[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF G. D. SEARLE AND CO.]

AUTONOMIC BLOCKING AGENTS. II. ALKAMINE ESTERS AND THEIR QUATERNARIES[1]

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In the preceding report (1) was described a group of aliphatic quaternary ammonium salts and analogous piperidinium and pyrrolidinium salts which possessed a relatively high potency as ganglion blocking agents. As stated in the first report, one objective of this work was to find a substance with oral activity. Since no great improvement in this respect was to be expected in simple quaternary salts due to their low rate of absorption, the syntheses were extended to include more complex quaternary salts of which a number of quaternary derivatives of basic esters are described in this report. Although the introduction of hydroxyalkyl groups into simple quaternaries is known to lower their ganglion blocking power, some restoration of activity on acylation might be expected. Accordingly, the quaternary ammonium derivatives of a large group of basic esters, many of which incorporated the amine groups from which highly active simple quaternaries were obtained, have been prepared.

Many similar tertiary basic esters have been extensively investigated for spasmolytic action and in instances where a comparison with the corresponding quaternary ammonium derivative was made it was usually observed that neurotropic action was increased while musculotropic action was diminished. The activity of the compounds of this series in relaxing acetylcholine-induced spasm was measured against atropine as a standard and the results are included in Tables I, II, and III.

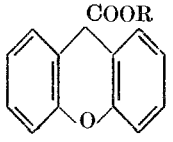
The tertiary basic esters were prepared by the method of Horenstein and Pählicke (2). Quaternization of the series by the addition of ethyl halides was not completed because some of the esters would not withstand the severe conditions necessary for quaternization. Two etho salts, 32 and 33 of Table I, of prime interest because they are related to the most active ganglion blocking agents, were prepared by reaction of the acid chloride with the hydroxyalkylammonium salts.

Pharmacology. When considered on a molar basis, the ganglion blocking power of the hydroxyalkylammonium salts was usually increased by acylation. Although the high activity of the corresponding simple quaternaries was not attained the activity was restored within a useful range. The incidence of good spasmolytic action was high in those esters derived from good ganglion blocking agents. Oral activity was considerably improved in this series. Compound 1 Table I, β-diethylaminoethyl-9-xanthenecarboxylate methobromide is an orally effective ganglion blocking agent which has recently been successfully employed in the control of peptic ulcer (4).

[1] Presented before the Medicinal Division of the American Chemical Society, April, 1950, Philadelphia, Pa.

TABLE I

ESTERS OF 9-XANTHENECARBOXYLIC ACID



NO.	R	M.P., °C. (Corr.)	FORMULA	NITROGEN		HALOGEN		GANGLION BLOCKING ACTION,[c] $Et_4N^+Br^-$ = 1	ANTIACETYLCHOLINE-ACTIVITY,[d] Atropine = 1
				Calc'd	Found	Calc'd	Found		
1	$CH_2CH_2\overset{+}{N}(C_2H_5)_2(CH_3)\ Br^-$[a]	175–176	$C_{21}H_{26}BrNO_3$			19.01	19.16	1.4	0.67
2	$CH_2CH_2\overset{+}{N}(C_2H_5)_3\ Br^-$[a]	195–196	$C_{22}H_{28}BrNO_3$			18.39	18.19	1.7	1.47
3	$CH_2CH_2\overset{+}{N}(C_2H_5)_2(C_3H_7)\ I^-$[a]	124–125	$C_{23}H_{30}INO_3$	55.76[b]	55.94[b]	25.62	25.23	1.5	0.15
4	$CH_2CH_2\overset{+}{N}(C_2H_5)_2(C_4H_9)\ Br^-$[a]	117–118	$C_{24}H_{32}BrNO_3$	3.03	3.11	17.28	17.36	1.0	.04
5	$CH_2CH_2\overset{+}{N}(C_2H_5)_2(CH_2CH_2OH)\ Br^-$[a]	148–149	$C_{22}H_{28}BrNO_4$	3.11	3.12	17.75	17.82	1.6	.08
6	$CH_2CH_2N(i\text{-}C_3H_7)(CH_3)\cdot HCl$	105–106	$C_{20}H_{24}ClNO_3$	3.87	3.89	9.80	9.82	<0.1	.04
7	$CH_2CH_2\overset{+}{N}(i\text{-}C_3H_7)(CH_3)_2\ Br^-$	188	$C_{21}H_{26}BrNO_3$	3.33	3.39	19.01	19.15	2.0	2.27
8	$CH_2CH_2N(i\text{-}C_3H_7)(C_2H_5)\cdot HCl$	172–173	$C_{21}H_{26}ClNO_3$	3.73	3.67	9.43	9.47	<0.01	0.07
9	$CH_2CH_2\overset{+}{N}(i\text{-}C_3H_7)(C_2H_5)(CH_3)\ Br^-$	178–179	$C_{22}H_{28}BrNO_3$	3.23	3.22	18.40	18.49	0.44	1.84
10	$CH_2CH_2N(i\text{-}C_3H_7)_2\cdot HCl$	111–112	$C_{22}H_{28}ClNO_3$	3.59	3.58	9.10	9.05	.5	0.24
11	$CH_2CH_2\overset{+}{N}(i\text{-}C_3H_7)_2(CH_3)\ Br^-$	156–157	$C_{23}H_{30}BrNO_3$	3.12	3.12	17.82	17.83	2.0	3.77
12	$CH_2CH_2CH_2\overset{+}{N}(C_2H_5)_2(CH_3)\ Br^-$	186–187	$C_{22}H_{28}BrNO_3$	60.83[b]	60.50[b]	18.40	18.50	2.0	0.45
13	$CH_2CH_2CH_2\overset{+}{N}(C_2H_5)_3\ Br^-$	123–124	$C_{23}H_{30}BrNO_3$	3.12	3.13	17.82	17.82	2.4	.60
14		128–129	$C_{20}H_{22}ClNO_3$	66.75[b]	66.75[b]	9.85	9.79	<0.1	.03
15		164–166	$C_{21}H_{24}BrNO_3$			19.10	19.39	1.0	.23
16		179–180	$C_{22}H_{26}BrNO_3$	61.11[b]	61.01[b]	18.48	18.33	1.2	.56

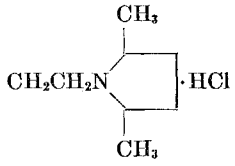
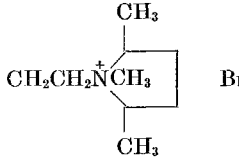
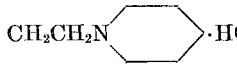
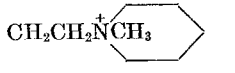
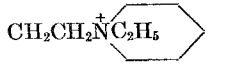
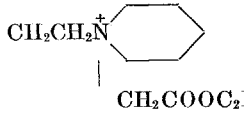
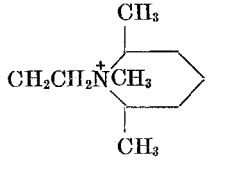
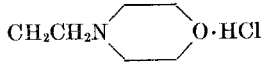
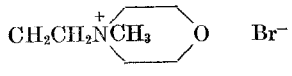
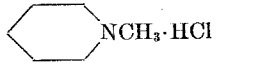
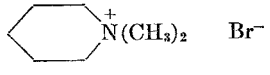
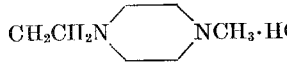
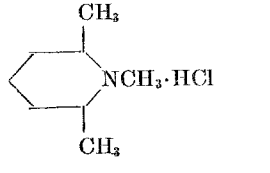
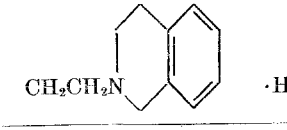
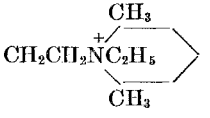
17		144	$C_{22}H_{26}ClNO_3$	68.11[b]	67.73[b]	9.14	9.2	0.7	.52
18		185–186	$C_{23}H_{28}BrNO_3$	61.88[b]	61.92[b]	17.90	17.91	1.1	1.86
19		146–147	$C_{21}H_{24}ClNO_3$	67.46[b]	67.65[b]	9.48	9.58	—	0.02
20		161–162	$C_{22}H_{26}BrNO_3$	—	—	18.48	18.42	1.4	.35
21		167–168	$C_{23}H_{28}BrNO_3$	61.88[b]	61.79[b]	17.90	17.97	1.4	.88
22		180–181	$C_{25}H_{30}BrNO_5$	59.53[b]	59.41[b]	15.84	15.85	3.0	.01
23		215	$C_{24}H_{30}BrNO_3$	62.61[b]	62.72[b]	17.36	17.55	2.36	.56

TABLE I—*Continued*

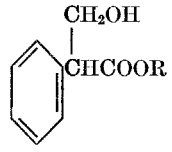
NO.	R	M.P., °C. (Corr.)	FORMULA	NITROGEN		HALOGEN		GANGLION BLOCKING ACTION,[c] $Et_4N^+Br^-$ = 1	ANTIACETYLCHOLINE ACTIVITY,[d] Atropine = 1
				Calc'd	Found	Calc'd	Found		
24		182–183	$C_{20}H_{22}ClNO_4$	3.73	3.67	9.43	9.30	0.1	.01
25		168–169	$C_{21}H_{24}BrNO$	3.23	3.23	18.40	18.43	0.82	.02
26		219–221	$C_{20}H_{22}ClNO_3$	3.89	3.96	9.85	9.8	<0.01	.95
27		226–227	$C_{21}H_{24}BrNO_3$	3.35	3.38	19.10	19.12	2.1	1.23
28		145–146	$C_{21}H_{25}ClN_2O_3$	7.21	7.16	9.12	9.09	—	<0.01
29		244–245	$C_{22}H_{24}ClNO_3$	68.12[b]	68.28[b]	9.14	9.12	—	0.1
30		163–165	$C_{25}H_{24}ClNO_3$	3.32	3.42	8.41	8.70	—	<0.01

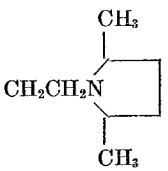
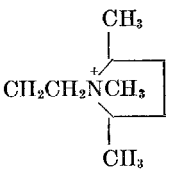
31	$CH_2CH(CH_3)\overset{+}{N}(CH_3)_3$	Br^-	175–177	$C_{20}H_{24}BrNO_3$	59.12[b]	59.02[b]	19.67	19.78	2.0	.45
32	$CH_2CH_2\overset{+}{N}(i\text{-}C_3H_7)_2(C_2H_5)$	Br^-	151–152	$C_{24}H_{32}BrNO_3$	3.03	2.98	17.28	17.10	1.56	4.42
33		Cl^-	203–204	$C_{25}H_{32}ClNO_3$	3.26	3.14	8.25	8.12	0.9	0.93
34	$CH_2CH_2\text{-}\overset{+}{N}(C_2H_5)_2(i\text{-}C_3H_7)$	Cl^-	—	$C_{23}H_{30}ClNO_3$	3.47	3.29	8.78	8.13	1.4	4.72

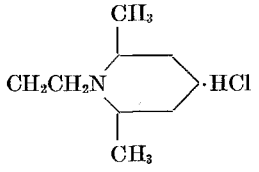
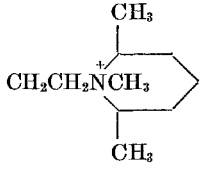
[a] The tertiary basic ester β-diethylaminoethyl 9-xanthenecarboxylate has been described by Burtner and Cusic (3). [b] Carbon analyses. [c] Sympathetic ganglion blockade (nictitating membrane) expressed as molar potency; $\frac{\text{mol. wt. of compound}}{\text{mol. wt. of } (C_2H_5)_4N^+Br^-} \times$ gram potency (4). [d] Anti-acetylcholine activity by the Magnus technique.

TABLE II

ESTERS OF TROPIC ACID



NO.	R	M.P., °C. (Corr.)	FORMULA	NITROGEN		HALOGEN		GANGLION BLOCKING ACTION,[b] $Et_4N^+Br^-$ = 1	ANTIACETYLCHOLINE ACTIVITY,[c] Atropine = 1
				Calc'd	Found	Calc'd	Found		
1	$CH_2CH_2\overset{+}{N}(i\text{-}C_3H_7)(CH_3)_2$ Br^-	115	$C_{16}H_{26}BrNO_3$	3.88	3.87	22.12	22.57	0.41	1.04
2	$CH_2CH_2N(i\text{-}C_3H_7)(C_2H_5)\cdot HCl$	93–94	$C_{16}H_{26}ClNO_3$	4.42	4.41	11.19	11.24	<0.1	0.1
3	$CH_2CH_2\overset{+}{N}(i\text{-}C_3H_7)(C_2H_5)(CH_3)$ Br^-	99–100	$C_{17}H_{28}BrNO_3$	3.73	3.75	21.29	21.69	.5	.66
4	$CH_2CH_2N(i\text{-}C_3H_7)_2\cdot HCl$	113–114	$C_{17}H_{28}ClNO_3$	4.15	4.23	10.51	10.75	.4	.06
5	$CH_2CH_2\overset{+}{N}(i\text{-}C_3H_7)_2(CH_3)$ Br^-	95–97	$C_{18}H_{30}BrNO_3$	3.61	3.61	20.58	20.54	3.5	.5
6	 $\cdot HCl$	106–108	$C_{17}H_{26}ClNO_3$	4.27	4.23	10.82	10.84	0.1	.58
7	 Br^-	185–186	$C_{18}H_{28}BrNO_3$	55.95[a]	55.93[a]	20.69	20.82	1.6	1.0

8		125–126	$C_{18}H_{23}ClNO_3$	4.10	4.05	10.37	10.24	0.44	0.2
9	 Br^-	169–170	$C_{19}H_{30}BrNO_3$	3.50	3.56	19.96	19.98	4.8	.14

[a] Carbon analysis. [b] See note (*c*) Table I. [c] See note (*d*) Table I.

TABLE III

MISCELLANEOUS ESTERS

NO.	ACID	AMINO ALCOHOL	SALT	M.P., °C.	FORMULA	NITROGEN		HALOGEN		GANGLION BLOCKING ACTION,[d] $Et_4N^+Br^-$ = 1	ANTIACETYLCHOLINE ACTIVITY[e] Atropine = 1
						Calc'd	Found	Calc'd	Found		
1	9-Methyl-9-fluorenecarboxylic	2-Diethylaminoethanol	HCl	118–120	$C_{21}H_{26}ClNO_2$	3.89	3.76	9.85	9.68		0.08
2	9-Fluorenecarboxylic	2-Dimethylaminoethanol	C_2H_5Br	200–210	$C_{20}H_{24}BrNO_2$	—	—	20.48	20.14	0.83	.33
3	9-Fluorenecarboxylic	2-Diisopropylaminoethanol	CH_3Br	124–125	$C_{23}H_{30}BrNO_2$	3.24	3.18	18.48	18.44	<0.1	.3
4	9-Fluorenecarboxylic	1-(2,6-Dimethylpiperidine)ethanol	HCl	206	$C_{23}H_{28}ClNO_2$	3.63	3.60	9.19	8.94	—	.06
5	9-Fluorenecarboxylic	1-(2,6-Dimethylpiperidine)ethanol	CH_3Br	180–195	$C_{24}H_{30}BrNO_2$	3.15	3.06	17.98	17.76	0.21	.14
6	9-Hydroxy-9-fluorenecarboxylic	2-Dimethylaminoethanol	CH_3Cl	223	$C_{19}H_{22}ClNO_3$	4.03	4.03	10.19	10.10	1.16	.16
7	9-Hydroxy-9-fluorenecarboxylic	2-Diethylaminoethanol[a]	C_2H_5Br	183–184	$C_{21}H_{26}BrNO_3$	3.33	3.31	19.01	19.24	0.63	.22
8	Diphenylacetic	2-Diethylaminoethanol[b]	CH_3Br	106–107	$C_{21}H_{28}BrNO_2$	3.45	3.40	19.67	19.47	.22	.013
9	Diphenylacetic	2-Diisopropylaminoethanol	HCl	84	$C_{22}H_{30}ClNO_2$	3.73	3.65	9.43	9.36	.54	<0.01
10	Diphenylacetic	2-Diisopropylaminoethanol	CH_3Br	176	$C_{23}H_{32}BrNO_2$	—	—	18.40	18.47	1.78	.02
11	Diphenylacetic	1-(2,6-Dimethylpiperidine)ethanol	HCl	—	$C_{23}H_{30}ClNO_2$	3.61	3.59	9.14	9.05	0.61	<0.01
12	Diphenylacetic	1-(2,6-Dimethylpiperidine)ethanol	CH_3Br	150–160	$C_{24}H_{32}BrNO_2$	—	—	17.90	17.92	5.65	0.014
13	9,10-Dihydro-9-anthroic	2-Diethylaminoethanol[a]	CH_3Br	161–162	$C_{22}H_{28}BrNO_2$	63.16[c]	63.37[c]	19.01	19.00		.08
14	9,10-Dihydro-9-anthroic	2-Dimethylaminoethanol	HCl	175–176	$C_{19}H_{22}ClNO_2$	4.22	4.18	10.69	10.59		<0.01
15	9,10-Dihydro-9-anthroic	1-Piperidineethanol	HCl	138	$C_{22}H_{26}ClNO_2$			9.53	9.56		<0.01
16	Benzilic	1-Pyrrolidineethanol	CH_3Br	205	$C_{21}H_{26}BrNO_3$		—	19.01	18.98	0.19	.2
17	Benzilic	2-Dimethylaminoethanol	$HOCH_2CH_2Br$	131–132	$C_{20}H_{24}BrNO_4$	3.30	3.15	18.83	18.75	.15	.33

[a] Burtner and Cusic (3). [b] Miescher, Hoffman, and Panizzonn, *Helv. Chim. Acta*, **24**, 458 (1941). [c] Carbon analysis. [d] See note (c) Table I. [e] See note (d) Table I.

The pharmacology of this series will be published by the Division of Biological Research of these laboratories.

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EXPERIMENTAL

The acids. The acids were prepared by the methods described by Burtner and Cusic (3).

The amino alcohols. The 2-dialkylaminoethanols which were not commercially available were prepared by the method of Burnett (5). The 4-piperidinol derivatives were prepared as described by Burtner and Cusic (3).

The dialkylaminoalkyl chlorides. The following method, which is essentially that of Reid (6), was employed for the preparation of the dialkylaminoalkyl chlorides.

1-(2-Chloroethyl)-2,5-dimethylpyrrolidine. 2,5-Dimethylpyrrolidineëthanol (107 g.), dissolved in 300 ml. of chloroform, was treated with hydrogen chloride (at 15–25°) to form the hydrochloride. Thionyl chloride (75 ml.) was added and the mixture was allowed to stand at room temperature for 48 hours. After distilling the solvent under diminished pressure the residue was washed with ether and butanone; yield 110 g., m.p. 135–136°. After recrystallization from butanone the hydrochloride melted at 137–138°.

Anal. Calc'd for $C_8H_{17}Cl_2N$: N, 7.07; Cl, 35.79; Cl^-, 17.9.
Found: N, 7.06; Cl, 35.5; Cl^-, 17.84.

1-(2-Chloroethyl)-2,6-lupetidine. Prepared in the same manner as the pyrrolidine derivative, m.p. 181°.

Anal. Calc'd for $C_9H_{19}Cl_2N$: N, 6.6; Cl, 33.42; Cl^-, 16.71.
Found: N, 6.61; Cl, 33.41; Cl^-, 16.67.

The dialkylaminoalkyl esters. The basic esters were prepared from the dialkylaminoalkyl chlorides and the free acids by the method of Horenstein and Pählicke (2). The esters of the piperidinols were produced by the action of the acid chloride upon the piperidinols (3).

β-Diisopropylaminoethyl ester of 9-xanthenecarboxylic acid. 9-Xanthenecarboxylic acid (83 g.) (m.p. 227–229°), 60 g. of 2-diisopropylaminoethyl chloride, and 150 ml. of 2-propanol refluxed 4 hours gave 120 g. of diisopropylaminoethyl 9-xanthenecarboxylate, m.p. 111–112°.

The quaternary salts. Quaternization was usually carried out in butanone solution. Diisopropylaminoethyl esters and others containing secondary alkyl groups gave colored impure products in butanone. The quaternization of such esters could be satisfactorily accomplished in chloroform solution.

β-Diisopropylaminoethyl 9-xanthenecarboxylate methobromide. The corresponding tertiary base (93 g.), 30 g. of methyl bromide and 150 ml. of chloroform were mixed and kept at 70–80° for 60 hours. The quaternary salt, which was soluble in chloroform, was precipitated by adding anhydrous ether and purified by two crystallizations from 2-propanol and ether. Yield 100 g.

β-Diisopropylaminoethyl 9-xanthenecarboxylate ethobromide. 2-Hydroxyethyldiisopropylethylammonium chloride (7 g.) and 10 g. of 9-xanthenecarbonyl chloride were mixed and warmed to 80–90° for one hour. The residue was washed with ether and crystallized from butanone and ether. The product was dissolved in butanone and precipitated as the iodide with sodium iodide. The iodide was purified by recrystallization first from chloroform and ether and then from 2-propanol. Yield 9 g., m.p. 148–149°. The iodide was converted to the bromide by the action of silver bromide in water. After removal of the silver iodide, the water solution was distilled to dryness at 25°. The crystalline product was dried *in vacuo* over phosphorus pentoxide. Yield 7 g.

SUMMARY

A number of basic esters and their quaternary ammonium derivatives, many of which are derived from active ganglion blocking agents, have been synthesized and evaluated as sympathetic ganglion blocking agents and for neurotropic spasmolytic action.

CHICAGO 80, ILLINOIS

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