Local Anesthetics III

Dialkylaminoalkoxyphenylethanol Esters

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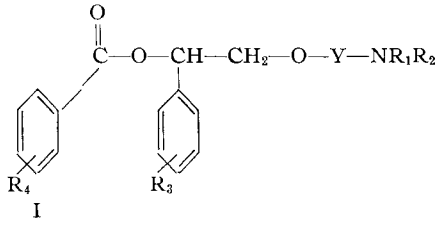
A series of "procaine analogs" (I) was prepared by reaction of dialkylaminoalkoxyphenylethanols with aromatic acid chlorides. Upon evaluation as anesthetics, selected compounds showed considerably more activity than procaine.

IN THE "PROCAINE" type of local anesthetics (1), lengthening of the alkylene chain separating the tertiary amino group and the ester group increases anesthetic activity as well as toxicity. These conclusions are substantiated in the recent work from other laboratories (2, 3).

Extension of our explorations (4) to compounds of type I was indicated in the hope of increasing anesthetic potency with no accompanying increase in toxicity.



I

R_1, R_2 = lower alkyl
$R_1 + R_2$ = lower alkylene
Y = ethylene, propylene, and trimethylene
R_3 = hydrogen and methyl
R_4 = hydrogen, alkyl, alkoxy, and halogen

For the reactant alcohols, the amino alcohol, R_1,R_2N-Y-OH (in excess) was condensed under alkoxide catalysis (5) with styrene oxide. This reaction, while affording the desired dialkylaminoalkoxyphenylethanols (Table I), was clearly not as straightforward as the condensation of secondary amines with stryene oxide (6). Under these reaction conditions the product formed is largely the secondary alcohol (5, 7, 8). A variety of nonbasic side products (9–12), including styrene glycol, was obtained in some of the preparations.

Alternatively, the substituted ethanols of Table I were preparable by palladium reduction of ω-(dialkylaminoalkoxy)-acetophenones which, in turn, were obtained from phenacyl halide and the reactant dialkylaminoethanol (see Experimental).

Treatment of the substituted ethanol with the acid chloride in benzene or in acetonitrile gave the ester I (Table II) isolated as the hydrochloride, or preferably, as the free base by distillation.

The pharmacological data (Table III) reflect that the compounds of Table II are more potent anesthetics, although slightly more toxic, than the esters of our previous series (4).

The most active $—NR_1R_2$ variant was pyrrolidino (compound 9). Variation of R_3 as hydrogen or methyl (compound 1 *vs.* 2) indicates superiority of hydrogen. The R_4 variant is desirably retained as hydrogen, although R_4 = *p*-CH_3O— (compound 5) combined high toxicity with anesthetic effectiveness.

With the ethanols of Table I, the antitremorine effect was noteworthy. Employing the procedure of Shapiro, et *al.* (4), the following observations were made: Compound No./$LD_{min.}$ mg./Kg./tremorine ED_{50} mg./Kg., respectively: 4/>1,000/32; 5/750/140; 9/750/90. On the other hand, compound 7 afforded moderate lasting hypotension (13).

Also of interest was the toxicity ($LD_{min.}$ of 100 mg./Kg.) of the dibutylamino derivative (compound 8) whereas the other amino alcohols had $LD_{min.}$ levels in the range 750 to >1,000 mg./Kg.; this compound in contrast to the others also showed some hypertensive effects.

EXPERIMENTAL[1]

2-(2-[N-Methyl-N-*i*-propylamino]ethoxy)-1-phenylethanol.—Sodium, 0.1 Gm. (0.005 gram atom) was added to 46.8 Gm. (0.4 mole) of N-methyl-N-isopropylaminoethanol while stirring. After solution was complete, the temperature was raised to 80° and 24.0 Gm. (0.2 mole) of styrene oxide added over one and one-half hours. Stirring was continued at this temperature for an additional five hours.

On distillation, 23.5 Gm. of N-methyl-N-isopropylaminoethanol was collected, b. p. 72° (30 mm.), followed by 28 Gm. (60%) of product, b. p. 120–128° (0.35 mm.).

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[1] Typical examples of the procedures used are given. Data shown in the tables are not reproduced. Initial reactants were all obtained from commercial sources.

TABLE I.—DIALKYLAMINOALKOXYPHENYLETHANOLS

R_1R_2N-Y-O-$CH_2CH(R_3C_6H_4)OH$[a, b]

Compd. No.	R_1	R_2	B. P., °C. (mm.)	Formula	Analyses[c] Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1	CH_3—	*i*-C_3H_7—	120–128 (0.35)	$C_{14}H_{23}NO_2$	70.9	71.1	9.8	9.4	5.9	5.6
2	HCl[d]			$C_{14}H_{24}ClNO_2$	61.4	61.1	8.8	8.3	5.1	5.4
3	C_2H_5—	C_2H_5—	131–134 (0.6)	$C_{14}H_{23}NO_2$	70.9	70.8	9.8	10.2	5.9	5.8
4[ba]	C_2H_5—	C_2H_5—	118–120 (0.1)	$C_{15}H_{25}NO_2$	71.7	71.7	10.0	9.7	...	...
5	—$(CH_2)_4$—		130–138 (0.1)	$C_{14}H_{21}NO_2$	...	...	...	...	6.0	5.7
6	HCl[e]		...	$C_{14}H_{22}ClNO_2$	61.9	62.1	8.2	8.3	5.2	5.5
7	—$(CH_2)_6$—		148–158 (0.4)	$C_{16}H_{25}NO_2$	73.0	73.2	9.6	9.6	...	...
8	*n*-C_4H_9—	*n*-C_4H_9—	136–145 (0.05)	$C_{18}H_{31}NO_2$	73.7	73.7	10.7	10.7	4.8	4.8
9[aa]	CH_3—	CH_3—	122–127 (0.1)	$C_{13}H_{21}NO_2$	69.9	70.1	9.5	9.2	...	...
10[ab]	C_2H_5—	C_2H_5	98–102 (0.04)	$C_{15}H_{25}NO_2$	71.7	71.8	10.0	9.8	5.6	5.5

[a] Y = —$(CH_2)_2$— unless otherwise shown; [aa] - $-CHCH_3CH_2$—; [ab] —$(CH_2)_3$—. [b] R_3—C_6H_4— = phenyl unless otherwise shown; [ba] *p*-tolyl. [c] Analyses are by Weiler and Strauss, Oxford, England. [d] Hydrochloride of compound immediately above, m. p. 133–137° (methyl ethyl ketone). [e] *Ibid.*, m. p. 125–130° (methyl ethyl ketone).

TABLE II.—ESTERS

(See Formula I), Y = —$(CH_2)_2$—[a, b]

Compd. No.	R_4	B. P., °C. (mm.)	Formula	Analyses Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1	H	162–164 (0.06)	$C_{21}H_{27}NO_3$	73.9	74.1	8.0	8.3	...	...
2[ba]	H	176–180 (0.2)	$C_{22}H_{29}NO_3$	74.3	74.1	8.2	8.1	3.9	3.6
3	*p*-CH_3—	156 (0.03)	$C_{22}H_{29}NO_3$	74.3	73.8	8.2	8.2	3.9	3.7
4	*o*-CH_3O—	178–180 (0.08)	$C_{22}H_{29}NO_4$	71.1	71.8	7.9	8.2	3.8	3.2
5	*p*-CH_3O—	188–192 (0.2)	$C_{22}H_{29}NO_4$	71.1	71.2	7.9	7.8	3.8	3.8
6	*p*-Cl—	198–200 (0.5)	$C_{21}H_{26}ClNO_3$	67.1	67.3	7.0	7.2	3.7	4.0
7	[c]	192–194 (0.08)	$C_{23}H_{29}NO_3$	75.2	74.9	8.0	7.9	3.8	3.8
8[aa]	H	160–162 (0.04)	$C_{21}H_{27}NO_3$	...	...	...	...	4.1	3.9
9[ab]	H	146–150 (0.05)	$C_{21}H_{25}NO_3$	...	...	...	...	4.1	4.2
10[ac]	H	187–190[d]	$C_{23}H_{30}ClNO_3$	...	...	...	...	3.5	3.4
11[ad]	H	161–164 (0.005)	$C_{25}H_{35}NO_3$	75.5	75.9	8.9	9.1	3.5	3.5

[a] R_1, R_2 = C_2H_5— unless otherwise shown; [aa] R_1 = CH_3—, R_2 = *i*-C_3H_7—; [ab] $R_1 + R_2$ = —$(CH_2)_4$—; [ac] $R_1 + R_2$ = —$(CH_2)_6$—; [ad] R_1R_2 = *n*-C_4H_9—. [b] R_3 = hydrogen unless otherwise shown; [ba] *p*-CH_3—. [c] Aryl group is cinnamoyl. [d] Melting point (isopropyl alcohol) of hydrochloride.

TABLE III.—ANESTHETIC EFFECTS[a]

Compd. No.	ED_{50}, mg./ml.	$LD_{min.}$, mg./Kg.	Reference Series[b] ED_{50}, mg./ml.	Reference Series[b] $LD_{min.}$, mg./Kg.
1	0.2	1000	0.32	>1,000
2	0.66	750	6	1,000
3	0.66	250	1.3	>1,000
4	0.4	200	0.17	400
5	0.06	150	[c]	750
6	0.26	750	1.3	>1,000
7	0.28	750	0.6	400
8	0.68	300	0.7	1,000
9	0.08	750	0.45	1,000
10	4.3	1000	0.88	1,000
11	2.6	750	0	>1,000
C[d]	13	200	...	...

[a] The anesthetic effect (ED_{50}) and toxicity ($LD_{min.}$) were established as described in (4). [b] These compounds have all R substituents the same as compounds in this series, and have been described (4); they differ from the present series in lacking the -O-Y- structural feature of the general formula I. [c] Not evaluated. [d] C = procaine introduced as a control.

2-(2-Diethylaminoethoxy)-1-phenylethyl Benzoate.—To a stirred refluxing solution of 4.2 Gm. (0.03 mole) of benzoyl chloride in 100 ml. of benzene was added 7.1 Gm. (0.03 mole) of 2-(2-diethylaminoethoxy)-1-phenylethanol over fifteen minutes. Reflux was continued for two hours and the solvent removed. The oily residue was taken up in 100 ml. of water, basified with 40% aqueous sodium hydroxide, and extracted with five 20-ml. portions of ether. The combined ether extracts were dried (anhydrous magnesium sulfate), filtered, and the solvent evaporated. Distillation of the residue gave 4.8 Gm. (47%) of product, b. p. 162–164° (0.06 mm.).

Isolation of Acid-Insoluble Products (Compound 10, Table I.)—In the preparation of compound 10, Table I, the fractions boiling at 118–138° (0.04 mm.) were dissolved in ether and the amino alcohol extracted with 3 *N* hydrochloric acid. The ether layer, containing the acid-insoluble fraction, was dried (anhydrous magnesium sulfate) and distilled. Styrene glycol (confirmed by mixed m. p. with authentic material) was collected at 132–142° (3 mm.) and a second product (fraction II) at 120–130° (1 mm.). In several runs, a high-boiling fraction III was obtained, b. p. 158–170° (0.05 mm.).

Fraction II, on redistillation, boiled at 106–108° (0.02 mm.). $\lambda_{242}^{\epsilon 1\%}$ (95% ethanol) 169. *Anal.*—Found: C, 76.6; H, 7.1.

Fraction III, on redistillation, boiled at 144–150° (0.01 mm.) $\lambda_{252}^{\epsilon 1\%}$, 257, 263 (95% ethanol) 34.8, 33.1, 28.5. *Anal.*—Found: C, 70.1; H, 7.4.

Fractions II and III slowly decolorized a solution of bromine in carbon tetrachloride with no evolution of hydrogen bromide, and have not as yet been characterized.

2-(2-Diethylaminoethoxy)acetophenone.—Sodium, 6.9 Gm. (0.3 gram atom), was dissolved in a solution of 35.1 Gm. (0.3 mole) of 2-diethylaminoethanol in 350 ml. of toluene. The solution, stirred and maintained at reflux, was treated with a solution of 19.9 Gm. (0.1 mole) of 2-bromoacetophenone in 100

ml. of toluene over a period of four hours. After an additional eight hours under reflux and cooling, the reaction mixture was diluted with 20 ml. of ethanol and 250 ml. of water. The aqueous layer was extracted with two 100-ml. portions of toluene followed by two 100-ml. portions of ether, the organic phase combined with the initial toluene layer, the whole washed with 0.5 L. of 0.6 *N* hydrochloric acid, the washings basified (pH 10), and the formed oil extracted with ether. After drying (anhydrous magnesium sulfate) and removal of solvent, distillation gave 1.8 Gm. (8%) of product, b. p. 116–120° (0.05 mm.), (n_D^{20} = 1.5136).

Anal.—Calcd. for $C_{14}H_{21}NO_2$: C, 71.5; H, 9.0; N, 6.0. Found: C, 71.1; H, 9.6; N, 6.5.

2-(2-Diethylaminoethoxy)-1-phenylethanol (14).—A solution of 3.3 Gm. (0.014 mole) of 2-(2-diethylaminoethoxy)acetophenone in 250 ml. of ethanol was quantitatively (one equivalent) hydrogenated over three 6-hour shaking periods with initial pressure of four atmospheres, using three 0.2-Gm. portions of 10% palladium-on-carbon as catalyst, and heating at a jacket temperature of 50°. After filtration and removal of solvent, there was obtained 2.0 Gm. (61%) of product, b. p. 119–122° (0.25 mm.), (n_D^{20} = 1.5090).

Anal.—Calcd. for $C_{14}H_{23}NO_2$: C, 70.9; H, 9.8; N, 5.9. Found: C, 70.5; H, 9.8; N, 5.9.

REFERENCES

(1) Burger, A., "Medicinal Chemistry," Vol. 1, Interscience Publishers, Inc., New York, N. Y., 1951, p. 100.
(2) Koelzer, P. P., and Wehr, K. H., *Arzneimittel-Forsch.*, **9**, 70, 113, 167, 683(1959).
(3) David, A., Leith-Ross, F., and Vallance, D. K., *J. Pharm. and Pharmacol.*, **9**, 446(1957).
(4) Shapiro, S. L., Soloway, H., Chodos, E., and Freedman, L., *J. Am. Chem. Soc.*, **81**, 203(1959).
(5) Reeve, W., and Christoffel, I., *ibid.*, **72**, 1480(1950).
(6) Shapiro, S. L., Soloway, H., and Freedman, L., *ibid.*, **80**, 6060(1958).
(7) Chapman, N. B., Isaacs, N. S., and Parker, R. E., *J. Chem. Soc.*, **1959**, 1925.
(8) Hayes, F. N., and Gutberlet, C., *J. Am. Chem. Soc.*, **72**, 3321(1950).
(9) Beasley, Y. M., Petrow, V., and Stephenson, O., *J. Pharm. and Pharmacol.*, **10**, 47(1958).
(10) Astle, M. J., and Jacobson, B. E., *J. Org. Chem.*, **24**, 1766(1959).
(11) Thomas, C. A., and Hochwalt, C. A., U. S. pat. 2,372,605 (1945).
(12) Emerson, W. S., *J. Am. Chem. Soc.*, **67**, 516(1945).
(13) Shapiro, S. L., Soloway, H., and Freedman, L., *ibid.*, **80**, 2743(1958).
(14) Corrigan, J. R., Sullivan, M. J., Bishop, H. W., and Ruddy, A. W., *ibid.*, **75**, 6258(1953).

Relative Potencies of Some Phenothiazines as Pecking Syndrome Inhibitors

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Members of a select group of chlorinated, fluorinated, and unhalogenated phenothiazines of known (i.e., reported) antiemetic potency in dogs were evaluated as pecking syndrome antagonists in pigeons. Assigning to chlorpromazine an arbitrary potency value of 1.0, it was calculated that promazine = 0.1, prochlorperazine = 2.3, trifluopromazine = 4.4, trifluoperazine = 7.2, and perphenazine = 10.2. The relationship of these data to the reported antiemetic activity of the compounds is discussed.

THE phenothiazines possess many diverse and apparently independent actions which require equally diverse methods for their quantitation. Of particular interest to us are those laboratory procedures designed to evaluate antiemetic activity since antiemesis represents one of the more important therapeutically useful characteristics of the phenothiazines.

The most frequently employed laboratory method for both screening and quantitatively evaluating antiemetics involves the administration of predetermined ED_{99} or "threshold" doses of apomorphine to dogs premedicated with the drug being investigated (e. g., 1–3). The use of the dog has been as much a matter of necessity as choice inasmuch as most of the other familiar laboratory animals are quite refractory to the emetic effects of apomorphine. The pigeon is one such animal. This bird has been the subject of our special attention because of its unusual, albeit nonemetic, response to apomorphine. The behaviorally distinct pecking syndrome in pigeons, described elsewhere (4–7), has been shown to be markedly influenced by several antiemetic substances, most notably the chlorinated phenothiazines (8). It has been observed that the more effective antiemetic agent (apomorphine antagonist in dogs) appeared to be the more efficient pecking syndrome inhibitor (apomorphine antagonist in pigeons).

The present communication deals with quantitation of antipecking activity of a select group of

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