hours on the steam-bath. The resulting needles (34 mg.) were recrystallized from dioxane–ether to give colchiceine; m.p. and mixed m.p. 175.5–177°.

Ultraviolet spectra were determined with a Cary recording quartz spectrophotometer, model 11M. The *infrared spectra* were measured with a Perkin–Elmer double beam spectrophotometer, model 21, either in chloroform solution, or as a glassy film obtained by evaporating a chloroform solution on a rock salt window.

PHILADELPHIA, PA. RECEIVED JULY 13, 1951

[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

Derivatives of 4-Amino-2-hydroxybenzoic Acid. II

BY R. O. CLINTON, U. J. SALVADOR, S. C. LASKOWSKI AND MARY WILSON

A series of 2-alkoxy-4-amino- and 4-alkylaminobenzoic acids has been utilized for the preparation of new local anesthetics. The size of the 2-alkoxy group varied from methoxy to *n*-hexyloxy; a number of very highly active local anesthetics were discovered among these compounds.

A previous communication[1] from these laboratories described a number of dialkylaminoalkyl 4-amino- and 4-alkylamino-2-hydroxybenzoates and dialkylaminoalkyl-4-amino- and 4-alkylamino-2-benzyloxybenzoates, prepared as part of a continuing investigation of new local anesthetics. In the present report this series is extended to include basic esters derived from 2-alkoxy-4-aminobenzoic acids and 2-alkoxy-4-alkylaminobenzoic acids.

Several position isomers of the compounds presently discussed have appeared in the literature. A German patent[2] covers a number of dialkylaminoalkyl 3-alkoxy-4-aminobenzoates and 4-alkoxy-3-aminobenzoates. The latter type of isomer has also been investigated by other workers.[3] The diethylaminoethyl 3-amino-4-propoxy- and 4-butoxybenzoates have been reported[3c] to possess a "low anesthetic index" in relation to procaine because of their high subcutaneous and intravenous toxicity. Both compounds produced slight erythema and edema on the human skin.[3c] The corresponding 4-ethoxy compound was described as "suitable for clinical trial,"[3c] although a side chain isomer[3a] was only about one-fifth as active topically as cocaine.

The compounds prepared in the present work were readily synthesized from the parent 2-alkoxy-4-nitrobenzoic acids. 2-Methoxy-4-nitrobenzoic acid has been prepared by several workers,[4] and since the completion of the present work Goldstein and Brochon[5] have described 2-ethoxy-4-nitrobenzoic acid and several of its derivatives. In each case these compounds were prepared by rather difficult and lengthy procedures.

The alkylation of 2-hydroxy-4-nitrobenzoic acid or of an alkyl 2-hydroxy-4-nitrobenzoate by means of an alkyl arylsulfonate in xylene solution, in the presence of potassium carbonate, gave nearly quantitative yields of alkyl 2-alkoxy-4-nitrobenzoates. These in turn could be saponified in very high yield to the free acids by means of an aqueous alcoholic sodium carbonate solution.

The alkylation experiments were of some interest because of the two opposing factors probably present during these syntheses: the solubilizing effect of an alkyl ester grouping on the potassium phenolate, and the steric opposition of this alkyl ester group to the entrance of a second alkyl group in the ortho position. The color changes observed during the alkylation of 2-hydroxy-4-nitrobenzoic acid indicated that alkylation proceeded from the initial ester formation (cream colored) to ester–potassium phenolate (deep red) to alkyl alkoxy ester (cream colored). The reaction was definitely stepwise; two stages of water elimination occurred.

The monoalkylation of methyl 2-hydroxy-4-nitrobenzoate by means of *n*-butyl benzenesulfonate was incomplete after 300 hours; conversely, the monoalkylation of *n*-butyl 2-hydroxy-4-nitrobenzoate by methyl benzenesulfonate was complete in three hours. These rates are thus apparently determined by the differing solubilities of the two ester-phenolates in the xylene solvent.

The dialkylation of 2-hydroxy-4-nitrobenzoic acid by means of methyl benzenesulfonate required about six hours for completion, whereas the dialkylation by means of ethyl benzenesulfonate required about 18 hours. The dialkylation time then dropped rapidly as the size of the alkyl group increased; dialkylation by means of *n*-hexyl benzenesulfonate was complete in about three hours. Based on these observations it seems justifiable to conclude that steric effects occupy a subordinate position in these reactions.

The alkylation of an alkyl 2-hydroxy-4-nitrobenzoate failed with cyclohexyl and cyclopentyl *p*-toluenesulfonates. This failure was not unexpected, since the ready cleavage of *p*-toluenesulfonic acid from these secondary esters is known. Similarly, alkylation by means of trimethylene bromohydrin resulted in the elimination of hydrogen bromide from the bromohydrin, and with thenyl bromide extensive decomposition occurred. When 4-chloroquinoline was tried as an alkylating agent no reaction occurred; this negative result was shown by models to be due to steric effects.

The synthesis of the 2-alkoxy-4-nitrobenzoic acids from the corresponding 2-alkoxy-4-nitrobenzonitriles[6] by the action of nitrous acid[7] on the intermediate amides gave excellent results with

(1) Clinton, Laskowski, Salvador and Wilson, THIS JOURNAL, **73**, 3674 (1951).

(2) German Patent 522,064 (*Frdl.*, **17**, 2285 (1930)); *cf.* Brit. Appln. 12,340 (May 5, 1948) and U. S. Patent 1,317,250 (1919).

(3) (a) Walter and Fosbinder, THIS JOURNAL, **61**, 1713 (1939); (b) Vliet and Moore, U. S. Patent 2,288,334; (c) McIntyre and Sievers, *J. Pharmacol.*, **61**, 107 (1937); **63**, 369 (1938); McIntyre, *et al.*, *Nebraska State Med. J.*, **35**, No. 4 (1950).

(4) (a) Kraut, *Ann.*, **150**, 1 (1869); (b) Hale and Robinson, *Am. Chem. J.*, **39**, 680 (1908); (c) Simonsen and Rau, *J. Chem. Soc.*, **111**, 220 (1917); (d) Froelicher and Cohen, *ibid.*, **121**, 1652 (1922).

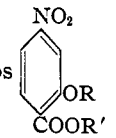
(5) Goldstein and Brochon, *Helv. Chim. Acta*, **32**, 2331 (1949).

(6) To be published in a separate communication.

(7) *Cf.* Bouveault, *Bull. soc. chim.*, [3] **9**, 370 (1893); Heyl and V. Meyer, *Ber.*, **28**, 2783 (1895).

TABLE I

ALKYL 2-ALKOXY-4-NITROBENZOATES AND 2-ALKOXY-4-NITROBENZOIC ACIDS

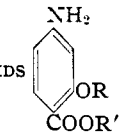


R	R'	M.p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
CH_3	CH_3	86.8–87.1[a]	$C_9H_9NO_5$	...	...	..	..	6.63	6.58
CH_3	C_2H_5	43.8–44.6	$C_{10}H_{11}NO_5$	53.33	53.56	4.92	5.06	6.22	6.34
C_2H_5	C_2H_5	53.9–54.4[c]	$C_{11}H_{13}NO_5$	55.24	55.55	5.48	5.42	5.86	5.73
C_3H_7[b]	CH_3	42.3–43.9	$C_{11}H_{13}NO_5$	55.24	55.38	5.48	5.36	5.86	6.06
C_4H_9[d]	C_2H_5	38.7–40.6	$C_{13}H_{17}NO_5$	...	...	..	..	5.24	5.22
CH_3	H	148.4–149.8[e]	$C_8H_7NO_5$	[f]	[f]	..	..	7.10	7.32
C_2H_5	H	147.3–148.2	$C_9H_9NO_5$	51.06	51.20	4.29	4.16	6.63	6.69
C_3H_7[b]	H	148.5–149.4	$C_{10}H_{11}NO_5$	53.33	53.32	4.97	5.23	6.22	6.40
C_4H_9[d]	H	120.9–122.8	$C_{11}H_{13}NO_5$	55.23	55.38	5.48	5.48	5.86	5.77
C_4H_9[g]	H	158.6–159.6	$C_{11}H_{13}NO_5$	55.23	55.44	5.48	5.37	5.86	5.90
C_6H_{13}[h]	H	86.3–87.0	$C_{13}H_{17}NO_5$	58.41	58.52	6.41	6.30	5.24	5.20

[a] Reported[4c] m.p. 88–89°. [b] *n*-Propyl. [c] Reported[5] m.p. 56°. [d] *n*-Butyl. [e] Reported[4c,d] m.p. 148–149°. [f] Neutral equivalent: calcd., 197.1; found, 193.7 [g] *i*-Butyl. [h] *n*-Hexyl.

TABLE II

ALKYL 2-ALKOXY-4-AMINOBENZOATES AND 2-ALKOXY-4-AMINOBENZOIC ACIDS



R	R'	M.p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
CH_3[a]	CH_3	157.3–158.1	$C_9H_{11}NO_3$	59.66	59.95	6.12	5.90	7.73	7.46
CH_3[b]	C_2H_5	130.8–132.6	$C_{10}H_{13}NO_3$	61.52	61.45	6.71	6.40	7.18	7.31
C_2H_5[c]	C_2H_5	120.7–121.8	$C_{11}H_{15}NO_3$	63.14	63.36	7.23	6.95	6.69	6.82
C_3H_7[d]	CH_3	85.8–87.4	$C_{11}H_{15}NO_3$	63.14	63.00	7.23	6.95	6.69	6.39
C_4H_9[e]	CH_3	140.6–142.3[f]	$C_{12}H_{18}ClNO_3$	55.49	55.62	6.98	6.98	[f]	[f]
C_4H_9[e]	C_2H_5	56.0–57.6	$C_{13}H_{19}NO_3$	65.80	65.56	8.07	8.14	5.90	6.03
CH_3[g]	H	150.5–151.4[h]	$C_8H_9NO_3$	57.48	57.79	5.43	5.44	8.38	8.39
C_2H_5	H	148.8–149.6[h]	$C_9H_{11}NO_3$	59.66	59.93	6.12	5.87	7.73	7.62
C_3H_7[d]	H	183.6–184.6[h]	$C_{10}H_{13}NO_3$	61.52	61.47	6.71	6.53	7.18	7.12
C_4H_9[e]	H	167.6–169.9[h]	$C_{11}H_{15}NO_3$	63.14	63.24	7.23	7.32	6.69	6.62
C_4H_9[i]	H	190.6–192.3[h]	$C_{11}H_{15}NO_3$	63.14	63.36	7.23	7.23	6.69	6.57

[a] The hydrochloride did not melt below 300°. *Anal.* Calcd. for $C_9H_{12}ClNO_3$: Cl, 16.29. Found: Cl, 16.17. [b] The hydrochloride did not melt below 300°. *Anal.* Calcd. for $C_{10}H_{14}ClNO_3$: Cl, 15.31. Found: Cl, 15.21. [c] The hydrochloride had m.p. 161.4–163.3°, resolidifying and remelting above 240°. *Anal.* Calcd. for $C_{11}H_{16}ClNO_3$: Cl, 14.43. Found: Cl, 14.25. [d] *n*-Propyl. [e] *n*-Butyl. [f] Hydrochloride. Calcd.: Cl, 13.65. Found: Cl, 13.62. [g] Reported[4d] m.p. 217–218°, see text. [h] With decomposition. [i] *i*-Butyl.

2-methoxy- and 2-ethoxy-4-nitrobenzonitriles. However, the method gave decreasing yields as the size of the alkoxy group increased, because of extensive cleavage of the alkoxy group during the hydrolysis of the nitrile to the amide (*e.g.*, with 2-*n*-propoxy-4-nitrobenzonitrile about 40% alkoxyl group cleavage occurred).

The crystalline alkyl 2-alkoxy-4-nitrobenzoates and the 2-alkoxy-4-nitrobenzoic acids prepared in the present work are listed in Table I. These compounds were also in most cases reduced to the corresponding 4-amino esters and acids, either by catalytic hydrogenation or by means of iron–hydrochloric acid. The 4-amino compounds so obtained are listed in Table II. It will be noted that the melting point (150.5–151.4°) of our 4-amino-2-methoxybenzoic acid differs from that reported (217–218°) by Froelicher and Cohen.[4d] We are unable to explain this discrepancy.

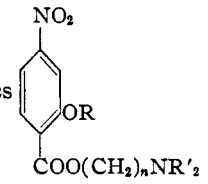
The conversion of the 2-alkoxy-4-nitrobenzoic acids to the dialkylaminoalkyl 2-alkoxy-4-nitrobenzoates was carried out in most cases by the conventional Horenstein–Pählicke reaction[8] or by the reaction of the acid chloride with a dialkylaminoalkanol. Because of the facile self-condensation of dimethylaminoethyl chloride in polar solvents it proved advantageous to prepare this type of ester from dimethylaminoethyl chloride, a 2-alkoxy-4-nitrobenzoic acid, and potassium carbonate in toluene solution. Further, it proved necessary in the preparation of the higher acid chlorides to conduct the reaction of the acid with thionyl chloride in the presence of pyridine, in order to obviate extensive alkoxy-group cleavage. The dialkylaminoalkyl 2-alkoxy-4-nitrobenzoates, with characterizing derivatives, are listed in Table III.

The reduction of the dialkylaminoalkyl 2-alkoxy-4-nitrobenzoates to the corresponding 2-alkoxy-4-aminobenzoates, and the reductive alkylation of the latter bases to the corresponding 2-alkoxy-4-alkylaminobenzoates, were carried out by procedures

(8) Horenstein and Pählicke, *Ber.*, **71**, 1644 (1938).

TABLE III

DIALKYLAMINOALKYL 2-ALKOXY-4-NITROBENZOATES



Hydrochloride

No.	R	R'2	n	M.p., °C.	Formula	Analyses, % Nitrogen[a] Calcd.	Nitrogen[a] Found	Chlorine Calcd.	Chlorine Found
1	CH_3	$(CH_3)_2$	2	158.0–159.8	$C_{12}H_{17}ClN_2O_5$	[e]	[e]	11.64	11.78
2	CH_3	$(C_2H_5)_2$	2	158.2–159.4	$C_{14}H_{21}ClN_2O_5$	8.42[d]	8.18[d]	10.65	10.57
3	CH_3	C_5H_{10}[e]	2	164.2–165.3	$C_{16}H_{21}ClN_2O_5$	8.12[d]	7.82[d]	10.28	10.25
4	CH_3	C_6H_{12}[f]	2	154.0–156.0	$C_{16}H_{23}ClN_2O_5$	3.90	4.09	9.88	9.59
5	CH_3	C_4H_8O[g]	2	170.5–172.5	$C_{14}H_{19}ClN_2O_6$	4.04	3.76	10.22	10.29
6	CH_3	$(CH_3)_2$	3	158.5–160.5	$C_{13}H_{19}ClN_2O_5$	...	...	11.12	10.92
7	CH_3	$(CH_3)_2$	[h]	189.6–190.4	$C_{13}H_{19}ClN_2O_5$	...	...	11.12	11.02
8	CH_3	$(C_2H_5)_2$	3	166.2–166.8	$C_{15}H_{23}ClN_2O_5$	8.07[d]	7.90[d]	10.22	10.02
9	CH_3	C_5H_{10}[e]	3	168.5–170.1	$C_{16}H_{23}ClN_2O_5$	3.90	3.80	9.88	9.97
10	CH_3	C_6H_{12}[f]	3	153.5–154.4	$C_{17}H_{25}ClN_2O_5$	7.51[d]	7.55[d]	9.51	9.65
11	CH_3	C_4H_8O[g]	3	203.0–204.5	$C_{15}H_{21}ClN_2O_6$	3.88	3.83	9.82	9.75
12	C_2H_5	$(CH_3)_2$	2	140.5–141.2	$C_{13}H_{19}ClN_2O_5$	4.39	4.55	11.12	11.03
13	C_2H_5	$(C_2H_5)_2$	2	131.0–132.0	$C_{15}H_{23}ClN_2O_5$	4.04	4.08	10.22	9.92
14	C_2H_5	$(C_2H_5)_2$	3	128.3–129.3	$C_{16}H_{25}ClN_2O_5$	3.89	3.94	9.83	9.64
15	C_2H_5	C_5H_{10}[e]	3	147.0–147.3	$C_{17}H_{25}ClN_2O_5$	7.51[d]	7.55[d]	9.51	9.28
16	C_3H_7[i]	$(CH_3)_2$	2	158.7–159.5	$C_{14}H_{21}ClN_2O_5$	4.21	4.12	10.65	10.46
17	C_3H_7[i]	$(C_2H_5)_2$	2	131.0–132.0	$C_{16}H_{25}ClN_2O_5$	3.89	4.01	9.83	9.75
18	C_3H_7[i]	$(C_2H_5)_2$	3	101.4–102.0	$C_{17}H_{27}ClN_2O_5$	3.74	3.94	9.46	9.51
19	C_3H_7[i]	C_5H_{10}[e]	3	147.3–148.6	$C_{18}H_{27}ClN_2O_5$	7.24[d]	7.12[d]	[j]	[j]
20	C_4H_9[k]	$(CH_3)_2$	2	108.8–110.7	$C_{15}H_{23}ClN_2O_5$	4.04	3.82	10.22	10.10
21	C_4H_9[k]	$(C_2H_5)_2$	2	108.0–110.4	$C_{17}H_{27}ClN_2O_5$	[l]	[l]	9.46	9.42
22	C_4H_9[k]	$(C_2H_5)_2$	3	123.0–124.2	$C_{18}H_{29}ClN_2O_5$	3.60	3.57	9.12	9.05
23	C_4H_9[k]	C_5H_{10}[e]	3	138.8–139.6	$C_{19}H_{29}ClN_2O_5$	6.98[d]	7.24[d]	[m]	[m]
24	C_4H_9[n]	$(C_2H_5)_2$	2	156.0–158.0	$C_{17}H_{27}ClN_2O_5$	3.74	3.76	9.46	9.36
25	C_4H_9[n]	C_5H_{10}[e]	3	163.3–165.0	$C_{19}H_{29}ClN_2O_5$	3.49	3.45	8.84	8.68
26	C_6H_{13}[o]	$(C_2H_5)_2$	2	77.5–78.5	$C_{19}H_{31}ClN_2O_5$	3.48	3.42	8.80	8.62
27	C_6H_{13}[o]	C_5H_{10}[e]	3	133.9–135.2	$C_{21}H_{33}ClN_2O_5$	3.27	3.26	8.27	8.20

Picrate

No.	M.p., °C.	Analyses, % Nitrogen[b] Calcd.	Nitrogen[b] Found	Nitrogen[a] Calcd.	Nitrogen[a] Found
2	135.2–136.2	2.67	2.68	10.68	10.70
8	153.2–154.2	..	..	10.38	10.33
12	159.2–160.2	2.74	2.76	10.96	11.23
13	157.2–158.0	2.60	2.61	10.40	10.13
14	120.0–120.8	2.53	2.54	10.12	10.30
15	120.4–121.5	2.47	2.49	9.88	10.00
16	155.2–155.8	2.67	2.67	10.68	10.74
17	124.0–125.0	2.53	2.55	10.12	10.01
18	121.4–123.0	2.47	2.50	9.88	9.63
19	110.0–111.0	2.41	2.37	9.64	9.68
20	149.2–150.0	2.60	2.62	10.40	10.42
21	147.8–148.6	2.47	2.49	9.88	9.94
22	109.4–111.0	2.41	2.42	9.64	9.77
23	105.2–106.0	2.36	2.36	9.44	9.43
24	149.2–150.1	2.47	2.47	9.88	9.93
25	125.6–127.0	2.36	2.36	9.44	9.44
26	118.4–119.6	2.35	2.36	9.40	9.43
27	114.6–115.4[p]	2.25	2.28	9.00	9.08

[a] Nitro nitrogen by titration with titanous chloride. [b] Basic amino nitrogen, by titration with perchloric acid in glacial acetic acid solution. [c] Calcd.: C, 47.29; H, 5.29. Found: C, 47.37; H, 5.48. [d] Total (Dumas) nitrogen. [e] 1-Piperidyl. [f] 2-Methyl-1-piperidyl. [g] 4-Morpholinyl. [h] 3-Dimethylamino-2-propyl. [i] *n*-Propyl. [j] Calcd.: C, 55.88; H, 7.03. Found: C, 56.07; H, 6.98. [k] *n*-Butyl. [l] Calcd.: C, 54.46; H, 7.26. Found: C, 54.49; H, 7.42. [m] Calcd.: C, 56.92; H, 7.29. Found: C, 57.09; H, 7.34. [n] *i*-Butyl. [o] *n*-Hexyl. [p] The flavinate had m.p. 161.7–163.0°. Calcd.: S, 4.54; C, 52.67; H, 5.42. Found: S, 4.52; C, 52.88; H, 5.37.

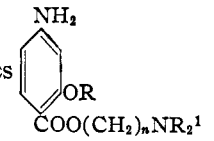
previously outlined.[1] These compounds, with derivatives, are listed in Tables IV and V, respectively.

In order that a direct comparison might be made between the compounds presently described and those tested by McIntyre,[3c] we have also synthesized the 2-diethylaminoethyl esters of 3-amino-4-butoxy- and -4-propoxybenzoic acids and of 4-amino-3-propoxybenzoic acid. These compounds have not been previously characterized in the literature.

Certain of the compounds prepared in the

TABLE IV

DIALKYLAMINOALKYL 2-ALKOXY-4-AMINOBENZOATES



R	R_1[1]	n	Type[a]	M.p., °C.	Formula	Compound Analyses, % Nitrogen Calcd.	Found	Calcd.[b]	Found[b]	Type[c]	M.p., °C.	Derivative Analyses, % Calcd.[d]	Found[d]
CH_3	$(CH_3)_2$	2	Ph	197.0-198.4	$C_{12}H_{21}N_2O_7P$	8.33	8.23	[e]	[e]	P	179.0-179.9	5.99	5.91
CH_3	$(C_2H_5)_2$	2	Ph	197.5-199.0	$C_{14}H_{25}N_2O_7P$	7.69	7.57	26.91	27.25	P	172.6-173.8	5.65	5.58
CH_3	C_5H_{10}[f]	2	Ph	171.7-172.3	$C_{15}H_{25}N_2O_7P$	7.44	7.41	26.05	26.07	P	180.4-181.4	5.52	5.38
CH_3	C_6H_{12}[g]	2	B	94.5-96.6	$C_{15}H_{24}N_2O_3$	9.58	9.33	...	...	...	.....	...	...
CH_3	C_6H_{12}[g]	2	Ph	219.0-220.0[h]	$C_{15}H_{27}N_2O_7P$	[i]	[i]	25.11	25.23	DP	149.5-150.5	11.22[j]	11.25[j]
CH_3	C_4H_8O[k]	2	Ph	173.0-174.1	$C_{14}H_{23}N_2O_8P$	7.40	7.40	25.91	25.70	P	189.6-190.2	5.50	5.20
CH_3	$(CH_3)_2$	3	B	113.4-114.4	$C_{13}H_{20}N_2O_3$	11.11	11.01	...	...	...	.....	...	...
CH_3	$(CH_3)_2$	3	Ph	183.8-184.5	$C_{13}H_{23}N_2O_7P$	7.99	8.14	27.98	28.07	P	138.0-138.8	[l]	[l]
CH_3	$(CH_3)_2$	[m]	B	99.0-100.6	$C_{13}H_{20}N_2O_3$	11.11	11.21	[n]	[n]	P	183.5-184.5	5.82	5.67
CH_3	$(C_2H_5)_2$	3	Ph	215.0-217.5	$C_{16}H_{27}N_2O_7P$	7.40	7.29	25.91	25.88	P	142.4-143.4	5.50	5.32
CH_3	C_5H_{10}[f]	3	Ph	219.1-220.0	$C_{16}H_{27}N_2O_7P$	7.17	7.30	25.11	25.28	P	168.8-170.0	5.37	5.13
CH_3	C_6H_{12}[g]	3	Ph	206.8-208.4	$C_{17}H_{29}N_2O_7P$	6.92	6.85	24.24	24.81	P	169.4-170.4	5.23	5.06
CH_3	C_4H_8O[k]	3	Ph	170.7-171.5	$C_{15}H_{25}N_2O_8P$	7.14	7.15	24.99	25.40	P	205.0-205.8	5.35	5.29
C_2H_5	$(CH_3)_2$	2	B	76.2-77.1	$C_{13}H_{20}N_2O_3$	11.11	11.12	[o]	[o]	P	152.0-153.0	5.82	5.88
C_2H_5	$(C_2H_5)_2$	2	B	92.0-93.8	$C_{15}H_{24}N_2O_3$	9.99	9.95	...	...	...	.....	...	...
C_2H_5	$(C_2H_5)_2$	2	Ph	151.8-152.8	$C_{15}H_{27}N_2O_7P$	7.40	7.34	25.91	25.89	P	177.0-178.2	5.50	5.37
C_2H_5	$(C_2H_5)_2$	3	DH	154.9-155.3[h]	$C_{16}H_{28}Cl_2N_2O_3$	[p]	[p]	19.30	19.05	F	163.8-165.4	5.27	5.38
C_2H_5	C_5H_{10}[f]	3	B	90.0-90.8	$C_{17}H_{26}N_2O_3$	9.14	9.01	4.57[q]	4.57[q]	...	.....	...	...
C_2H_5	C_5H_{10}[f]	3	DH	171.6-176.6	$C_{17}H_{28}Cl_2N_2O_3$	[r]	[r]	18.69	18.40	F	184.2-186.0	5.16	5.24
C_3H_7[s]	$(CH_3)_2$	2	DH	157.0-160.0[h]	$C_{14}H_{24}Cl_2N_2O_3$	8.26	8.14	[t]	[t]	F	194.2-194.8[h]	5.52	5.56
C_3H_7[s]	$(C_2H_5)_2$	2	H	148.3-150.0	$C_{16}H_{27}ClN_2O_3$	8.46	8.40	10.72	10.71	...	.....	...	...
C_3H_7[s]	$(C_2H_5)_2$	2	DH	132.8-136.8	$C_{16}H_{28}Cl_2N_2O_3$	7.62[u]	7.49[u]	19.30	19.13	DP	137.0-137.8	3.72[gg]	3.60
C_3H_7[s]	$(C_2H_5)_2$	3	DH	152.5-154.5	$C_{17}H_{30}Cl_2N_2O_3$	[v]	[v]	18.59	18.30	F	130.4-133.2	5.15	5.27
C_3H_7[s]	C_5H_{10}[f]	3	B	62.8-64.0	$C_{18}H_{28}N_2O_3$	8.74	8.93	...	...	...	.....	...	...
C_3H_7[t]	C_5H_{10}[f]	3	DH	169.4-172.0[h]	$C_{18}H_{30}Cl_2N_2O_3$	7.12	7.30	[w]	[w]	DF	151.0[h]	6.75	6.73
C_4H_9[x]	$(CH_3)_2$	2	DH	156.8-159.0[h]	$C_{15}H_{26}Cl_2N_2O_3$	7.93	7.97	[y]	[y]	DF	191.2-192.5	7.06	7.11
C_4H_9[x]	$(C_2H_5)_2$	2	H	125.4-126.4	$C_{17}H_{29}ClN_2O_3$	8.12	8.10	10.28	10.12	DP	96.2-96.9	14.60[z]	14.61[z]
C_4H_9[x]	$(C_2H_5)_2$	3	DH	148.3-150.9	$C_{18}H_{32}Cl_2N_2O_3$	[aa]	[aa]	17.94	17.77	F	139.6-146.8	5.04	5.18
C_4H_9[x]	C_5H_{10}[f]	3	Ph	80.0-83.0	$C_{19}H_{31}N_2O_7$	6.47	6.64	[bb]	[bb]	DP	84.2-85.6	3.53[ff]	3.27
C_4H_9[cc]	$(C_2H_5)_2$	2	H	128.6-129.6	$C_{17}H_{29}ClN_2O_3$	8.12	7.88	10.28	10.20	DP	131.0-131.6	3.65[hh]	3.58
C_4H_9[cc]	C_5H_{10}[f]	3	H	178.7-179.8	$C_{19}H_{31}ClN_2O_3$	7.55	7.61	9.56	9.27	DF	157.0-159.0	6.66	6.83
C_5H_{11}[dd]	$(C_2H_5)_2$	2	H	130.5-133.5	$C_{19}H_{33}ClN_2O_3$	7.51	7.33	9.51	9.22	DF	166.2-168.1	6.64	6.66
C_5H_{11}[dd]	C_5H_{10}[f]	3	H	133.2[ee]	$C_{21}H_{35}ClN_2O_3$	7.02	7.11	8.89	8.70	DF	198.0-199.6	6.48	6.50

[a] B, base; Ph, phosphate; H, monohydrochloride; DH, dihydrochloride. [b] Phosphoric acid analyses on phosphates; chlorine analyses on hydrochlorides. [c] P, monopicrate; DP, dipicrate; F, monoflavianate; DF, diflavianate. [d] Sulfur analyses on flavianates, basic amino nitrogen on picrates (by titration with perchloric acid in glacial acetic acid solution). [e] Calcd.: C, 42.85; H, 6.30. Found: C, 42.60; H, 6.14. [f] 1-Piperidyl. [g] 2-Methyl-1-piperidyl. [h] With decomposition. [i] Calcd.: C, 49.22; H, 6.98. Found: C, 49.28; H, 6.71. [j] Nitro nitrogen by titration with titanous chloride. [k] 4-Morpholinyl. [l] Calcd.: C, 47.40; H, 4.83. Found: C, 47.19; H, 4.76. [m] 3-Dimethylamino-2-propyl. [n] Calcd.: C, 61.88; H, 7.99. Found: C, 61.85; H, 7.70. [o] Calcd.: C, 61.88; H, 7.99. Found: C, 61.88; H, 8.27. [p] Calcd.: C, 52.31; H, 7.68. Found: C, 52.15; H, 7.90. [q] Primary aromatic amine by diazotization. [r] Calcd.: C, 53.82; H, 7.43. Found: C, 53.41; H, 7.50. [s] *n*-Propyl. [t] Calcd.: C, 49.56; H, 7.13. Found: C, 49.52; H, 7.08. [u] Calcd.: C, 52.31; H, 7.68. Found: C, 52.30; H, 7.60. [v] Calcd.: C, 53.54; H, 7.93. Found: C, 53.84; H, 8.14. [w] Calcd.: C, 54.96; H, 7.68. Found: C, 55.19; H, 7.83. [x] *n*-Butyl. [y] Calcd.: C, 50.99; H, 7.42. Found: C, 51.04; H, 7.31. [z] Total (Dumas) nitrogen. [aa] Calcd.: C, 54.68; H, 8.15. Found: C, 54.45; H, 8.19. [bb] Calcd.: C, 52.76; H, 7.69. Found: C, 52.48; H, 7.89. [cc] *i*-Butyl. [dd] *n*-Hexyl. [ee] To a wax. [ff] Calcd.: N, 14.14. Found: N, 14.09. [gg] Calcd.: N, 14.89. Found: N, 14.89. [hh] Calcd.: N,[j] 10.95. Found: N,[j] 10.51.

present work possessed outstanding local anesthetic activity,[9] both topically and by infiltration. In addition, the simple alkyl 2-alkoxy-4-aminobenzoates were considerably more active as surface anesthetics than benzocaine.

Experimental[10]

Alkyl 2-Alkoxy-4-nitrobenzoates.—A mixture of 18.3 g. (0.10 mole) of pure 2-hydroxy-4-nitrobenzoic acid, 30.4 g. (0.22 mole) of powdered anhydrous potassium carbonate and 500 ml. of dry xylene was stirred and refluxed under a water separator until the evolution of water ceased (*ca.* two hours). To the cream-colored mixture was added 56.1 g. (0.28 mole) of ethyl *p*-toluenesulfonate (or an equivalent quantity of ethyl benzenesulfonate) and stirring and refluxing were continued for an additional 24 hours. During this period an additional quantity of water was collected in the trap; the contents of the flask changed color from cream through deep red and thence back to cream again.[11] The mixture was filtered, the solid material on the funnel was washed thoroughly with hot toluene, and the combined filtrates were evaporated *in vacuo*. The residual oil crystallized on cooling and scratching. Recrystallization from methanol gave 22.2 g. (93% yield) of ethyl 2-ethoxy-4-nitrobenzoate as yellow needles, m.p. 48–52°.

On a larger scale it was found advantageous to decrease the amount of anhydrous potassium carbonate to 2.2 *equivalents*, to add the alkyl arylsulfonate in two portions of 2.0 and 0.8 equivalents (the second portion after a 12-hour interval) and to decrease the amount of solvent appreciably.

The substitution of an alkyl 2-hydroxy-4-nitrobenzoate for 2-hydroxy-4-nitrobenzoic acid in the above procedure also gave excellent results, although in certain cases considerably longer reflux periods were necessary (see text).

The following alkyl alkoxynitrobenzoates were also prepared by the above procedure (although these esters were at

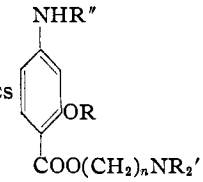
(9) Preliminary pharmacological results have been published by Luduena and Hoppe, *Federation Proc.*, **9**, 297 (1950).

(10) All melting points are corrected. They were determined in a modified Hershberg apparatus, using total-immersion N.B.S. calibrated thermometers. The sample was immersed 15° below the melting point, 3.0° rise per minute. The analyses were done by Mr. Morris E. Auerbach and staff.

(11) This final color change is an indication of the completion of the reaction (see text).

TABLE V

DIALKYLAMINOALKYL 2-ALKOXY-4-ALKYLAMINOBENZOATES



Compound

No.	R	R_2'	R″	n	Type[a]	M.p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
1	CH_3	$(CH_3)_2$	C_4H_9	2	DH	143.1–145.6	$C_{16}H_{28}Cl_2N_2O_3$	[d]	[d]	..	...	..	..
2	CH_3	$(CH_3)_2$	C_6H_{11}	2	DH	152.8–158.2	$C_{17}H_{30}Cl_2N_2O_3$	53.54	53.61	7.93	7.76	[e]	[e]
3	CH_3	$(CH_3)_2$	$HO(CH_2)_5$	2	B	Oil	$C_{17}H_{28}N_2O_4$	[f]	[f]	..	...	8.68	8.58
4	CH_3	$(C_2H_5)_2$	C_4H_9	2	DH	143.1–144.4	$C_{18}H_{32}Cl_2N_2O_3$	[g]	[g]	..	...	7.08	7.00
5	CH_3	C_5H_{10}[h]	C_4H_9	2	B	Oil	$C_{19}H_{30}N_2O_3$	68.23	67.93	9.04	9.24	8.37	8.53
6	CH_3	C_6H_{12}[i]	C_4H_9	2	B	Oil	$C_{20}H_{32}N_2O_3$	68.93	69.15	9.25	8.98	8.04	7.94
7	CH_3	C_6H_{12}[i]	$HO(CH_2)_5$	2	B	Oil	$C_{21}H_{34}N_2O_4$	66.63	66.72	9.05	8.92	7.40	7.15
8	CH_3	C_4H_8O[j]	C_4H_9	2	B	Oil	$C_{18}H_{28}N_2O_4$	64.26	64.48	8.38	8.28	8.32	8.09
9	CH_3	$(CH_3)_2$	C_3H_7	3	Ph	164.6–165.8	$C_{16}H_{29}N_2O_7P$	[k]	[k]	..	...	7.14	7.06
10	CH_3	$(CH_3)_2$	C_4H_9	3	B	Oil	$C_{17}H_{28}N_2O_3$	66.20	66.21	9.15	9.27	9.08	9.05
11	CH_3	$(CH_3)_2$	C_5H_{11}	3	DH	9.70–100.0	$C_{18}H_{32}Cl_2N_2O_3$	...	...	..	...	7.08	7.05
12	CH_3	$(C_2H_5)_2$	C_4H_9	3	B	Oil	$C_{19}H_{32}N_2O_3$	67.82	67.82	9.58	9.72	8.32	8.05
13	CH_3	C_5H_{10}[h]	C_4H_9	3	B	Oil	$C_{20}H_{32}N_2O_3$	68.93	68.89	9.25	9.29	8.04	7.70
14	CH_3	C_6H_{12}[i]	C_4H_9	3	B	Oil	$C_{21}H_{34}N_2O_3$	69.58	69.64	9.45	9.56	7.73	8.03
15	CH_3	C_4H_8O[j]	C_4H_9	3	B	Oil	$C_{19}H_{30}N_2O_4$	65.11	65.32	8.62	8.36	7.99	7.98
16	C_2H_5	$(C_2H_5)_2$	C_4H_9	2	B	Oil	$C_{19}H_{32}N_2O_3$	67.82	67.74	9.58	9.30	8.32	8.27
17	C_2H_5	C_5H_{10}[h]	C_4H_9	3	DH	143.4–146.8	$C_{21}H_{36}Cl_2N_2O_3$	57.92	58.04	8.33	8.36	6.43	6.17
18	C_3H_7	$(C_2H_5)_2$	C_4H_9	2	DH	136.8–138.0	$C_{20}H_{36}Cl_2N_2O_3$	56.73	56.81	8.57	8.35	6.61	6.50
19	C_3H_7	C_5H_{10}[h]	C_4H_9	3	DH	136.2–137.5	$C_{22}H_{38}Cl_2N_2O_3$	58.79	58.98	8.52	8.30	[m]	[m]
20	C_4H_9[n]	$(C_2H_5)_2$	C_4H_9	2	B	Oil	$C_{21}H_{36}N_2O_3$	69.19	69.44	9.95	9.67	7.68	7.38
21	C_4H_9[n]	C_5H_{10}[h]	C_4H_9	3	B	Oil	$C_{23}H_{38}N_2O_3$	70.93	70.86	9.80	9.67	7.17	7.13
22	C_4H_9[n]	C_5H_{10}[h]	C_5H_{11}	3	B	Oil	$C_{24}H_{40}N_2O_3$	71.24	71.19	9.96	10.02	6.92	7.07

Derivative

No.	Type[b]	M.p., °C.	Analyses, % Sulfur Calcd.[c]	Sulfur Found[c]	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
1	F	164.0–166.0[l]	..	..	51.30	51.01	5.30	5.55
2	F	155.5–157.0	5.15	5.18	....	....	..	..
3	F	167.0–168.2	5.02	5.32	....	....	..	.
5	P	141.5–142.6	4.97	4.67	7.46[o]	7.35[o]	..	..
8	P	146.1–148.0	4.95	4.88	7.43[o]	7.68[o]	..	.
9	F	170.0[l]	5.26	5.23	....	....	..	..
11	F	161.0–162.2	5.03	5.29	....	....	..	..
12	F	165.2–167.5	4.92	4.90	53.53	53.22	5.88	5.74
13	P	132.4–134.4	4.85	4.70	7.28[o]	7.42[o]	..	..
14	F	167.0–168.2	4.73	4.84	55.01	55.17	5.95	6.00
15	P	159.6–161.6	4.83	4.82	51.81	52.06	5.74	5.77
16	F	149.9–151.7	4.92	5.01	53.52	53.35	5.88	5.71
17	F	166.4–168.0	4.73	5.01	55.01	54.92	5.95	5.66
18	F	168.5–169.0[l]	4.82	4.93	54.20	54.03	6.06	5.83
19	F	167.8–169.7	4.64	4.84	55.63	55.40	6.12	5.79
21	F	186.6–187.2	4.54	4.56	56.23	56.29	6.29	6.04
22	F	192.5–193.2	4.46	4.52	56.80	56.63	6.45	6.19

[a] B, base, Ph, phosphate; DH, dihydrochloride. [b] P, picrate; F, flavianate. [c] Sulfur analyses on flavianates, basic amino nitrogen (by perchloric acid titration) analyses on picrates. [d] Calcd.: Cl, 19.30; OCH_3 8.44. Found: Cl, 19.29; OCH_3, 8.44. [e] Calcd.: Cl, 18.60. Found: Cl, 18.41. [f] Calcd.: OCH_3, 9.56. Found: OCH_3, 9.27. [g] Calcd.: Cl, 17.93; OCH_3, 7.84. Found: Cl, 17.72; OCH_3, 7.62. [h] 1-Piperidyl. [i] 2-Methyl-1-piperidyl. [j] 4-Morpholinyl. [k] Calcd.: H_3PO_4, 24.98. Found: H_3PO_4, 25.12. [l] With decomposition. [m] Calcd.: Cl, 15.78. Found: Cl, 15.71. [n] *n*-Butyl. [o] Nitro nitrogen by titration with titanous chloride.

least 95% pure, as shown by the high yields obtained on hydrolysis to the acid, the presence of unused alkylating agent coupled with the (presumed) low melting points prevented crystallization): *n*-propyl 2-*n*-propoxy-4-nitrobenzoate, *n*-butyl 2-*n*-butoxy-4-nitrobenzoate, *i*-butyl 2-*i*-butoxy-4-nitrobenzoate, *n*-hexyl 2-*n*-hexoxy-4-nitrobenzoate, *n*-butyl 2-methoxy-4-nitrobenzoate, ethyl 2-*i*-butoxy-4-nitrobenzoate, ethyl 2-*n*-hexoxy-4-nitrobenzoate, *n*-propyl 4-*n*-propoxy-3-nitrobenzoate, *n*-butyl 4-*n*-butoxy-3-nitrobenzoate and *n*-propyl 3-*n*-propoxy-4-nitrobenzoate. The new intermediate alkyl *p*-toluenesulfonates, *i.e.*, *i*-butyl, *n*-hexyl and cyclopentyl *p*-toluenesulfonates, were prepared by the general method of Hückel, *et al.*,[12] and used without purification other than a stripping at 110° and 0.5 mm.

When cyclohexyl *p*-toluenesulfonate[12] was utilized in the

(12) Hückel, Neunhoeffer, Gercke and Frank, *Ann.*, **477**, 143 (1930); *cf.* Braker, Pribyl and Lott, THIS JOURNAL, **69**, 866 (1947).

above procedure with 2-hydroxy-4-nitrobenzoic acid (240 hours of reflux), the only product isolated in addition to starting materials was a 5% yield of **cyclohexyl 2-hydroxy-4-nitrobenzoate**, rosettes of elongated pale yellow plates from Skellysolve B, m.p. 91.4–92.4°.

Anal. Calcd. for $C_{13}H_{15}NO_5$: C, 58.86; H, 5.70; N, 5.28. Found: C, 59.07; H, 5.92; N, 5.17.

The reactions between ethyl 2-hydroxy-4-nitrobenzoate and cyclopentyl *p*-toluenesulfonate, cyclohexyl *p*-toluenesulfonate, thenyl bromide, 4-chloroquinoline and 3-bromopropanol gave none of the desired products. With *p*-toluenesulfonyl chloride there was obtained a high yield of **2-carbethoxy-5-nitrophenyl *p*-toluenesulfonate**, platelets from absolute alcohol, m.p. 101.0–102.0°.

Anal. Calcd. for $C_{16}H_{15}NO_7S$: C, 52.60; H, 4.14; N, 3.83; S, 9.07. Found: C, 52.90; H, 4.32; N, 3.79; S, 8.78.

The alcoholysis of 2-methoxy-4-nitrobenzonitrile by means of an alcohol–sulfuric acid mixture (10 hours reflux) gave a 20% conversion to ethyl 2-methoxy-4-nitrobenzoate. The use of homologous alkoxy nitriles[6] proved unfeasible because of extensive alkoxyl cleavage during the alcoholysis.

The new alkyl 2-alkoxy-4-nitrobenzoates, prepared as outlined above, are listed in Table I.

2-Alkoxy-4-nitrobenzoic Acids.—A mixture of 164 g. (0.78 mole) of methyl 2-methoxy-4-nitrobenzoate, 247 g. (2.3 moles, anhydrous basis) of sodium carbonate, 1600 ml. of water and 1600 ml. of alcohol was stirred and refluxed for 12 hours. The alcohol was removed *in vacuo* and the residual clear aqueous solution was acidified to congo red with concentrated hydrochloric acid. The yellow precipitate of 2-methoxy-4-nitrobenzoic acid was filtered off, washed well with water, and dried *in vacuo*. There was thus obtained 146.8 g. (96.5%) of material melting at 146–148°. Recrystallization from dilute alcohol gave pure material with but little loss.

The crude (semi-crystalline or oily) alkyl 2-alkoxy-4-nitrobenzoates, obtained as the residue after the removal of xylene in the alkylation procedure (*vide supra*), were saponified directly by the above procedure, using equivalent amounts. Products of good melting point were obtained in yields of 90–97% based on 2-hydroxy-4-nitrobenzoic acid or an ester thereof. Hydrolysis by means of an aqueous alcoholic potassium hydroxide solution gave high-melting polymers. Acidic hydrolysis, using 5% aqueous alcoholic hydrochloric acid, resulted in partial de-etherification.

A mixture of 100 g. of 2-methoxy-4-nitrobenzonitrile and 300 ml. of concentrated sulfuric acid was stirred and heated on the steam-bath to an internal temperature of 95°. At this point heating was interrupted; the internal temperature rose to 108°. When the spontaneous reaction had subsided the mixture was further stirred and heated on the steam-bath for one hour, cooled to 20° and slowly treated with a solution of 39.4 g. of 95% sodium nitrite in 75 ml. of water. The temperature was maintained at 20–23° during this addition. The solution was stirred at 20° for a further 20 minutes and then slowly heated (foaming!) to 95°. When gas evolution had ceased the mixture was quenched in 2000 g. of crushed ice, and the precipitated solid was filtered off and washed thoroughly with water. After purification through the sodium salt there was obtained 76.6 g. (69% yield) of 2-methoxy-4-nitrobenzoic acid, m.p. 148–149°. This method was not adaptable to homologs higher than 2-ethoxy-4-nitrobenzonitrile because of extensive alkoxyl cleavage.

Saponification of 2-carbethoxy-5-nitrophenyl *p*-toluenesulfonate under similar conditions produced cleavage of the sulfonate grouping. The new 2-alkoxy-4-nitrobenzoic acids prepared in the present work are listed in Table I. In addition the following isomers were prepared from the corresponding esters (*vide supra*). Sodium carbonate solution failed to achieve complete saponification with these esters, but in contrast to the 2-alkoxy series the saponification with an aqueous alcoholic sodium hydroxide solution proceeded smoothly and without resinification.

4-Propoxy-3-nitrobenzoic acid, pale yellow prisms from dilute alcohol, m.p. 167.5–169.7°.

Anal. Calcd. for $C_{10}H_{11}NO_5$: C, 53.33; H, 4.89; N, 6.22. Found: C, 53.59; H, 4.78; N, 5.92.

4-Butoxy-3-nitrobenzoic acid, cream colored needles from dilute alcohol, m.p. 166.0–167.0°.

Anal. Calcd. for $C_{11}H_{13}NO_5$: C, 55.23; H, 5.48; N, 5.86. Found: C, 55.48; H, 5.51; N, 5.66.

3-Propoxy-4-nitrobenzoic acid, pale yellow needles from absolute alcohol, m.p. 197.5–198.2°.

Anal. Calcd. for $C_{10}H_{11}NO_5$: N, 6.22. Found: N, 6.43.

Alkyl 2-Alkoxy-4-aminobenzoates.—A general procedure for the reduction of the nitro esters (including dialkylaminoalkyl esters—*vide infra*) is exemplified by the following:

To a stirred, boiling mixture of 150 g. of powdered iron (excess of a six mole proportion), 700 ml. of alcohol, 200 ml. of water and 1 ml. of concentrated hydrochloric acid was added in small portions 90.5 g. (0.377 mole) of ethyl 2-ethoxy-4-nitrobenzoate. The source of heat was removed during this addition. After completion of the exothermic addition the mixture was stirred and gently boiled for 20 minutes, cautiously treated with 20 g. of powdered sodium bicarbonate (initial foaming) and stirred at the boiling point for a further 10 minutes. The hot mixture was filtered through a pad of Filtercel and the insoluble material was thoroughly washed with hot alcohol. The alcohol was removed from the combined filtrates *in vacuo*, the residual paste was cooled, filtered, and the solid material was washed with water. One recrystallization of the product from benzene–Skellysolve B gave 76.3 g. (96.5% yield) of ethyl 4-amino-2-ethoxybenzoate, m.p. 119–121°.

Heating the latter compound with acetic anhydride on the steam-bath gave a quantitative yield of **ethyl 4-acetamido-2-ethoxybenzoate**, white needles from benzene–Skellysolve B, m.p. 141.6–143.2°.

Anal. Calcd. for $C_{13}H_{17}NO_4$: C, 62.13; H, 6.82; N, 5.57. Found: C, 62.28; H, 6.72; N, 5.62.

The amino esters were also prepared by the catalytic reduction of the nitro esters in alcoholic solution at 50°, using platinum oxide as catalyst. The yields by this method varied from 87–95%. By this means (but not by iron–hydrochloric acid reduction) there was also prepared **5-amino-2-carbethoxyphenyl *p*-toluenesulfonate**, rosettes of white needles from alcohol, m.p. 104.5–106.6°.

Anal. Calcd. for $C_{16}H_{17}NO_5S$: N, 4.18; S, 9.56. Found: N, 4.19; S, 9.56.

The hydrochlorides of the alkyl 2-alkoxy-4-aminobenzoates were prepared in absolute alcohol and precipitated with absolute ether. These compounds slowly lost hydrogen chloride when heated in solution.

The new alkyl 2-alkoxy-4-aminobenzoates are listed in Table II.

2-Alkoxy-4-aminobenzoic Acids.—Forty-six grams (0.192 mole) of 2-ethoxy-4-nitrobenzoic acid was reduced by the general iron–hydrochloric acid procedure described above, but the amount of added sodium bicarbonate was increased to 40 g. The alcohol was removed *in vacuo* from the combined filtrates and the clear aqueous solution was acidified to congo red with concentrated hydrochloric acid. The mixture (precipitate present) was then adjusted to basicity to congo red by means of solid sodium acetate, stirred well and filtered. After washing and drying *in vacuo* there was obtained 32.0 g. (92% yield) of 4-amino-2-ethoxybenzoic acid, m.p. 147–149° (dec.). The compound crystallized from ethyl acetate in white needles. Treatment with hot acetic anhydride gave **4-acetamido-2-ethoxybenzoic acid**, white needles from water, m.p. 148.0–152.2°.

Anal. Calcd. for $C_{11}H_{13}NO_4$: C, 59.19; H, 5.87; N, 6.28. Found: C, 59.00; H, 5.98; N, 6.29.

The new 2-alkoxy-4-aminobenzoic acids are listed in Table II.

4-Butylamino-2-ethoxybenzoic Acid.—The reductive alkylation of ethyl 4-amino-2-ethoxybenzoate by means of *n*-butyraldehyde, zinc dust and acetic acid, by the general procedure previously outlined,[1] gave a quantitative yield of the non-crystalline ethyl 4-*n*-butylamino-2-ethoxybenzoate. Hydrolysis by means of an aqueous alcoholic potassium hydroxide solution gave the desired acid; white prisms from benzene–Skellysolve B, m.p. 98.0–98.8°.

Anal. Calcd. for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90. Found: C, 66.00; H, 8.15; N, 6.01.

Dialkylaminoalkyl 2-Alkoxy-4-nitrobenzoates. A.—A mixture of 23.9 g. (0.10 mole) of 2-*n*-butoxy-4-nitrobenzoic acid, 16.3 g. of 2-diethylaminoethyl chloride (0.12 mole) and 200 ml. of isopropyl alcohol was stirred and refluxed for six hours. The mixture was concentrated to a small volume *in vacuo* and the residue was diluted with ether until precipitation was complete. The solid material was filtered off, washed with ether and recrystallized three times from ethyl

acetate. There was thus obtained 27.0 g. of 2-diethylaminoethyl 2-*n*-butoxy-4-nitrobenzoate hydrochloride, m.p. 108.0–110.4°.

Alternatively, in certain cases where a crystalline hydrochloride could not be obtained directly from the reaction mixture, the isopropyl alcohol was completely removed *in vacuo* and the residue was dissolved in warm water. The aqueous solution, after decolorization, was treated with excess solid potassium carbonate and the liberated base was taken up in ethyl acetate. After drying over Drierite the extract was evaporated *in vacuo;* from these purified bases crystalline derivatives could usually be prepared with little difficulty.

B.—A mixture of 22.5 g. (0.10 mole) of 4-nitro-2-*n*-propoxybenzoic acid, 11.0 g. (0.11 mole) of potassium bicarbonate and 400 ml. of dry toluene was stirred and refluxed under a water trap until dehydration was complete (two hours). The water trap was removed and there was added 12.9 g. (0.12 mole) of 2-dimethylaminoethyl chloride. Stirring and refluxing were continued for 20 hours. The mixture was filtered while hot and the filtercake was washed well with hot toluene. The toluene was removed from the combined filtrates *in vacuo* and the residual oil was dissolved in dilute hydrochloric acid. After decolorization, etc., as above outlined, there was obtained 24.0 g. (81% yield) of oily 2-dimethylaminoethyl 4-nitro-2-*n*-propoxybenzoate.

C.—A mixture of 51.6 g. (0.26 mole) of 2-methoxy-4-nitrobenzoic acid and 155 g. (1.3 moles) of pure thionyl chloride was refluxed for one hour. The excess thionyl chloride was distilled off at atmospheric pressure and the residual solid acid chloride was triturated thoroughly with Skellysolve B. After drying *in vacuo* over paraffin–phosphorus pentoxide there was obtained 49.5 g. (87.5% yield) of crude 2-methoxy-4-nitrobenzoyl chloride, m.p. 33–36°. To a solution of this material in 300 ml. of dry benzene was added with stirring 36.2 g. (0.23 mole) of 3-(2-methyl-1-piperidyl)-propanol. The heterogeneous mixture was heated to boiling, cooled, diluted with 500 ml. of absolute ether, and filtered. Two recrystallizations of the solid product from absolute alcohol–ether gave an 88% yield of 3-(2-methyl-1-piperidyl)-propyl 2-methoxy-4-nitrobenzoate hydrochloride, m.p. 153.5–154.4°.

When alkoxy acids with the alkoxy group larger than ethoxy were used in this procedure the acyl chloride formation was carried out in the presence of anhydrous pyridine[1] in order to prevent alkoxyl group cleavage.

The dialkylaminoalkyl 2-alkoxy-4-nitrobenzoates and their characterizing derivatives are listed in Table III.

In addition, the following isomers were prepared by the Horenstein–Pählicke reaction:

2-Diethylaminoethyl 4-propoxy-3-nitrobenzoate hydrochloride, pale yellow leaflets from absolute alcohol–absolute ether, m.p. 124.8–126.8°.

Anal. Calcd. for $C_{16}H_{25}ClN_2O_5$: Cl, 9.83; N,[13] 3.88. Found: Cl, 9.54; N,[13] 3.95.

The corresponding **picrate** melted at 130.4–131.4°.

Anal. Calcd. for $C_{22}H_{27}N_5O_{12}$: N,[14] 2.53; N,[13] 10.12. Found: N,[14] 2.51; N,[13] 10.00.

2-Diethylaminoethyl 4-butoxy-3-nitrobenzoate hydrochloride, cream-colored leaflets from absolute alcohol–absolute ether, m.p. 138.4–140.0°.

Anal. Calcd. for $C_{17}H_{27}ClN_2O_5$: Cl, 9.46; N,[13] 3.74. Found: Cl, 9.26; N,[13] 3.70.

The picrate had m.p. 124.2–125.0°.

Anal. Calcd. for $C_{23}H_{29}N_5O_{12}$: N,[14] 2.47; N,[13] 9.88. Found: N,[14] 2.42; N,[13] 9.85.

2-Diethylaminoethyl 3-propoxy-4-nitrobenzoate hydrochloride, white needles from absolute alcohol–absolute ether, m.p. 134.9–136.9°.

Anal. Calcd. for $C_{16}H_{25}ClN_2O_5$: N,[13] 3.88; Cl, 9.82. Found: N,[13] 4.00; Cl, 10.00.

The picrate had m.p. 127.9–128.8°.

Anal. Calcd. for $C_{22}H_{27}N_5O_{12}$: N,[14] 2.53; N,[13] 10.12. Found: N,[14] 2.51; N,[13] 10.15.

Dialkylaminoalkyl 2-Alkoxy-4-aminobenzoates.—The dialkylaminoalkyl 2-alkoxy-4-nitrobenzoate bases or hydrochlorides were reduced either by the general iron–hydrochloric acid procedure outlined above, or by catalytic reduction with platinum oxide. The yields were very high in all cases and no manipulative difficulties were encountered either in these reductions or in the preparation of derivatives. The monohydrochlorides were best prepared by the catalytic method. The 2-alkoxy-4-amino compounds and their derivatives are listed in Table IV.

The following structural isomers were prepared by similar methods:

2-Diethylaminoethyl 3-amino-4-propoxybenzoate hydrochloride, white prisms from absolute alcohol–ethyl acetate, m.p. 182.0–183.3°.

Anal. Calcd. for $C_{16}H_{27}ClN_2O_3$: Cl, 10.72; N, 8.47. Found: Cl, 10.88; N, 8.56.

The flavianate had m.p. 162.0–163.0° (dec.).

Anal. Calcd. for $C_{26}H_{32}N_4O_{11}S$: S, 5.27. Found: S, 5.22.

2-Diethylaminoethyl 3-Amino-4-butoxybenzoate hydrochloride, white needles from absolute alcohol-ethyl acetate, m.p. 158.8–160.0°.

Anal. Calcd. for $C_{17}H_{29}ClN_2O_3$: Cl, 10.28; N, 8.12. Found: Cl, 10.54; N, 7.97.

The flavianate had m.p. 172.6–174.6°.

Anal. Calcd. for $C_{27}H_{34}N_4O_{11}S$: S, 5.15. Found: S, 5.17.

2-Diethylaminoethyl 4-amino-3-propoxybenzoate hydrochloride, white needles from absolute alcohol, m.p. 172.5–173.2°.

Anal. Calcd. for $C_{16}H_{27}ClN_2O_3$: Cl, 10.72; N, 8.46. Found: Cl, 10.66; N, 8.60.

The diflavianate crystallized from acetic acid in canary-yellow needles, m.p. 208.8–210.0°.

Anal. Calcd. for $C_{36}H_{38}N_6O_{19}S_2$: S, 6.94. Found: S, 7.02.

Dialkylaminoalkyl 2-Alkoxy-4-alkylaminobenzoates.—The dialkylaminoalkyl 2-alkoxy-4-aminobenzoates were reductively alkylated by means of an aldehyde, zinc dust and acetic acid,[1] or by catalytic reductive alkylation.[1] With the majority of the compounds a crystalline water-soluble salt could not be obtained, and it was necessary to purify the bases.[1] Preparation *via* a 2-alkoxy-4-*n*-butylaminobenzoyl chloride hydrochloride gave fair to poor yields, but the products so obtained were difficult to purify.

The compounds and their derivatives are listed in Table V.

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(13) Nitro nitrogen, by titration with titanous chloride.

(14) Basic amino nitrogen, by titration with perchloric acid in glacial acetic acid solution.