little glacial acetic acid[8] was added and the solution was let stand a few weeks (method V-C).

It is interesting to note that from a reaction of methyl iodide with 2-dimethylaminobutyl 3-dimethylaminopropionate in acetone in which the temperature was permitted to rise to reflux, considerable quantities of tetramethylammonium iodide and 2-trimethylammoniobutyl acrylate iodide were isolated; this suggests that there may have been dissociation of the starting amino ester under these conditions, since the product, I-25, is stable to recrystallization from boiling methanol.

Route 4.—This was used only for two ammonioesters, 2-trimethylammonioethyl 2,2-dimethyl-3-trimethylammoniopropionate diiodide (I-14) and 1,1-dimethyl-2-trimethylammonioethyl 2,2-dimethyl-3-trimethylammoniopropionate diiodide (I-17). The 3-amino-2,2-dimethylpropionic acid[9] was N,N-dimethylated with formaldehyde and catalytic hydrogenation[10] and converted to the acid chloride hydrochloride by thionyl chloride.[11]

Route 5.—This approach, which permits each of the six N-alkyl groups to differ from the others, was used for the synthesis of several of the diammonioesters. It was the only one of the five routes that could yield 2-(1-ethylpiperidinio)-ethyl 3-trimethylammoniopropionate diiodide (I-34) and 2-trimethylammoniobutyl 3-(1-ethylpiperidinio)-propionate diiodide (I-41).

In the preparation of 2-(1-methylpiperidinio)-ethyl 3-trimethylammoniopropionate (I-33) by this method the analytically pure product probably contained 5–10% of methyl 3-trimethylammoniopropionate iodide[12]; this was removed by an additional recrystallization. Presumably this contaminant arose from an unsuccessful attempt to crystallize the oily intermediate 2-(1-methylpiperidinio)-ethyl 3-iodopropionate iodide (plus unreacted 3-iodopropionyl chloride) from methanol. The methyl 3-iodopropionate produced here then reacted with trimethylamine in the next step to give the highly cholinergic and toxic by-product (C.R. 10,000; MLD 0.5 mg./kg.; as defined in Table I, footnotes *a* and *b*). Although its presence was not shown by elemental analysis (because its values were so similar to those of I-33) or by melting point be-

(4) F. W. Schueler and H. H. Keasling, *J. Pharmacol. Exptl. Therap.*, **103**, 222 (1951).

(5) F. W. Schueler and H. H. Keasling, *J. Am. Pharm. Assoc., Sci. Ed.*, **43**, 98 (1954).

(6) C. E. Rehberg and W. A. Faucette, THIS JOURNAL, **71**, 3164 (1949).

(7) G. D. Graves, U. S. Patent 2,138,031 (1938).

(8) D. W. Adamson, *J. Chem. Soc.*, S144 (1955).

(9) J. Lincoln, U. S. Patent 2,500,317 (1950).

(10) R. E. Bowman and H. H. Stroud, *J. Chem. Soc.*, 1342 (1950).

(11) O. Dalmer, C. Diehl and H. Pieper, U. S. Patent 2,370,015 (1945).

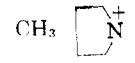
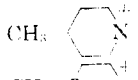
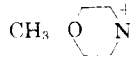
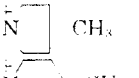
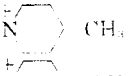
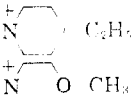
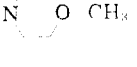
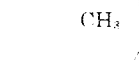
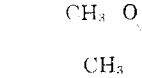
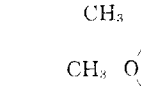
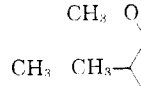
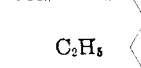
(12) R. Willstätter, *Ber.*, **35**, 610 (1902).

TABLE I

AMMONIOALKYL AMMONIOALKANOATE HALIDES

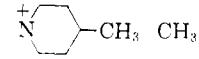
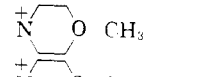
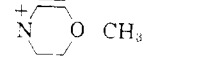
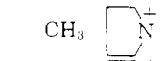
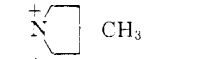
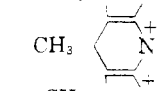
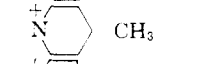
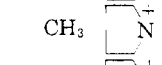
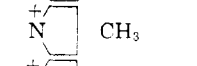
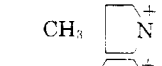
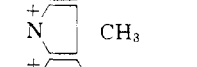
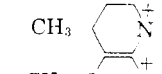
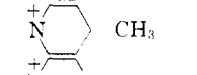
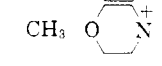
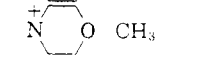
$$R_1R_2R_3\overset{+}{N}CH_2CH_2COOCH_2CH_2\overset{+}{N}R_4R_5R_6\cdot 2X^-$$

(1′, 2′, 3′, 4′)

Cmpd.	R_1 R_2 R_3 $\overset{+}{N}$	C-Alkyl (1′,2′,3′,4′) if present	$\overset{+}{N}$ R_4 R_5 R_6	X	C.R.[a]	Hypotensive activity Dose/MLD[b] (mg./kg.)	H.R.[c]	Method[d]	Yield[e]	M.p., °C.[f]
1	$(CH_3)_2N^+$		$^+N(CH_3)_3$	I	100	1/125	3	A	67	195.5–196.5[g]
								B	61	196–197
2	$C_2H_5(CH_3)_2N^+$		$^+N(CH_3)_2C_2H_5$	I	50	2/50	10	A	60	182–184.5
								B	36	177–179
3	$CH_3(C_2H_5)_2N^+$		$^+N(C_2H_5)_2CH_3$	I	0	1/38	20	A	83	169–171[h]
4	$(C_2H_5)_3N^+$		$^+N(C_2H_5)_3$	I	2	1/50	0	A	25	160.5–162.5[i]
5	$(CH_3)_3N^+$	1′-CH_3	$^+N(CH_3)_3$	I	0	2/75	5	A	68	199–201.5
6	$(CH_3)_3N^+$	2′-CH_3	$^+N(CH_3)_3$	I	0	1/150	25	A	90	166–168.5
7	$(CH_3)_3N^+$	3′-CH_3	$^+N(CH_3)_3$	I	20	1/175	15	A	80	203.5–204.5
								C	88	203–204
8	$(CH_3)_3N^+$	4′-CH_3	$^+N(CH_3)_3$	I	30	4/100	30	A	50	205–208
9	$C_2H_5(CH_3)_2N^+$	1′-CH_3	$^+N(CH_3)_2C_2H_5$	I	0	1.5/25	5	A	38	174–178
10	$C_2H_5(CH_3)_2N^+$	2′-CH_3	$^+N(CH_3)_2C_2H_5$	I	0	2/50	45	A	33	150.5–153[i]
11	$C_2H_5(CH_3)_2N^+$	3′-CH_3	$^+N(CH_3)_2C_2H_5$	I	0	1/75	60	A	45	159–161.5
12	$C_2H_5(CH_3)_2N^+$	4′-CH_3	$^+N(CH_3)_2C_2H_5$	I	0	1.5/50	50	A	19	180–181
13	$(CH_3)_3N^+$	1′,1′-$(CH_3)_2$	$^+N(CH_3)_3$	I	0	2/50	25	A	58	186–187.5
14	$(CH_3)_3N^+$	2′,2-$(CH_3)_2$	$^+N(CH_3)_3$	I	0	1/150	25	A	88	216.5–220.5
15	$(CH_3)_3N^+$	3′,3′-$(CH_3)_2$	$^+N(CH_3)_3$	I	0	1/150	55	A	62	224.5–226.5
16	$(CH_3)_3N^+$	4′,4′-$(CH_3)_2$	$^+N(CH_3)_3$	I	10	1/50	25	A	70	224.5–225
								C	74	222
17	$(CH_3)_3N^+$	2′,2′,3′,3′-$(CH_3)_4$	$^+N(CH_3)_3$	I	0	1/50	0	A	91	208–209
18	$CH_3(C_2H_5)_2N^+$		$^+N(CH_3)_3$	I	100	1/150	15	A	83	159–162.5
19	$(CH_3)_3N^+$		$^+N(C_2H_5)_2CH_3$	I	0	3/100	10	A	86	177.5–180.5
20	*i*-$C_3H_7(CH_3)_2N^+$		$^+N(CH_3)_2$*i*-C_3H_7	I	3	1/10	0	A	24	167.5–168.5
21	*n*-$C_3H_7(CH_3)_2N^+$		$^+N(CH_3)_2$*n*-C_3H_7	I	2	2/25	4	A	3	154–155[i]
22	*n*-$C_4H_9(CH_3)_2N^+$		$^+N(CH_3)_2$*n*-C_4H_9	I	2	5/25	0	A	16	149.5–150.5
23	$CH_2{=}CHCH_2(CH_3)_2N^+$		$^+N(CH_3)_2CH_2CH{=}CH_2$	Br	3	1/12	0	A	63	131–133[i]
24	$C_6H_5CH_2(CH_3)_2N^+$		$^+N(CH_3)_2CH_2C_6H_5$	Br	0	2/12	0	A	66	163.5–165.5
25	$(CH_3)_3N^+$	4′-C_2H_5	$^+N(CH_3)_3$	I	10	1/125	25	A	85	183–185
26	$C_2H_5(CH_3)_2N^+$	4′-C_2H_5	$^+N(CH_3)_2C_2H_5$	I	0	1/50	30	A	27	174–176[i]
27	$CH_3(C_2H_5)_2N^+$	4′-C_2H_5	$^+N(CH_3)_3$	I	5	2/75	70	A	61	163–164
28			$^+N(CH_3)_3$	I	100	2/75	20	A	35	168–170
29			$^+N(C_2H_5)(C_2H_5)CH_3$	I	0	1/25	105	A	40	155–156
30			$^+N(CH_3)_3$	I	100	2/125	15	A	11	158.5–162
31			$^+N(CH_3)_3$	I	100	2/75	20	A	75	164.5–168.5
32	$(CH_3)_3N^+$			I	10	4/50	10	C	74[g]	190
33	$(CH_3)_3N^+$			I	10	1/50	10	C	51[g]	170–171
								A	52	170–172
34	$(CH_3)_3N^+$			I	0	2/75	40	C	65[g]	175–178
35	$(CH_3)_3N^+$			I	2	4/100	15	C	53[g]	188–190
36		1′-CH_3	$^+N(CH_3)_2C_2H_5$	I	0	1/25	20	A	39	185–186[i]
37		1′-CH_3	$^+N(CH_3)_3$	I	0	4/150	10	A	62	200.5–202
38		2′-CH_3	$^+N(CH_3)_3$	I	0	2/100	40	A	83	155–157.5
39		2′-CH_3	$^+N(CH_3)_3$	I	0	1.5/150	15	A	69	166–167
40		3′-CH_3	$^+N(CH_3)_3$	I	0	4/50	0	A	45	184–185
41		4′-C_2H_5	$^+N(CH_3)_3$	I	0	4/50	0	C	22	175–176

	Recrystn. solvent	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Halogen, % Calcd.	Halogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1	95% EtOH MeOH	$C_{11}H_{26}I_2N_2O_2$	27.98	28.16	5.55	5.60	53.76	53.98	5.93	5.66
2	1:3 MeOH–*i*-PrOH	$C_{13}H_{30}I_2N_2O_2$	31.21	31.40	6.05	5.95	50.74	51.14	5.60	5.42
3	Abs. EtOH	$C_{15}H_{34}I_2N_2O_2$	34.10	34.19	6.49	6.30	48.05	48.04	5.30	5.01
4	1:2 MeOH–*i*-PrOH	$C_{17}H_{38}I_2N_2O_2$	36.70	35.65[j]	6.89	6.71	45.62	45.80	5.04	5.09
5	1:1:20 H_2O–MeOH–Me_2CO	$C_{12}H_{28}I_2N_2O_2$	29.65	29.62	5.81	5.91	52.21	51.86	5.76	5.60
6	1:7:10 H_2O–MeOH–Me_2CO	$C_{12}H_{28}I_2N_2O_2 \cdot H_2O$[k]	28.59	28.78	6.00	6.02	50.34	50.10	5.56	5.53
7	95% EtOH MeOH	$C_{12}H_{28}I_2N_2O_2$	29.65	29.35	5.81	5.78	52.21	52.62	5.76	5.54
8	1:5 MeOH–EtOH	$C_{12}H_{28}I_2N_2O_2$	29.65	29.39	5.81	5.78	52.21	51.92	5.76	5.79
9	1:10 MeOH–Me_2CO	$C_{14}H_{32}I_2N_2O_2$	32.70	32.56	6.27	6.16	49.36	49.32	5.45	5.21
10	1:6 MeOH–Me_2CO	$C_{14}H_{32}I_2N_2O_2$	32.70	32.53	6.27	6.13	49.36	49.56	5.45	5.16
11	Abs. EtOH	$C_{14}H_{32}I_2N_2O_2$	32.70	31.02[j]	6.27	5.96	49.36	49.66	5.45	5.28
12	Abs. EtOH	$C_{14}H_{32}I_2N_2O_2$	32.70	31.44[j]	6.27	6.20	49.36	49.58	5.45	5.17
13	95% EtOH	$C_{13}H_{30}I_2N_2O_2$	31.21	30.94	6.05	5.98	50.74	50.78	5.60	5.39
14	95% EtOH	$C_{13}H_{30}I_2N_2O_2$	31.21	31.13	6.05	6.20	50.74	51.08	5.60	5.45
15	95% EtOH	$C_{13}H_{30}I_2N_2O_2$	31.21	31.63	6.05	6.30	50.74	51.08	5.60	5.42
16	1:4 H_2O–Me_2CO MeOH	$C_{13}H_{30}I_2N_2O_2$	31.21	31.44	6.05	6.09	50.74	50.95	5.60	5.58
17	95% EtOH	$C_{15}H_{34}I_2N_2O_2$	34.10	34.00	6.49	6.66	48.05	48.62	5.30	4.97[m]
18	1:3 MeOH–Me_2CO	$C_{13}H_{30}I_2N_2O_2$	31.21	31.29	6.05	6.06	50.74	50.80	5.60	5.52
19	1:2 MeOH–Me_2CO	$C_{13}H_{30}I_2N_2O_2$	31.21	30.91	6.05	6.15	50.74	50.42	5.60	5.54
20	1:5 MeOH–Me_2CO	$C_{15}H_{34}I_2N_2O_2 \cdot 0.5H_2O$[n]	33.53	33.54	6.57	6.29	47.24	47.35	5.21	5.17
21	MeOH	$C_{15}H_{34}I_2N_2O_2$	34.10	31.9[j]	6.49	5.7[j]	48.05	47.7	5.30	5.2
22	1:2 Me_2CO–abs. EtOH	$C_{17}H_{38}I_2N_2O_2$	35.70	34.01[j]	6.89	6.00[j]	45.62	45.50	5.04	5.12
23	1:50 MeOH–*i*-PrOH	$C_{15}H_{30}Br_2N_2O_2$	41.87	41.4	7.03	7.1	37.15	37.22	6.51	6.40
24	1:8 MeOH–Me_2CO	$C_{23}H_{34}Br_2N_2O_2$	52.07	51.42	6.46	6.72	30.14	30.52	5.28	5.22
25	MeOH	$C_{13}H_{30}I_2N_2O_2$	31.21	31.54	6.05	6.04	50.74	51.08	5.60	5.62
26	Abs. EtOH	$C_{15}H_{34}I_2N_2O_2$	34.10	33.8	6.49	6.4	48.05	48.0	5.30	5.2
27	1:30 H_2O–Me_2CO	$C_{15}H_{34}I_2N_2O_2$	34.10	33.89	6.49	6.46	48.05	47.98	5.30	5.32
28	MeOH	$C_{13}H_{28}I_2N_2O_2$	31.34	31.46	5.67	5.32	50.95	49.72	5.62	5.61
29	MeOH–Me_2CO	$C_{17}H_{36}I_2N_2O_2$	36.84	36.90	6.55	6.60	45.79	45.73	5.05	4.79
30	1:3 MeOH–Me_2CO	$C_{14}H_{30}I_2N_2O_2$	32.83	32.18[j]	5.90	5.74	49.55	49.38	5.47	5.26
31	MeOH	$C_{13}H_{28}I_2N_2O_2$	30.37	30.89	5.49	5.59	49.36	49.62	5.45	5.38
32	MeOH	$C_{13}H_{28}I_2N_2O_2$	31.34	31.08	5.67	5.52	50.95	50.92	5.62	5.49
33	MeOH	$C_{14}H_{30}I_2N_2O_2 \cdot H_2O$[p]	31.71	31.72	6.08	6.11	47.87	48.38	5.28	5.22
	1:14 H_2O–Me_2CO	$C_{14}H_{30}I_2N_2O_2$	32.83	31.13[j]	5.90	5.86	49.55	50.40	5.47	5.45
34	MeOH	$C_{15}H_{32}I_2N_2O_2$	34.24	34.12	6.13	6.57	48.23	48.18	5.32	5.00
35	MeOH	$C_{13}H_{28}I_2N_2O_2$	30.37	30.42	5.49	5.46	49.36	49.89	5.45	5.33
36	99% *i*-PrOH	$C_{15}H_{32}I_2N_2O_2$	34.24	33.35[j]	6.13	6.38	48.23	48.05	5.32	5.39
37	1:10 H_2O–Me_2CO	$C_{14}H_{30}I_2N_2O_2$	31.83	31.84	5.72	5.55	48.05	47.81	5.30	5.19
38	1:3 MeOH–Me_2CO	$C_{14}H_{30}I_2N_2O_2$	32.83	32.33	5.90	5.78	49.55	49.30	5.47	5.47
39	MeOH–Me_2CO	$C_{14}H_{30}I_2N_2O_2$	31.83	31.38	5.72	5.79	48.05	48.18	5.30	5.25
40	MeOH–Me_2CO	$C_{16}H_{34}I_2N_2O_2$	35.57	35.52	6.34	5.89	46.98	46.74	5.19	5.01
41	Abs. EtOH	$C_{17}H_{36}I_2N_2O_2$	36.84	36.56	6.55	6.42	45.79	45.92	5.05	4.82

TABLE I (*Continued*)

Cmpd.	R_1 R_2 R_3 $\overset{+}{N}$	C-Alkyl (1′,2′,3′,4′) if present	$\overset{+}{N}$ R_4 R_5 R_6	X	C.R.[a]	Hypotensive activity Dose/MLD[b] (mg./kg.)	H.R.[c]	Method[d]	Yield[e]	M.p., °C.[f]
42	$(CH_3)_3N^+$	3′-CH_3		I	0	1/100	45	A	40	170–172
43	$(CH_3)_3N^+$	4′-CH_3		I	0	4/200	30	A	8	170–175
44	$(CH_3)_3N^+$	4′-C_2H_5		I	0	2/125	20	A	23	170–172
45				I	4	1/50	15	A	61	176–177
46				I	0	3/50	20	A	58	165–167
47		3′-CH_3		I	0	1/50	115	A	74	160–161
48		3′3′-$(CH_3)_2$		I	0	1/50	100	A	87	90–93[l]
49		3′-CH_3		I	0	2/25	85	A	52	198–200
59		3′-CH_3		I	0	1/200	70	A	76	203–205
51	$^+NC_5H_5$		$^+NC_5H_5$	Br	0	5/75	15	B	38	215–216[l]

[a] Cholinergic rating: determined *in vitro* on rabbit ileum, compound 1 being arbitrarily rated 100; on this scale, acetylcholine is 10,000. [b] *Minimum lethal dose: the smallest intravenous dose killing all of the mice tested.* [c] Hypotensor rating: the time during which the specified intravenous dose of bis-quaternary ester reduced the blood pressure of a rat by at least 20 mm., expressed as per cent. of the corresponding time produced by 1 mg./kg. of pentolinium tartrate (M.L.D. = 50 mg./kg.); values above 5 are rounded to the nearest 5%. [d] Methods of preparation: A, ditertiary aminoester plus alkyl halide; B, dihaloester plus tertiary amine; C, ammonioalkyl halopropionate plus tertiary amine. [e] This is the yield of purified material. [f] Taken on a Fisher–Johns microblock; most of these salts melt with decomposition. [g] Ref. 3, m.p. 190°. [h] One preparation m.p. 184–185°; it analyzed well. [i] Another preparation m.p. 192–195°; it analyzed well. [j] Carbon–hydrogen values for some of these bis-quaternary salts are consistently low, presumably due to erratic decomposition during combustion. [k] H_2O, calcd. 3.6, found 3.4 (Fischer). [l] Hygroscopic. [m] This compound gave low, erratic results by the usual micro-Dumas and micro-Kjeldahl methods. [n] H_2O, calcd. 1.7, found 1.1 (Fischer). [o] Based on the corresponding 2-ammonioalkanol iodide; the intermediate ammonioalkyl 3-iodopropionate iodide was an oil. [p] H_2O, calcd. 3.4; found 2.6 (Fischer). [q] H_2O, calcd. 1.7; found 2.2 (Fischer).

havior, it was revealed by its unusual pharmacological properties.

Preparation of Quaternary Ammonium Salts.—The quaternization reactions were usually run in low molecular weight polar organic solvents such as acetone, methanol, ethanol, chloroform, ether and combinations of these. The preferred halogen compounds were iodides, occasionally bromides were used, and chlorides were not as satisfactory; usually the smallest alkyl group was introduced last, methyl iodide being the most reactive reagent. Two attempts to use methyl chloride as the quaternizing reagent, with 2-diethylaminoethyl 3-diethylaminopropionate and with 2-dimethylaminobutyl 3-dimethylaminopropionate, did not give the desired product. The second of these cases was investigated more thoroughly and was shown to give, reproducibly, a compound whose physical properties, analyses and derivatives did not agree with those of a dichloride prepared by anionic exchange of chloride for the iodide of 2-trimethylammoniobutyl 3-trimethylammoniopropionate diiodide; its structure was not determined.

In the preparation of additional salts of these bisquaternary ammonium esters (Table II) by replacing iodide with some other anion, the reaction conditions had to be relatively mild, to avoid decomposition. The picrates were easily precipitated from an aqueous solution (method II-F), but for other salts the most general method was the use of anion exchange resin (method II-D) although nitrates and bitartrates could be obtained from the silver salts (method II-E). A few examples are given in Table II, others were isolated but were too hygroscopic or poorly crystalline to characterize.

Pharmacology.—The compounds of Table I have been shown to exert their hypotensive action through ganglionic blockade; the details of this and other pharmacological data will be reported elsewhere.[13] Three columns in Table I summarize these results: C.R., the cholinergic rating (compared to compound I-1 on rabbit ileum *in vitro*); dose/M.L.D., the fraction of the intravenous minimum lethal dose (mg./kg. in mice) which was given to rats to obtain H.R., the hypotensor rating (compared to 1 mg./kg. of pentolinium tartrate).

As can be seen in Table I, the cholinergic rating tended to decrease as the weight of the cation increased, although three heterocyclic compounds, I-28, I-30 and I-31, do not show this. It is evident, however, that an increase of one or two carbons in the N-alkyls reduced the cholinergic rating much more when it occurred on the "alcohol" side of the ester (I-18) than when on the "acid" side (I-19) whereas with C-alkyls, substitution on the "acid" side gave the greater decrease (I-5 and I-6 *vs.* I-7 and I-8). The comparison of I-9 and I-10 *vs.*

(13) J. Hidalgo, W. Wilken and V. P. Seeberg, *Arch. intern. pharmacodyn.*, **118**, 210 (1959).

	Recrystn. solvent	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Halogen, % Calcd.	Halogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
42	1:10 H_2O–Me_2CO	$C_{16}H_{34}I_2N_2O_2$	35.57	35.18	6.34	5.84	46.98	46.28	5.19	4.85
43	95% EtOH	$C_{14}H_{30}I_2N_2O_3 + 0.5H_2O$[q]	31.30	31.53	5.82	5.94	47.25	47.03	5.21	5.02
44	1:25 H_2O–Me_2CO	$C_{15}H_{32}I_2N_2O_3$	33.23	32.72	5.95	6.25	46.81	46.46	5.17	5.18
45	2:5 MeOH–*i*-PrOH	$C_{15}H_{30}I_2N_2O_2 \cdot 0.5H_2O$	33.79	33.98	5.86	5.65	47.60	47.56	5.25	5.00
46	Abs. EtOH	$C_{17}H_{34}I_2N_2O_2$	36.97	37.09	6.21	5.91	45.96	46.20	5.07	5.50
47	MeOH–Me_2CO	$C_{16}H_{32}I_2N_2O_2$	35.70	35.53	5.99	5.99	47.16	46.90	5.20	4.76
48	Abs. EtOH	$C_{17}H_{34}I_2N_2O_2$	36.97	37.2	6.21	6.5	45.96	45.8	5.07	4.8
49	1:20 H_2O–Me_2CO	$C_{18}H_{36}I_2N_2O_2$	38.18	38.35	6.41	6.30	44.82	44.82	4.95	5.05
50	1:4 H_2O–Me_2CO	$C_{16}H_{32}I_2N_2O_4$	33.70	33.68	5.66	5.70	44.51	44.60	4.91	4.85
51	Abs. EtOH	$C_{15}H_{18}Br_2N_2O_2$	43.09	43.4	4.34	4.4	38.22	37.62	6.70	6.50

I-11 and I-12 does not show this, presumably because the addition of another carbon to each nitrogen, as in I-2 *vs.* I-1, depressed the C.R. into a range in which our test was not sufficiently discriminating. In the case of the *gem*-dimethyl compounds, I-13 and I-14 *vs.* I-15 and I-16, some of this relationship was demonstrable.

A comparison of the toxicities (M.L.D.) of I-6 and I-7 *vs.* I-5 and I-8 suggests that C-alkylation gives less toxic compounds if it is adjacent to the ester group (2′ and 3′) than if adjacent to the ammonio group (1′ and 4′); this is confirmed by I-10 and I-11 *vs.* I-9 and I-12 and emphasized by I-14 and I-15 *vs.* I-13 and I-16.

The values of the hypotensor rating (H.R.) show that I-47 and I-48 were comparable in potency to pentolinium tartrate; I-29 and I-49 were also quite active although more toxic; I-50 was of interest because of its much lower toxicity. None of these had significant cholinergic action, but another compound, I-25, which had a C.R. of 10, was investigated extensively to see if it would prevent the intestinal stasis often produced by ganglionic blockade. This proved to be the case, but the hypotensive activity was low.

Among the shorter acting compounds, where rapid detoxification and absence of cholinergic action were desired for use in producing controlled hypotension during surgical operations, I-3 and I-6 were given special testing and the latter appeared quite promising.

In vitro studies of the hydrolysis of 5 of these compounds by pseudocholinesterase, true (red blood cell) cholinesterase, and plasma by the method of Michel[14] showed that none was hydrolyzed. This is in harmony with the report of Strack and Frunder[15] that esters of β-homobetaine are not hydrolyzed by serum esterases.

(14) H. O. Michel, *J. Lab. Clin. Med.*, **34**, 1564 (1949).

(15) E. Strack and H. Frunder, *Hoppe-Seyler's Z. physiol. Chem.*, **286**, 51 (1950).

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Experimental[16]

Acid Chlorides.—3-Bromopropionyl chloride and crotonyl chloride were purchased. 3-Iodopropionyl chloride, b. p. 75–80° (18 mm.), was prepared from β-propiolactone *via* 3-iodopropionic acid by the method of Gresham, *et al.*,[17] and Hamilton and Simpson[18]; the yields for the two steps were 93 and 92%, respectively. Acrylyl chloride was prepared from propiolactone through 3-chloropropionic acid by the method of Gresham, *et al.*,[17] in yields of 73 and 71%, respectively. Senecioyl chloride, b p. 59–60° (29 mm.), was obtained in 90% yield from commercial senecioic acid by the method of Smith and Engelhardt.[19]

3-Dimethylamino-2,2-dimethylpropionyl Chloride Hydrochloride. 3-Dimethylamino-2,2-dimethylpropionic Acid.—A solution of 10.54 g. (0.09 mole) of 3-amino-2,2-dimethylpropionic acid[9] and 16.2 g. (0.20 mole) of 37% formaldehyde in 150 ml. of water was shaken overnight with 1 g. of 5% palladium-on-charcoal catalyst and 50 p.s.i. of hydrogen. The catalyst was filtered off, the filtrate concentrated *in vacuo* at 40° to a partially crystalline sirup and slurried with 75 ml. of acetone. This precipitate was recrystallized from 50 ml. of boiling acetone and the mother liquor reconcentrated and retreated twice, to give two smaller crops of crystals. The combined yield was dissolved in 100 ml. of hot acetone, filtered, concentrated to 45 ml. and let crystallize, yielding 9.21 g. of colorless product melting at 106–107° (lit.[11] m.p. 100°). Additional material of similar purity was obtained from the mother liquor, raising the total to 10.35 g. (79%).

Anal. Calcd. for $C_7H_{15}NO_2$: C, 57.90; H, 10.41; N, 9.65. Found: C, 58.02; H, 10.47; N, 9.54.

(16) All boiling points are uncorrected; all melting points were taken on a Fisher–Johns microblock. The carbon–hydrogen determinations and most of the halogen and nitrogen analyses were by Microchemical Specialties Co., Berkeley, Calif.

(17) T. L. Gresham, J. E. Jansen and F. W. Shaver, THIS JOURNAL, **72**, 72 (1950).

(18) C. S. Hamilton and C. L. Simpson, *ibid.*, **51**, 3159 (1929).

(19) L. I. Smith and V. A. Engelhardt, *ibid.*, **71**, 2671 (1949).

TABLE II: ADDITIONAL SALTS OF AMMONIOALKYL AMMONIOALKANOATES

Bis cation (Table I)[a]	X	Method[b]	Yield[c]	M.p., °C.[d]	Recrystn. solvent	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Halogen, % Calcd.	Halogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
3A	Cl	D	81	200–204.5[e]	1:20 *i*-PrOH–Me_2CO	$C_{15}H_{34}Cl_2N_2O_2$	52.17	52.2	9.92	10.0	20.53	20.3	8.11	7.7
3B	NO_3	E	40	155[e]	*i*-PrOH	$C_{15}H_{34}N_4O_8 \cdot H_2O$	43.26	43.8	8.71	8.6			13.45	13.1
4A	Br	A	22	179.5–180.5[e]	*i*-PrOH	$C_{17}H_{38}Br_2N_2O_2$	44.16	43.4[f]	8.28	8.0	34.57	35.6	6.06	6.3
7A	NO_3	E	53	147–148	Abs. EtOH	$C_{12}H_{28}N_4O_8$	40.44	40.42	7.92	7.92			15.72	15.51
7B	Pic[g]	F	68	178–179	MeOH	$C_{24}H_{32}N_8O_{16}$	41.86	42.05	4.68	4.84			16.27	16.13
25A	Cl	D	32	187–189[e]	1:4 *i*-PrOH–Me_2CO	$C_{13}H_{30}Cl_2N_2O_2$	49.21	49.6	9.53	9.4	22.35	22.2	8.83	8.6
		C	32[h]	208–209[e]	1:4 *i*-PrOH–Me_2CO			49.2		9.6		22.0		
25B	NO_3	E	70	166–167	*i*-PrOH	$C_{13}H_{30}N_4O_8$	42.15	41.99	8.16	8.09			15.13	15.04
25C	Pic[g]	F	68	191–192	MeOH	$C_{25}H_{34}N_8O_{16}$	42.74	42.86	4.88	4.97			15.95	15.79
34A	NO_3	E	78	142–144	*i*-PrOH	$C_{15}H_{32}N_4O_8$	45.44	45.16	8.14	7.86			14.13	14.01
34B	Bit[i]	E	7	123–126[e]	Abs. EtOH	$C_{23}H_{42}N_2O_{14}$	48.41	48.8	7.42	7.6			4.91	4.6
34C	Pic[g]	F	72	182–183	95% EtOH	$C_{27}H_{36}N_8O_{16}$	44.51	44.26	4.98	5.08			15.38	15.13
39A	Pic[g]	F	94	169–170	MeOH	$C_{26}H_{34}N_8O_{17}$	42.74	42.91	4.69	4.82			15.34	14.70
47A	NO_3	D	45	143–144[e]	*i*-PrOH	$C_{16}H_{32}N_4O_8$	47.05	46.8	7.90	7.9			13.72	13.5
47B	Bit[i]	D	51	145–148	1:2 MeOH–Me_2CO	$C_{24}H_{42}N_2O_{14}$	49.48	49.73	7.27	7.32			4.81	4.82
		E	11	145–146	MeOH–Et_2O									
47C	Pic[g]	F	87	172	MeOH	$C_{28}H_{38}N_8O_{16}$	45.41	45.34	4.90	4.99			15.13	14.96

[a] These numbers identify the cationic portion of the salt and refer to Table I. [b] Methods of preparation: A, ditertiary aminoester plus alkyl halide; B, dihaloester plus tertiary amine; C, ammonioalkyl halopropionate plus tertiary amine; D, diammonioester dihalide plus anion exchange resin; E, diammonioester dihalide plus silver salt of the appropriate acid; F, diammonioester dihalide plus picric acid. [c] This is the yield of purified material. [d] Taken on a Fisher–Johns microblock; most of these salts melt with decomposition. [e] Hygroscopic. [f] Carbon–hydrogen values for some of these bis-quaternary salts are consistently low, presumably due to erratic decomposition during combustion. [g] Picrate. [h] Based on 2-trimethylammonio-1-butanol chloride. [i] Bitartrate.

This 3-dimethylamino-2,2-dimethylpropionic acid was converted to the acid chloride hydrochloride[11] and used *without purification*.

Dihalogenated Esters.—2-Chloroethyl 3-chloropropionate, b.p. 109–112° (20 mm.), was obtained in 94% yield by the method of Marvel, *et al.*[20] 2-Bromoethyl 3-bromopropionate, b.p. 126–130° (15 mm.), was prepared in 77% yield by the method of Schueler and Keasling.[5] 2-Iodoethyl 3-iodopropionate, b.p. 111–114° (1 mm.), was prepared in 66% yield from the acid chloride and 2-iodoethanol and in 51% yield by refluxing 2-chloroethyl 3-chloropropionate with sodium iodide in 2-butanone.

Anal. Calcd. for $C_5H_8I_2O_2$: I, 71.71. Found: I, 71.49.

Aminoalkyl Alkanoates (Table IV). (a) **2-Dimethylaminoethyl Acrylate (Method IV-A).**[6]—A solution of 178 g. (2.0 moles) of 2-dimethylaminoethanol in 730 ml. (8.1 moles) of methyl acrylate was treated with 20 g. of N-phenyl-2-naphthylamine and 40 ml. of distillate was slowly (5 hours) removed through a 30-plate distilling column to dry the system. A 20-g. portion of commercial aluminum isopropoxide was added and during the next 17 hours 210 ml. of distillate (containing *ca.* 70 ml. of methanol) was withdrawn at 62–65°. The residue was distilled under nitrogen and then refractionated from fresh inhibitor to give 147 g. (51%) of colorless ester (IV-1) boiling at 59.5–61.5° (11 mm.), reported[6] b.p. 61° (11 mm.). Considerable polymer remained in the original reaction vessel.

(b) **2-Dimethylaminoethyl Senecioate (Method IV-B).**[7]—A solution of 53.38 g. (0.45 mole) of senecioyl chloride[19] in 350 ml. of dry benzene was treated dropwise during one hour with a solution of 40.10 g. (0.45 mole) of 2-dimethylaminoethanol in 50 ml. of dry benzene. The flask was shaken occasionally and the rate of addition regulated so that the temperature remained at 40–50°. The mixture was refluxed for two hours, cooled in an iced water-bath and shaken with a cold solution of 70 g. (0.56 mole) of potassium carbonate in 100 ml. of water. The aqueous layer was extracted with three 100-ml. portions of benzene; all benzene phases were united, washed with 25 ml. of cold, saturated aqueous sodium chloride solution and dried over anhydrous magnesium sulfate. Distillation through a small Vigreux column gave 59.30 g. (77%) of clear, yellowish liquid (IV-10), boiling at 85–86° (6 mm.).

2-Aminoalkyl 3-Aminoalkanoates (Table V). (a) **Method V-A (1). 2-Dimethylaminoethyl 3-Dimethylamino-2,2-dimethylpropionate.**—A solution of 43.4 g. (0.96 mole) of anhydrous dimethylamine in 119.4 g. (0.76 mole) of 2-dimethylaminoethyl methacrylate (IV-6) was prepared in an ice-cooled pressure bottle, stoppered and let stand at room temperature for 18 days. Distillation of the solution gave 145.6 g. (95%) of colorless ester (V-6) boiling at 78–81° (2.5 mm.).

(2) **1-Methyl-2-(1-pyrrolidinyl)-ethyl 1-Pyrrolidinepropionate.**—To 108.5 g. (0.59 mole) of 1-methyl-2-(1-pyrrolidinyl)-ethyl acrylate (IV-14) was added, over a 15-min. period, 46.3 g. (0.65 mole) of pyrrolidine; the heat of reaction brought the solution to a gentle boil. This refluxing was continued on a steam-bath for 30 min. and then the product was distilled. The yield of colorless ester (V-31) was 128.7 g. (85%) boiling at 168–170° (15 mm.).

(b) **Method V-B. 2-Diethylaminoethyl 3-Diethylaminopropionate Dihydrochloride.**—A solution of 52 g. (0.20 mole) of 2-bromoethyl 3-bromopropionate in 250 ml. of benzene was treated with 58.6 g. (0.80 mole) of diethylamine

(20) C. S. Marvel, J. Dec, H. G. Cooke, Jr., and J. C. Cowan, THIS JOURNAL, **62**, 3495 (1940).

TABLE III

TERTIARY AMINOALCOHOLS $HOCH_2CH_2NR_4R_5$ (3′ 4′)

Number	C-Alkyl (3′,4′) if present	NR_4R_5	Method[a]	Yield	B.p. °C.	B.p. Mm.[b]
1		$N(C_2H_5)CH_3$	A	52	145–150[c]	
2		$N(C_4H_9)C_2H_5$	B	52	79–82	12[d]
3	3′-CH_3	$N(CH_3)_2$	[e]		124–126	
4	4′-CH_3	$N(CH_3)_2$	C	59	68–69	38[f]
5	4′-C_2H_5	$N(CH_3)_2$	C[g]	84	164–166[h]	
6	3′,3′-$(CH_3)_2$	$N(CH_3)_2$	B	64	129.5–131.5[i]	
7	4′,4′-$(CH_3)_2$	$N(CH_3)_2$	C	66	158–160[j]	
8		NC_4H_8[t]	B	45	188–191[k]	
9		NC_5H_{10}[u]	B	66	199–202[l]	
10	3′-CH_3	NC_4H_8[t]	A	76	75–78	15[m]
11	3′-CH_3	NC_5H_{10}[u]	A	84	195–197[n]	
12	3′-CH_3	$NC_5H_9CH_3$[v]	A	81	210–212[o]	
13	3-′CH_3	NC_4H_8O[w]	A	69	102–103	17.5[p]
14	4′-CH_3	NC_4H_8O[w]	D	65	112–113	16[q]
15	4′-C_2H_5	NC_4H_8O[w]	D	54	84–88	2.5[r]
16	3′,3′-$(CH_3)_2$	NC_4H_8[t]	B	66	77–79	18[s]

[a] Methods of preparation: A, secondary amine plus epoxide; B, secondary amine plus halogen alcohol; C, aminoalcohol plus formaldehyde and formic acid; D, aminoalcohol plus bis-(2-chloroethyl) ether. [b] Atmospheric pressures are not indicated. [c] B. Emmert, *Ber.*, **45**, 432 (1912), reported b.p. 149–150°. [d] H. C. Brill, THIS JOURNAL, **54**, 2486 (1932), reported b.p. 195°. [e] Commercial. [f] J. Attenburrow, J. Elks, B. A. Hems and K. N. Speyer, *J. Chem. Soc.*, 514 (1949), reported b.p. 65° (37 mm.). [g] The more dilute reaction conditions of C. H. Tilford and M. G. Van Campen, Jr., THIS JOURNAL, **76**, 2432 (1954), were used; the yield by unmodified method C was 40–50%. [h] *Anal.* Calcd. for $C_6H_{15}NO$: N, 11.95. Found: N, 11.75. [i] B. K. Campbell and K. N. Campbell, THIS JOURNAL, **60**, 1373 (1938), reported b.p. 130°. [j] V. Rosnati, *Gazz. chim. ital.*, **80**, 663 (1950), reported b.p. 159–161°. [k] J. v. Braun, O. Braunsdorf and K. Räth, *Ber.*, **55**, 1673 (1922), reported b.p. 187–189°. [l] R. Hazard, J. Cheymol, P. Chabrier, E. Corteggiani and F. Nicholas, *Arch. intern. pharmacodyn.*, **84**, 237 (1950), reported b.p. 198°. [m] J. H. Hunter and W. B. Reid, U. S. Patent 2,483,998 (1949), reported b.p. 116–117° (110 mm.). [n] A. Ladenburg, *Ber.*, **14**, 1880 (1881), reported b.p. 194°. [o] *Anal.* Calcd. for $C_9H_{19}NO$: N, 8.91. Found: N, 9.02. [p] $n^{20}D$ 1.4633; L. C. Cheney and W. G. Bywater, THIS JOURNAL, **64**, 970 (1942), reported b.p. 82–84° (1.5 mm.), $n^{20}D$ 1.4638. [q] J. Attenburrow, J. Elks, B. A. Hems and K. N. Speyer, *J. Chem. Soc.*, 510 (1949), reported b.p. 121–124° (18 mm.). [r] *Anal.* Calcd. for $C_8H_{17}NO_2$: N, 8.80. Found: N, 8.76. [s] *Anal.* Calcd. for $C_5H_{17}NO$: N, 9.78. Found: N, 9.30. [t] NC_4H_8 = 1-pyrrolidinyl. [u] NC_5H_{10} = 1-piperidinyl. [v] $NC_5H_9CH_3$ = 4-methyl-1 piperidinyl. [w] NC_4H_8O = 4-morpholinyl.

TABLE IV

AMINOALKYL ALKENOATES $CH_2{=}CHCOOCH_2CH_2NR_4R_5$ (1′ 2′ 3′ 4′)

Number	C-Alkyl (1′,2′,3′,4′) if present	NR_4R_5	Method[a]	Yield	B.p. °C.	B.p. Mm.	Formula	Nitrogen, % Calcd.	Nitrogen, % Found
1		$N(CH_3)_2$	A	51	59.5–61.5	11[b]			
2		$N(C_2H_5)_2$	[c]		69–71	5[d]			
3		$N(C_4H_9)C_2H_5$	B	76	105–107	12	$C_{11}H_{21}NO_2$	7.03	6.69
4	1′-CH_3	$N(CH_3)_2$	B	85	76–78	6	$C_8H_{15}NO_2$	8.91	8.73
5	1′-CH_3	$N(C_2H_5)CH_3$	B	75	58–62	2.5	$C_9H_{17}NO_2$	8.18	8.55
6	2′-CH_3	$N(CH_3)_2$	[c]		62–65	6[e]			
7	3′-CH_3	$N(CH_3)_2$	B	73	72–74	21	$C_8H_{15}NO_2$	8.91	8.59
8	4′-CH_3	$N(CH_3)_2$	B	50	85–86	23	$C_8H_{15}NO_2$	8.91	8.43
9	4′-C_2H_5	$N(CH_3)_2$	A	49	79–81	10	$C_9H_{17}NO_2$	8.18	8.09
			B	85	90–92	18			8.00
10	1′,1′-$(CH_3)_2$	$N(CH_3)_2$	B	77	85–86	6	$C_9H_{17}NO_2$	8.18	8.12
11	3′,3′-$(CH_3)_2$	$N(CH_3)_2$	B	75	75–77	20	$C_9H_{17}NO_2$	8.18	7.75
12	4′,4′-$(CH_3)_2$	$N(CH_3)_2$	B	58	93–96	18	$C_9H_{17}NO_2$	8.18	8.11
13		NC_5H_{10}[f]	B	68	100–103	8.5	$C_{10}H_{17}NO_2$	7.64	7.48
14	3′-CH_3	NC_4H_8[g]	B	83	101–104	15	$C_{10}H_{17}NO_2$	7.64	7.73
15	3′-CH_3	NC_5H_{10}[f]	B	72	117–121	21	$C_{11}H_{19}NO_2$	7.10	7.18
16	3′-CH_3	$NC_5H_9CH_3$[h]	B	69	84–86	2.5	$C_{12}H_{21}NO_2$	6.63	6.42
17	3′-CH_3	NC_4H_8O[i]	B	83	98–100	4.5	$C_{10}H_{17}NO_3$	7.03	6.98
18	4′-CH_3	NC_4H_8O[i]	B	67	86–91	1.5	$C_{10}H_{17}NO_3$	7.03	6.89
19	4′-C_2H_5	NC_4H_8O[i]	B	62	115–119	5	$C_{11}H_{19}NO_3$	6.57	6.76
20	3′,3′-$(CH_3)_2$	NC_4H_8[g]	B	75	109–113	18	$C_{11}H_{19}NO_2$	7.10	6.93

[a] Methods of preparation: A, aminoalcohol plus methyl acrylate (ref. 6); B, aminoalcohol plus acid chloride (ref. 7). [b] Ref. 6, b.p. 61° (11 mm.). [c] Commercial. [d] Ref. 6, b.p. 70° (5 mm.). [e] G. D. Graves, U. S. Patent 2,138,763 (1938), reported b.p. 62–65° (6 mm.). [f] NC_5H_{10} = 1-piperidinyl. [g] NC_4H_8 = 1-pyrrolidinyl. [h] $NC_5H_9CH_3$ = 4-methyl-1-piperidinyl. NC_4H_8O = 4-morpholinyl.

TABLE V

2-AMINOALKYL 3-AMINOALKANOATES $R_2R_3NCH_2CH_2COOCH_2CH_2NR_4R_5$ (1′ 2′ 3′ 4′)

Number	R_2R_3N	C-Alkyl (1′,2′,3′,4′) if present	NR_4R_5	Method[a]	Yield	B.p. °C.	B.p. Mm.	Formula	Nitrogen anal. Calcd.	Found
1	$(CH_3)_2N$		$N(CH_3)_2$	A	91	86–86.5	4[b]	$C_9H_{20}N_2O_2$	14.88	14.90
				B	65	108–110	14[c]			
2	$(C_2H_5)_2N$		$N(CH_3)_2$	A	84	104–106	4	$C_{11}H_{24}N_2O_2$	12.95	13.00
3	$(CH_3)_2N$		$N(C_2H_5)_2$	A	89	103–105	4	$C_{11}H_{24}N_2O_2$	12.95	13.10
4	$(C_2H_5)_2N$		$N(C_2H_5)_2$	A	92	113.5–115	2.5	$C_{13}H_{28}N_2O_2$	11.46	11.35
4A	$(C_2H_5)_2N$		$N(C_2H_5)_2\cdot 2HCl$	B	63[d]	m. p. 229–230		$C_{13}H_{30}Cl_2N_2O_2$[e]	8.83	8.51
5	$(CH_3)_2N$	1′-CH_3	$N(CH_3)_2$	A	94	91.5–93.5	3	$C_{10}H_{22}N_2O_2$	13.85	14.03
6	$(CH_3)_2N$	2′-CH_3	$N(CH_3)_2$	A	95	78–81	2.5	$C_{10}H_{22}N_2O_2$	13.85	13.61
7	$(CH_3)_2N$	3′-CH_3	$N(CH_3)_2$	A	96	90.5–91	5.5	$C_{10}H_{22}N_2O_2$	13.85	14.01
8	$(CH_3)_2N$	4′-CH_3	$N(CH_3)_2$	A	50	124–127	16.5	$C_{10}H_{22}N_2O_2$	13.85	13.50
9	$(CH_3)_2N$	4′-C_2H_5	$N(CH_3)_2$	A	86	102–106	5	$C_{11}H_{24}N_2O_2$	12.95	13.25
10	$(C_2H_5)_2N$	4′-C_2H_5	$N(CH_3)_2$	A	73	117–119	5	$C_{13}H_{28}N_2O_2$	11.46	11.63
11	$(CH_3)_2N$	1′,1′-$(CH_3)_2$	$N(CH_3)_2$	C	60	87–89.5	2	$C_{11}H_{24}N_2O_2$	12.95	12.51
				A	0					
12	$(CH_3)_2N$	2′,2′-$(CH_3)_2$	$N(CH_3)_2$	D	52[f]	90–93	2.5	$C_{11}H_{24}N_2O_2$	12.95	12.70
13	$(CH_3)_2N$	3′,3′-$(CH_3)_2$	$N(CH_3)_2$	A	98	89–91	4	$C_{11}H_{24}N_2O_2$	12.95	12.58
14	$(CH_3)_2N$	4′,4′-$(CH_3)_2$	$N(CH_3)_2$	A	96	93.5–96.5	2	$C_{11}H_{24}N_2O_2$	12.95	13.06
15	$(CH_3)_2N$	2′,2′,3′,3′-$(CH_3)_4$	$N(CH_3)_2$	D	47[f]	87–89	2.5	$C_{13}H_{28}N_2O_2$	11.46	11.29
16	C_4H_8N[h]		$N(CH_3)_2$	A	65	105–109	3	$C_{11}H_{22}N_2O_2$	13.07	12.59
17	C_4H_8N[h]		$N(C_4H_9)C_2H_5$	A	66	149–154	3	$C_{15}H_{30}N_2O_2$	10.36	10.23
18	$C_5H_{10}N$[i]		$N(CH_3)_2$	A	87	100–103	1.5	$C_{12}H_{24}N_2O_2$	12.27	11.82
19	OC_4H_8N[j]		$N(CH_3)_2$	A	73	95–98	1.5	$C_{11}H_{22}N_2O_3$	12.16	11.96
20	$(CH_3)_2N$		NC_5H_{10}[i]	A	77	126–128	5	$C_{12}H_{24}N_2O_2$	12.27	11.82
21	C_4H_8N[h]	1′-CH_3	$N(C_2H_5)CH_3$	A	43	103–104	1.5	$C_{13}H_{26}N_2O_2$	11.56	11.94
22	OC_4H_8N[j]	1′-CH_3	$N(CH_3)_2$	A	78	124–128	1	$C_{12}H_{24}N_2O_3$	11.47	11.46
23	C_4H_8N[h]	2′-CH_3	$N(CH_3)_2$	A	69	82–87	1	$C_{12}H_{24}N_2O_2$	12.27	12.15
24	OC_4H_8N[j]	2′-CH_3	$N(CH_3)_2$	A	70	137–140	6	$C_{12}H_{24}N_2O_3$	11.47	11.21
25	$CH_3C_5H_9N$[k]	3′-CH_3	$N(CH_3)_2$	A	67	126–128	2	$C_{14}H_{28}N_2O_2$	10.93	10.84
26	$(CH_3)_2N$	3′-CH_3	$NC_5H_9CH_3$[k]	A	88	113–115	1.5	$C_{14}H_{28}N_2O_2$	10.93	10.96
27	$(CH_3)_2N$	4′-CH_3	NC_4H_8O[j]	A	36	138–140	3.5	$C_{12}H_{24}N_2O_3$	11.47	11.14
28	$(CH_3)_2N$	4′-C_2H_5	NC_4H_8O[j]	A	64	117–120	1	$C_{13}H_{26}N_2O_3$	10.84	11.00
29	C_4H_8N[h]		NC_4H_8[h]	B	29	165–168	18	$C_{13}H_{24}N_2O_2$	11.66	11.67
30	C_5H_{10}[i]		NC_5H_{10}[i]$\cdot 2HCl$	B	31[g]	m. p. 229		$C_{15}H_{30}Cl_2N_2O_2$	8.21	8.22
31	C_4H_8N[h]	3′-CH_3	NC_4H_8[h]	A	85	168–170	15	$C_{14}H_{26}N_2O_2$	11.01	11.00
32	$C_5H_{10}N$[i]	3′-CH_3	$NC_5H_{10}N$[i]	A	96	114.5–115	1.5	$C_{16}H_{30}N_2O_2$	9.92	9.97
33	OC_4H_8N[j]	3′-CH_3	NC_4H_8O[j]	A	91	159–163	1	$C_{14}H_{26}N_2O_4$	9.78	9.88
34	OC_4H_8N[j]	4′-C_2H_5	NC_4H_8O[j]	A	61	161–164	1	$C_{15}H_{28}N_2O_4$	9.33	9.55
35	C_4H_8N[h]	3′,3′-$(CH_3)_2$	NC_4H_8[h]	A	64	165–169	18	$C_{15}H_{28}N_2O_2$	10.44	9.85

[a] Methods of preparation: A, secondary amine plus aminoalkyl acrylate; B, secondary amine plus dihaloester; C, method A plus 0.3 equivalent of glacial acetic acid; D, *t*-aminoacyl chloride hydrochloride plus aminoalcohol. [b] Ref. 3, b.p. 85° (3 mm.) by method B. [c] Contained 3% bromine (contaminant from dibromoester). [d] Based on dibromoester. [e] Calcd.: Cl, 22.35. Found: Cl, 22.21. [f] Based on 2,2-dimethyl-3-dimethylaminopropionic acid. [g] Based on diiodo ester. [h] C_4H_8N = 1-pyrrolidinyl. [i] $C_5H_{10}N$ = 1-piperidinyl. [j] OC_4H_8N = 4-morpholinyl. [k] $CH_3C_5H_9N$ = 4-methyl-1-piperidinyl.

in 30 min. and cooled occasionally to prevent refluxing. After standing at room temperature for four days it was refluxed for 24 hours, chilled, and the diethylamine hydrobromide filtered off. The filtrate was treated with a solution of 18.2 g. (0.50 mole) of hydrogen chloride in 500 ml. of acetone and cooled in an iced water-bath. The colorless crystals were filtered and recrystallized from 300 ml. of methanol to give 32 g. of the desired diaminoester dihydrochloride (V-4A) melting at 229–230°. An additional 8 g. of similar purity was isolated from the mother liquors, bringing the yield to 63%.

(c) **Method V-C. 2-Dimethylaminoethyl 3-Dimethylamino-3-methylbutyrate**.—A solution of 6 g. (0.10 mole) of glacial acetic acid and 24 g. (0.53 mole) of anhydrous dimethylamine in 51.37 g. (0.30 g.) of 2-dimethylaminoethyl senecioate (IV-10) was prepared in an ice-cooled pressure bottle and stoppered. The contents were kept at 40° (homogeneous) for three days and then let stand at room temperature (the diethylammonium acetate separated as a heavier phase) for one month. The upper phase was fractionally distilled to yield 38.76 g. (60%) of almost colorless ester (V-11) boiling at 87–89.5° (2 mm.).

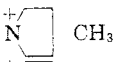
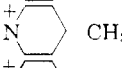
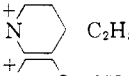
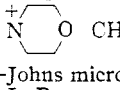
A similar experiment in which the glacial acetic acid was omitted gave none of the desired product.

(d) **Method V-D. 2-Dimethylaminoethyl 3-Dimethylamino-2,2-dimethylpropionate**.—To 2.90 g. (0.020 mole) of 3-dimethylamino-2,2-dimethylpropionic acid was added carefully 8.0 ml. (0.11 mole) of thionyl chloride. There was an immediate vigorous reaction and the mixture was refluxed on a steam-bath for one hour. After standing overnight, the excess thionyl chloride was removed *in vacuo* and the crystalline residue twice treated with 10-ml. portions of dry benzene and concentrated to dryness *in vacuo*.

The crude acid chloride hydrochloride was treated with a solution of 1.78 g. (0.020 mole) of 2-dimethylaminoethanol in 10 ml. of alcohol-free chloroform and refluxed one hour to yield a crystalline mush. The solvent was removed *in vacuo* and the residue was dissolved in 5 ml. of water. This solution was cooled in iced water, made alkaline with a cold solution of 7 g. (0.050 mole) of potassium carbonate in 5 ml. of water and extracted with three 10-ml. portions of benzene. These were combined, dried over magnesium sulfate and distilled through a semi-micro Vigreux column.

TABLE VI

AMMONIOALCOHOL IODIDES $HOCH_2CH_2\overset{3'}{N}R_4R_5R_6\overset{4'}{}\cdot I^-$

Number	C-Alkyl (3',4') if present	$NR_4R_5R_6$	Yield	M.p., °C.[a]	Recrystn. solvent	Formula	Iodine, % Calcd.	Iodine, % Found
1	3'-CH_3	$N(CH_3)_3$	70[b]	158–159	MeOH	$C_6H_{16}INO$		
2	4'-C_2H_5	$N(CH_3)_3$	30[c]	223–226	MeOH–Et_2O	$C_7H_{18}INO$[d]	48.97	49.40
3	4',4'-$(CH_3)_2$	$N(CH_3)_3$	60[c]	239–240[e]	EtOH	$C_7H_{18}INO$	48.97	48.88
4			74[f]	179–180[g]	MeOH–Me_2CO–Et_2O	$C_7H_{16}INO$	49.36	49.80
5			93[f]	235–238[h]	MeOH–Et_2O	$C_8H_{18}INO$		
6			87[f]	260	MeOH–Me_2CO–Et_2O	$C_9H_{20}INO$	44.50	44.30
7			94[f]	128–129[i]	MeOH	$C_7H_{16}INO_2$		

[a] Taken on a Fisher–Johns microblock; most of these salts melt with decomposition. [b] Prepared from propylene oxide and trimethylamine [J. L. Brannon, U. S. Patent 2,475,005 (1949)], followed by hydriodic acid; the product is 1-trimethylammonio-2-propanol iodide [E. M. Schultz and J. M. Sprague, THIS JOURNAL, **70**, 50 (1948), reported m.p. 153–154°], rather than the 2-trimethylammonio-1-propanol iodide which the patent would predict; the yield was based on trimethylamine. [c] Based on primary aminoalcohol; prepared by treatment with excess methyl iodide and sodium hydroxide in methanol. [d] The corresponding chloride was prepared in 74% yield, m. 166–170°, very hygroscopic, from this iodide and anion exchange resin. *Anal.* Calcd.: Cl, 21.14. Found: Cl, 20.47. [e] V. Rosnati, *Gazz. chim. ital.*, **80**, 663 (1950), reported m.p. 237–238°. [f] Based on heterocyclic aminoalcohol; prepared by treatment with alkyl iodide. [g] J. v. Braun, O. Braunsdorf and K. Rath, *Ber.*, **55**, 1666 (1922), reported no m.p. [h] Footnote *g* reference reported m.p. 238°. [i] A. H. Ford-Moore, A. G. Lidstone and W. A. Waters, *J. Chem. Soc.*, 819 (1946), reported m.p. 127°.

TABLE VII

AMMONIOALKYL 3-IODOPROPIONATE IODIDES[a] $ICH_2CH_2COOCH_2CH_2\overset{3'}{N}R_4R_5R_6\overset{4'}{}\cdot I^-$ (1' 2')

Number	C-Alkyl (1',2',3',4') if present	$NR_4R_5R_6$	Yield	M.p., °C.[b]	Recrystn. solvent	Formula	Iodine, % Calcd.	Iodine, % Found
1	3'-CH_3	$N(CH_3)_3$	63	117–118	5:1:5 Me_2CO–MeOH–Et_2O	$C_9H_{19}I_2NO_2$	59.43	59.24
2	4'-C_2H_5	$N(CH_3)_3$	75	125–127	MeOH	$C_{10}H_{21}I_2NO_2$	57.54	57.87
3	4',4'-$(CH_3)_2$	$N(CH_3)_3$	30	180–181	Abs. EtOH	$C_{10}H_{21}I_2NO_2$	57.54	57.40

[a] Other esters which were prepared and used as oily intermediates without further purification were the 1-methylpyrrolidinio-, 1-methylpiperidinio-, 1-ethylpiperidinio- and 4-methylmorpholinio-ethyl 3-iodopropionate iodides. [b] Taken on a Fisher–Johns microblock.

The yield of colorless oil (V-12) boiling at 90–93° (2.5 mm.) was 2.24 g. (52%).

2-Ammonioalkyl 3-Iodopropionate Iodides (Table VII). 1-Methyl-2-trimethylammonioethyl 3-Iodopropionate Iodide.—A mixture of 12.25 g. (0.050 mole) of 1-trimethylammonio-2-propanol iodide and 12.3 g. (0.056 mole) of 3-iodopropionyl chloride in a flask was heated gently with a free flame until it melted and then kept on a steam-bath for one hour. The reddish-brown oil was digested with three portions of ether and the insoluble residue recrystallized from 50 ml. of hot acetone. The colorless crystals were recrystallized from 50 ml. of acetone, 10 ml. of methanol and 50 ml. of ether to give 13.5 g. (63%) of colorless ester, melting at 117–118°.

2-Ammonioalkyl 3-Ammonioalkanoate Salts (Table I). (a) Method I-A. (1) 2-Trimethylammoniobutyl 3-Trimethylammoniopropionate Diiodide.—A solution of 324 g. (1.50 moles) of 2-dimethylaminobutyl 3-dimethylaminopropionate (V-9) in 3 liters of acetone was seeded with the desired product and treated with 568 g. (4.00 moles) of methyl iodide in 90 min., stirring continuously and cooling the flask as needed to keep the temperature below 25°. After crystallizing overnight, the product was filtered off, dried (crude yield 95%), dissolved in 2 liters of boiling methanol and filtered hot. The filtrate was let crystallize overnight at +5° and the colorless product (I-25) filtered and dried *in vacuo* at 60°; the yield was 635 g. (85%) melting at 183–185°.

Another run, in which the heat of reaction was allowed to bring the solution to reflux, gave a more complex mixture of products, from which were isolated a 37% yield of the diammonioester diiodide, a 25% yield of tetramethylammonium iodide and a 33% yield of 2-trimethylammoniobutyl acrylate iodide. The structure of this latter compound was confirmed by treating 2-dimethylaminobutyl acrylate (IV-9) in acetone with methyl iodide and recrystallizing the product twice from the same solvent to give a 78% yield of material melting at 120–121°.

Anal. Calcd. for $C_{10}H_{20}INO_2$: I, 40.52. Found: I, 40.77.

(2) 2-(*n*-Butyldimethylammonio)-ethyl 3-(*n*-Butyldimethylammonio)-propionate Diiodide.—A solution of 1.88 g. (0.010 mole) of 2-dimethylaminoethyl 3-dimethylaminopropionate (V-1) in 20 ml. of acetone was treated with 5.52 g. (0.030 mole) of *n*-butyl iodide, seeded and let stand at room temperature for one week. The nicely crystalline product was filtered and washed with a little acetone; 2.30 g., m.p. 116–122°. This was dissolved in 6 ml. of absolute ethanol, centrifuged twice to remove some insoluble material and the supernate was treated with 3 ml. of acetone and kept at +2° for four days. The crystals were filtered in a dry-box and washed with a little cold mixed solvent and with acetone. The yield was 0.91 g. (16%) of colorless product (I-22) melting at 149.5–150.5°; this melting point was not raised by another recrystallization.

The carbon–hydrogen values for I-22 are too low, but we have found that several of these trialkylammonio compounds give erratic combustion results; in such cases we place more reliance on the iodine and nitrogen values.

(3) 2-Triethylammonioethyl 3-Triethylammoniopropionate Diiodide.—A seeded solution of 4.89 g. (0.020 mole)

of 2-diethylaminoethyl 3-diethylaminopropionate (V-4) and 9.36 g. (0.060 mole) of ethyl iodide was let stand at room temperature for one month while crystals slowly deposited; these were filtered, washed and dried to yield 6.87 g. (61%), m. p. 145–175°. This was refluxed briefly with 150 ml. of isopropyl alcohol and let stand overnight; the 4.35 g. of precipitate was recrystallized from 5 ml. of methanol plus 10 ml. of isopropyl alcohol to yield 3.50 g., m.p. 158.5–164°. Two more recrystallizations, each from 2 ml. of methanol plus 4 ml. of isopropyl alcohol, gave 2.84 g. (25%) of (I-4) melting at 160.5–162.5°.

(4) 2-Triethylammonioethyl 3-Triethylammoniopropionate Dibromide.—A seeded solution of 4.89 g. (0.020 mole) of 2-diethylaminoethyl 3-diethylaminopropionate (V-4) and 6.54 g. (0.060 mole) of ethyl bromide in 20 ml. of acetone stood at room temperature for one month while crystals slowly deposited; these were filtered (in a dry-box, −40° dew point), washed and dried; the crude yield of very hygroscopic product was 5.63 g. (61%). It was refluxed briefly with 30 ml. of isopropyl alcohol, cooled to room temperature, filtered, and the filtrate concentrated on a steam-bath to one-half its original volume and treated with 30 ml. of ether to precipitate tan needles. After several days these were separated (in the dry-box) and recrystallized twice from 5-ml. portions of isopropyl alcohol to yield 2.05 g. (22%) of colorless needles (II-4A), m.p. 179.5–180.5°, very hygroscopic.

These properties agreed completely with those of another sample, prepared in somewhat lower yield by shaking an aqueous solution of 2-triethylammonioethyl 3-triethylammoniopropionate diiodide (I-4) with excess freshly precipitated silver bromide for two hours; the filtrate was dried and recrystallized twice from isopropyl alcohol–ether.

For comparison, we repeated the preparation for "RACET" given by Schueler and Keasling.[5] To 6.5 g. (0.025 mole) of 2-bromoethyl 3-bromopropionate was added 70 ml. (0.50 mole) of anhydrous triethylamine. A colorless solid began to precipitate at once and after 18 hours at room temperature it was filtered and washed with 200 ml. of anhydrous ether; yield 4.4 g. after air drying for 3 days. The crystals, on heating, commenced to grow at 165°, sublimed slowly at 220° and melted at 248–250°; a sample of commercial triethylamine hydrobromide behaved similarly and a mixed melting point was not depressed. Schueler and Keasling reported that their "RACET" sublimed slowly at 163°, and melted at 244°; it was non-hygroscopic.

Anal. Calcd. for $C_6H_{16}BrN$: C, 39.57; H, 8.86; Br, 43.88; N, 7.69. Found: C, 39.86; H, 8.33; Br, 43.66; N, 7.80.

The intravenous minimal lethal dose in mice for our preparation of "RACET" was 190 mg./kg.; this agrees well with a value of 150 mg./kg. for triethylamine hydrochloride and is much higher than the 50 mg./kg. reported in Table I for 2-triethylammonioethyl 3-trimethylammoniopropionate diiodide (I-4).

(b) Method I-B. (1) 2-Trimethylammonioethyl 3-Trimethylammoniopropionate Diiodide.—A solution of 10 g. (0.028 mole) of 2-iodoethyl 3-iodopropionate and 15 g. (0.25 mole) of trimethylamine in 500 ml. of dioxane (freshly distilled from sodium) was let stand at room temperature for four days. The 12.3-g. crop of pale yellow crystals (m.p. 138–145°) was recrystallized from methanol three times to yield 7.0 g. (61%) of almost colorless product (I-1) melting at 196–197°.

(2) 2-Pyridinioethyl 3-Pyridinopropionate Dibromide.—A solution of 5.2 g. (0.020 mole) of 2-bromoethyl 3-bromopropionate and 7.9 g. (0.10 mole) of pyridine in 50 ml. of dry benzene was refluxed for 7 hours and let cool to room temperature. The precipitated oil was recrystallized twice from absolute ethanol (25 and 30 ml., respectively) to yield 3.2 g. (38%) of moderately hygroscopic, colorless crystals (I-51) melting at 215–216°.

(c) Method I-C. (1) 1-Methyl-2-trimethylammonioethyl 3-Trimethylammoniopropionate Diiodide.—A mixture of 2.0 g. (0.0047 mole) of 1-methyl-2-trimethylammonioethyl 3-iodopropionate iodide (VII-1) and 1.5 g. (0.025 mole) of trimethylamine in 15 ml. of chloroform was shaken vigorously for 5 minutes, at which time the solid material had changed to a colorless oil, which crystallized on standing overnight at room temperature. The crystals were washed with chloroform by decantation and crystallized twice from 10-ml. portions of methanol to give 2.0 g. (88%) of colorless crystals (I-7), melting at 203–204°.

(2) 2-(1-Methylpiperidinio)-ethyl 3-Trimethylammoniopropionate Diiodide.—A mixture of 13 g. (0.048 mole) of 2-(1-methylpiperidinio)-ethanol iodide (VI-5) and 15 g. (0.069 mole) of 3-iodopropionyl chloride was allowed to react spontaneously and became homogeneous in 15 minutes. It was heated on a steam-bath for one hour and then extracted with three 50-ml. portions of ether to remove unreacted acid chloride (but perhaps not all of it). The ether-insoluble residue was dissolved in 20 ml. of methanol and, when this deposited no crystals after one day, it was treated with a solution of 5 g. (0.085 mole) of trimethylamine in 50 ml. of chloroform and a little ether to turbidity. After one day at +5°, a few crystals had formed and 50 ml. of ether was added, precipitating an oil which began to crystallize. This was separated and crystallized by digestion with acetone, the product being recrystallized from 25 ml. of methanol plus 20 ml. of ether. This was crystallized from methanol to yield 12.9 g. (51%) melting at 170–171°; analytical results for the desired product as a monohydrate (I-33) were quite acceptable. However, it was very cholinergic and toxic (C.R. 1000; MLD 12.5 mg./kg.); another recrystallization gave values (C.R. 10; MLD 50 mg./kg.) which were identical with those obtained for another batch of I-33 prepared by method I-A.

In investigating the nature of this highly cholinergic material which was removed by the final recrystallization, we prepared methyl 3-dimethylaminopropionate, b.p. 151.5–154° (literature[12] value 154.5°) in 86% yield from dimethylamine and methyl acrylate (method V-A); with methyl iodide, this gave 73% of methyl trimethylammoniopropionate iodide, m.p. 194–195° (literature[12] value, 191–192°) after two recrystallizations from methanol. This product was shown to be extremely cholinergic and toxic (C.R. 10,000; MLD 0.5 mg./kg.). It seems likely that it comprised 5–10% of the I-33 as first tested.

(Table II) (a). Method II-D. 2-(Diethylmethylammonio)-ethyl 3-(Diethylmethylammonio)-propionate Dichloride.—A 3" diameter plastic column was charged with 2400 ml. of Duolite A-40 anion exchange resin[21] in the chloride form and a solution of 211.3 g. (0.40 mole) of 2-(diethylmethylammonio)-ethyl 3-(diethylmethylammonio)-propionate diiodide (I-3) in 250 ml. of water was placed on it and eluted by distilled water at the rate of 1200 ml. per hour. The product was collected in a 2000-ml. fraction, concentrated to 300 ml. *in vacuo* at room temperature and diluted with 2000 ml. of isopropyl alcohol. This solution was again concentrated *in vacuo* at 35° to remove water until the residual volume was 350 ml. It was filtered (rinsing with 100 ml. of isopropyl alcohol) and diluted with 9 liters of acetone to precipitate a nearly colorless crystalline product which weighed 124.4 g., m. 192–198°, after washing with mixed solvent and with acetone and drying in the dry-box (dew point, −40°) at room temperature. Two more recrystallizations, from 400 ml. of isopropyl alcohol plus 8 liters of acetone and from 350 ml. of isopropyl alcohol plus 7 liters of acetone gave 112.1 g. (81%) of colorless product (II-3A) melting at 200–204.5°. The compound was extremely hygroscopic and was handled in the dry-box.

Method II-E. 2-Trimethylammoniobutyl 3-Trimethylammoniopropionate Dinitrate.—A solution of 1.25 g. (0.0025 mole) of 2-trimethylammoniobutyl 3-trimethylammoniopropionate diiodide (I-25) in 15 ml. of water was mixed with a solution of 0.86 g. (0.005 mole) (an excess should be avoided) of silver nitrate in 10 ml. of water, shaken for a few minutes, filtered and the filtrate evaporated under reduced pressure to a colorless solid. This was recrystallized from two 25-ml. portions of isopropyl alcohol to give 0.65 g. (70%) of colorless crystals (II-25B) melting at 166–167°.

Method II-F. 2-Trimethylammonioethyl 2-Methyl-3-(4-methylmorpholinio)-propionate Dipicrate.—A solution of 1.0 g. (0.0019 mole) of 2-trimethylammonioethyl 2-methyl-3-(4-methylmorpholinio)-propionate diiodide (I-39) in 15 ml. of water was added to 2.3 g. (0.010 mole) of picric acid in 150 ml. of warm water. On cooling, a yellow oil precipitated and slowly crystallized. It was recrystallized from 300 ml. of methanol to give 1.3 g. (94%) of canary yellow crystals (II-39A) melting at 169–170°.

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(21) A quaternary ammonium resin manufactured by Chemical Process Co., Redwood City, Calif.