VII. Crystallization from benzene gave material of m.p. 226–227°. The infrared spectrum[13] exhibited carbonyl absorption at 1680 and hydroxyl absorption at 3380 cm.$^{-1}$.

Anal. Calcd. for $C_{16}H_{18}O_5$: C, 66.18; H, 6.26. Found: C, 66.32; H, 6.23.

3-Hydroxymethyl-5-isopropyl-6,7-dimethoxy-1-naphthol (VIII).—To 4 g. of lithium aluminum hydride in 200 ml. of absolute ether there was added dropwise a solution of 4.5 g. of VII in 100 ml. of ether. The mixture was refluxed for 90 minutes and allowed to stand overnight. After cooling, the mixture was decomposed by the dropwise addition of water and then acidified with dilute hydrochloric acid. After separation, the ethereal extract was washed twice with water and dried over anhydrous sodium sulfate. The ether was removed over a steam-bath and the residue crystallized from benzene to give 3.9 g. (93%) of VIII, m.p. 207–209°. The infrared spectrum[13] showed hydroxyl group absorption at 3420 and 3300 cm.$^{-1}$.

Anal. Calcd. for $C_{16}H_{20}O_4$: C, 69.53; H, 7.31. Found: C, 69.71; H, 7.20.

5-Isopropyl-6,7-dimethoxy-3-methyl-1-naphthol (IX).—To 0.15 g. of palladium-on-charcoal (10%) in 35 ml. of methanol there was added 0.5 g. of VIII in 65 ml. of methanol. One drop of concd. hydrochloric acid in 1 ml. of water was added to this mixture. It was then hydrogenated for 20 minutes in a Parr low pressure hydrogenator. Anhydrous sodium sulfate was added and the mixture suction filtered. After removal of the methanol over a steam-bath, the product was recrystallized from chloroform–petroleum ether (30–60°) to give 0.192 g. (41%) of IX, m.p. 129–130°. The infrared spectrum[13] showed the presence of an hydroxyl group (sharp band at 3570 and a broad band at 3310 cm.$^{-1}$).

Anal. Calcd. for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.76; H, 7.78.

2,2′-Bi-1-(5-isopropyl-6,7-dimethoxy-3-methyl)-naphthol (X).—A test-tube containing 0.2 g. of IX was placed in an oil-bath heated to 150°; the temperature was allowed to rise to 215° and held there for 20 minutes or until the material had melted and solidified. The product was recrystallized from benzene–methanol to give a quantitative yield of X, m.p. 271–274°.

Anal. Calcd. for $C_{32}H_{38}O_6$: C, 74.10; H, 7.38; mol. wt., 518. Found: C, 74.21; H, 7.39; mol. wt. (Rast), 447.

2,2′-Bi-5-isopropyl-1,6,7-trimethoxy-3-methylnaphthyl (III).—To a solution of 0.24 g. of X in 25 ml. of purified dioxane[14] there was added 5 ml. of an aqueous solution of 0.49 g. of potassium hydroxide. To this mixture there was added 1.1 g. of dimethyl sulfate which was then heated under reflux until reaction was complete as indicated by litmus paper. The additions of potassium hydroxide and dimethyl sulfate were repeated two times. After cooling, water was added and the reaction mixture extracted with dichloromethane. The dichloromethane phase was extracted several times with water. After drying over anhydrous sodium sulfate, the dichloromethane was removed over a steam-bath and the residue taken up in 25 ml. of diethyl ether and filtered. Upon standing 0.1 g. (42%) of 2,2′-bi-5-isopropyl-1,6,7-trimethoxy-3-methylnaphthyl (III) crystallized. It was recrystallized several times from benzene–methanol, m.p. 277–279°; mixture m.p. with apogossypol hexamethyl ether prepared from gossypol, 277–278°. The infrared[13] spectra of the natural and synthetic product were indistinguishable.

(14) L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., Boston, Mass., 1955, p. 285.

HOUSTON, TEXAS

[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

Derivatives of 4-Amino-2-hydroxybenzoic Acid. IV. Amides

BY R. O. CLINTON, S. C. LASKOWSKI, U. J. SALVADOR, HELEN G. BATES AND PATRICIA M. CARROLL

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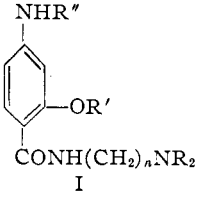
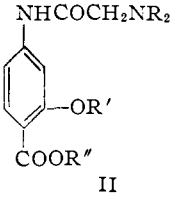
Several types of amides derived from the 4-amino-2-hydroxybenzoic acid nucleus have been prepared. The first type consisted of N-(dialkylaminoalkyl)-4-amino-2-hydroxybenzamides and the related 2-alkoxy and 4-alkylamino compounds. Several of these compounds possessed outstanding activity as antifibrillatory agents. The second series was of the general type represented by an alkyl 4-(dialkylaminoacetylamino)-2-alkoxybenzoate and its related derivatives. The latter compounds were, in general, only fair local anesthetics but in certain cases possessed substantial analgesic properties. Finally, a series of variants on the 4-amino-2-alkoxybenzamide nucleus were prepared; certain of these compounds were potent oral analgesics.

The observation[1] that a very high degree of local anesthetic activity was associated with certain basic ester and thiol ester derivatives of 4-amino-2-hydroxy- and 2-alkoxybenzoic acids[2] prompted an extension of the synthetic work to two types of basic amides related to these series, as depicted in I and II.



I



II

Previously published investigations[3-5] of N-ω-dialkylaminoalkylbenzamides have shown that the simple amides were considerably less active as local anesthetics than their ester counterparts and that even in the cases of 3-alkoxy-[4] or 4-alkoxy-[5] substitution the local anesthetic activity does not surpass that of the esters. However, since in the present series a very high degree of local anesthetic activity was associated with the basic ester counterparts[1] of I, it was felt that a reduction in the degree of local anesthetic activity would not be a serious defect. Further, the increased stability of the amide linkage toward hydrolysis might well be reflected in more desirable physiological properties.

The synthesis of the amides of type II was based upon the premise that the low toxicity associated

(1) F. P. Luduena and J. O. Hoppe, *J. Pharmacol. Exptl. Therap.*, **104**, 40 (1952), and subsequent papers.

(2) (a) R. O. Clinton, S. C. Laskowski, U. J. Salvador and Mary Wilson, THIS JOURNAL, **73**, 3674 (1951); (b) **74**, 592 (1952); (c) R. O. Clinton, U. J. Salvador and S. C. Laskowski, *ibid.*, **76**, 5121 (1954).

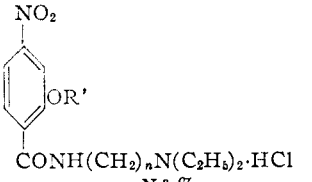
(3) H. Wenker, *ibid.*, **60**, 1081 (1938); F. F. Blicke, H. C. Parke and E. L. Jenner, *ibid.*, **62**, 3316 (1940); R. O. Clinton, U. J. Salvador and S. C. Laskowski, *ibid.*, **71**, 3839 (1949).

(4) J. Büchi, E. Stünzi, M. Flury, R. Hirt, P. Labbart and L. Ragaz, *Helv. Chim. Acta*, **34**, 1002 (1951).

(5) P. Kolosy, P. Teyssie and H. Vanderhaeghe, *J. Pharm. Pharmacol.*, **7**, 477 (1955).

TABLE I

N-(DIETHYLAMINOALKYL)-2-ALKOXY- OR 2-HYDROXY-4-NITROBENZAMIDE HYDROCHLORIDES



n	R′	M.p., °C.	Formula	Chlorine, % Calcd.	Found	N,[a] % Calcd.[a]	Found[a]
2	H	149.6–150.2	$C_{13}H_{20}ClN_3O_4$	11.16	11.12	[c]	[c]
3	H	137.8–138.8	$C_{14}H_{22}ClN_3O_4$	10.69	10.62	4.22[d]	4.21[d]
4	H	146.0–146.9	$C_{15}H_{24}ClN_3O_4$	10.25	10.09	[e]	[e]
2	CH_3	161.2–162.7	$C_{14}H_{22}ClN_3O_4$	10.69	10.49	4.22	4.14
3	CH_3[g]	149.1–150.0	$C_{15}H_{24}ClN_3O_4$	10.25	10.33	[f]	[f]
4	CH_3	116.4–119.6	$C_{16}H_{26}ClN_3O_4$	9.85	10.10	..	..
[b]	CH_3[h]	153.6–155.0	$C_{15}H_{24}ClN_3O_5$	9.80	9.62	3.87	3.99
3	C_2H_5[i,j]	133.4–135.0	$C_{16}H_{26}ClN_3O_4$	9.85	9.99	3.89	3.83
2	n-C_3H_7[k,l,m]	164.8–167.9	$C_{16}H_{26}ClN_3O_4$	9.85	9.96	3.89	4.14
2	n-C_4H_9[n,o,p]	133.2–134.2	$C_{17}H_{28}ClN_3O_4$	9.48	9.57	3.74	3.74
2	n-C_6H_{13}[q]	90.1–108.9	$C_{19}H_{32}ClN_3O_4$	8.82	8.77	3.49	3.44
2	n-C_8H_{17}[r]	128.0–129.4	$C_{21}H_{36}ClN_3O_4$	8.25	8.35	3.26	3.30

[a] Ref. 10. [b] 3-Diethylamino-2-hydroxy-1-propyl. [c] Calcd.: C, 49.13; H, 6.34. Found: C, 49.35; H, 6.10. [d] Calcd.: C, 50.67; H, 6.68. Found: C, 50.72; H, 6.50. [e] Calcd.: C, 52.09; H, 7.00. Found: C, 52.23; H, 6.70. [f] Calcd.: C, 52.09; H, 7.00. Found: C, 52.16; H, 6.88. [g] Picrate m.p. 152.8–153.8°. Calcd.: neut. equiv., 538; basic N, 2.60. Found: neut. equiv., 546; basic N, 2.62. [h] Picrate m.p. 151.0–152.0°. Calcd.: neut. equiv., 554; basic N, 2.52. Found: neut. equiv., 549; basic N, 2.33. [i] Base, m.p. 62.0–62.9°. Calcd.: N[a], 4.33; basic N, 4.33. Found: N[a], 4.24; basic N, 4.31. [j] Flavianate m.p. 185.9–187.1°. Calcd.: S, 5.03. Found: S, 5.04. [k] Base m.p. 64.4–65.0°. Calcd.: N, 12.99. Found: N, 13.28. [l] Methiodide m.p. 169.8–170.5°. Calcd.: N[a], 3.01; I, 27.28. Found: N[a], 3.05; I, 27.28. [m] Picrate m.p. 161.6–162.6°. Calcd.: neut. equiv., 552; basic N, 2.53. Found: neut. equiv., 546; basic N, 2.48. [n] Base m.p. 49.9–50.9°. Calcd.: N, 12.45. Found: N, 12.32. [o] Methiodide m.p. 136.5–137.6°. Calcd.: N[a], 2.92; I, 26.48. Found: N[a], 3.09; I, 26.40. [p] Picrate m.p. 164.5–165.3°. Calcd.: neut. equiv., 566; basic N, 2.47. Found: neut. equiv., 563; basic N, 2.41. [q] Picrate m.p. 110.2–112.0°. Calcd.: N[a], 9.42. Found: N[a], 9.29. [r] Base m.p. 51.8–52.7°. Calcd.: N, 10.68. Found: N, 10.70.

with Nirvanine[6] [methyl 5-(diethylaminoacetylamino)-2-hydroxybenzoate] might well be retained in the corresponding 4-dialkylaminoacetylamino series, while simultaneously achieving a very desirable reduction in irritation. Since the completion of this investigation, two examples of compounds related to II have been published.[7] Both compounds were hydroxy acids (II, R′ = R″ = H), prepared for testing as antitubercular agents.

In the two formulas shown, I and II, the various indicated substituent R, R′ and R″ groups were varied sufficiently to ensure the attainment, if possible, of a wide range of local anesthetic activity. In addition to the alkyl esters of II, several of the related benzamides and benzoic acids were prepared for comparison.

The benzamides of type I were prepared either by the aminolysis of a 4-nitrosalicylic ester or by the reaction between an alkoxynitrobenzoyl chloride and an amine. Subsequent reduction by conventional means led to the 4-aminobenzamides and thence by reductive alkylation to the 4-alkylaminobenzamides. These compounds are listed in Tables I, II and III and are described in the Experimental section.

The amides of type II were in general prepared by the reaction of an alkyl 2-alkoxy-4-aminobenzoate with chloroacetyl chloride, followed by amination by the appropriate secondary amine. Similar methods were used for the amide types (II, $CONH_2$ in place of COOR″). This series is summarized in Tables IV and V.

(6) A. Einhorn and M. Oppenheimer, *Ann.*, **311**, 155 (1900).

(7) R. Hirt and H. Hurni, *Helv. Chim. Acta*, **32**, 378 (1949); British Patents 665,675 and 676,363.

The initial observation[8] that 4-amino-2-alkoxybenzamides possessed oral analgesic activity of the order of aminopyrine in the standard Radiant Thermal Stimulus test, prompted the synthesis of a large number of variants on the former nucleus. These compounds were synthesized by straightforward methods with little difficulty; they are summarized in Table VI and in the Experimental section.

Pharmacological testing[9] of the N-dialkylaminoalkyl benzamide types, I, has indicated a high degree of local anesthetic activity for those compounds where R′ is greater than ethyl. In general this activity is less than that found for the corresponding esters, while toxicity and irritancy are similar to those found for the esters. Several of the higher members of the series, in particular N-(2-diethylaminoethyl)-4-amino-2-hexoxybenzamide (Win 8568), have shown outstanding properties as antifibrillatory agents.

The dialkylaminoacetylamino compounds, II, possessed a relatively low order of local anesthetic activity, comparable to that of procaine. However, many of these compounds showed a high order of analgesic activity[8] in the Standard Radiant Thermal Stimulus test and have undergone further testing as oral analgesics.

Experimental[10]

N-(Diethylaminoethyl)-2-hydroxy-4-nitrobenzamide Hydrochloride.—A mixture of 16.7 g. (0.079 mole) of ethyl 4-

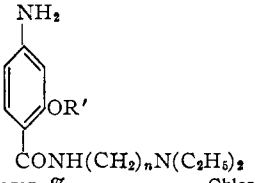
(8) J. R. Lewis and J. O. Hoppe, to be published.

(9) L. Grumbach and J. O. Hoppe, to be published.

(10) All melting points were determined in a modified Hershberg Apparatus, using total immersion N.B.S. calibrated thermometers

TABLE II

N-DIETHYLAMINOALKYL-4-AMINO-2-ALKOXY- OR 2-HYDROXYBENZAMIDES

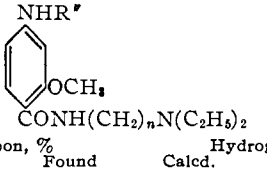


n	R′	M.p. °C.	Formula	Type[a]	Nitrogen, % Calcd.	Nitrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found
3	H	179.0–182.0	$C_{14}H_{25}Cl_2N_3O_2$	DH	[b]	[b]	20.96	20.70
4	H	156.8–159.6	$C_{15}H_{26}ClN_3O_2$	H	13.31	13.16	11.23	11.12
2	CH_3[c]	167.9–170.8	$C_{14}H_{26}N_3O_6P$	P	11.56	11.41	26.98[d]	27.35[d]
2	CH_3[e,f]	212.0–213.1	$C_{15}H_{28}N_3O_6P$	P	11.13	10.91	25.98[d]	25.92[d]
4	CH_3[g]	197.0–199.0	$C_{16}H_{30}N_3O_6P$	P	10.74	10.43	...	...
3	C_2H_5[h]	204.0–205.6	$C_{16}H_{28}ClN_3O_2$	H	12.74	12.75	10.75	10.52
2	n-C_3H_7[i,j]	232.7–233.7	$C_{16}H_{28}ClN_3O_2$	H	12.74	12.72	10.75	10.88
2	n-C_4H_9[k,l]	199.0–199.6	$C_{17}H_{30}ClN_3O_2$	H	12.22	12.24	10.31	10.39
2	n-C_6H_{13}	137.9–139.7	$C_{19}H_{34}ClN_3O_2$	H	11.30	11.38	9.52	9.47
2	n-C_8H_{17}	87.6–90.2	$C_{21}H_{38}ClN_3O_2$	H	10.51	10.55	8.86	8.87

[a] P = phosphate; H = hydrochloride; DH = dihydrochloride. [b] Calcd.: C, 49.71; H, 7.45. Found: C, 49.47; H, 7.27. [c] Flavianate m.p. 199.8–202.8°. Calcd.: N, 12.08. Found: N, 12.08. [d] Phosphoric acid analysis. [e] Flavianate m.p. 186.5–188.2°. Calcd.: S, 5.24. Found: S, 5.26. [f] Calcd.: C, 47.73; H, 6.67. Found: C, 47.74; H, 6.83. [g] Flavianate m.p. 231.2–231.9° dec. Calcd.: neut. equiv., 303; N^a, 4.61. Found: neut. equiv., 298; N^a, 4.54. [h] Flavianate m.p. 208.8–209.1°. Calcd.: S, 5.28. Found: S, 5.40. [i] Diflavianate m.p. 209.0–210.0°. Calcd.: N^a, 6.07. Found: N^a, 5.90. [j] Methiodide m.p. 138.8–141.0°. Calcd.: N, 9.65; I, 29.15. Found: N, 9.66; I, 28.99. [k] Diflavianate m.p. 165.8–167.8°. Calcd.: N^a, 5.98. Found: N^a, 5.78. [l] Methiodide m.p. 173.3–174.5°. Calcd.: C, 48.11; H, 7.17; N, 9.35. Found: C, 48.02; H, 6.97; N, 9.28.

TABLE III

N-(DIETHYLAMINOALKYL)-2-METHOXY-4-ALKYLAMINOBENZAMIDES



n	R″	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
2	n-C_4H_9[a]	$C_{18}H_{31}N_3O_2$	13.07	12.78	...	...	...	...
3	n-C_4H_9[b,c]	$C_{19}H_{33}N_3O_2$	12.53	12.33	68.02	68.08	9.91	9.79
3	n-C_5H_{11}[d]	$C_{20}H_{35}N_3O_2$	...	...	68.73	69.06	10.09	9.77
3	$C_5H_{10}O$[e,f]	$C_{20}H_{35}N_3O_3$	...	...	63.43	63.41	9.14	9.08
4	n-C_4H_9	$C_{20}H_{35}N_3O_2$	12.02	12.00	68.73	68.63	10.09	10.26

[a] Dipicrate m.p. 117.0–121.4°. Calcd.: neut. equiv., 390; basic N, 3.59. Found: neut. equiv., 383; basic N, 3.63. [b] Base m.p. 58.4–59.8°. [c] Flavianate m.p. 169.3–171.2°. Calcd.: O, 24.6; N^a, 4.32. Found: O, 25.0; N^a, 4.32. [d] Flavianate m.p. 166.0–166.5°. Calcd.: neut. equiv., 332; N^a, 4.22. Found: neut. equiv., 336; N^a, 4.22. [e] 5-Hydroxyamyl. [f] Flavianate m.p. 140.0–141.7°. Calcd.: neut. equiv., 340; N^a, 4.12. Found: neut. equiv., 346; N^a, 4.18.

nitrosalicylate, 23.2 g. (0.20 mole) of 2-diethylaminoethylamine and 250 ml. of dry toluene was refluxed for 8 hr. On cooling, the orange-colored solution separated into two layers. The toluene was removed *in vacuo* and the residual solid (essentially a phenolate-type salt of the base with excess 2-diethylaminoethylamine)[11] was dissolved in an excess of hot alcoholic hydrogen chloride solution. The solution was cooled, diluted with anhydrous ether and the precipitated hydrochloride was filtered. It was obtained analytically pure after a single recrystallization from absolute alcohol. The yield of bright yellow solid was 18.9 g. (75%). The physical properties of this compound, as well as those of analogous 2-hydroxy compounds prepared by the same procedure, are listed in Table I. The free bases (usually oils) were prepared by liberation from the pure hydrochlorides with potassium carbonate solution, under nitrogen. The picrates, flavianates and methiodides were prepared from the free bases in the usual manner.

and are corrected. The analyses were done by Mr. M. E. Auerbach, Mr. K. D. Fleischer and their staffs. In the text and Tables the following abbreviations are used: N^a for nitro-nitrogen by titanous chloride titration; neutral equivalent by titration with sodium methoxide in anhydrous methanol; basic N for nitrogen by titration with perchloric acid in acetic acid.

(11) *Cf.* R. O. Clinton and S. C. Laskowski, THIS JOURNAL, **74**, 2226 (1952).

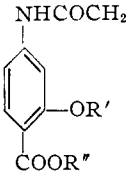
N-(Diethylaminoalkyl)-2-alkoxy-4-nitrobenzamides.—Aminolysis of an alkyl 2-alkoxy-4-nitrobenzoate[2b] by means of a dialkylaminoalkylamine as above gave fair to poor yields; the yields decreased as the size of the 2-alkoxy group increased. A better procedure involved the reaction between a 2-alkoxy-4-nitrobenzoyl chloride and the amine in benzene or ether solution.

To a stirred solution of 40.0 g. (0.186 mole) of 2-methoxy-4-nitrobenzoyl chloride[2b] in 250 ml. of dry benzene, there was slowly added a solution of 21.6 g. (0.186 mole) of 2-diethylaminoethylamine in 50 ml. of dry benzene. The addition required about 0.5 hr.; the internal temperature was held at about 20° by means of a cooling bath. The resulting gummy mixture was heated to boiling, diluted with 700 ml. of dry *n*-hexane and cooled. The tan-colored solid was filtered and washed with 1:1 benzene–hexane mixture. After three recrystallizations from an absolute alcohol–*n*-hexane mixture, with decolorization by means of Darco G-60 during the first recrystallization, the product was obtained pure in 77% yield.

With the higher 2-alkoxy-4-nitrobenzoic acids it was necessary to prepare the benzoyl chloride *in situ* in the presence of pyridine, to prevent cleavage of the alkoxyl group.[2b] Under these conditions, wherein a slight initial excess of the acid over thionyl chloride was present, the excess acid was removed by a basic wash of an ethereal solution of the product before conversion to the hydrochloride.

TABLE IV

ALKYL 4-(DIALKYLAMINOACETYLAMINO)-2-ALKOXY- OR -2-HYDROXYBENZOATES

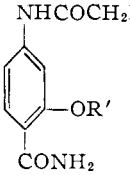


R_2	R'	R''	Type[a]	M.p., °C.	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found
$(C_2H_5)_2$	C_2H_5	C_2H_5[c]	H	171.7–172.5	$C_{17}H_{27}ClN_2O_4$	7.81	7.82	9.88	9.64
C_6H_{12}[b]	C_2H_5	C_2H_5[d]	H	194.4–196.0	$C_{19}H_{29}ClN_2O_4$	7.28	7.22	9.21	9.04
$(C_2H_5)_2$	n-C_4H_9	C_2H_5[e]	H	133.0–134.4	$C_{19}H_{31}ClN_2O_4$	7.24	7.23	9.16	9.30
C_6H_{12}[b]	n-C_4H_9	C_2H_5	B	70.2–71.8	$C_{21}H_{32}N_2O_4$	7.46	7.52	..	..
C_6H_{12}[b]	n-C_4H_9	C_2H_5	H	186.1–187.1	$C_{21}H_{33}ClN_2O_4$	6.78	6.99	8.59	8.82
$(C_2H_5)_2$	C_7H_7[f]	C_2H_5[g]	H	119.8–121.4	$C_{22}H_{29}ClN_2O_4$	6.66	6.68	8.42	8.14
C_6H_{12}[b]	C_7H_7[f]	C_2H_5[h]	H	169.6–171.0	$C_{24}H_{31}ClN_2O_4$	6.27	6.32	7.93	7.90

[a] B = base; H = hydrochloride. [b] 2-Methyl-1-piperidyl. [c] Picrate m.p. 147.8–148.9°. Calcd.: neut. equiv., 552; basic N, 2.54. Found: neut. equiv., 559; basic N, 2.50. [d] Flavianate m.p. 200.1–201.2°. Calcd.: neut. equiv., 332; S, 4.84. Found: neut. equiv., 338; S, 4.94. [e] Picrate m.p. 134.8–135.4°. Calcd.: neut. equiv., 580; basic N, 2.42. Found: neut. equiv., 583; basic N, 2.40. [f] Benzyl. [g] Picrate m.p. 146.2–147.6°. Calcd.: neut. equiv., 614; basic N, 2.28. Found: neut. equiv., 611; basic N, 2.29. [h] Picrate m.p. 154.0–155.2°. Calcd.: neut. equiv., 640; basic N, 2.19. Found: neut. equiv., 652; basic N, 2.19.

TABLE V

4-(DIETHYLAMINOACETYLAMINO)-2-ALKOXY- OR -2-HYDROXYBENZAMIDES

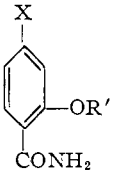


R'	Type[a]	M.p., °C.	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found
C_2H_5[c]	B	138.4–138.8	$C_{15}H_{23}N_3O_3$	14.31	14.32	...	...
C_2H_5	H	234.6–236.0[b]	$C_{15}H_{24}ClN_3O_3$	12.74	12.84	10.75	10.66
n-C_4H_9[d]	B	154.0–155.2	$C_{17}H_{27}N_3O_3$	13.07	13.34	..	..
n-C_4H_9	H	228.6–230.2	$C_{17}H_{28}ClN_3O_3$	11.74	11.59	9.91	9.73
C_7H_7[e,f]	B	137.6–138.0	$C_{20}H_{25}N_3O_3$	11.82	11.55	...	...
C_7H_7	H	199.2–199.6	$C_{20}H_{26}ClN_3O_3$	10.72	10.56	9.05	8.85

[a] B = base; H = hydrochloride. [b] With decomposition. [c] Dipicrate m.p. 155.2–156.4. Calcd.: neut. equiv., 376; basic N, 1.86. Found: neut. equiv., 381; basic N, 1.98. [d] Picrate m.p. 166.5–167.4. Calcd.: N^a, 7.63. Found: N^a; 7.65. [e] Benzyl. [f] Picrate m.p. 179.9–180.9°. Calcd.: neut. equiv., 585; basic N, 2.40. Found: neut. equiv., 590; basic N, 2.64.

TABLE VI

2,4-DISUBSTITUTED BENZAMIDES



X	R'	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
NO_2	CH_3	255.7–256.6	$C_8H_8N_2O_4$	[a]	[a]	..	..	14.28	14.44
NO_2	C_2H_5	188.2–190.0	$C_9H_{10}N_2O_4$	51.42	51.29	4.80	4.68	13.33	13.09
NO_2	n-C_3H_7	191.0–191.7	$C_{10}H_{12}N_2O_4$	[b]	[b]	..	..	12.49	12.23
NO_2	n-C_4H_9	166.6–167.6	$C_{11}H_{14}N_2O_4$	55.45	55.73	5.92	5.65	11.76	11.76
NO_2	i-C_4H_9	198.4–199.4	$C_{11}H_{14}N_2O_4$	55.45	55.43	5.92	5.82	11.76	11.68
NO_2	n-C_6H_{13}	136.3–138.0	$C_{13}H_{18}N_2O_4$	58.63	58.90	6.81	6.52	10.52	10.34
NO_2	C_7H_7[c,d]	180.9–181.9	$C_{14}H_{12}N_2O_4$	61.76	61.75	4.44	4.47	[g]	[g]
NH_2	CH_3	193.9–195.6	$C_8H_{10}N_2O_2$	[e]	[e]	..	..	16.86	16.59
NH_2	C_2H_5	191.6–193.1	$C_9H_{12}N_2O_2$	59.98	60.28	6.71	6.58	15.51	15.56
NH_2	n-C_3H_7	159.6–160.9	$C_{10}H_{14}N_2O_2$	61.83	62.13	7.26	7.39	14.43	14.32
NH_2	n-C_4H_9	178.7–180.2	$C_{11}H_{16}N_2O_2$	63.44	63.62	7.75	7.49	13.45	13.53
NH_2	i-C_4H_9	175.7–177.3	$C_{11}H_{16}N_2O_2$	63.44	63.47	7.75	7.47	13.45	13.12
NH_2	n-C_6H_{13}	127.6–129.0	$C_{13}H_{20}N_2O_2$	66.07	66.09	8.53	8.75	11.86	11.78
NH_2	C_7H_7[c,f]	150.0–151.8	$C_{14}H_{14}N_2O_2$	69.40	69.15	5.82	5.82	11.57	11.27

[a] Calcd.: N^a, 7.19. Found: N^a, 6.96. [b] Calcd.: N^a, 6.25. Found: N^a, 6.24. [c] Benzyl. [d] K. A. Jensen and H. Ingvorsen, *Acta Chem. Scand.*, 6, 161 (1952), reported m.p. 178°. [e] Calcd.: OCH_3, 18.67. Found: OCH_3, 18.50. [f] Reported, without physical properties, in British Patent 670,424. [g] Calcd.: N^a, 5.15. Found: N^a, 5.12.

An alternative procedure involved the addition of the benzoyl chloride in alcohol-free chloroform solution to a mixture of the amine, water and sodium bicarbonate.[12] The crude yields obtained by this method were usually somewhat lower than those resulting by the direct reaction mentioned above, but the products in some cases proved to be purified more easily. For example, this method gave excellent results when applied to the preparation of N-(3-diethylamino-2-hydroxy-1-propyl)-2-methoxy-4-nitrobenzamide, whereas the direct reaction in benzene gave an almost inseparable mixture of benzoate and benzamide.

In addition to those compounds listed in Table I, there was prepared: **N-(3-(2-methyl-1-piperidyl)-(propyl)-2-methoxy-4-nitrobenzamide hydrochloride**, from the benzoyl chloride and 3-(2-methyl-1-piperidyl)-propylamine[13] in benzene solution; 82% yield. The compound formed pale yellow prisms from absolute alcohol–*n*-hexane; m.p. 167.5–169.3°.

Anal. Calcd. for $C_{17}H_{26}ClN_3O_4$: N^a, 3.76; Cl, 9.53. Found: N^a, 3.71; Cl, 9.18.

4-Nitro-2-octyloxybenzoic Acid.—The alkylation of ethyl 2-hydroxy-4-nitrobenzoic acid by means of *n*-octyl benzenesulfonate (from *n*-octyl alcohol, benzenesulfonyl chloride and pyridine) was carried out by the method previously described.[2b] Hydrolysis of the crude oily ethyl ester gave a 97% over-all yield of the acid, m.p. 92–93°. The compound crystallized from *n*-hexane in cream-colored feathery needles, m.p. 93.1–94.2°.

Anal. Calcd. for $C_{15}H_{21}NO_5$: C, 61.00; H, 7.16; N, 4.74. Found: C, 60.94; H, 7.20; N, 4.91.

Conversion to the acid chloride by means of thionyl chloride–pyridine and thence to the ethyl ester, gave the latter as a mobile oil; reduction by means of iron–hydrochloric acid gave a 77% yield of **ethyl 4-amino-2-octyloxybenzoate**, white prisms from *n*-hexane; m.p. 61.8–63.4°.

Anal. Calcd. for $C_{17}H_{27}NO_3$: C, 69.59; H, 9.27; N, 4.77. Found: C, 69.58; H, 9.02; N, 4.82.

N-(Diethylaminoalkyl)-4-amino-2-hydroxybenzamides.—The 2-hydroxy-4-nitrobenzamide hydrochlorides were reduced catalytically by hydrogen in alcoholic solution at 50 lb. pressure and 25°, using 7% palladium chloride on Darco G-60 as catalyst. Precautions were taken in the isolation procedure to minimize air oxidation of the sensitive products.

N-(Dialkylaminoalkyl)-2-alkoxy-4-aminobenzamides.—Reduction of the 2-alkoxy-4-nitrobenzamide hydrochlorides (or the free bases) was carried out by the usual iron–hydrochloric acid procedure.[2b] The isolated bases were converted into the acid salts, picrates, etc., in the usual manner. In the case of N-(3-diethylamino-2-hydroxy-1-propyl)-4-amino-2-methoxybenzamide, the compound was obtained impure (possibly due to some amide–ester interconversion); it was characterized as the **picrate**, m.p. 88.0–97.0° dec.

Anal. Calcd. for $C_{21}H_{28}N_6O_{10}$: N, 16.00. Found: N, 15.91.

N-(3-(2-Methyl-1-piperidyl)-propyl)-4-amino-2-methoxybenzamide dihydrochloride monohydrate crystallized from absolute alcohol–ether in white needles, m.p. 143.8–146.0°.

Anal. Calcd. for $C_{17}H_{29}Cl_2N_3O_2 \cdot H_2O$: N, 10.60; Cl, 17.89; H_2O, 4.54. Found: N, 10.85; Cl, 17.61; H_2O, 4.57.

The flavianate formed yellow cottony needles from dilute alcohol, m.p. 193.8–195.5°. *Anal.* Calcd. for $C_{27}H_{33}N_5O_{10}S$: S, 5.17. Found: S, 5.32.

The 2-alkoxy-4-aminobenzamide methiodides shown in Table II were prepared by the catalytic reduction (platinum oxide) of the nitrobenzamide precursors.

N-(Dialkylaminoalkyl)-4-alkylamino-2-methoxybenzamides.—Reductive alkylation of the 4-amino-2-methoxybenzamides by means of an aldehyde, zinc dust and acetic acid was carried out as usual.[2b] The products in all cases were viscous, high boiling oils; purification was carried out as previously outlined.[2a,b] **N-(3-(2-Methyl-1-piperidyl)-propyl)-4-butylamino-2-methoxybenzamide** was a glassy, straw-colored resin.

Anal. Calcd. for $C_{21}H_{35}N_3O_2$: C, 69.76; H, 9.75; N, 11.62. Found: C, 69.93; H, 9.58; N, 11.31.

The diflavianate crystallized from alcohol in bright yellow prisms, m.p. 160.9–163.9°. *Anal.* Calcd. for $C_{41}H_{47}N_7O_{18}S_2$: N, 9.90. Found: N, 9.84.

Ethyl 4-(Chloroacetylamino)-2-ethoxybenzoate.—To a solution of 20.9 g. (0.10 mole) of ethyl 4-amino-2-ethoxybenzoate in 250 ml. of warm, dry benzene there was added 12.4 g. (0.11 mole) of chloroacetyl chloride in one portion. The resulting heterogeneous mixture, which contained a gelatinous precipitate, was refluxed for 3.5 hr. Solution of the precipitate was completed in 15 minutes; the evolution of hydrogen chloride practically ceased after 2 hr. The mixture was then concentrated to a small volume *in vacuo* and diluted with about five volumes of *n*-hexane. After two recrystallizations from benzene–*n*-hexane, there was obtained 24.8 g. (87%) of pure product which crystallized in brilliant white prisms, m.p. 112.8–113.8°.

Anal. Calcd. for $C_{13}H_{16}ClNO_4$: C, 54.64; H, 5.65; N, 4.90. Found: C, 54.47; H, 5.38; N, 4.91.

With compounds which contained 2-alkoxy groups larger than ethoxy, recourse was had to the acetic acid–sodium acetate methods of Löfgren,[14] in order to prevent alkoxy cleavage.

Ethyl 4-(chloroacetylamino)-2-butoxybenzoate, 81% yield, white prisms from Skellysolve C; m.p. 81.4–83.4°. *Anal.* Calcd. for $C_{15}H_{20}ClNO_4$: Cl, 11.30. Found: Cl, 11.61.

Ethyl 4-(chloroacetylamino)-2-benzoyloxybenzoate, nearly quantitative yield, white prisms from benzene–*n*-hexane, m.p. 120 4–121.6°. *Anal.* Calcd. for $C_{18}H_{18}ClNO_4$: Cl, 10.19; N, 4.03. Found: Cl, 10.42; N, 3.99.

4-(Chloroacetylamino)-2-ethoxybenzamide, obtained in 75% yield from 4-amino-2-ethoxybenzamide (see below) by the acetic acid method, formed white needles from absolute alcohol; m.p. 194.0–198.0° dec. *Anal.* Calcd. for $C_{11}H_{13}ClN_2O_3$: N, 10.91. Found: N, 10.92.

4-(Chloroacetylamino)-2-benzyloxybenzamide, obtained from the amide (see below) by the acetic acid method in 98% yield, rosettes of white needles, from absolute alcohol–ethyl acetate; m.p. 208.0–209.3°. *Anal.* Calcd. for $C_{16}H_{15}ClN_2O_3$: N, 8.79. Found: N, 8.73.

Alkyl 4-(Dialkylaminoacetylamino)-2-alkoxybenzoates.—A mixture of the alkyl 4-(chloroacetylamino)-2-alkoxybenzoate, an amine and the appropriate alcohol was refluxed for 4 to 6 hr. After removal of the alcohol and excess amine *in vacuo*, the product was converted to the base in the usual manner. The yields of the crude bases were 75–85%. The picrates, hydrochlorides, etc., were prepared in the usual manner; *cf.* Table IV.

4-(Dialkylaminoacetylamino)-2-alkoxybenzamides.—The benzamide derivatives were prepared either from the 4-(chloroacetylamino)-benzamide by the above method, or *via* the free acid.

A mixture of 24.5 g. (0.076 mole) of ethyl 4-(diethylaminoacetylamino)-2-ethoxybenzoate, 6.4 g. (0.11 mole) of potassium hydroxide, 200 ml. of alcohol and 100 ml. of water was refluxed for 1 hr. The alcohol was removed *in vacuo* and the aqueous solution was made acidic to congo red paper with hydrochloric acid and saturated with salt. The resulting precipitate was filtered, dried thoroughly and recrystallized from absolute alcohol and from an absolute alcohol–isopropyl alcohol mixture, yielding pure **4-(diethylaminoacetylamino)-2-ethoxybenzoic acid hydrochloride**, m.p. 203.6–204.1° dec.

Anal. Calcd. for $C_{15}H_{23}ClN_2O_4$: Cl, 10.72. Found: Cl, 10.64.

To a stirred suspension of 19.1 g. (0.058 mole) of 4-(diethylaminoacetylamino)-2-ethoxybenzoic acid hydrochloride in 5.2 g. (0.066 mole) of pure pyridine and 200 ml. of dry benzene was added 7.5 g. (0.063 mole) of pure thionyl chloride. The resulting mixture was refluxed and stirred for 15 minutes; solution was not effected. The resulting slurry was poured into a mixture of 200 ml. of concentrated ammonium hydroxide and 500 ml. of water with vigorous stirring. After 15 minutes the benzene layer was separated, washed once with water, dried over Drierite and decolorized with Darco G-60. Evaporation of the benzene gave 13.4 g. of **4-(diethylaminoacetylamino)-2-ethoxybenzamide**, m.p. 135–137°. Two recrystallizations from dilute alcohol gave pure material; *cf.* Table V.

(12) R. O. Clinton, U. J. Salvador, S. C. Laskowski and C. M. Suter, THIS JOURNAL, **70**, 950 (1948).

(13) R. O. Clinton, U. J. Salvador and S. C. Laskowski, *ibid.*, **71**, 3839 (1949).

(14) N. Löfgren, *Arkiv. Kemi, Mineral. Geol.*, **22A**, No. 18 (1946) (*C. A.*, **43**, 1021 (1949)).

Similarly prepared were: **4-(Diethylaminoacetylamino)-2-butoxybenzoic acid hydrochloride**, m.p. 205.4–206° dec. *Anal.* Calcd. for $C_{17}H_{27}ClN_2O_4$: N, 7.81. Found: N, 7.65.

4-(Diethylaminoacetylamino)-2-benzyloxybenzoic acid hydrochloride, m.p. 180.7–182.0°. *Anal.* Calcd. for $C_{20}H_{25}ClN_2O_4$: N, 7.13; Cl, 9.02. Found: N, 7.34; Cl, 8.90.

2-Methoxy-4-nitrobenzamide.—To 1 liter of cooled, stirred, concentrated ammonium hydroxide (28%) there was added, portionwise, 70 g. of pure 2-methoxy-4-nitrobenzoyl chloride.[2b] When the addition was completed, the resulting suspension was stirred for 15 minutes, filtered and the insoluble product was washed thoroughly with water and dried at 70°. The finely powdered, crude material was stirred at 50° for 15 minutes with 500 ml. of 5% aqueous sodium hydroxide solution and the insoluble material was filtered, washed thoroughly with water and recrystallized twice from glacial acetic acid; *cf.* Table VI.

2-Ethoxy-4-nitrobenzamide.—A mixture of 32 g. (0.166 mole) of 2-ethoxy-4-nitrobenzonitrile[11] and 100 ml. of concentrated sulfuric acid was stirred and heated until the temperature of the mixture was 97°. The heat source was removed; the internal temperature spontaneously rose to 109°. When the internal temperature had dropped to 95°, the mixture was held at 96–97° for a further 1-hr. period. After quenching in 500 ml. of water, the insoluble product was filtered off, washed thoroughly with water and dried at 80°. Three recrystallizations from absolute alcohol furnished 13 g. (37%) of the pure 2-ethoxy-4-nitrobenzamide.

2-Butoxy-4-nitrobenzamide.—General method for alkoxy groups larger than ethoxy: The preparation of 2-butoxy-4-nitrobenzoyl chloride was carried out in benzene solution in the presence of pyridine.[2b] The resulting benzene suspension was added slowly to an excess of concentrated ammonium hydroxide solution, with vigorous stirring. The emulsion was filtered and the insoluble material was washed well with water. The benzene layer was separated from the filtrate and washed with water; evaporation gave a small additional amount of product. The combined fractions, after three recrystallizations from ethyl acetate, gave a 67% yield of pure 2-butoxy-4-nitrobenzamide.

4-Amino-2-alkoxybenzamides.—The reduction of the 2-alkoxy-4-nitrobenzamides was carried out either by means of iron–hydrochloric acid in dilute alcohol[2a] or by catalytic reduction with platinum oxide in alcoholic solution. The yields were good in all cases (80–95%).

RENSSELAER, NEW YORK

[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

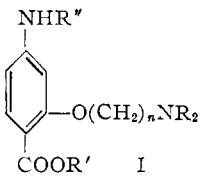
Derivatives of 4-Amino-2-hydroxybenzoic Acid. V. Basic Ethers

BY R. O. CLINTON, S. C. LASKOWSKI, U. J. SALVADOR AND PATRICIA M. CARROLL

RECEIVED OCTOBER 15, 1956

A series of alkyl 4-amino-2-(dialkylaminoalkoxy)-benzoates was prepared for testing as potential local anesthetics. The compounds proved to be good local anesthetics; of more interest was the observation that quaternary salts of these compounds exhibited a high degree of activity as ganglionic blocking agents.

Previous communications[1] from these laboratories have described basic esters, thiol esters and amides derived from 4-amino-2-hydroxybenzoic acids. In these compounds, either the carboxyl or the 4-amino group served as a linkage point for the attachment of a dialkylaminoalkyl chain, which was introduced to confer local anesthetic activity. A third point of attachment for the basic moiety, *viz.*, the 2-hydroxy group, is considered in the present communication. These compounds have the general structure shown by I.



I

Although a compound of type I has not appeared in the literature, a number of related des-amino and des-carboxy analogs have been reported. Chapman, *et al.*,[2] prepared bis-diethylaminoethoxy compounds derived from stilbestrol and hexylresorcinol. Peak and co-workers[3] synthesized several series of basic ethers derived from various chlorinated phenols, catechol, hydroquinone, etc. Furthermore Einhorn and Rothlauf[4] have prepared several alkyl 2- and 4-(2-diethylaminoethoxy)-benzoates and phenolic monobasic ethers, and Rohmann and Friedrich[5] reported the preparation of 4-(2-diethylaminoethoxy)-aniline and a number of its derivatives. In most of these cases pharmacological data have not been reported for the compounds.

Reference should also be made to the dialkylaminoalkoxyaryl compounds and related benzodioxane derivatives, which have been extensively studied by Bovet and co-workers[6] and found to have a wide variety of pharmacodynamic activities.

The alkyl 4-amino-2-(dialkylaminoalkoxy)-benzoates prepared during this investigation were tested for local anesthetic activity[7] by standard methods. In general the compounds were highly active in the intracutaneous wheal and sciatic nerve block tests but less active as corneal local anesthetics. Increasing the side chain length (*e.g.*, from 2-(2-diethylaminoethoxy)- to 2-(3-diethylaminopropoxy)-) or altering the terminal basic moiety (*e.g.*, from dimethylamino to 2-methyl-1-piperidyl) produced a substantial increase in activity. Similarly, changing the ester group from methyl to butyl increased the subcutaneous local anesthetic activity moderately and the topical (corneal) activity markedly. The

(1) (a) R. O. Clinton, S. C. Laskowski, U. J. Salvador, Mary Wilson, Helen Bates and Patricia Carroll, THIS JOURNAL, **73**, 3674 (1951); (b) **74**, 592 (1952); (c) **76**, 5121 (1954); (d) **79**, 2285 (1957).

(2) C. W. Chapman, G. P. Hager and D. E. Shay, *J. Am. Pharm. Assoc.*, **36**, 78 (1947).

(3) D. J. Drain, D. A. Peak and F. F. Whitmore, *J. Chem. Soc.*, 2680 (1949); J. L. Lowe, D. A. Peak and T. I. Watkins, *ibid.*, 3286 (1951).

(4) A. Einhorn and L. Rothlauf, *Ann.*, **382**, 237 (1911); *cf.* C. Rohmann and B. Scheurle, *Arch. Pharm.*, **274**, 110 (1936).

(5) C. Rohmann and K. Friedrich, *Ber.*, **72**, 1333 (1939).

(6) D. Bovet and A. Simon, *Compt. rend. soc. biol.*, **117**, 958 (1934); subsequent papers by D. Bovet, E. Zinz, J. Levy and I. A. M. Staub.

(7) F. P. Luduena and J. O. Hoppe, to be published.