ride precipitated as a gum which upon trituration with additional portions of dry ether yielded 4.0 g. of solid; yield after recrystallization, 9%.

Di-(2-pyrrolidino-1-phenylethyl) Phthalate Dihydrochloride. Method C (Table I, Compound 10).—A mixture of phthalic anhydride (4.55 g., 0.033 mole) and 100 ml. of toluene was stirred and heated to reflux in a flask fitted with a Dean–Stark water trap. Upon addition of 12.4 g. (0.06 mole) of 2-pyrrolidino-1-phenyl-ethanol,[1] a clear homogeneous solution was obtained. Dry hydrogen chloride was passed through the reaction mixture for a total of 32 hours with continued stirring and azeotropic reflux. A precipitate which formed immediately, remained throughout the process. Separation of water was substantially completed at the end of the 32-hour period. The precipitate was separated and triturated with ether yielding 16.4 g. of crude product; yield after recrystallization was 41%.

Di-(2-diethylamino-1-phenylethyl) Succinate. Method D (Table I, Compound 3).—A solution of 7.8 g. (0.04 mole) of 2-diethylamino-1-phenylethanol in 100 ml. of chlorobenzene was treated with 1.6 g. (0.04 mole) of dry hydrogen chloride. Succinyl chloride (3.1 g., 0.02 mole) was added at reflux temperature during a 0.5-hour period and refluxing and stirring were continued for 30 hours. At the end of this period, evolution of hydrogen chloride had practically ceased and a black, gummy reaction product had separated. The chlorobenzene was removed by decantation and the product was dissolved in water, the solution was washed with ether and made basic with 40% sodium hydroxide. The resultant oil which separated was extracted with five 20-ml. portions of ether and the combined extracts dried (magnesium sulfate). Filtration of the solution and evaporation of the solvent gave 2.4 g. of residue which was distilled to yield a small fore-run of 2-diethylamino-1-phenylethanol and then 0.9 g. (8%) of product boiling at 196° (0.06 mm.).

Di-(2-pyrrolidino-1-phenylethyl) Succinate Dimethobromide (Table I, Compound 5).—A solution of 4.3 g. (0.008 mole) of di-(2-pyrrolidino-1-phenylethyl) succinate dihydrochloride dihydrate in water was made basic with 40% sodium hydroxide and the free base extracted with ether. The ether extracts were dried (magnesium sulfate), filtered, the solvent removed and the residue of the free base was dissolved in 60 ml. of acetonitrile and treated with 3.0 g. of methyl bromide. After standing 20 hours, 3.1 g. of product was obtained; the yield after recrystallization was 52%.

2-Pyrrolidino-1-phenylethyl Dichloroacetate Hydrochloride (Table II, Compound 4).—A solution of 4.9 g. (0.033 mole) of dichloroacetyl chloride in 70 ml. of ether was cooled in an ice-bath. To this was added, with stirring, a solution of 5.8 g. (0.03 mole) of 2-pyrrolidino-1-phenylethanol[1] in 30 ml. of ether over a 20-minute period. Stirring and cooling were continued for an additional hour. The precipitate, after recrystallization from ethanol, weighed 6.9 g. (65%).

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE U. S. VITAMIN CORPORATION]

Local Anesthetics. II.[1] Esters of 2-Amino-1-phenyl- and 2-Amino-2-phenyl-ethanols

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A series of 2-amino-1-phenylethanols and 2-amino-2-phenylethanols have been esterified with benzoic, aryloxyacetic and cinnamic acids, and the resultant basic esters and their quaternary ammonium salts have been examined for pharmacological activity. Many compounds have been found which show a high order of local anesthetic activity, and within this series significant relationships between structure and activity are indicated. Certain compounds in this series show anti-tremorine action, hypotensive and ganglionic blocking effects, as well as adrenergic blocking and adrenergic potentiation effects.

Much of the published work on local anesthetics concerns procaine analogs of the type $RCOO–Y–NR_1R_2$ wherein R represents a substituted aryl or styryl group, Y is an alkylene radical and $–NR_1R_2$ is a secondary amino function.

This investigation was concerned chiefly with the effect on local anesthetic response when the alkylene linking element Y was varied as $–CH(R_4)CH_2–$ and $–CH_2CH(R_4)–$. The group R_4 represented phenyl, *p*-tolyl, *p*-chlorophenyl, α-naphthyl and cyclohexyl, but was largely retained as phenyl.

This structural feature of the R_4 substituent was retained throughout the work while R and $–NR_1R_2$ were varied principally to encompass factors contributing to anesthetic activity noted by other workers. In addition to the free bases and salts of the anesthetics described, a fairly broad evaluation of the quaternary ammonium salts (R_3X) was undertaken.

Typical of the compounds studied were I and II, and the products prepared have been described in Tables I and II, respectively.

$$RCOOCH(R_4)CH_2NR_1R_2\cdot R_3X \quad (I)$$

$$RCOOCH_2CH(R_4)NR_1R_2\cdot R_3X \quad (II)$$

The synthesis of the compounds listed in Tables I and II was effected by conventional procedures through reaction of the acid chloride RCOCl with the aminophenylethanol,[2] $R_1R_2NCH_2CH(R_4)OH$ or $R_1R_2NCH(R_4)CH_2OH$, with acetonitrile proving to be the preferred solvent. In most instances the hydrochloride of the desired compound precipitated or it could be recovered in sufficiently pure state for recrystallization upon evaporation of the solvent. In those instances in which the hydrochloride was not crystalline or granular, it was converted to the free base and the ester was purified by distillation.

The nitro compounds were reduced to the corresponding amino derivatives by familiar procedures.

Pharmacology.—The results and methods of the pharmacological tests have been given in Tables III and IV. The local anesthetic effect shows strong dependence on structure. Variation of the substituent R^3 correlates with Burger's[4] order in

(1) Paper I of this series, S. L. Shapiro, H. Soloway, E. Chodos and L. Freedman, THIS JOURNAL, **81**, 201 (1959).

(2) S. L. Shapiro, H. Soloway and L. Freedman, *ibid.*, **80**, 6060 (1958).

(3) For papers citing many references to this type of variation, see (a) J. S. Pierce and H. A. Rutter, Jr., *ibid.*, **74**, 3954 (1952); (b) W. H. Houff and R. D. Schuetz, *J. Org. Chem.*, **18**, 916 (1953).

(4) A. Burger, "Medicinal Chemistry," Vol. I, Interscience Publishers, Inc., New York, N. Y., 1951, p. 100.

TABLE I

ESTERS OF 2-AMINO-1-PHENYLETHANOLS $RCOOCHCH_2NR_1R_2 \cdot R_3X$[a]

R_3

No.	R_1	R_2	R_3X	Yield, %	M.p.,[b] °C., or b.p. (mm.)	RS[c]	Formula	Analyses,[d] % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
					R = C_6H_5–								
1	CH_3–	CH_3–		55	122–124 (0.02)		$C_{17}H_{19}NO_2$	75.8	75.4	7.1	7.7	5.2	4.9
2	CH_3–	CH_3–	HCl	53	213–215	A	$C_{17}H_{20}ClNO_2$	66.8	66.5	6.9	6.9	4.6	5.0
3	CH_3–	CH_3–	CH_3I	54	153–155	A	$C_{18}H_{22}INO_2$	52.6	52.8	5.4	5.7		
4	CH_3–	CH_3–	C_2H_5I	55	150–153	Z	$C_{19}H_{24}INO_2$	53.7	54.2	5.7	5.6	3.3	3.2
5	CH_3–	*i*-C_3H_7–	HCl	47	147–148	B	$C_{19}H_{24}ClNO_2$	68.4	68.4	7.3	7.4	4.2	4.0
6	CH_3–	*i*-C_3H_7–	CH_3I	53	222–223	C	$C_{20}H_{26}INO_2$					3.2	2.9
7	CH_3–	C_6H_{11}–[e]	HCl	68	197–198	D	$C_{22}H_{28}ClNO_2$	70.7	70.7	7.6	7.9	3.8	3.9
8	CH_3–	C_6H_5–		14	182–184 (0.08)		$C_{22}H_{21}NO_2$	79.7	79.7	6.4	6.5	4.2	3.9
9	CH_3–	C_8H_9–		24	168–170 (0.03)		$C_{24}H_{25}NO_2$	80.2	80.2	7.0	7.3	3.9	3.8
10	CH_3–	$C_6H_5CH_2$–		51	165–168 (0.18)		$C_{23}H_{23}NO_2$	80.0	80.2	6.7	6.6	4.1	3.9
11	C_2H_5–	C_2H_5–	HCl	65	140–142	D	$C_{19}H_{24}ClNO_2$	68.4	67.9	7.3	7.5	4.2	3.7
12	C_2H_5–	C_2H_5–	CH_3Cl	20	164–166	B	$C_{20}H_{26}ClNO_2$					4.0	3.9
13	*C_2H_5–*	*C_2H_5–*	*CH_2Br*	*58*	*191–192*	*D*	*$C_{20}H_{26}BrNO_2$*	*61.2*	*61.1*	*6.7*	*6.7*		
14	C_2H_5–	C_2H_5–	CH_3I	66	212–213	B	$C_{20}H_{26}INO_2$	54.7	54.7	6.0	6.0	3.2	3.1
15	C_2H_5–	C_2H_5–	DMS[g1]	73	148–149	E	$C_{21}H_{29}NO_6S$	59.6	60.0	6.9	6.8	3.3	3.0
16	C_2H_5–	C_2H_5–	C_2H_5Br	16	188–190	B	$C_{21}H_{28}BrNO_2$	62.0	62.0	6.9	6.8		
17	C_2H_5–	C_2H_5–	C_2H_5I	41	156–158	D	$C_{21}H_{28}INO_2$					3.1	2.8
18	C_2H_5–	C_2H_5–	DES[g2]	51	154–155	B	$C_{23}H_{33}NO_6S$	61.2	61.3	7.4	7.2	3.1	3.0
19	C_2H_5–	C_2H_5–	EBA[h]	10	167–169	E	$C_{23}H_{30}BrNO_4$	59.5	59.1	6.5	6.7	3.0	3.1
20	C_2H_5–	C_2H_5–	C_3H_5Br	25	108–109	B	$C_{22}H_{26}BrNO_2$	63.5	63.2	6.3	6.4		
21	C_2H_5–	C_2H_5–	$C_6H_5CH_2Cl$	12	181–183	B	$C_{26}H_{30}ClNO_2$	73.7	73.8	7.1	7.4	3.3	3.0
22[aa]	C_2H_5–	C_2H_5–	HCl	54	160–161	D	$C_{19}H_{23}Cl_2NO_2$	62.0	62.1	6.3	6.2	3.8	3.7
23[ab]	C_2H_5–	C_2H_5–	CH_3I	83	127–129	D	$C_{14}H_{22}INO_2$	46.3	46.5	6.1	6.2	3.9	4.0
24[ab]	C_6H_5–	C_2H_5–	C_2H_5I	40	137–140	B	$C_{15}H_{24}INO_2$	47.8	47.6	6.4	6.4	3.7	4.0
25[ac]	C_2H_5–	C_2H_5–		43	176–178 (0.8)		$C_{20}H_{25}NO_2$	77.1	77.2	8.1	8.3		
26	*n*-C_3H_7–	*n*-C_3H_7–		63	180–184 (0.9)		$C_{21}H_{27}NO_2$	77.5	78.2	8.4	8.2	4.3	4.2
27	*i*-C_3H_7	$C_6H_5CH_2$–	HCl	24	153–155	B	$C_{25}H_{28}ClNO_2$	73.2	73.0	6.9	7.3		
28	*n*-C_4H_9–	*n*-C_4H_9–		41	154 (0.05)		$C_{23}H_{31}NO_2$	78.1	78.5	8.8	9.1		
29		–$(CH_2)_4$–	HCl	80	190–192	A	$C_{19}H_{22}ClNO_2$	68.8	68.7	6.7	6.7	4.2	4.0
30		–$(CH_2)_4$–	CH_3I	37	204–207	I	$C_{20}H_{24}INO_2$	54.9	55.2	5.5	5.0		
31		–$(CH_2)_4$–	EBA[h]	63	125–127	I	$C_{23}H_{28}BrNO_4$	59.7	59.7	6.1	6.2	3.0	3.0
32		–$(CH_2)_5$–	HCl	64	206–208	A	$C_{20}H_{24}ClNO_2$	69.5	69.2	7.0	6.4	4.1	3.8
33		–C_8H_{16}–		46	178–180 (0.05)		$C_{23}H_{29}NO_2$	78.6	77.7	8.3	8.6	3.6	3.3
34		–$(CH_2)_6$–	HCl	49	195–197	D	$C_{21}H_{26}ClNO_2$	70.1		7.3	7.3	3.9	4.1
35		–$C_6H_{11}N$–[k]	HCl	21	220–223	A	$C_{26}H_{34}Cl_2N_2O_2$	60.5	60.5	6.6	6.9	7.1	7.4
36		–$(CH_2)_2O(CH_2)_2$–		12	161–165 (0.07)		$C_{18}H_{21}NO_3$	73.3	73.1	6.8	7.3	4.5	4.5
37		–$C_6H_{12}O$–[l]	HCl	26	163–165	H	$C_{20}H_{22}ClNO_3$	67.1	67.6	7.0	7.1	3.7	4.1
					R = 2-$CH_3C_6H_4$–								
38	C_2H_5–	C_2H_5–		29	142–143 (0.15)		$C_{21}H_{27}NO_2$	77.1	77.1	8.1	8.3	4.5	4.5
39		–$(CH_2)_5$–	HCl	86	165–167	B	$C_{21}H_{26}ClNO_2$	70.1	70.3	7.3	7.8	3.9	3.7
					R = 3-$CH_3C_6H_4$–								
40	C_2H_5–	C_2H_5–		68	144–145 (0.1)		$C_{21}H_{27}NO_2$	77.1	77.3	8.1	8.2	4.5	4.5
41		–$(CH_2)_4$–	HCl	75	172–173	B	$C_{20}H_{24}ClNO_2$	69.5	69.5	7.0	7.1	4.1	4.0
42		–$(CH_2)_4$–	CH_3I	56	163–164	D	$C_{21}H_{26}INO_2$	55.9	56.1	5.8	5.6		
43		–$(CH_2)_5$–	HCl	60	185–188	K	$C_{21}H_{26}ClNO_2$					3.9	3.5
					R = 4-$CH_3C_6H_4$–								
44	C_2H_5–	C_2H_5–	HCl	60	132–134	B	$C_{20}H_{26}ClNO_2$	69.0	68.7	7.5	7.5	4.0	3.7
45		–$(CH_2)_4$–	HCl	73	188–189	E	$C_{20}H_{24}ClNO_2$	69.5	69.5	7.0	7.1		
46		–$(CH_2)_4$–	CH_3I	53	111–113	M	$C_{21}H_{26}INO_2$	55.9	56.2	5.8	6.0	3.1	2.9
					R = 4-*t*-$C_4H_9C_6H_4$–								
47	C_2H_5–	C_2H_5–	HCl	51	156–157	B	$C_{23}H_{32}ClNO_2$	70.8	70.8	8.3	8.2	3.6	4.0
48		–$(CH_2)_4$–	HCl	66	178–179	H	$C_{23}H_{30}ClNO_4$	71.2	71.1	7.8	7.7	3.6	3.5
49		–$(CH_2)_4$–	CH_3I	55	204–205	A	$C_{24}H_{32}INO_2$	58.4	58.5	6.5	6.6	2.8	2.8
50		–$(CH_2)_5$–	HCl	62	167–169	H	$C_{24}H_{32}ClNO_2$	71.7	71.3	8.0	8.2	3.5	3.1
					R = 2-$CH_3OC_6H_4$–								
51	CH_3–	CH_3–	HCl	57	180–182	A	$C_{18}H_{22}ClNO_3$	64.4	64.6	6.6	6.9	4.2	3.9
52	CH_3–	*s*-C_4H_9–		33	160–161 (0.08)		$C_{21}H_{27}NO_3$	73.9	74.3	8.0	7.9		
53	CH_3–	$C_6H_5CH_2$–		37	181–184 (0.08)		$C_{24}H_{25}NO_3$	76.8	76.9	6.7	7.0		
54	CH_3–	C_6H_{11}–[e]		36	215–216 (0.5)		$C_{23}H_{29}NO_3$					3.8	3.6
55	CH_3–	C_6H_{11}–[e]	Pic.[m]		157–159	A	$C_{29}H_{32}N_4O_{10}$	58.4	58.0	5.4	5.5	9.4	9.2
56	CH_3–	C_6H_5–		56	218–220 (0.04)		$C_{23}H_{23}NO_3$	76.4	75.9	6.4	6.4	4.0	3.9
57	C_2H_5–	C_2H_5–	HCl	55	117–118	O	$C_{20}H_{26}ClNO_3$	66.0	66.3	7.2	7.2	3.9	3.9
58	C_2H_5–	C_2H_5–	CH_3I	84	185–188	A	$C_{21}H_{28}INO_3$	53.7	53.6	6.0	5.9		
59[ac]	C_2H_5–	C_2H_5–		12	184–190 (0.8)		$C_{21}H_{27}NO_3$	73.9	73.5	8.0	7.8	4.1	4.3
60	*n*-C_3H_7–	*n*-C_3H_7–		4	138–140 (0.5)		$C_{22}H_{29}NO_3$					3.9	3.5
61	*n*-C_3H_7–	*n*-C_3H_7–	Pic.[m]		115–116	T	$C_{28}H_{32}N_4O_{10}$	57.5	57.6	5.5	5.5	9.6	9.7
62	*i*-C_3H_7–	$C_6H_5CH_2$–	HCl	18	148–149	B	$C_{26}H_{30}ClNO_3$	71.0	71.4	6.9	6.8		
63	*n*-C_4H_9–	*n*-C_4H_9–		20	168–170 (0.04)		$C_{24}H_{35}NO_3$	75.2	75.1	8.7	8.9	3.7	4.0
64		–$(CH_2)_4$–	HCl	54	183–185	P	$C_{20}H_{24}ClNO_3$	66.4	66.7	6.7	7.0	3.9	4.2
65		–$(CH_2)_5$–	HCl	62	138–140	B	$C_{22}H_{28}ClNO_3$	67.8	68.1	7.2	7.3	3.6	3.9
66		–$(C_6H_{11}N$–[k]	2HCl	39	211–213	Q	$C_{27}H_{38}Cl_2N_2O_3$	59.0	59.1	6.6	6.6	6.6	6.8
67		–$(CH_2)_2O(CH_2)_2$–		11	184 (0.05)		$C_{20}H_{23}NO_4$	70.4	70.2	6.8	6.6	4.1	4.1

TABLE I (*Continued*)

No.	R_1	R_2	R_3X	Yield, %	M.p.,[b] °C., or b.p. (mm.)	RS[c]	Formula	Analyses,[d] % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
					R = 4-$CH_3OC_6H_4$–								
68	C_2H_5–	C_2H_5–		27	142–144 (0.06)		$C_{20}H_{25}NO_3$	73.4	73.4	7.7	7.8	4.3	4.1
69[ac]	C_2H_5–	C_2H_5–		45	180–186 (0.12)		$C_{21}H_{27}NO_3$	73.9	73.8	8.0	8.0	4.1	4.2
70	–$(CH_2)_4$–		HCl	74	196–198	D	$C_{20}H_{24}ClNO_3$	66.4	66.0	6.7	6.6	3.9	3.6
71	–$(CH_2)_4$–		CH_3I	77	198–199	A	$C_{21}H_{26}INO_3$					3.0	2.7
72	–C_8H_{16}–			23	182–186 (0.06)		$C_{24}H_{31}NO_2$	75.6	75.7	8.2	8.0	3.7	3.7
					R = 3,5-di-$CH_3OC_6H_3$–								
73	C_2H_5–	C_2H_5–		53	184–186 (0.3)		$C_{21}H_{27}NO_4$	70.6	70.6	7.6	7.3	3.9	3.6
74	C_2H_5–	C_2H_5–	CH_3I	56	163–164	A	$C_{22}H_{30}INO_4$	52.9	52.9	6.1	5.9		
75	–$(CH_2)_4$–		HCl	27	199–202	D	$C_{21}H_{26}ClNO_4$	64.4	64.3	6.7	7.2	3.6	3.7
					R = 3,4,5-tri-$CH_3OC_6H_2$–								
76	C_2H_5–	C_2H_5–	HCl	75	147–149	A	$C_{22}H_{30}ClNO_5$	62.3	62.2	7.1	6.8		
77	C_2H_5–	C_2H_5–	CH_3I	65	183–185	A	$C_{23}H_{32}INO_5$	52.2	52.7	6.1	6.0	2.7	2.8
78	C_2H_5–	C_2H_5–	C_2H_5I	57	92–95	M	$C_{24}H_{34}INO_5$	53.0	53.3	6.3	6.6		
					R = 2-$C_2H_5OC_6H_4$–								
79	CH_3–	CH_3–	HCl	55	183–184	A	$C_{19}H_{24}ClNO_3$	65.2	65.3	6.9	7.0	4.0	3.8
80	CH_3–	i-C_3H_7–		27	166–168 (0.15)		$C_{21}H_{27}NO_3$	73.9	74.3	8.0	8.1	4.1	3.8
81	C_2H_5–	C_2H_5–		44	154–156 (0.15)		$C_{21}H_{27}NO_3$	73.9	74.1	8.0	7.8	4.1	4.1
82	C_2H_5–	C_2H_5–	HCl	29	113–114	N	$C_{21}H_{28}ClNO_3$	66.7	66.7	7.5	7.4	3.7	3.8
83	C_2H_5–	C_2H_5–	CH_3I	70	145–146	R	$C_{22}H_{30}INO_3$	54.7	55.0	6.3	6.2	2.9	2.7
84[ac]	C_2H_5–	C_2H_5–		6	166 (0.12)		$C_{22}H_{29}NO_3$	74.3	74.1	8.2	8.2	3.9	4.1
85	i-C_3H_7–	$C_6H_5CH_2$–		17	151–154 (0.07)		$C_{27}H_{31}NO_3$	77.7	77.6	7.5	7.8		
86	–$(CH_2)_4$–		HCl	69	186–187	D	$C_{21}H_{26}ClNO_3$	67.1	66.8	7.0	7.1	3.7	3.7
87	–$(CH_2)_4$–		CH_3I	54	138–139	A	$C_{22}H_{28}INO_3$	54.9	55.3	5.9	6.2	2.9	2.8
88	–$(CH_2)_4$		EBA[h]	51	136–137	B	$C_{25}H_{32}BrNO_5$					2.8	2.7
89	–$(CH_2)_5$–		HCl	76	194–196	P	$C_{22}H_{28}ClNO_3$	67.8	67.9	7.2	7.3	3.6	3.4
90	–$(CH_2)_6$–		HCl	43	176–177	A	$C_{23}H_{30}ClNO_3$	68.4	68.1	7.5	7.1	3.5	3.5
91	–$C_6H_{11}N$–[k]		2HCl	50	185–188	D	$C_{22}H_{30}Cl_2N_2O_3$	59.9	60.1	6.9	6.8	6.4	6.5
92	–$(CH_2)_2O(CH_2)_2$–		HCl	37	171–172	K	$C_{21}H_{28}ClNO_4$	64.4	64.2	6.7	6.8		
					R = 4-$C_2H_5OC_6H_4$–								
93	C_2H_5–	C_2H_5–	HCl	30	143–145	B	$C_{21}H_{28}ClNO_3$	66.7	66.9	7.5	7.5	3.7	3.9
94	n-C_4H_9–	n-C_4H_9–		16	183–184 (0.05)		$C_{25}H_{35}NO_3$					3.7	3.7
95	n-C_4H_9–	n-C_4H_9–	Pic.[m]	33	122–123	A	$C_{31}H_{38}N_4O_{10}$	59.4	59.3	6.1	6.2		
96	–$(CH_2)_4$–		HCl	75	168–169	D	$C_{21}H_{26}ClNO_3$	67.1	67.4	7.0	7.1	3.7	3.9
97	–$(CH_2)_4$–		CH_3I	52	193–194	D	$C_{22}H_{28}INO_3$	54.9	55.4	5.9	6.0	2.9	2.6
98	–C_8H_{16}–[i]			12	194–196 (0.02)		$C_{26}H_{32}NO_3$	75.9	75.8	8.4	8.6	3.5	3.5
					R = 4-n-$C_4H_9OC_6H_4$–								
99	C_2H_5–	C_2H_5–		11	160–166 (0.06)		$C_{23}H_{31}NO_3$					3.8	4.0
100	–$(CH_2)_4$–		HCl	36	155–156	O	$C_{23}H_{30}ClNO_3$					3.5	3.8
101	–$(CH_2)_4$–		CH_3I	53	150–151	A	$C_{24}H_{32}INO_3$	56.6	56.8	6.3	6.2	2.8	2.8
					R = 4-FC_6H_4–								
102	C_2H_5–	C_2H_5–	HCl	28	111–113	H	$C_{19}H_{23}ClFNO_2$	64.9	65.0	6.6	6.7	3.4	3.9
103	–$(CH_2)_4$–		HCl	11	151–154	S	$C_{19}H_{21}ClFNO_2$	65.2	64.4	6.1	7.6	4.0	3.5
					R = 2-ClC_6H_4–								
104	C_2H_5–	C_2H_5–		38	164–165 (0.4)		$C_{19}H_{22}ClNO_2$	68.8	69.0	6.7	6.8	4.2	4.3
105	C_2H_5–	C_2H_5–	CH_3I	28	90–92	J	$C_{20}H_{25}ClINO_2$	50.7	50.8	5.3	5.6		
106	–$(CH_2)_4$–		HCl	73	172–175	D	$C_{19}H_{21}Cl_2N_2O_2$	62.3	62.4	5.8	6.1	3.8	4.2
107	–$(CH_2)_4$–		EBA[h]	72	168–170	D	$C_{23}H_{27}BrClNO_4$	55.6	55.9	5.6	6.0		
					R = 4-ClC_6H_4–								
108	CH_3–	i-C_3H_7–	HCl	58	168–170	B	$C_{19}H_{23}Cl_2NO_2$	62.0	62.2	6.3	6.1	3.8	4.0
109	CH_3–	i-C_3H_7–	CH_3I	70	231–232	T	$C_{20}H_{25}ClINO_2$	50.7	50.6	5.3	5.4	3.0	3.0
110	C_2H_5–	C_2H_5–	HCl	58	135–141	B	$C_{19}H_{23}Cl_2NO_2$	61.8	62.2	6.6	6.5	3.8	3.8
111	C_2H_5–	C_2H_5–	CH_3I	59	163–165	A	$C_{20}H_{25}ClINO_2$	50.7	50.7	5.3	5.3		
112	C_2H_5–	C_2H_5–	EBA[h]	38	164–166	B	$C_{23}H_{29}BrClNO_4$	55.4	55.7	5.9	5.5	2.8	2.7
113[ad]	C_2H_5–	C_2H_5–	HCl	32	187–189	P	$C_{23}H_{24}Cl_2NO_2$	66.0	65.8	6.0	5.9	3.4	3.3
114	n-C_3H_7–	n-C_3H_7–		36	159–162 (0.13)		$C_{21}H_{26}ClNO_2$	70.1	70.4	7.3	7.7	3.9	3.8
115	n-C_4H_9–	n-C_4H_9–		36	170–172 (0.03)		$C_{23}H_{30}ClNO_2$	71.2	71.2	7.8	7.9	3.6	3.5
116	–$(CH_2)_4$–		HCl	71	198–199	A	$C_{19}H_{21}Cl_2NO_2$					3.8	3.8
117	–$(CH_2)_4$–		CH_3I	64	193–195	A	$C_{20}H_{23}ClINO_2$	50.9	50.7	4.9	4.6	3.0	2.7
118	–$(CH_2)_6$–		HCl	58	206–208	A	$C_{21}H_{25}Cl_2NO_2$	64.0	64.1	6.4	6.6	3.6	3.9
119	–$(CH_2)_6$–		CH_3I	60	190–191	A	$C_{22}H_{27}ClINO_2$	52.9	52.8	5.5	5.1	2.8	2.3
					R = 2,4-di-ClC_6H_3–								
120	C_2H_5–	C_2H_5–		17	180–184 (0.4)		$C_{19}H_{21}Cl_2NO_2$	62.3	62.3	5.8	6.0	3.8	4.0
121	–$(CH_2)_4$–		HCl	50	178–180	A	$C_{19}H_{20}Cl_3NO_2$	56.9	56.4	5.0	5.3	3.5	3.7
					R = 3,4-di-ClC_6H_3–								
122	C_2H_5–	C_2H_5–	HCl	28	186–187	A	$C_{19}H_{22}Cl_3NO_2$	56.7	57.2	5.5	5.6	3.5	3.3
123	C_2H_5–	C_2H_5–	CH_3I	37	181–183	U	$C_{20}H_{24}Cl_2INO_2$	47.3	47.4	4.8	5.0	2.8	2.9
124	–$(CH_2)_4$–		HCl	35	185–186	D	$C_{19}H_{20}Cl_3NO_2$	56.9	57.5	5.0	5.7	3.5	3.9

TABLE I (*Continued*)

No.	R_1	R_2	R_3X	Yield, %	M.p.,[b] °C., or b.p. (mm.)	RS[c]	Formula	Analyses,[d] % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
					R = 3-BrC_6H_4–								
125	C_2H_5–	C_2H_5–	HCl	60	127–128	B	$C_{19}H_{22}BrClNO_2$	55.3	55.3	5.6	5.6		
126	–$(CH_2)_4$–		HCl	67	176–177	B	$C_{19}H_{21}BrClNO_2$	55.6	55.4	5.2	5.1	3.4	3.1
127	–$(CH_2)_4$–		CH_3I	37	195–197	A	$C_{20}H_{23}BrINO_2$					2.7	2.9
128	CH_3–	C_6H_5–		10	202–204 (0.06)		$C_{22}H_{20}BrNO_2$	64.4	64.3	4.9	5.0	3.4	3.3
129	CH_3–	C_8H_9		7	202–204 (0.07)		$C_{24}H_{24}BrNO_2$	65.8	66.0	5.5	5.8	3.2	3.6
					R = 4-BrC_6H_4–								
130	C_2H_5–	C_2H_5–	HCl	13	146–148	D	$C_{19}H_{23}BrClNO_2$	55.3	55.2	5.6	5.7		
131	–$(CH_2)_4$–		HCl	67	215–218	A	$C_{19}H_{21}BrClNO_2$	55.6	55.5	5.2	4.9		
132	–$(CH_2)_4$–		CH_3I	37	108–109	D	$C_{20}H_{23}BrINO_2$	46.5	46.6	4.5	4.2	2.7	2.7
133	–$(CH_2)_5$–		EBA[h]	57	159–162	D	$C_{23}H_{27}BrNO_4$	51.0	51.2	5.0	5.1		
					R = 3-$NO_2C_6H_4$–								
134	C_2H_5–	C_2H_5–	HCl	60	143–145	B	$C_{19}H_{23}ClN_2O_4$	60.2	59.8	6.1	5.9		
135[ab]	C_2H_5–	C_2H_5–	HCl	80	186–188	A	$C_{13}H_{19}ClN_2O_4$	51.6	51.9	6.3	6.4		
136	–$(CH_2)_4$–		HCl	66	196–197	A	$C_{19}H_{21}ClN_2O_4$	60.6	60.5	5.6	6.0	7.4	7.4
137	–$(CH_2)_4$–		CH_3I	28	123–126	A	$C_{20}H_{23}IN_2O_4$	49.8	49.6	4.8	4.8	5.8	5.5
					R = 4-$NO_2C_6H_4$–								
138	CH_3–	CH_3–	HCl	66	195–198	D	$C_{17}H_{19}ClN_2O_4$	58.2	57.9	5.5	5.4	8.0	8.2
139	CH_3–	*i*-C_3H_7–	HCl[g]	24	111–113	B	$C_{19}H_{25}ClN_2O_4$	57.5	58.0	6.4	6.1	7.1	7.3
140	C_2H_5–	C_2H_5–	HCl	64	151–153	D	$C_{19}H_{23}ClN_2O_4$	60.2	60.5	6.1	6.1	7.4	7.0
141[aa]	C_2H_5–	C_2H_5–	HCl[f]	69	101–102	B	$C_{19}H_{22}Cl_2N_2O_4$	54.0	54.5	5.5	5.5	6.6	7.0
142[ad]	C_2H_5–	C_2H_5–	HCl	46	186–187	B	$C_{23}H_{25}ClN_2O_4$	64.4	64.2	5.9	5.6	6.5	6.6
143	–$(CH_2)_4$–		HCl	79	201–203	D	$C_{18}H_{21}ClN_2O_4$	60.6	60.1	5.6	5.4	7.4	7.3
144[ae]	–$(CH_2)_4$–		HCl	77	236–237	A	$C_{19}H_{27}ClN_2O_4$	59.6	59.8	7.1	7.0	7.3	7.0
145[aa]	–$(CH_2)_4$–		HCl[n]	83	138–139	A	$C_{19}H_{20}ClN_2O_4$	54.3	54.8	5.0	5.2	6.7	6.8
146	–$(CH_2)_5$–		HCl[o]	72	156–159	A	$C_{20}H_{25}ClN_2O_5$	58.8	58.5	6.2	6.6	6.9	6.8
147	–$(CH_2)_5$–		CH_3I	20	178–180	A	$C_{21}H_{25}IN_2O_4$	50.8	50.5	5.1	4.7		
148	–$(CH_2)_6$–		HCl	70	193–194	A	$C_{21}H_{25}ClN_2O_4$	62.3	62.4	6.2	5.9	6.9	7.2
149	–$(CH_2)_2O(CH_2)_2$–		HCl[o]	49	179–182	V	$C_{19}H_{23}ClN_2O_5$	55.5	55.4	5.6	6.0	6.8	7.1
					R = 3-$NH_2C_6H_4$–								
150[ab]	C_2H_5–	C_2H_5–	HCl	67	115–117	D	$C_{19}H_{21}ClN_2O_2$	57.2	56.9	7.8	7.8	10.3	10.1
151	–$(CH_2)_4$–		HCl	39	153–155	V	$C_{19}H_{23}ClN_2O_2$	65.8	65.6	6.7	7.0	8.1	7.9
					R = 4-$NH_2C_6H_4$–								
152	CH_3–	CH_3–	HCl[o]	28	223–225	X	$C_{17}H_{23}ClN_2O_3$	60.3	60.8	6.8	6.8	8.3	8.3
153	CH_3–	*i*-C_3H_7–	2HCl	24	183–186	O	$C_{19}H_{26}Cl_2N_2O_2$	59.2	59.1	6.8	7.0	7.3	7.2
154	C_2H_5–	C_2H_5–	HCl[n]	71	200–201	A	$C_{19}H_{25}ClN_2O_2$	63.8	64.0	7.3	7.3	7.8	7.1
155[aa]	C_2H_5–	C_2H_5–		21	96–97	V	$C_{19}H_{23}ClN_2O_2$	65.8	65.8	6.7	6.6	8.1	8.2
156[ad]	C_2H_5–	C_2H_5–	HCl[n]	41	211–214	V	$C_{23}H_{27}ClN_2O_2$	67.7	68.3	6.9	6.9	6.9	7.4
157	–$(CH_2)_4$–		HCl[o]	42	194–196	A	$C_{19}H_{23}ClN_2O_3$	62.5	63.0	6.9	6.4	7.7	7.8
158	–$(CH_2)_5$–		HCl	33	200–203	C	$C_{20}H_{25}ClN_2O_2$	66.6	66.2	7.0	7.3	7.8	8.2
159	–$(CH_2)_2O(CH_2)_2$–		HCl[n]	59	218–220	V	$C_{19}H_{23}ClN_2O_3$	61.4	61.1	6.5	6.3	7.5	7.9
					R = 4-pyridyl-								
160	C_2H_5–	C_2H_5–	2HCl	37	195–196	A	$C_{15}H_{23}Cl_2N_3O_2$	57.9	57.8	7.0	6.6	7.6	7.8
161	–$(CH_2)_4$–		2HCl	10	201–203	A	$C_{18}H_{22}Cl_2N_2O_2$					7.6	7.9
					R = 2-furyl-								
162	C_2H_5	C_2H_5	HCl	55	118–120	O	$C_{17}H_{22}ClNO_3$	63.1	62.7	6.9	7.1	4.3	4.1
163	–$(CH_2)_4$–		HCl	83	205–208	A	$C_{17}H_{20}ClNO_3$	63.5	63.6	6.3	6.2		
					R = 2-thienyl-								
164	–$(CH_2)_4$–			11	160–166 (0.3)		$C_{17}H_{19}NO_2S$	67.7	68.3	6.4	6.8	4.7	4.8
					R = 2-cyclopentylethyl-								
165	C_2H_5–	C_2H_5–		53	144–146 (0.1)		$C_{20}H_{31}NO_2$	75.7	76.0	9.8	10.0		
					R = C_6H_5CH=CH–								
166	CH_3–	CH_3–	HCl	62	201–203	P	$C_{19}H_{22}ClNO_2$	68.8	68.7	6.7	6.9	4.2	4.5
167	CH_3–	*i*-C_3H_7–	HCl	58	164–166	B	$C_{21}H_{26}ClNO_2$	70.1	69.8	7.3	7.1		
168	C_2H_5–	C_2H_5–		34	176–178 (0.2)		$C_{21}H_{25}NO_2$	78.0	77.6	7.8	7.6	4.3	4.3
169	C_2H_5–	C_2H_5–	HCl	74	118–120	O							
170[aa]	C_2H_5–	C_2H_5–	HCl	19	93–96	D	$C_{21}H_{25}Cl_2NO_2$	64.0	63.2	6.4	6.9	3.4	3.7
171	–$(CH_2)_4$–		HCl	21	200–202	B	$C_{21}H_{24}ClNO_2$	70.5	70.5	6.8	6.6	3.9	3.2
172	–$(CH_2)_5$–		HCl	54	202–204	P	$C_{22}H_{26}ClNO_2$	71.1	71.2	7.1	6.9	3.8	3.8
173	–$(CH_2)_6$–		HCl	67	208–210	V	$C_{23}H_{28}ClNO_2$	71.6	72.1	7.3	7.3	3.6	3.9
174	–$(CH_2)_2O(CH_2)_2$–		HCl	21	225–227	V	$C_{21}H_{24}ClNO_3$	67.5	67.2	6.5	6.7	3.8	3.7
					R = 3,4-$(OCH_2O)C_6H_3CH$=CH–								
175	–$(CH_2)_4$–		HCl	63	188–189	B	$C_{21}H_{24}ClNO_4$	64.7	64.7	6.2	5.9	3.6	4.0
					R = 2-$NO_2C_6H_4CH$=CH–								
176	–$(CH_2)_4$–		HCl	49	127–130	B	$C_{21}H_{23}ClN_2O_4$	62.6	62.0	5.8	5.8	7.0	6.7
					R = $C_6H_5OCH_2$–								
177	CH_3–	CH_3–	HCl	72	165–167	A	$C_{18}H_{22}ClNO_3$	64.4	64.1	6.6	6.5	4.2	4.4
178	CH_3–	*i*-C_3H_7–	HCl	76	187–188	D	$C_{20}H_{26}ClNO_3$	66.0	66.0	7.2	7.1	3.9	4.1
179	C_2H_5–	C_2H_5–	HCl	80	138–140	D	$C_{20}H_{26}ClNO_3$	66.0	66.0	7.2	7.3	3.9	4.0

TABLE I (*Concluded*)

No.	R_1	R_2	R_3X	Yield, %	M.p.,[b] °C., or b.p. (mm.)	RS[c]	Formula	Analyses,[d] % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
180	C_2H_5–	C_2H_5–	C_2H_5I	43	93–95	B	$C_{22}H_{30}INO_2$					2.9	2.6
181	C_2H_5–	C_2H_5–	EBA[h]	52	148–149	D	$C_{24}H_{32}BrNO_5$	58.3	58.2	6.5	6.4	2.8	2.8
182	–(CH_2)$_4$–		HCl	73	205–206	A	$C_{20}H_{24}ClNO_3$	66.4	66.4	6.7	6.7	3.9	3.7
183	–(CH_2)$_4$–		EBA[h]	80	139–140	B	$C_{24}H_{30}BrNO_5$	58.5	58.4	6.1	6.3	2.8	2.7
	R = 4-Cl-2-$CH_3C_6H_3OCH_2$–												
184	C_2H_5–	C_2H_5–	HCl	28	144–147	B	$C_{21}H_{27}Cl_2NO_3$	61.2	60.7	6.6	6.2		
185	–(CH_2)$_4$		HCl	37	126–129	B	$C_{21}H_{25}Cl_2NO_3$	61.5	61.3	6.1	6.2	3.4	3.3
	R = $C_6H_5OCHCH_3$–												
186	CH_3–	CH_3–	HCl	32	123–125	D	$C_{19}H_{24}ClNO_2$					4.0	3.7
187	CH_3–	*i*-C_3H_7	HCl	17	162–164	O	$C_{21}H_{28}ClNO_2$					3.7	3.9
188	C_2H_5–	C_2H_5–		36	158–160 (0.18)		$C_{21}H_{21}NO_3$	73.9	73.6	8.0	7.7		
189	C_2H_5–	C_2H_5–	CH_3I	19	118–120	B	$C_{22}H_{30}INO_3$	54.7	54.8	6.3	6.2	2.9	2.7
190	–(CH_2)$_4$–			42	180–181 (0.5)		$C_{21}H_{25}NO_2$	74.3	74.5	7.4	7.6	4.1	3.8
191	–(CH_2)$_{4}$–		CH_2I	67	115–120	B	$C_{22}H_{25}INO_4$	54.9	54.6	5.9	6.0		

[a] R_4 = C_6H_5 unless otherwise shown as superscript in the compound no. column; [aa] = *p*-chlorophenyl; [ab] = H; [ac] = *p*-tolyl; [ad] = 1-naphthyl; [ae] = cyclohexyl. [b] Melting points are not corrected and were taken on a Fisher–Johns melting point block. [c] RS = solvent for recrystallization: A = ethanol, B = methyl ethyl ketone, C = ethanol–acetonitrile, D = isopropyl alcohol, E = methyl ethyl ketone–ethanol, F = methyl ethyl ketone–isopropyl alcohol, G = isoamyl alcohol–ethanol, H = methyl ethyl ketone–isopropyl ether, I = ethyl acetate–ethanol–isopropyl alcohol, J = ethyl acetate–ethanol, K = acetone–ethanol, L = methyl ethyl ketone–isopropyl alcohol, M = methyl ethyl ketone–ethyl acetate, N = acetone, O = isopropyl alcohol–isopropyl ether, P = acetonitrile, Q = acetone–methanol, R = ethanol–isopropyl alcohol, S = methyl ethyl ketone–ethyl acetate, T = 95% ethanol, U = ethyl acetate–methanol, V = methanol, W = 1-propanol, X = methanol–ethanol, Y = hexane, Z = ethanol–isopropyl ether. [d] Analyses by Weiler and Strauss, Oxford, England. [e] C_6H_{11} = cyclohexyl. [f] C_8H_9 = 2,6-dimethylphenyl. [g] Sulfate quaternizing group; g_1 = dimethyl sulfate; g_2 = diethyl sulfate. [h] EBA = quaternizing group is ethyl bromoacetate. [i] C_3H_3Br = quaternizing group is propargyl bromide. [j] C_8H_{16} is derived with the attached N, and R_1 + R_2 from 2-methyl-5-ethylpiperidine. [k] $C_5H_{11}N$– is derived with attached N from 4-methylpiperazine. [l] $C_6H_{12}O$– with attached N is derived from 2,6-dimethylmorpholine. [m] Pic. = picric acid. [n] The compound crystallized as a hemihydrate; the elements of water are not shown in the empirical formula. [o] The compound crystallized as a monohydrate. [p] Compounds 1, 11 and 166 are described pharmacologically without chemical data by G. A. Alles and P. K. Knoefel, *Arch. intern. pharm.*, **47**, 96 (1934); compound 32 has been reported by F. F. Blicke and E. S. Blake, THIS JOURNAL, **52**, 235 (1930), m.p. 193–194°; compound 154 has been reported by C. S. Marvel and V. du Vigneaud, *ibid.* **46**, 2093 (1924), m.p. 210–212°.

TABLE II

ESTERS OF 2-AMINO-2-PHENYLETHANOLS $RCOOCH_2CH(C_6H_5)NR_1R_2 \cdot R_3X$[a]

No.	R	R_3X	Yield, %	M.p.,[b] °C., or b.p. (mm.)	RS[c]	Formula	Analyses,[d] % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
				R_1, R_2 = C_2H_5–								
192	C_6H_5–	HCl	52	151–152	B	$C_{19}H_{24}ClNO_2$	68.4	68.4	7.3	7.5	4.2	4.0
193	C_6H_5–	CH_3I	73	217–219	X	$C_{20}H_{26}INO_2$	54.7	54.6	6.0	5.8		
194	2-$CH_3OC_6H_4$–		30	158–160 (0.12)		$C_{20}H_{25}NO_3$	73.4	72.9	7.7	7.7	4.3	4.3
195	2-$CH_3OC_6H_4$–	CH_3I	67	175–177	R	$C_{21}H_{28}INO_3$	53.7	53.9	6.0	5.8		
196	2-$C_2H_5OC_6H_4$–		15	158 (0.1)		$C_{21}H_{27}NO_3$	73.9	73.4	8.0	8.3	4.1	4.4
				R_1 + R_2 = –(CH_2)$_4$–								
197	4-$NO_2C_6H_4$–	HCl	29	222–225	A	$C_{19}H_{21}ClN_2O_4$	60.6	60.7	5.6	5.8	7.4	7.4
198	4-$NH_2C_6H_4$–	HCl	47	216–218	C	$C_{19}H_{23}ClN_2O_2$	65.8	65.9	6.7	6.8	8.1	7 9
199	C_6H_5CH=CH–	HCl	8	156–159	Z	$C_{21}H_{24}ClNO_2$	70.5	70.0	6.8	7.0	3.9	4.3

[a] Footnotes of Table II have same significance as in Table I.

that greatest activity is obtained with R = phenyl, followed by 2-furyl, 2-thienyl and 4-pyridyl in decreasing order of activity.

Substitution of R as cyclopentylethyl[5] (compound 165) was not associated with a particularly good anesthetic response.

The cinnamates[6] compared favorably with the benzoates except where R_1R_2N– was dimethylamino (compound 2 *vs.* 166), and morpholino (compound 36 *vs.* 174). When substituted cinnamates were used, activity was depressed (compounds 175, 176 *vs.* 171).

Although acylation of the usual amino alcohols with aralkyl groups has been associated with relatively poor activity[7] the use of the aryloxyacetic acids[8] as acylating agents with the amino alcohols of this series yielded potent and relatively nontoxic anesthetics (compounds 178, 182, 185).

The factor of substitution in the system R = phenyl was explored extensively.

Various workers have utilized alkyl groups to introduce steric factors making the resultant ester less vulnerable to hydrolysis,[9,10] or introduced bulky groups[11] with the presumed objective of

(5) For a discussion on anesthetic effects of esters of aliphatic acids, see T. E. Jones and C. O. Wilson, *J. Am. Pharm. Assoc., Sci. Ed.*, **42**, 340 (1953).

(6) R. P. Perry, D. C. Jones and C. Pratt, THIS JOURNAL, **78**, 3340 (1956), found cinnamates superior to benzoates.

(7) O. Kamm, *ibid.*, **42**, 1030 (1920).

(8) F. C. G. Hoskin, *ibid.*, **78**, 3121 (1958), prepared a series of diethylaminoethyl esters of the plant growth-regulating phenoxyacetic acids but did not assess these for anesthetic activity.

(9) I. Dvoretzky and G. H. Richter, *J. Org. Chem.*, **18**, 615 (1953).

(10) N. Rabjohn, J. W. Fronabarger and W. W. Linstromberg, *ibid.*, **20**, 271 (1955).

(11) (a) L. B. Dale, Jr., and E. Voss, *J. Am. Pharm. Assoc., Sci. Ed.*, **42**, 685 (1953); (b) G. C. Gross and E. Voss, *ibid.*, **46**, 167 (1957).

TABLE III

PHARMACOLOGICAL TESTS[a]

No.[a]	LDmin,[b] mg./kg.	ANED$_{50}$,[c,g] mg./ml.	TED$_{50}$,[d,f] mg./kg.	No.[a]	LDmin,[b] mg./kg.	ANED$_{50}$,[c,g] mg./ml.	TED$_{50}$,[d,f] mg./kg.
2	450	0.54		85	750	0	
3	250	0	80	86	400	0.21	
4	100		31	87	200	17.5	45
5	1000	0.7		88	200	14	0
6	750	1.3	110	89	300	7.2	
7	>1000	4		90	>1000	2.9	
8	>1000	12		91	500	1.9	0
10	>1000	0		92	>1000	11	
11	>1000	0.32		93	>1000	0.47	
14	300	0.76	1.6	94	>1000	0	
16	75	20.5	11	96	1000	0.5	
18	100	13.5	10	97	200	7.6	
19	75		Sl.	98	>1000	0	0
20	50	16	5.6	99	>1000	0	0
21	50	6.5	17	100	1000	1.2	
22	>1000	9.4		101	200	21	0
23	250		0	102	>1000	0.5	
24	200	>20	0	104	750		
25	1000	6	0	105	250	13	37
26	1000	>20	0	106	200	0.44	
27	>1000	0		107	75	5.4	
28	>1000	0	Sl.	108	>1000	6.5	
29	1000	0.45		109	400	10	105
30	150	31	42	110	>1000	1.3	
31	150	13.5	Sl.	111	250	0	86
32	1000	3.8		112	400	25	
33	>1000	0		113	>1000	0	
34	>1000	0.88		114	>1000	0	0
35	750	4.2		115	>1000	0	0
36	>1000	8.2		116	750	0.4	
37	>1000	>10		117	200	29	35
38	300	2.6		119	200	0	38
39	750	10.3		120	>1000	22	
40	>1000	0.43		121	>1000	7.5	
41	>1000	0.46		122	>1000	15	
42	100	>20	0	123	300	0	72
43	>1000	9		124	1000	1.1	
44	>1000	1.3		125	>1000	0	
45	1000	0.67		126	>1000	0.23	
46	250	>20	85	127	300	0	100
47	1000	0	0	128		11	
48	400	0.9		129		5.5	
49	80	0	0	130	>1000	7.8	
50	>1000	>30		131	>1000	1.8	
51	250	0.4		132	200	0	0
52	750	6.9		133	250	27.5	
53	>1000	0		134	>1000	4.5	
54	1000	7		135	750	16.8	
56	750	11		136	200	0.17	
57	400	0.17		137	300	0	
58	150	0	37.5	138	750	10.5	
59	100	2		139	>1000	1	
60	750	3		140	350	8.4	
62	>1000	0		141	>1000	>30	
63	>1000	0	0	142	>1000	0	
64	500	0.35		143	250	0.3	
65	1000	0.4		144	750		
66	500	9	275	145	1000	3.3	
67	>1000	1.5		146	>1000	8.8	
68	750			147	>1000	0	270
69	>1000	7		149	>1000	0	
70	750	0.55		150	>1000	15	
71	200	0	0	151	150	0.21	
72	>1000	0		152	100	0	
73	750			153	100	9.4	
74	200	0	60	154	50	0.11	
75	>1000	0.48		155	300	4.1	
76	400	0.33	130	157	50	0.71	
77	200	20	70	158	75	0.2	
78	75	8	25	159	750	12.5	
79	300	0.26		160	200	22	
80	500	0.14		161	250	37	
81	1000	0.52		162	750	2	
83	150	0	37.5	163	450	2.5	
84	750	0.32		164	300	5	
165	>1000	23		183	1000	15	0
166	500	5.4	0	184	1000	0	0
167	>1000	1.5		185	>1000	3.2	
168	400	0.6		186	1000	8.9	
170	>1000	2.7		187	750	8.5	
171	>1000	2.8		188	>1000		
172	>1000	5.2		189	350	13	120
173	750	0.45		190	450		
174	1000	0		191	750	9.8	0
175	>1000	7.4	0	192	>1000	1.9	
176	1000	>30		193	150	>20	0
177	>1000	>20		194	350	0.9	0
178	400	0.9		195	200	>10	0
179	750	17.2		196	750	0.54	0
180	350	>20	0	197	600	14	
181	1000	14.8	0	198	250	3.2	
182	450	0.65		199	750	8	

[a] The number refers to the compound listed by this number in Tables I and II. [b] The LD$_{min.}$ is the minimum lethal dose established subcutaneously (s.c.) in mice and expressed in mg./kg. [c] The method used for testing has been described; S. L. Shapiro, K. Weinberg, T. Bazga and L. Freedman, THIS JOURNAL, **80**, 3734 (1958). The ANED$_{50}$ is reported as anesthetic dose in mg./ml. Control drugs: procaine, LD$_{min.}$ 200 mg./kg., ANED$_{50}$ 15 mg./ml; xylocaine, LD$_{min.}$ 225 mg./kg., ANED$_{50}$ 6.8 mg./ml. [d] The TED$_{50}$ is the dosage level in mg./kg. for mice which protects 50% of the animals from the neurotoxicity (tremors) induced by the administration of tremorine. The test as herein performed was developed by Dr. G. Ungar of our Pharmacology Laboratories. The compound to be tested is injected s.c. in mice at levels corresponding to $^1/_3$, $^1/_6$, $^1/_{12}$, etc., of the LD$_{min.}$ Four mice are used at each test level. Ten minutes later, tremorine ditartrate is injected s.c. at a level of 30 mg./kg. One hour after the injection of tremorine, the mice are observed for the presence of tremors by holding the animals by the tail for ten seconds. If no tremors are noted the animal is adjudged protected by the test compound. A graphic plot of the percentage of animals protected at each dose level of the test drug is made and the dosage level which protects 50% of the animals is established and reported as the TED$_{50}$ (effective dose protecting 50% of the animals from tremors). [e] The procedure for evaluation of the blood pressure response described in the discussion of the pharmacological results has been reported by S. L. Shapiro, H. Soloway and L. Freedman, THIS JOURNAL, **80**, 2743 (1958). The ganglionic blocking effects were established in similarly anesthetized dogs. [f] Control drugs evaluated by this method give a TED$_{50}$: atropine 4 mg./kg.; α-cycloehxyl-α-phenyl-1-piperidine-propanol hydrochloride (Artane) 2 mg./kg. [g] A zero (0) in the ANED$_{50}$ column is indicative of no noted anesthetic activity in the dosage ranges evaluated.

TABLE IV

ANESTHETIC *vs.* ADRENALIN EFFECT

ANED$_{50}$, mg./ml.	Effect on Adrenalin[a,b] Potentiation			No effect						Inhibition
	2	96	154	5	43	66	93	136	170	38
	32	108	157	7	44	67	100	138	173	41
	39	121	158	11	45	69	102	146	178	76
	52	122	164	22	48	75	106	153	185	126
<15	56	124	171	29	51	80	110	159	186	143
	57	139	175	34	54	81	116	162	196	172
	70	140	182	35	59	89	130	163	198	187
	79	145	194	36	64	90	131	166		192
	92	151	197	40	65	91	134	167		
	27	94	161	10	99	141	160			179
15+	33	98	177	50	113	142	174			
	37	114		53	125	149	176			
	72	120		62	135	150	184			

[a] The test procedure was a modification of the method outlined by G. E. Ullyot and J. F. Kerwin, "Medicinal Chemistry," Vol. II, John Wiley and Sons, Inc., New York, N.Y., 1956, p. 267, method 5. [b] The numbers refer to the compound listed by this number in Tables I and II.

conferring maximal lipophilic character[12] to the aromatic moiety of the ester. In this series, no considerable differences were noted relative to the unsubstituted phenyl structures upon introducing methyl groups in the benzoyl radical.

With the halogenated[13] substituents, the *p*-fluoro derivative (compound 102) showed the anticipated similarity to its hydrogen equivalent,[14,15] while a 3-bromo derivative (compound 126) was the most active of the halogen substitution products studied. Certain of the halogen derivatives, in contrast to the majority of the structures evaluated, and in particular compounds 110 and 122, were irritant at levels considerably higher than the $ANED_{50}$ when test solutions were administered directly on the eye.

With the nitro compounds good anesthetic activity was noted, the *m*-nitro group being more effective than the *p*-nitro group. When assessed against the corresponding amino structures, many of the nitro derivatives proved to be superior (compound 136 *vs.* 151; 138 *vs.* 152; 139 *vs.* 153; 143 *vs.* 157). However, in selected instances, considerable improvement in the anesthetic potency was noted upon reduction to the amino compounds (compound 140 *vs.* 154; 146 *vs.* 158).

In contrast to the majority of the structures evaluated, the amino derivatives showed fairly high toxicities (compounds 151, 152, 153, 154, 157, 158) with the noted lethality occurring at dosage levels of the order of 1/20 that observed with many of the other equally active structures. Consequently, this toxicity factor, coupled with a more difficult synthetic path as well as potential difficulties in stabilization of the final product in solution form, discouraged a more extensive study of amino derivatives.

One additional facet explored, in view of the significance of substitution in the *m*-position, was the preparation of the *meta* analog of procaine (compound 150) which proved to be about as active as procaine and considerably less toxic.

In recent years, the significance of ring-substituted alkoxy[16] and polyalkoxy substituents[17] has been the subject of intensive study. Certain generalizations may be made from the observations of the various workers. In the monoalkoxy series, ethoxy is superior to methoxy[16f] and activity reaches a maximum with increasing chain length of the alkoxy substituent up to six carbon atoms,[16d] then falls abruptly. The fall in activity with the larger substituents probably is due to a solubility factor.[16d,17d] Polyalkoxylation has been associated with enhanced activity using two alkoxy groups,[17a] and disappearance of activity with three alkoxy groups.[17d] While the position of the alkoxy group is significant in many of the series, no generalizations can be made as to the locus for optimal anesthetic effect. In this series, the methoxy and ethoxy derivatives were relatively non-toxic and extremely potent compounds except in the instance where the R_1R_2N- group was dimethylamino (compounds 51, 79) in which the toxicities approached that of procaine. With the monoalkoxy structures the data do not clearly distinguish between the absolute anesthetic potency of structures bearing methoxy *vs.* ethoxy groups, although the ethoxy structures are uniformly less toxic (see compound 51 *vs.* 79; 57 *vs.* 82; 64 *vs.* 86; 65 *vs.* 90; 67 *vs.* 92 for comparison of *o*-alkoxy derivatives; and 71 *vs.* 96 for *p*-alkoxy derivatives). When the bulk of the alkoxy group was increased as *n*-butoxy, noted activity in otherwise active structures was decreased (compound 100 *vs.* 96) or disappeared (compound 99 *vs.* 93). Failure to note the augmented response on increasing the size of the alkoxy group, as observed by others,[16d] might be reconciled with the possibility of insufficient solubility of these *n*-butoxy structures due to the presence of the additional phenyl group (R_4) in the alkylene linking element in our series.

Polyalkoxy derivatives where examined showed excellent activity (compounds 75, 76). In view of the high activity of compound 76, it is of particular interest that the β-diethylaminoethyl 3,4,5-triethoxybenzoate[17d] does not possess local anesthetic properties.

In the assessment of the role of the secondary amino group on the noted anesthetic activity, in the majority of cases the pyrrolidino group[18] showed the best response. With only two exceptions, moreover (compounds 80, 173), either the pyrrolidino or the diethylamino group afforded the most active structure in terms of relationship to other structural parameters. The dimethylamino structures showed lessened activity and, most important, heightened toxicity (compounds 2, 51, 79), while the more bulky nitrogeneous substituents afforded diminished anesthetic potency.

The critical and distinctive structural feature of this investigation concerned the linking elements $-CH((R_4)CH_2-$ and $-CH_2CH(R_4)-$. In the initial contemplation of this work it was hoped that introduction of R_4 = phenyl, particularly in the type I structures, would afford substitution on the key carbon to effect steric inhibition of hydrolysis of the anesthetic esters under conditions of Newman's "Rule of Six."[19]

(12) J. R. Boissier, C. Malen, C. Dumont and R. Maugé, *Compt. rend.*, **243**, 529 (1956).

(13) (a) M. Rubin, H. C. Marks, H. Wishinsky and A. Lanzilotti, THIS JOURNAL, **68**, 623 (1946); (b) S. J. Childress, M. G. Cordasco, O. J. Plekss and L. Reiner, *ibid.*, **76**, 3988 (1954); (c) E. R. Andrews, M. G. Van Campen and E. L. Schumann, *ibid.*, **75**, 4003 (1953).

(14) H. L. Friedman, American Chemical Society, Abstracts New York Meeting, September, 1954, p. 23-N.

(15) G. A. Oláh, A. E. Pavlath, J. A. Oláh and F. Herr, *J. Org. Chem.*, **22**, 879 (1957).

(16) (a) J. S. Pierce, M. J. Fletcher and S. L. Cooke, Jr., THIS JOURNAL, **76**, 1956 (1954); (b) M. B. Winstead, S. H. Wishnoff and R. W. Bost, *ibid.*, **77**, 772 (1955); (c) F. P. Luduena and J. O. Hoppe, *J. Pharmacol. Exp. Therap.*, **117**, 89 (1956); (d) H. Vanderhaeghe, P. Kolosy and M. Claesen, *J. Pharm. and Pharmacol.*, **6**, 119 (1954); (e) S. M. McElvain and T. P. Carney, THIS JOURNAL, **68**, 2592 (1946); (f) H. B. Wright and M. B. Moore, *ibid.*, **76**, 4396 (1954); (g) A. Sekera, A. Borovanský, I. Jakubec, K. Palát and Č. Vrba, *Československ. farm.*, **5**, 388 (1956) [*C. A.*, **51**, 8669a (1957)].

(17) (a) R. P. Perry, D. C. Jones and C. Pratt, THIS JOURNAL, **78**, 3403 (1956); (b) E. Epstein and M. Meyer, *ibid.*, **77**, 4059 (1955); (c) N. Rabjohn and A. Mendel, *J. Org. Chem.*, **21**, 218 (1956); (d) N. Rabjohn and A. Mendel, *ibid.*, **22**, 986 (1957).

(18) For outstanding effects with pyrrolidino substituents in another series, see P. P. Koelzer and K. H. Wehr, *Arzneimittel-Forsch.*, **8**, 270 (1958).

(19) (a) M. S. Newman, "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1956, p. 204 *et seq.*; (b) L. Tsai, T. Miwa and M. S. Newman, THIS JOURNAL, **79**, 2530 (1957); (c) S. Sarel, I. Tsai and M. S. Newman, *ibid.*, **78**, 5420 (1956); (d) C. T. Chmiel and F. A. Long, *ibid.*, **78**, 3326 (1956); (e) G. L.

The importance of the retention of the ester linkage to avoid inactivation through hydrolysis by plasma esterases is well recognized.[20] Methyl groups introduced to yield steric factors on the phenyl ring[10] or in the linking element[4,21] have yielded compounds with high anesthetic potency. The long series of compounds of type I showing very high anesthetic potency clearly confirms this approach to active anesthetic structures.

Further evidence is obtained on comparison of the compounds of type I which show "Rule of Six" structural inhibition, and the isomeric structures of type II which do not. While all the structures compared exceed procaine activity, with the sole exception of the paired isomers (compounds 81, 196) both of which are extremely active, the type I structure is by far the more active (compound 11 *vs.* 192; 57 *vs.* 194; 143 *vs.* 197; 157 *vs.* 198; 171 *vs.* 199) of the two isomers.

The rationalization of the basis for enhanced activity as advanced above suffers somewhat upon consideration of the anesthetic response when R_4 in the type I structures is substituted as other than phenyl. Thus, when R_4 = *p*-tolyl, in one instance, compound 84 *vs.* 81, an improved effect is noted; however, see compound 25 *vs.* 11, and 59 *vs.* 57. This pattern of superiority of phenyl over the other R_4 substitutents is noted when R_4 = *p*-chlorophenyl (compound 22 *vs.* 11; 141 *vs.* 140; 145 *vs.* 143; 155 *vs.* 154; 170 *vs.* 169), and α-naphthyl (compound 113 *vs.* 110; 142 *vs.* 140).

It is not likely that such substituents would materially differ in their hydrolysis rates from those of congeners bearing a phenyl group and, undoubtedly, many other factors including solubility, enter into the fully defined spectrum of effects associated with maximum anesthetic potency.

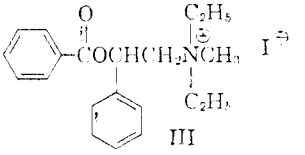
While the structures of the types I and II are in every instance a racemic mixture, we have not at this point attempted the resolution to establish whether a difference in activity of the optical isomers exists.[22]

More detailed description of the time of onset and duration of anesthetic activity, cutaneous absorption and lack of irritancy of selected anesthetics in this work will be given at a later date.

With the availability of the free bases of these anesthetic esters of the types I and II it was of interest as well to prepare the quaternary ammonium derivatives.[23] These might provide compounds of interesting potential divorced from the anesthetic response and might have anesthetic effect[24] in spite of the requisites of current concepts of the action of anesthetic agents[25] which require that the free base and not a quaternary nitrogen be available.

In this study no definite correlations were noted in the anesthetic response with the quaternaries. In one instance (compound 181 *vs.* 179) the quaternary with ethyl bromoacetate was superior in anesthetic effect to the free base.

A particularly interesting property of some of the quaternary structures was the reversal of the neurotoxicity of tremorine. This effect has been implied as affording a possible screening procedure for anti-Parkinson drugs.[26] The required tremorine was prepared as tremorine ditartrate and a convenient synthesis is indicated in the Experimental section. Although anti-tremorine activity was shown in a variety of structures, peak activity was confined exclusively to compound 14 (III).



III

If the grouping was varied so that the nitrogen bore three methyl groups, two methyl and one ethyl group, or three ethyl groups (compounds 3, 4, 16) activity decreased. If the phenyl group in the linking element was withdrawn (compounds 23, 24) or the phenyl placed on the carbon alpha to the amino structure (compound 193), no activity was noted. Substituents introduced into the phenyl ring of the benzoyl group (compounds 74, 77, 111), or methiodides of variants of the amino component R_1R_2N- other than diethylamino (compound 30), yielded markedly reduced effects.

The structures other than III which showed reasonably potent effect (compounds 16, 18, 20) were also somewhat more toxic than III. It is of interest that III retained a fair amount of the anesthetic effect noted with the free base. Although a number of free bases were evaluated for anti-tremorine activity, none showed any response of interest.

Upon examination for their effect on blood pressure most of the compounds showed a normotensive pattern or at most, transient hypotension. Sustained effects were obtained with some of the quaternaries (compounds 105, 183, 14, 16, 77, 83, 88, 97, 101, 111, 123, 180 and 181). More interesting, was the noted hypotensive effect with some of the free bases,[27] with the R_1R_2N- = N-methylpiperazyl structures (compounds 35, 66, 91) showing the only correlative feature. Others of the tertiary amino bases which showed sustained hypotension were compounds 7, 35, 44, 59, 72, 94, 158. A few of the compounds showed a hypertensive response (compounds 56, 79, 171, 198).

Goerner, Abstracts of Papers, 130th American Chemical Society Meeting, Atlantic City, N. J., September, 1956, p. 14-O.

(20) K. H. Beyer and A. R. Latven, *J. Pharmacol. Exp. Therap.*, **106**, 37 (1952).

(21) I. N. Nazarov and R. I. Kruglikova, *Zhur. Obshchei Khim.*, **27**, 316 (1957) [*C. A.*, **51**, 15521h (1957)].

(22) Reference 4, p. 102, states that the optically active forms of ester type local anesthetics whose amino alcohol portion contains asymmetric carbon atoms rarely differ in their activity.

(23) (a) R. O. Clinton, S. C. Laskowski, U. J. Salvador and P. M. Carroll, THIS JOURNAL, **79**, 2290 (1957); (b) A. L. Mindzhoyan, V. G. Afrikyan and A. N. Oganesyan, *Doklady Akad. Nauk Armyan. S. S. R.*, **24**, 105 (1957) [*C. A.*, **52**, 9021d (1958)]; (c) R. Hazard, M. Beauvallet, R. Giudicelli, P. Chabrier and G. Thullier, *Compt. rend.*, **147**, 1744 (1953); (d) **147**, 1927 (1953).

(24) (a) K. Nador, F. Herr, G. Pataky and J. Borsy, *Nature*, **171**, 788 (1953). (b) K. Nador, F. Herr and B. Losonczy, *Acta Chim. Acad. Sci. Hung.*, **3**, 497 (1953) [*C. A.*, **49**, 2363d (1955)] have observed anesthetic effects upon quaternization of active anesthetics, although activity never reached the levels of the unquaternized anesthetic agents.

(25) R. B. Barlow, "Chemical Pharmacology," John Wiley and Sons, Inc., New York, N. Y., 1955, p. 99.

(26) (a) G. M. Everett, *Nature*, **177**, 1238 (1956); (b) G. M. Everett, L. E. Blockus and I. M. Shepperd, *Science*, **124**, 79 (1956).

(27) S. L. Shapiro, H. Soloway and L. Freedman, THIS JOURNAL, **80**, 2743 (1958).

A complete ganglionic block was restricted to the quaternaries and was noted with compounds 74, 83, 101, 105, 180. Less complete blockage was obtained with compounds 77, 109 and 137. Partial ganglionic block was obtained with the following amines: compounds 7, 18, 114, 72 and 76. In this pharmacological category as well, no clear-cut structure *vs.* activity effects were evident.

It was of interest to correlate the anesthetic response with the noted cardiovascular effect of the various basic compounds on the response to adrenalin as established in the anesthetized dog. Where available, the data so obtained have been gathered, and the effect on adrenalin which varied as potentiation, no effect and inhibition, has been collated with the anesthetic $ANED_{50}$ as shown in Table IV.

It will be seen that the distribution of the adrenalin response shows a paralleling effect whether involved with the more active anesthetic drugs or not. However, since in clinical application, local anesthetics are often co-administered with adrenalin it will be of interest, and we plan to assess, the pattern of activity of selected highly active compounds within each of the adrenalin response categories.

Experimental

Material.—The amino alcohols have been previously described.[2] The acid chlorides which were not commercially available were prepared by published procedures. The *o*-, *m*- and *p*-toluyl chlorides,[28] 3,5-dimethoxybenzoyl chloride,[29] 3,4,5-trimethoxybenzoyl chloride,[30] *o*-, and *p*-*n*-butoxybenzoyl chloride[31] and β-piperonylacryloyl chloride[32] were prepared from the carboxylic acids.

The acid chlorides were prepared following the method described below for 4-chloro-2-methylphenoxyacetyl chloride.

4-Chloro-2-methylphenoxyacetyl Chloride.—To a stirred suspension of 140 g. (0.7 mole) of 4-chloro-2-methylphenoxyacetic acid in 100 ml. of benzene there was added 107 g. (0.91 mole) of thionyl chloride during a period of 45 minutes. The reaction mixture was heated under reflux for 3.5 hours. The benzene and excess thionyl chloride were removed under diminished pressure and the residue was distilled to give 116 g. (76%) of product, b.p. 118–130° (5–7 mm.).

(28) J. F. Norris and H. H. Young, Jr., THIS JOURNAL, **57**, 1420 (1935).

(29) F. Mauthner, *J. prakt. Chem.*, [2] **87**, 404 (1913).

(30) J. Koo, THIS JOURNAL, **75**, 720 (1953).

(31) J. S. Pierce, J. M. Salsbury and J. M. Fredericksen, *ibid.*, **64**, 1691 (1942).

(32) H. Thoms and F. Thumen, *Ber.*, **44**, 3726 (1911).

Anal. Calcd. for $C_9H_8Cl_2O_2$: C, 49.4; H, 3.7. Found: C, 49.2; H, 4.0.

Esters Reported in Tables I and II. General Procedure.—To a solution of 0.07 mole of acid chloride in 150 ml. of refluxing benzene (or acetonitrile) there was added, dropwise, during 0.5 hour, 0.07 mole of the amino alcohol.[2] Reflux and stirring were continued for 2 hours. In many instances adequate yields of the formed hydrochloride of the product could be separated readily by filtration. If the hydrochloride did not precipitate, the solvent was removed under diminished pressure and the residue was purified by recrystallization. In those cases where the physical state of the residue rendered crystallization difficult, the hydrochloride was dissolved in water, the solution was made alkaline, the free base extracted with ether, and after drying (magnesium sulfate) and removal of the ether, the product was distilled.

***p*-Aminobenzoate Esters.**—The following procedure was typical: A solution of 0.05 mole of the corresponding nitrobenzoate ester hydrochloride in 230 ml. of ethanol containing 0.01 g. of platinum dioxide was hydrogenated in a Parr hydrogenator. When hydrogenation was completed, the catalyst was separated, the solvent removed and the residue recrystallized.

1,4-Dipyrrolidino-2-butyne (Tremorine).—A solution of 34 g. (0.48 mole) of pyrrolidine and 14.8 g. (0.12 mole) of 1,4-dichloro-2-butyne in 180 ml. of toluene was heated under reflux for 1 hour. After cooling, the solution was decanted from the tarry precipitate and upon removal of the toluene, 10.8 g. (47%) of product was obtained, b.p. 92–99° (1 mm.).

Anal. Calcd. for $C_{12}H_{20}N_2$: N, 14.6. Found: N, 15.0.

Tremorine Ditartrate.—To a solution of 5.76 g. (0.03 mole) of 1,4-dipyrrolidino-2-butyne in 500 ml. of ethanol, there was added a hot solution of 9 g. (0.06 mole) of tartaric acid in 100 ml. of ethanol. After cooling, 12 g. of the pure salt separated, m.p. 126–127°.

Anal. Calcd. for $C_{20}H_{32}N_2O_2$: C, 48.8; H, 6.6; N, 5.7. Found: C, 48.7; H, 7.1; N, 5.6.

In previous work[2] it had been shown that acetylation of 2-pyrrolidino-2-phenylethanol afforded a mixture of acetates with 58% of the expected product and 15% of the rearranged product, 2-pyrrolidino-1-phenylethyl acetate. To ensure that the product isolated in the benzoylations of the $R_1R_2NCH(C_6H_5)CH_2OH$ alcohols was not a rearranged product, several mixed melting points were run, mixed m.p. (compounds 192 and 11), 139–149°; (compounds 197 and 143), 190–193°.

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