[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, RESEARCH LABORATORIES, THE WM. S. MERRELL COMPANY]

Local Anesthetics. Aminoesters of Chlorobenzoic and Chlorocinnamic Acids[1]

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A series of aminoesters of various chlorine-substituted benzoic and cinnamic acids was prepared for pharmacological evaluation as local anesthetics and against auricular flutter. Thirty-seven esters and related derivatives are reported.

In a search for new local anesthetic agents suitable for infiltration use, a series of aminoesters of various chloro- and dichlorobenzoic and cinnamic acids was investigated. Although 2-diethylaminoethyl 4-chlorobenzoate hydrochloride, the only previously described compound in this series, was reported[2] to have little anesthetic activity, most of the compounds in the series reported here were effective local anesthetics.

The aminoester hydrochlorides were prepared in moderate to good yields by the reaction of acid chlorides with aminoalcohols in benzene solution. Variations in the number and position of the chlorine atoms on the aromatic nucleus, the length of the ester side chain and the length of the N-alkyl substituents were made. In addition, an amine oxide and a basic amide were prepared. The ester hydrochlorides, in general, were white, crystalline, water-soluble solids. Aqueous solutions of the hydrochlorides were acidic and the compounds were rapidly hydrolyzed by alkali. Physical constants and pharmacological data for the reported compounds are given in Table I.

Pharmacological.—We are indebted to the Pharmacology Department of The Wm. S. Merrell Co. for the local anesthetic and acute toxicity data given in Table I. The compounds are identified in the discussion by their numbers given in column 1 of Table I.

Structure, Activity Relationships.—The influence of the number and position of the chlorine substituents on toxicity and local anesthetic activity can be shown by a comparison of the 2-diethylaminoethyl esters of the various acids used. Benzoic esters containing chlorine atoms in the 2,5- and 2,6-positions were the most toxic and the 2,6-dichlorobenzoate, compound 25, was much less active than the other benzoates. Cinnamic esters, in general, were somewhat more toxic than corresponding benzoic esters. A comparison of compounds 35 and 37 shows that hydrogenation of a cinnamic ester to a hydrocinnamic ester decreases both toxicity and potency.

In the 2,4-dichlorobenzoate series, compounds 8, 9, 11, 13, 15 and 16 comprise a series of 2-dialkylaminoethyl esters in which the N-alkyl group was increased in size from methyl to *n*-amyl. Increasing the size of the alkyl group appears to increase toxicity and reduce local anesthetic activity. Branching of the N-alkyl substituents usually reduced toxicity and decreased or abolished local anesthetic action, as is shown by compounds 12, 13 and 14, 15.

The most important variable in obtaining maximum activity appeared to be the length of the ester side chain. A series of diethylaminoalkyl 2,4-dichlorobenzoates in which the length of the side chain was increased from two to five carbon atoms, compounds 9, 18, 19 and 22, indicated that local anesthetic activity increased at a greater rate than did the toxicity. Branching of the ester side chain reduced potency and usually increased toxicity as illustrated by compounds 17, 18 and 20, 21, 22.

Esters of *l*- and *dl*-novol alcohols, compounds 20 and 21, showed almost identical pharmacological properties and the one basic amide described, compound 28, showed much less local anesthetic activity than the comparable ester.

Most of the ester hydrochlorides studied were highly irritating and caused necrosis when injected subcutaneously or intramuscularly in animals. Several, however, on the basis of low intravenous toxicity were screened for action against auricular flutter.[3] Although the compounds, particularly 9 and 19, appeared to show considerable anti-flutter activity in dogs, clinical results were disappointing.

Experimental[4]

Aminoalcohols.—In addition to the commercially available aminoalcohols used, 2-(1-piperidyl)-ethanol,[5] 2-diisopropylaminoethanol,[6] 2-di-*n*-propylaminoethanol,[7] 2-diisobutylaminoethanol,[8] 2-di-*n*-amylaminoethanol,[9] 4-diethylamino-1-butanol[10] and 5-diethylamino-1-pentanol[11] were prepared according to known methods. All aminoalcohols were dried over anhydrous potassium carbonate and redistilled before use.

The sample of *l*-5-diethylamino-2-pentanol used for the preparation of compound 20 was provided by Dr. W. R. Brode.[12]

Acids and Acid Chlorides.—Most of the acids and acid chlorides were commercially available. The preparation of 2,6-dichlorobenzoic acid from 2,6-dichlorotoluene[13] was carried out according to the directions of Norris and Bearse.[14] 4-Chlorocinnamic acid[15] and 2,4-dichlorocinnamic acid[16] were prepared from the corresponding aldehydes by means of the Perkin reaction.

Acid chlorides were prepared by refluxing a mixture of equal weights of an acid and thionyl chloride in benzene for

(1) Presented before the Division of Medicinal Chemistry at the American Chemical Society Meeting in Milwaukee, Wisconsin, March 30 to April 3, 1952.

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(4) All melting and boiling points are uncorrected.

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TABLE I

PROPERTIES OF CHLOROBENZOATES AND CHLOROCINNAMATES

No.	Ester	M.p., °C.[a]	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Halide Calcd.	Halide Found	Yield, %	Recryst. solv.[b]	Soly. in H_2O[c]	Approx. LD_{50}, i.v., mice, mg./kg.[d]	Duration of local anesthesia, procaine = 1[e]
				2-Chlorobenzoates										
1	2-Diethylaminoethyl	126–127	$C_{13}H_{18}O_2NCl\cdot HCl$	53.43	53.31	6.55	6.35	12.13	12.07	82	A	5	100	1.1
2	2-Diisobutylaminoethyl	113–115	$C_{17}H_{26}O_2NCl\cdot HCl$	58.62	58.71	7.81	7.49	10.18	10.15	76	B	5	200	0
				4-Chlorobenzoates										
3	2-Dimethylaminoethyl	194–195	$C_{11}H_{14}O_2NCl\cdot HCl$	50.02	50.00	5.72	5.39	13.42	13.53	64	A	5	150	0.8
4	2-Diethylaminoethyl	136–139	$C_{13}H_{18}O_2NCl\cdot HCl$	53.43	53.43	6.55	6.40	12.13	12.07	86	A	5	150	1.2
5	2-Diisobutylaminoethyl	144–147	$C_{17}H_{26}O_2NCl\cdot HCl$	58.62	58.49	7.81	7.63	10.18	10.14	69	C	5	300	0.7
6	2-Di-*n*-butylaminoethyl	105–107	$C_{17}H_{26}O_2NCl\cdot HCl$	58.62	58.49	7.81	8.05	10.18	10.09	65	C	6	50	1.0
7	4-Diethylamino-1-butyl	152–153	$C_{15}H_{22}O_2NCl\cdot HCl$	56.25	56.40	7.24	7.50	11.07	11.12	66	D	6	75	1.0
				2,4-Dichlorobenzoates										
8	2-Dimethylaminoethyl	164–165	$C_{11}H_{13}O_2NCl_2\cdot HCl$	44.24	44.32	4.73	4.95	11.87	11.90	82	E	5	200	1.2
9	2-Diethylaminoethyl	147–148[f]	$C_{13}H_{17}O_2NCl_2\cdot HCl$	47.80	47.90	5.56	5.65	10.85	10.77	81	D	5	150	1.0
10	2-Diethylaminoethyl	133–134	$C_{13}H_{17}O_2NCl_2\cdot CH_3Br$	43.66	43.82	5.23	5.28	20.75	20.78	94	D	5	70	0.3
11	2-(1-Piperidyl)-ethyl	176–177	$C_{14}H_{17}O_2NCl_2\cdot HCl$	49.65	49.80	5.36	5.54	10.47	10.35	59	E	6	75	1.0
12	2-Diisopropylaminoethyl	167–168	$C_{15}H_{21}O_2NCl_2\cdot HCl$	50.79	50.92	6.25	6.29	10.00	10.06	59	F	30	75	0
13	2-Di-*n*-propylaminoethyl	148–149	$C_{15}H_{21}O_2NCl_2\cdot HCl$	50.79	50.65	6.25	6.39	10.00	10.15	82	F	40	85	1.0
14	2-Diisobutylaminoethyl	105–107	$C_{17}H_{25}O_2NCl_2\cdot HCl$	53.34	53.57	6.85	7.06	9.26	9.20	71	C	5	300	0
15	2-Di-*n*-butylaminoethyl	123–124	$C_{17}H_{25}O_2NCl_2\cdot HCl$	53.34	53.43	6.85	6.97	9.26	9.15	80	D	40	75	0.5
16	2-Di-*n*-amylaminoethyl	94–95	$C_{19}H_{29}O_2NCl_2\cdot HCl$	55.55	55.41	7.36	7.27	8.63	8.75	51	C	700	...	...
17	1-Diethylamino-2-propyl	147–148	$C_{14}H_{19}O_2NCl_2\cdot HCl$	49.35	49.55	5.92	6.04	10.41	10.41	73	F	5	150	0.6
18	3-Diethylaminopropyl	164–165	$C_{14}H_{19}O_2NCl_2\cdot HCl$	49.35	49.52	5.92	5.89	10.41	10.37	84	E	6	100	1.1
19	4-Diethylamino-1-butyl	122–123	$C_{15}H_{21}O_2NCl_2\cdot HCl$	50.79	50.90	6.25	6.38	10.00	10.19	80	D	6	75	1.5
20	*l*-5-Diethylamino-2-amyl	80–83	$C_{16}H_{23}O_2NCl_2\cdot HCl$[g]	52.11	51.58	6.56	6.81	9.62	9.75	37	G	10	53	2.8
21	*dl*-5-Diethylamino-2-amyl	104–106[h]	$C_{16}H_{23}O_2NCl_2\cdot HCl$[i]	52.11	51.90	6.56	6.62	9.62	9.49	28	F	10	44	2.8
22	5-Diethylamino-1-amyl	125–126	$C_{16}H_{23}O_2NCl_2\cdot HCl$	52.11	52.11	6.56	6.69	9.62	9.53	90	D	6	75	4.6
				2,5-Dichlorobenzoates										
23	2-Diethylaminoethyl	187–188[j]	$C_{13}H_{17}O_2NCl_2\cdot HCl$	47.80	48.03	5.56	5.46	10.85	10.94	82	E	60	75	1.3
24	3-Diethylaminopropyl	143–144	$C_{14}H_{19}O_2NCl_2\cdot HCl$	49.35	49.54	5.92	6.18	10.41	10.32	84	F	10	75	1.0
				2,6-Dichlorobenzoates										
25	2-Diethylaminoethyl	178	$C_{13}H_{17}O_2NCl_2\cdot HCl$	47.80	47.99	5.56	5.67	10.85	10.95	10	D	5	35	0.5
				3,4-Dichlorobenzoates										
26	2-Diethylaminoethyl	172	$C_{13}H_{17}O_2NCl_2\cdot HCl$	47.80	47.92	5.56	5.54	10.85	10.97	79	A	5	200	1.1
27	2-Diisobutylaminoethyl	149–150	$C_{17}H_{25}O_2NCl_2\cdot HCl$	53.34	53.37	6.85	6.79	9.26	9.25	94	A	7	200	0.8

TABLE I (*Continued*)

No.	Ester	M.p., °C.[a]	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Halide Calcd.	Halide Found	Yield, %	Re-cryst. solv.[b]	Soly. in H_2O[c]	Approx. LD_{50}, i.v., mice, mg./kg.[d]	Duration of local anesthesia, procaine = 1[e]
				Other Derivatives										
28	N-2-Diethylaminoethyl 2,4-dichlorobenzamide	137–138	$C_{13}H_{18}ON_2Cl_2 \cdot HCl$	47.94	47.65	5.88	5.94	10.89	10.99[k]	37	C	6	100	0.4
29	2-Diethylaminoethyl 2,4-dichlorobenzoate N-oxide	114–115	$C_{13}H_{17}O_3NCl_2 \cdot C_7H_4O_2Cl_2$[l]	48.31	48.11	4.26	4.41	...	...[m]	9	D	1000	...	...
				2-Chlorocinnamates										
30	2-Dimethylaminoethyl	147–148	$C_{13}H_{16}O_2NCl \cdot HCl$	53.80	53.44	5.91	5.80	12.22	12.33	87	A	5	75	1.0
31	2-Diethylaminoethyl	170–171	$C_{15}H_{20}O_2NCl \cdot HCl$[n]	56.61	56.94	6.65	6.51	11.14	11.09	78	E	6	75	1.0
32	1-Diethylamino-2-propyl	150–151	$C_{16}H_{22}O_2NCl \cdot HCl$	57.83	57.73	6.98	6.68	10.67	10.76	77	D	5	75	1.0
				4-Chlorocinnamates										
33	2-Diethylaminoethyl	192–193	$C_{15}H_{20}O_2NCl \cdot HCl$	56.61	56.77	6.65	6.69	11.14	11.09	77	E	40	140	1.0
34	3-Diethylaminopropyl	133–134	$C_{16}H_{22}O_2NCl \cdot HCl$	57.83	57.88	6.98	7.04	10.67	10.53	36	D	5	93	1.0
				2,4-Dichlorocinnamates										
35	2-Diethylaminoethyl	208–209	$C_{15}H_{19}O_2NCl_2 \cdot HCl$	51.08	51.15	5.72	5.90	10.05	10.06	79	E	75	100	1.0
36	3-Diethylaminopropyl	172–173	$C_{16}H_{21}O_2NCl_2 \cdot HCl$	52.40	52.58	6.05	6.17	9.67	9.74	74	A	10	120	1.0
				2,4-Dichlorohydrocinnamates										
37	2-Diethylaminoethyl	128–129	$C_{15}H_{21}O_2NCl_2 \cdot HCl$	50.79	50.76	6.25	6.37	10.00	9.98	60	D	6	155	0.7

[a] All temperatures are uncorrected. [b] Recrystallization solvents: A, absolute ethanol–anhydrous ether; B, ethyl acetate–anhydrous ether; C, ethyl acetate; D, butanone; E, absolute ethanol; F, butanone–anhydrous ether; G, benzene–petroleum ether (40–60°). [c] The values indicate the approximate parts of water required to dissolve one part of the salt at room temperature. Solubilities were not determined for concentrations of greater than 1:5. [d] The approximate i.v. LD_{50} was determined in female mice weighing from 16 to 21 g. at an approximate injection rate of 100 mg./kg. per minute of a 1% solution. In dosages above 288 mg./kg., a 2% solution of the test compound was used. Using this method, the approximate i.v. LD_{50} of procaine was 100 mg./kg. [e] The numbers represent the ratio of duration of action of the test compound to the duration of action of procaine. Duration of anesthesia was determined in guinea pigs. 0.1 cc. of 0.25% solution of the anesthetic agent was injected intracutaneously on a line previously plotted on the abdomen by stimulation of the skin and obtaining a twitch of the vulva. Weak tetanizing stimuli were applied peripheral to the point of injection, and the duration of the block measured. Standard or control values were obtained by employing procaine on the contra-lateral side. [f] The free base boiled at 128–130° at 1 mm.; $n^{25}D$ 1.5249. [g] Very hygroscopic. [h] Some previous sintering. [i] Hygroscopic. [j] Melted with some decomposition. [k] *Anal.* Calcd. for $C_{13}H_{18}ON_2Cl_2 \cdot HCl$: N, 8.41. Found: N, 8.43. [l] 2,4-Dichlorobenzoic acid salt. [m] *Anal.* Calcd. for $C_{13}H_{17}O_3NCl_2 \cdot C_7H_4O_2Cl_2$: N, 2.82; Cl, 28.53. Found: N, 2.54; Cl, 28.28. [n] The free base boiled at 157° at 0.5 mm.; $n^{25}D$ 1.5451.

several hours or until a homogeneous solution was obtained. After removal of the solvent and excess thionyl chloride, the acid chloride was distilled or recrystallized.

New intermediate acids and acid chlorides are described below.

4-Chlorocinnamoyl Chloride.—Treatment of 4-chlorocinnamic acid[15] with thionyl chloride as described above gave 98% of crude acid chloride melting at 79–81°. An analytical sample recrystallized twice from petroleum ether (40–60°) melted at 78–79°.

Anal. Calcd. for $C_9H_6OCl_2$: C, 53.76; H, 3.01; Cl, 35.27. Found: C, 53.64; H, 3.09; Cl, 34.87.

2,4-Dichlorocinnamoyl Chloride.—This compound was prepared by a similar procedure (87% crude yield). An analytical sample recrystallized from petroleum ether (70–90°) melted at 81–82°.

Anal. Calcd. for $C_9H_5OCl_3$: C, 45.90; H, 2.14; Cl, 45.17. Found: C, 46.17; H, 2.28; Cl, 45.02.

2,4-Dichlorohydrocinnamic Acid.—A mixture of 65 g. (0.3 mole) of 2,4-dichlorocinnamic acid,[16] 1 g. of platinum oxide and 600 cc. of purified anhydrous dioxane[17] was hydrogenated at room temperature under an initial pressure of 50 p.s.i. Hydrogen absorption was complete in two hours. After filtration and removal of the solvent under reduced pressure, the residue was washed with water and air-dried. Two recrystallizations from benzene–petroleum ether (70–90°) followed by two from aqueous ethanol gave 42.5 g. (65%) of pure product which melted at 95–97°.

Anal. Calcd. for $C_9H_8O_2Cl_2$: C, 49.36; H, 3.68; Cl, 32.39; neut. equiv., 219. Found: C, 49.00; H, 3.52; Cl, 32.35; neut. equiv., 220.

2,4-Dichlorohydrocinnamoyl chloride, obtained in 75% yield, boiled at 159–160° (18 mm.), $n^{25}D$ 1.5576.

Anal. Calcd. for $C_9H_7OCl_3$: C, 45.51; H, 2.97; Cl, 44.78. Found: C, 45.67; H, 3.15; Cl, 44.38.

Aminoester Hydrochlorides.—A solution of 0.21 mole of an acid chloride in 100 cc. of dry benzene was added fairly rapidly to a stirred solution of 0.20 mole of an aminoalcohol in 500 cc. of dry benzene. After the addition, the mixture was refluxed for six hours, then allowed to cool. In most cases, the aminoester hydrochloride precipitated on standing overnight and was separated by filtration, washed with benzene and ether and recrystallized. When the product did not precipitate on standing and seeding, the mixture was diluted with anhydrous ether until the hydrochloride precipitated.

N-2-Diethylaminoethyl 2,4-Dichlorobenzamide Hydrochloride.—A solution of 32.6 g. (0.156 mole) of 2,4-dichlorobenzoyl chloride in 100 cc. of dry benzene was added, during a 15 minute period, to a stirred solution of 20.0 g. (0.172 mole) of 2-diethylaminoethylamine in 400 cc. of dry benzene. The mixture was refluxed for six hours after the addition, then allowed to cool. Seeding the oily precipitate (seeds from butanone–ether) gave 42 g. of crude, solid product. Three recrystallizations from butanone and one from ethyl acetate yielded 18.8 g. (37%) of pure hydrochloride melting at 137–138°. Analyses are given in Table I.

2-Diethylaminoethyl 2,4-Dichlorobenzoate N-Oxide 2,4-Dichlorobenzoic Acid Salt.—A solution of 24 g. (0.073 mole) of 2-diethylaminoethyl 2,4-dichlorobenzoate hydrochloride in 300 cc. of water was covered with 300 cc. of ether and stirred during the rapid addition of 0.1 mole of aqueous sodium bicarbonate solution. The ether layer was separated immediately, dried over magnesium sulfate, filtered and evaporated. After addition of 79 g. (0.7 mole) of 30% hydrogen peroxide to the residual base, the mixture was allowed to stand at room temperature for six days with occasional shaking.

The precipitated white solid was separated by filtration, washed with a small amount of cold water and air-dried. Recrystallization from a 1:3 mixture of butanone and petroleum ether (70–90°), then from butanone alone gave 3.3 g. of pure product which melted at 114–115°.

Hydrolysis of a part of the ester apparently furnished sufficient free 2,4-dichlorobenzoic acid to form the salt. The possibility of the product being a 2,4-dichloroperbenzoic acid salt of the unoxidized ester was precluded by the failure of an aqueous solution of the product to give a peroxide test.

2-Diethylaminoethyl 2,6-Dichlorobenzoate Hydrochloride.—A solution of 20 g. (0.0956 mole) of 2,6-dichlorobenzoyl chloride in 50 cc. of dry benzene was added to a stirred solution of 10.7 g. (0.0910 mole) of 2-diethylaminoethanol in 250 cc. of dry benzene. After refluxing for six hours and standing for several days, the mixture was evaporated to dryness on the steam-bath, diluted with anhydrous ether and filtered to remove the solid material. The ether filtrate was evaporated and the procedure of dilution with dry ether, removal of solid and re-evaporation to dryness was repeated several times. The first two crops of solid were very hygroscopic and were discarded. Subsequent crops were combined and recrystallized from butanone to obtain 3 g. (10%); m.p. 178°. Analyses are given in Table I.

CINCINNATI, OHIO

(17) L. F. Fieser, "Experiments in Organic Chemistry," Second Edition, D. C. Heath and Co., New York, N. Y., 1941, p. 369.

[CONTRIBUTION FROM ABBOTT LABORATORIES]

Antispasmodics. Basic Esters and Amides of Some Heterocyclic N-Carboxylic Acids

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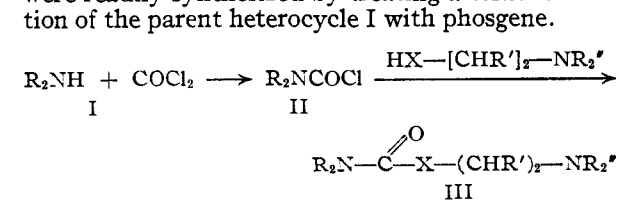
A series of N,N-disubstituted aminoalkyl esters and amides of phenothiazine-10-, carbazole-9-, acridane-10- and 5,10-dihydro-5-methylphenazine-10-carboxylic acids is described. These products, prepared by condensing the N-carboxylic acid chlorides with an aminoalcohol or diamine, and some of their quaternary salts have been evaluated as antispasmodics.

In continuing our search for substances with antispasmodic properties,[1] the investigation of basic carbamates and ureas represented by Formula III was undertaken. In this paper are reported basic esters and amides of some heterocyclic N-carboxylic acids which may be considered basic carbamates and ureas in which one of the nitrogen atoms forms part of a heterocyclic ring. In addition, the quaternary salts of some of these compounds were prepared for comparative purposes.

The tertiary amines III were obtained by condensation of an N-carboxylic acid chloride II with two moles of the dialkylaminoalkanol or dialkylaminoalkylamine in dry benzene. The acid chlorides were readily synthesized by treating a toluene solution of the parent heterocycle I with phosgene.



R_2NH = phenothiazine, carbazole, acridan, 5,10-dihydro-5-methylphenazine
X = O, S, NH, NCH_3
R' = H or CH_3
NR_2'' = dimethylamino, diethylamino, pyrrolidino, morpholino

(1) Previous paper, A. W. Weston and W. B. Brownell, THIS JOURNAL, 74, 653 (1952).