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Mono- and Dialkylaminoethyl Esters of *m*-Aminoalkoxybenzoic Acids

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Several mono- and dialkylaminoethyl esters of 2-, 5- and 6-alkoxy-3-aminobenzoic acids were prepared and tested for both topical and conductive anesthesia. Many of these proved to be highly potent and non-irritating local anesthetics with relatively low toxicities. 2′-*n*-Amylaminoethyl 3-amino-5-heptoxybenzoate hydrochloride when tested topically on the rabbit cornea was shown to be 210 times as efficient (ratio of potency to toxicity) as cocaine. Other members of this series were many times more efficient than procaine as determined on the sciatic nerve of the guinea pig. 2′-Diethylaminoethyl-2-butoxy-3-aminobenzoate hydrochloride (Primacaine hydrochloride) was found clinically to be a remarkably potent and safe local anesthetic for use in dentistry.

The toxicity of *m*-aminobenzoic acid esters of monoalkylaminoethanol has been shown by Nevin, Epstein and Nevin[1] in the instance of the isobutylaminoethyl ester of *m*-aminobenzoic acid and by Ringk and Epstein[2] in a series of monoalkylamino 2,2-dimethylethyl *m*-aminobenzoates, to be exceedingly low.

Both mono- and dialkylaminoethyl esters have been prepared from alkoxybenzoates.[3,4] Dialkylaminoethyl esters have been prepared from 2- and 3-alkoxy-4-aminobenzoates[5] and 4-alkoxy-3-aminobenzoates.[6] These compounds differ from ours in the position of the alkoxy and amino groups. The diethylaminoethyl esters of 4-alkoxy-3-aminobenzoates have been reported to have a low anesthetic index (ratio of anesthetic potency to toxicity) when compared with procaine.[7] Derivatives of 2-alkoxy-4-aminobenzoates have been reported[8] to be potent anesthetics. Of these diethylaminoethyl 2-propoxy-4-aminobenzoate hydrochloride recently has been introduced as a mixture with procaine hydrochloride in a local anesthetic solution.

It was of interest to prepare and evaluate a series of mono- and dialkylaminoethyl esters of 2-, 5- and 6-alkoxy-3-aminobenzoic acids. It was felt that the position of the amino group *meta* to the carboxyl group would produce compounds exhibiting high anesthetic potency, low toxicity and low irritation.

The method of preparation consisted of condensing an N-substituted 2-aminoethanol with a substituted benzoyl chloride and then reducing the resulting nitro ester with iron filings, or catalytically with hydrogen. The amino alcohols which were not available were prepared by condensing an alkylamine with ethylene oxide[9] (method A) or by treating an alkyl bromide with ethanolamine.[10] Other methods have been reported on the preparation of N-substituted amino alcohols.[11]

A mixture of 2- and 6-hydroxy-3-nitrobenzoic acids was prepared by the nitration of 2-hydroxybenzoic acid with dilute nitric acid[12] (method B). The two isomers were isolated by taking advantage of the relative solubility of the acids and their salts.[13]

3-Nitro-5-hydroxybenzoic acid was prepared from 3,5-dinitrobenzoic acid by reduction with ammonium sulfide to 3-nitro-5-aminobenzoic acid and subsequent diazotization and hydrolysis of the amino group[14] (method C).

The alkoxy derivatives of the various hydroxy nitro acids were prepared by three general methods. (1) Reaction of the methyl esters of the hydroxynitrobenzoic acids with an alkyl iodide or bromide in the presence of freshly precipitated silver oxide (method D). (2) Reaction of an alkyl arylsulfonate with the hydroxynitro acid in the presence of anhydrous potassium carbonate[5] (method E). (3) Reaction of alkyl iodide or bromide with an alcoholic solution of sodium methylate and the methyl ester of a hydroxynitrobenzoic acid (method F).

The acid chlorides were prepared by refluxing the alkoxynitro acid with an excess of thionyl chloride (method G). They were purified whenever possible by distillation under very high vacuum. Where the acid chloride would not distil without decomposition the excess thionyl chloride was removed by vacuum distillation and the crude acid chloride was used without further purification. All of the alkoxy acids were prepared for the first time. Their melting points and analyses are listed in Table I.

The nitroalkoxy esters were prepared by one of three general methods: (1) the Schotten–Baumann method as described by Ringk and Epstein[2] was used for the monoalkylaminoethyl esters (method H). (2) Direct condensation of the acid chloride and the aminoalcohol in a non-aqueous solvent was used for the dialkylaminoethyl esters (method I). (3) Condensation of the acid chloride with the monoalkylaminoethanol hydrochloride in refluxing toluene (method J). This method was used to prepare 2′-isobutylaminoethyl 2-butoxy-3-nitrobenzoate hydrochloride. The nitro esters were isolated as their hydrochlorides. The nitro ester hydrochlorides were reduced to the corresponding amino compounds by either iron reduction (method K) or by means of catalytic hydrogenation with a palladium catalyst (method L). The anesthetic bases

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(6) German Patent 522,064 (*Frdl.*, **17**, 2285 (1930)).

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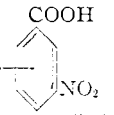
(13) H. Hubner, *Ann.*, **195**, 1 (1879).

(14) J. J. Blanksma, *Chem. Weekblad*, **11**, 59 (1914); P. H. Beyer, *Rec. trav. chim.*, **40**, 621 (1921).

TABLE I

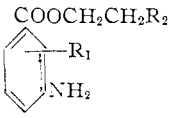
x-ALKOXY-3-NITROBENZOIC ACIDS



-OR	M.p., °C.	Formula	Nitrogen, % Calcd.	Found	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found
2-$OCH(CH_3)_2$	84–85	$C_{10}H_{11}O_5N$	6.20		53.33	53.21	4.93	5.09
2-$OCH_2CH_2CH_3$	88–89	$C_{10}H_{11}O_5N$	6.20		53.33	53.51	4.93	4.67
2-$OCH_2(CH_2)_2CH_3$	68–71	$C_{11}H_{13}O_5N$	5.85	5.90	55.22	55.71	5.47	5.49
2-$OCH_2(CH_2)_3CH_3$	54–55.5	$C_{12}H_{15}O_5N$	5.54	5.43	56.89	57.34	5.97	5.97
2-$OCH_2(CH_2)_5CH_3$	52–53.5	$C_{14}H_{19}O_5N$	4.98		59.76	59.96	6.81	6.50
6-$OCH_2(CH_2)_2CH_3$	116–119	$C_{11}H_{13}O_5N$	5.85	5.76	55.22	55.54	5.47	5.63
5-$OCH_2(CH_2)_2CH_3$	123–125	$C_{11}H_{13}O_5N$	5.85	5.58	55.22	55.67	5.47	5.28
5-$OCH_2(CH_2)_5CH_3$	95–98	$C_{14}H_{19}O_5N$	4.98	4.74	59.76	60.01	6.81	6.60

TABLE II

2-ALKYLAMINOETHYL 3-AMINO-*x*-ALKOXYBENZOATE HYDROCHLORIDES



R_1	R_2	Base B.p., °C.	Press., μ	Hydrochloride m.p., °C.	Formula	Nitrogen, % Calcd.	Found
2-$OCH(CH_3)_2$	$-N(C_2H_5)_2$	..		142–146	$C_{16}H_{27}O_3N_2Cl$	8.48	8.53
2-$OCH_2CH_2CH_3$	$-N(C_2H_5)_2$	..		127–130	$C_{16}H_{27}O_3N_2Cl$	8.48	8.15
2-$OCH_2(CH_2)_2CH_3$	$-N(CH_3)_2$	..		132–136	$C_{15}H_{25}O_3N_2Cl$	8.84	8.90
2-$OCH_2(CH_2)_2CH_3$	$-N(C_2H_5)_2$	134	10	118–120	$C_{17}H_{29}O_3N_2Cl$	8.11	8.09
2-$OCH_2(CH_2)_2CH_3$	$-NHCH_2CH(CH_3)_2$	..		98–101	$C_{17}H_{29}O_3N_2Cl$	8.11	8.15
2-$OCH_2(CH_2)_2CH_3$	$-N(C_4H_9)_2$	180	20	Oil	$C_{21}H_{37}O_3N_2Cl$	6.99	7.05
2-$OCH_2(CH_2)_3CH_3$	$-N(C_2H_5)_2$	138	10	Oil	$C_{18}H_{31}O_3N_2Cl$	7.79	7.83
2-$OCH_2(CH_2)_5CH_3$	$-N(C_2H_5)_2$	..		Oil	$C_{20}H_{35}O_3N_2Cl$	7.24	7.61
5-$OCH_2(CH_2)_2CH_3$	$-NHC_5H_{11}$	..		190–192	$C_{15}H_{31}O_3N_2Cl$	7.81	7.50
5-$OCH_2(CH_2)_2CH_3$	$-NHCH(CH_3)C_6H_{13}$	..		128–130	$C_{21}H_{37}O_3N_2Cl$	6.99	6.82
5-$OCH_2(CH_2)_5CH_3$	$-NHC_5H_{11}$	..		176–178	$C_{21}H_{37}O_3N_2Cl$	6.99	6.97
6-$OCH_2(CH_2)_2CH_3$	$-N(CH_3)_2$	155	7	128–132	$C_{15}H_{25}O_3N_2Cl$	8.84	8.94
6-$OCH_2(CH_2)_2CH_3$	$-N(C_2H_5)_2$	174	50	104–106	$C_{17}H_{29}O_3N_2Cl$	8.12	8.20
6-$OCH_2(CH_2)_2CH_3$	$-NHC_4H_7$	166	15	159–162	$C_{16}H_{27}O_3C_2Cl$	8.46	8.20
6-$OCH_2(CH_2)_2CH_3$	$-NHCH_2CH(CH_3)_2$	..		196–197	$C_{17}H_{29}O_3N_2Cl$	8.17	7.64
6-$OCH_2(CH_2)_2CH_3$	$-NHC_5H_{11}$	..		203–205	$C_{18}H_{31}O_3N_2Cl$	7.80	7.70
6-$OCH_2(CH_2)_2CH_3$	$-NHCH(CH_3)C_3H_7$	..		159–163	$C_{18}H_{31}O_3N_2Cl$	7.80	7.40
6-$OCH_2(CH_2)_2CH_3$	$-NHCH_2CH(C_2H_5)C_4H_9$	..		179–181	$C_{21}H_{37}O_3N_2Cl$	6.99	6.80
6-$OCH_2(CH_2)_2CH_3$	$-NHCH(CH_3)C_6H_{13}$	..		194–196	$C_{21}H_{37}O_3N_2Cl$	6.99	6.49

were isolated and whenever possible distilled under very high vacuum. We found this to be a good method of purification. The hydrochloride salts were prepared by adding an equivalent amount of concentrated hydrochloric acid to an alcoholic solution of the base. Table II summarizes the physical properties of the bases and acid salts with their analyses.

Pharmacology.—A preliminary pharmacological investigation of these compounds on experimental animals shows them to be potent and non-irritating local anesthetics with relatively low toxicities when compared with procaine and cocaine.

The toxicities were determined intraperitoneally on white mice. This mode of injection was chosen as it gives values somewhat between that of an intravenous injection with very rapid absorption and subcutaneous injection with slow absorption. The toxicities of these compounds range from one-third to twice as toxic as procaine.

The topical anesthetic potency was determined by noting the length of anesthesia on the rabbit cornea produced by various concentrations of the anesthetic. The conductive anesthesia was determined by blocking the sciatic nerve of the intact guinea pig, using the method originally introduced by Shackell.[15] The details of these procedures have been described previously.[1]

All of these compounds exhibited local anesthetic properties and almost all were more efficient (ratio of potency to toxicity) on topical application than cocaine and more efficient in nerve block than procaine.

2′-*n*-Amylaminoethyl 3-amino-5-heptoxybenzoate hydrochloride when tested topically on the rabbit cornea was shown to be 210 times as efficient as cocaine. 2′-Diethylaminoethyl 2-butoxy-3-aminobenzoate hydrochloride (Primacaine hydrochloride) was found clinically to be a remarkably potent and safe local anesthetic for use in dentistry.

Detailed pharmacological and clinical studies of these compounds will be published elsewhere.

Experimental

Method A. Preparation of Isobutylaminoethanol.—To 220 g. of isobutylamine (3 moles) dissolved in 400 ml. of water and 400 g. of crushed ice was added slowly 44 g. of ethylene oxide (1 mole). The temperature of the mixture was kept between 10 and 20° during the addition. The

(15) L. Shackell, *Current Researches, Anesthesia and Analgesia*, **14**, 20 (1935).

solution was allowed to stand at room temperature for four hours. One hundred and fifty grams of sodium hydroxide was added slowly while keeping the temperature below 40°. The solution was extracted with ether and the extract dried overnight over sodium hydroxide pellets. The isobutylaminoethanol was isolated by distillation through an efficient column and the fraction distilling at 98–101° at 28 mm. was collected. The yield of isobutylaminoethanol was 71 g. (60%).

Method B. 2-Hydroxy-3- and 5-Nitrobenzoic Acids.—Two hundred grams of 2-hydroxybenzoic acid was nitrated with 10% nitric acid at 50–65°. The precipitated product was suspended in 1500 ml. of boiling water and the insoluble 2-hydroxy-5-nitrobenzoic acid was filtered. The yield was 118 g. (46%), m.p. 230–233°. The 2-hydroxy-3-nitrobenzoic acid was isolated through its barium salt. The yield of anhydrous 2-hydroxy-3-nitrobenzoic acid was 38 g. (15%), m.p. 146–149°.

Method C. 3-Nitro-5-hydroxybenzoic Acid.—Three hundred grams of 3,5-dinitrobenzoic acid was dissolved in 400 ml. of concentrated ammonium hydroxide and 700 ml. of water. Hydrogen sulfide was bubbled in until a sample of the solution was completely soluble in concentrated hydrochloric acid. The mixture was filtered hot, acidified with glacial acetic acid and cooled. The precipitate of crude 3-nitro-5-aminobenzoic acid was recrystallized from water. The yield was 200 g. (80%), m.p. 208–211°.

One hundred grams of the 3-nitro-5-aminobenzoic acid was dissolved in 180 ml. of water and 130 ml. of concentrated sulfuric acid at room temperature. Forty-two grams of sodium nitrate dissolved in 100 ml. of water was added slowly until the test for sodium nitrite was obtained with starch–iodide paper. The warm diazonium mixture was added slowly to a vigorously boiling mixture of 300 ml. of water and 400 ml. of concentrated sulfuric acid. The mixture then was boiled for an additional 30 minutes. After diluting with 500 ml. of crushed ice, the mixture was cooled to 0° and filtered. The crude 3-nitro-5-hydroxybenzoic acid was recrystallized from water. The yield was 77 g. (70%), m.p. 192–194°.

Method D. 3-Nitro-5-butoxybenzoic Acid.—A slurry of 46.4 g. (0.2 mole) of freshly prepared silver oxide in 200 ml. of water was added to a suspension of 39 g. (0.2 mole) of methyl 3-nitro-5-hydroxybenzoate (prepared from the acid by esterification by dry hydrogen chloride in methanol) and 80 g. (0.44 mole) of butyl iodide in 300 ml. of methanol. After refluxing with stirring for four to six hours, the mixture was filtered and the precipitate washed with ether. The alcohol was distilled from the filtrate and the residue extracted with ether. The combined ether solutions were washed with dilute ammonium hydroxide and the ether removed on a steam-bath. The residual oil, which was crude methyl 3-nitro-5-butoxybenzoate, was dissolved in 100 ml. of methanol and added to 300 ml. of 10% sodium hydroxide solution and refluxed for two hours. The alcohol was distilled from the solution which was then cooled, neutralized to a *p*H of 7 with concentrated hydrochloric acid, bone-charred and filtered. The solution was then acidified to a *p*H of 4 and the precipitate formed was recrystallized from 50% isopropyl alcohol. The yield of 3-nitro-5-butoxybenzoic acid was 41 g. (85%), m.p. 123–125°.

Method E.—3-Nitro-5-hydroxybenzoic acid was butylated according to the method of Clinton, Salvador, Laskowski and Wilson.[5] The product was isolated in a manner described in method D. The yield of 3-nitro-5-butoxybenzoic acid was 19 g. (80%), m.p. 122–124°.

Method F. 3-Nitro-5-butoxybenzoic Acid.—19.7 g. (0.1 mole) of methyl 3-nitro-5-hydroxybenzoate in 30 ml. of methanol was added to a solution of 2.3 g. (0.1 mole) of metallic sodium in 70 ml. of methanol. 13.7 g. (0.1 mole) of butyl bromide was added and the mixture was refluxed with stirring for 24 hours. Thirty-two grams (0.3 mole) of sodium carbonate in 150 ml. of water was added and reflux was continued for three hours. The alcohol was removed by distillation and the cooled water solution was acidified to a *p*H of 7, bone-charred and filtered. The solution was acidified to a *p*H of 4 and the precipitate formed was recrystallized from 50% isopropyl alcohol. The yield of 3-nitro-5-butoxybenzoic acid was 19 g. (80%), m.p. 123–125°.

Method G. 3-Nitro-5-butoxybenzoyl Chloride.—Thirty-six grams (0.15 mole) of 3-nitro-5-butoxybenzoic acid was mixed with 10 ml. of toluene and 60 g. (0.5 mole) of thionyl chloride. The mixture was refluxed for four to six hours, and the excess thionyl chloride and toluene were removed by distillation. The residue was distilled under high vacuum. The yield of 3-nitro-5-butoxybenzoyl chloride (amber oil) was 32 g. (83%), b.p. 141–143° at 700 μ pressure.

Method H. 2′-*n*-Amylaminoethyl 3-Nitro-5-butoxybenzoate Hydrochloride.—A solution of 5.8 g. of sodium hydroxide and 15.4 g. of *n*-amylaminoethanol, in 100 ml. of water was added rapidly with vigorous stirring to 32 g. of 3-nitro-5-butoxybenzoyl chloride dissolved in 50 ml. of trichloroethylene. Stirring was continued for an additional ten minutes while keeping the temperature below 40°. The trichlorethylene layer was acidified with 15 ml. of concentrated hydrochloric acid. The mixture was heated to boiling and then allowed to cool to 10°. The precipitate which formed was filtered and then recrystallized from water to give 28 g. (63%) of 2′-*n*-amylaminoethyl 3-nitro-5-butoxybenzoate hydrochloride (white crystals), m.p. 114–115°.

Method I. 2′-Diethylaminoethyl 3-Nitro-2-butoxybenzoate Hydrochloride.—To a solution of 39.8 g. of diethylethanol in 500 ml. of benzene was added 87.7 g. of 2-butoxy-3-nitrobenzoyl chloride. The mixture was refluxed with stirring for one hour. After cooling, the precipitate was filtered off and then recrystallized from 600 ml. of isopropyl alcohol. The yield of 2′-diethylaminoethyl 3-nitro-2-butoxybenzoate hydrochloride was 100 g. (79%) as white crystals, m.p. 132–134°. Concentration of the mother liquid yielded an additional 18 g. for a total yield of 118 g. (92%).

Method J. 2′-Isobutylaminoethyl 2-Butoxy-3-nitrobenzoate Hydrochloride.—A solution of 4.7 g. of isobutylaminoethanol in 125 ml. of toluene was saturated with dry HCl and 11.3 g. of 2-butoxy-3-nitrobenzoyl chloride was added. The mixture was refluxed for 24 hours, cooled and extracted with an equal volume of water. The water solution was made basic with sodium carbonate and extracted with two 50-ml. portions of ether. The combined extracts were dried over anhydrous sodium sulfate and saturated with dry HCl. The precipitated oil was washed with ether and vacuum dried. The yield of 2′-isobutylaminoethyl 2-butoxy-3-nitrobenzoate hydrochloride was 5 g. (30%) as a pale yellow oil.

Method K. 2′-Diethylaminoethyl 3-Amino-6-butoxybenzoate Hydrochloride.—To 10 g. of 2′-diethylaminoethyl 3-nitro-6-butoxybenzoate hydrochloride dissolved in 100 ml. of water at 70° was added 10 g. of iron filings. The mixture was stirred at this temperature for three hours, and then filtered. One gram of citric acid and 0.5 g. of sodium hydrosulfite was added to the filtrate which then was made alkaline with excess sodium carbonate solution and extracted with ether. The ether solution after drying over anhydrous sodium sulfate was evaporated on the steam-bath. The residue was dissolved in 10 ml. of methanol and acidified with concentrated hydrochloric acid to a *p*H of 5. The alcohol was removed by evaporation and the residual oil vacuum-dried over phosphorus pentoxide until crystallization occurred. Recrystallization from ethyl acetate yielded 5 g. of 2′-diethylaminoethyl 3-amino-6-butoxybenzoate hydrochloride (52%) as white crystals, m.p. 104–106°.

Method L. 2′-Diethylaminoethyl 2-Butoxy-3-aminobenzoate Hydrochloride.—Ten grams of diethylaminoethyl 2-butoxy-3-nitrobenzoate hydrochloride, 100 ml. of water and 0.5 g. of 5% palladium oxide-on-charcoal was shaken for three hours under 40 pounds pressure of hydrogen in a Parr hydrogenation apparatus. The catalyst was removed by filtration and 0.25 g. of sodium hydrosulfite was added to the filtrate. The solution was made strongly alkaline with sodium carbonate and extracted with ether. The ether extract was dried over anhydrous sodium sulfate and the ether removed by evaporation. The residue was distilled under vacuum and the fraction distilling at 132–136° at 10 μ pressure was collected as a pale yellow oil (yield 5 g.). The amino ester was dissolved in 10 ml. of isopropyl alcohol and acidified with anhydrous hydrochloric acid to a *p*H of 4.5. The white precipitate was recrystallized from isopropyl alcohol to give 5 g. (52%) of diethylaminoethyl 2-butoxy-3-aminobenzoate hydrochloride, m.p. 118–120°.

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