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LOWER ALKYL 4-SUBSTITUTED-2-(TERTIARY-AMINOALKOXY)BENZOATES AND THEIR PREPARATION

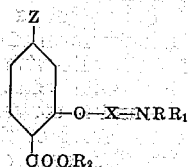
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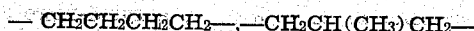
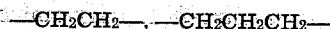
This invention relates to lower alkyl 4-substituted-2-(tertiary-aminoalkoxy) benzoates and to their preparation.

The compounds of our invention have the general formula



where Z is nitro, amino, lower alkylamino or lower hydroxyalkylamino; X is a lower alkylene radical; NRR₁ is a tertiary-amino radical and R₂ is a lower alkyl radical. These benzoates, especially the compounds where Z is NO₂, have utility as intermediates, for instance, in the preparation of the corresponding quaternary salts which are disclosed and claimed in our co-pending application Serial No. 245,248, filed September 5, 1951. In addition, some of these alkyl 4-substituted-2-(tertiary-aminoalkoxy) benzoates have useful pharmacological properties, such as, local anesthetic activity and analgesic activity.

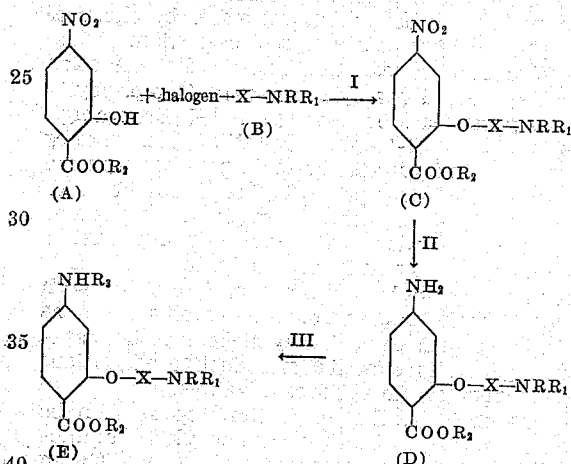
In the above general formula, the lower alkylene radical designated as X has preferably two to four carbon atoms and has its two free valence bonds on different carbon atoms. Thus, X includes such examples as



and the like. The tertiary-amino radical shown above as NRR₁ comprehends dialkylamino radicals where R and R₁ are lower alkyl groups, alike or different and each alkyl group having one to six carbon atoms, such dialkylamino radicals including dimethylamino, diethylamino, ethylmethylamino, diisopropylamino, ethyl-n-propylamino, di-n-butylamino, di-n-hexylamino, and the like. Further, the tertiary-amino radical designated as NRR₁ encompasses saturated N-heteromonocyclic radicals having five to six ring atoms, illustrated by examples such as 1-piperidyl; (lower alkylated) 1-piperidyl such as 2-methyl-1-piperidyl, 3-ethyl-1-piperidyl, 4-methyl-1-piperidyl, 2,6-dimethyl-1-piperidyl; 1-pyrrolidyl; (lower alkylated) 1-pyrrolidyl such as 2-methyl-1-pyrrolidyl, 2,5-dimethyl 1-pyrrolidyl; 4-mor-

pholinyl; and the like. In the above formula, when Z stands for lower alkylamino, the lower alkyl radical, designated as R₃ hereinbelow, has preferably one to six carbon atoms, including such radicals as methyl, ethyl, n-propyl, n-butyl, isobutyl, n-amyl, 2-amyl, n-hexyl, and the like. When Z represents lower hydroxyalkylamino, the lower hydroxyalkyl radical, designated as R₃ hereinbelow, has preferably two to six carbon atoms, including radicals such as 2-hydroxyethyl, 2-hydroxypropyl, 3-hydroxypropyl, 3-hydroxy-2-methylpropyl, 3-hydroxy-2,2-dimethylpropyl, 2-hydroxybutyl, 4-hydroxybutyl, 3-hydroxyamyl, 5-hydroxyamyl, 6-hydroxyhexyl, and the like.

The compounds of our invention can be prepared preferably according to the procedure represented by the following series of equations where X, NRR₁, R₂ and R₃ have the meanings given hereinabove and halogen is chlorine, bromine, iodine or fluorine:



Thus, in step I, a lower alkyl 4-nitro-2-hydroxybenzoate (A) is converted into a lower alkyl 4-nitro-2-(tertiary-aminoalkoxy)benzoate (C) by reaction with a tertiary-aminoalkyl halide (B). In step II, the lower alkyl 4-nitro-2-(tertiary-aminoalkoxy)benzoate (C) is reduced to yield the corresponding lower alkyl 4-amino-2-(tertiary-aminoalkoxy)benzoate (D), which is then alkylated to form the corresponding lower alkyl 4-alkylamino- or 4-hydroxyalkylamino-2-(tertiary-aminoalkoxy)benzoate (E). A specific illustration of this series of reactions is the formation of ethyl 4-n-butylamino-2-(2-diethylaminoethoxy)benzoate by first reacting ethyl 4-nitro-2-hydroxybenzoate, preferably in the form

Additional lower alkyl 4-amino-2-(tertiary-aminoalkoxy)benzoates which can be prepared according to the foregoing procedures include the following: ethyl 4-amino-2-(2-dimethylami-

no-1-ethoxy)benzoate, isopropyl 4-amino-2-(2-dimethylamino-1-ethoxy)benzoate, n-butyl 4-amino-2-(2-dimethylamino-1-ethoxy)benzoate, isobutyl 4-amino-2-(2-dimethylamino-1-ethoxy)benzoate, sec-butyl 4-amino-2-(2-dimethylamino-1-ethoxy)benzoate, tert-butyl 4-amino-2-(2-dimethylamino-1-ethoxy)benzoate, n-pentyl 4-amino-2-(2-dimethylamino-1-ethoxy)benzoate, isopentyl 4-amino-2-(2-dimethylamino-1-ethoxy)benzoate, n-hexyl 4-amino-2-(2-dimethylamino-1-ethoxy)benzoate, isohexyl 4-amino-2-(2-dimethylamino-1-ethoxy)benzoate, n-octyl 4-amino-2-(2-dimethylamino-1-ethoxy)benzoate, isooctyl 4-amino-2-(2-dimethylamino-1-ethoxy)benzoate, n-decyl 4-amino-2-(2-dimethylamino-1-ethoxy)benzoate, isodecyl 4-amino-2-(2-dimethylamino-1-ethoxy)benzoate, n-dodecyl 4-amino-2-(2-dimethylamino-1-ethoxy)benzoate, and n-tetradecyl 4-amino-2-(2-dimethylamino-1-ethoxy)benzoate.

of their monohydrochlorides, are ethyl 4-n-propylamino-2-(2-diethylaminoethoxy)benzoate, ethyl 4-n-ethylamino-2-(2-diethylaminoethoxy)benzoate and ethyl 4-n-butylamino-2-(2-diethylaminoethoxy)benzoate.

Other lower alkyl 4-amino-2-(tertiary-aminoalkoxy)benzoates which can be prepared according to the foregoing procedures include the following: ethyl 4-amino-2-(2-diethylaminoethoxy)benzoate, isopropyl 4-amino-2-(2-diethylaminoethoxy)benzoate, n-butyl 4-amino-2-(2-diethylaminoethoxy)benzoate, isobutyl 4-amino-2-(2-diethylaminoethoxy)benzoate, sec-butyl 4-amino-2-(2-diethylaminoethoxy)benzoate, tert-butyl 4-amino-2-(2-diethylaminoethoxy)benzoate, n-pentyl 4-amino-2-(2-diethylaminoethoxy)benzoate, isopentyl 4-amino-2-(2-diethylaminoethoxy)benzoate, n-hexyl 4-amino-2-(2-diethylaminoethoxy)benzoate, isohexyl 4-amino-2-(2-diethylaminoethoxy)benzoate, n-octyl 4-amino-2-(2-diethylaminoethoxy)benzoate, isooctyl 4-amino-2-(2-diethylaminoethoxy)benzoate, n-decyl 4-amino-2-(2-diethylaminoethoxy)benzoate, isodecyl 4-amino-2-(2-diethylaminoethoxy)benzoate, n-dodecyl 4-amino-2-(2-diethylaminoethoxy)benzoate, and n-tetradecyl 4-amino-2-(2-diethylaminoethoxy)benzoate.

treating the solution with an excess of 20% ethereal hydrogen chloride solution. The resulting precipitate of ethyl 4-nitro-2-(2-diethylaminoethoxy)benzoate hydrochloride was collected and recrystallized twice from isopropanol, yielding 45.5 g. of purified product, M. P. 144.4–145.2° C. (cor.).

Anal.—Calcd. for $C_{15}H_{22}N_2O_5 \cdot HCl$: C, 51.94; H, 6.40; Cl, 10.22. Found: C, 52.08; H, 6.48; Cl, 10.12.

Ethyl 4-nitro-2-(2-diethylaminoethoxy)benzoate was also prepared stepwise as follows:—A mixture of 84.4 g. of ethyl 4-nitro-2-hydroxybenzoate, 60.8 g. of powdered anhydrous potassium carbonate and 2000 ml. of meta-xylene was refluxed with stirring under a water trap until no more water was collected (three hours). The water trap was removed and 112.7 g. of 2-chloroethyl para-toluenesulfonate was added in one portion. Refluxing and stirring were continued for an additional nineteen hours. The mixture was filtered while hot and the filter-cake was washed with hot toluene. The combined filtrate and washings were evaporated to dryness in vacuo, yielding a cream-colored solid as residue. Several recrystallizations of this solid from methanol and from n-pentane gave a 60% yield of ethyl 4-nitro-2-(2-chloroethoxy)benzoate as pale yellow platelets, M. P. 56.6–57.2° C. (cor.).

Anal.—Calcd. for $C_{11}H_{12}ClNO_5$: Cl, 12.96. Found: Cl, 12.62.

On heating a mixture of ethyl 4-nitro-2-(2-chloroethoxy)benzoate, diethylamine, sodium iodide and absolute ethanol, there was obtained, in only a fair yield, ethyl 4-nitro-2-(2-diethylaminoethoxy)benzoate. Following this same procedure but using dimethylamine or 2-methylpiperidine in place of diethylamine, there is obtained, ethyl 4-nitro-2-(2-dimethylaminoethoxy)benzoate or ethyl 4-nitro-2-[2-(2-methyl-1-piperidyl)ethoxy]benzoate, respectively.

Ethyl 4-nitro-2-[3-(1-piperidyl)propoxy]benzoate was prepared as follows: To a stirred refluxing solution of 84.4 g. of ethyl 4-nitro-2-hydroxybenzoate in 1500 ml. of absolute ethanol was added in a fine stream a solution of 9.2 g. of sodium in 500 ml. of absolute ethanol. To the resulting solution was added dropwise over a period of fifteen minutes 65 g. of 3-(1-piperidyl)propyl chloride and the resulting solution was refluxed for twenty-four hours. The sodium chloride was filtered off and washed with ethyl acetate. The combined filtrate and washings were taken to dryness under reduced pressure yielding a mixture of an oily residue and a small amount of a red solid. To this mixture was added 2 liters of ether and the insoluble red solid was filtered off. The filtrate was evaporated to dryness under reduced pressure, yielding as an oily material, ethyl 4-nitro-2-[3-(1-piperidyl)propoxy]benzoate. This ester was converted into its hydrochloride salt by dissolving it in a little ethyl acetate and adding to the solution an excess of ethanolic hydrogen chloride. The solid hydrochloride separated slowly. The mixture was diluted with absolute ether, cooled, and the precipitate was collected and washed with absolute ether. The precipitate was recrystallized three times from isopropanol, yielding, as pale yellow needles, ethyl 4-nitro-2-[3-(1-piperidyl)propoxy]benzoate hydrochloride, M. P. 160.4–161.6° C. (cor.).

Anal.—Calcd. for $C_{17}H_{24}N_2O_5 \cdot HCl$: N, 7.52; Cl, 9.51. Found: N, 7.37; Cl, 9.33.

N_D stands for total nitrogen as determined by the Dumas method.

n-Butyl 4-nitro-2-(2-diethylaminoethoxy)benzoate was prepared as follows: To a stirred refluxing solution of 9.2 g. of sodium in 2000 ml. of n-butanol was added 95.7 g. of n-butyl 4-nitro-2-hydroxybenzoate. The red insoluble sodium phenolate separated immediately. After addition had been complete, refluxing was continued for an additional ten minutes, and then 54.2 g. of 2-diethylaminoethyl chloride was added dropwise over a period of about twenty minutes. When the addition had been completed, the color had already changed from a deep red to a pale orange-yellow. The reaction mixture was then refluxed for five hours, cooled and filtered. The filtrate was taken down to dryness under reduced pressure yielding an oily residue and a small amount of red solid. This mixture was treated with 2500 ml. of absolute ether, and the red solid was filtered off. The filtrate was taken down to dryness under reduced pressure, yielding as an oil, the product, n-butyl 4-nitro-2-(2-diethylaminoethoxy)benzoate. This ester was converted into its hydrochloride addition salt by dissolving it in a little absolute ether and treating the solution with an excess of ethereal hydrogen chloride. A pale cream-colored solid separated. The mixture was cooled and the solid was collected and washed with absolute ether. Three recrystallizations of this solid from ethyl acetate yielded, as pale yellow needles, n-butyl 4-nitro-2-(2-diethylaminoethoxy)benzoate hydrochloride, M. P. 117.6–118.6° C. (cor.).

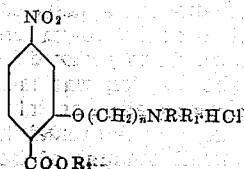
Anal.—Calcd. for $C_{17}H_{26}N_2O_5 \cdot HCl$: N_D, 7.47; Cl, 9.46. Found: N_D, 7.66; Cl, 9.44.

Ethyl 4-nitro-2-(2-dimethylaminoethoxy)benzoate was prepared as follows: To a solution of 126.6 g. of ethyl 4-nitro-2-hydroxybenzoate in 1000 ml. of absolute ethanol was added a solution of 13.8 g. of sodium in 500 ml. of absolute ethanol. The ethanol was then removed by distillation while simultaneously adding toluene (1000 ml.). To the resulting bright red suspension of the sodium salt of ethyl 4-nitro-2-hydroxybenzoate in toluene was added 66.3 g. of 2-dimethylaminoethyl chloride and the mixture was refluxed with stirring for forty-eight hours. The mixture was filtered while hot and the filter-cake was washed with hot toluene. The combined filtrate and washings were evaporated in vacuo, leaving a quantitative yield of ethyl 4-nitro-2-(2-dimethylaminoethoxy)benzoate, as an oil. Treatment of an ethyl acetate solution of this compound with an excess of 20% ethereal hydrogen chloride gave a gummy precipitate, which crystallized from isopropanol in pale yellow needles, M. P. 202.2–202.6° C. (cor.). This product was ethyl 4-nitro-2-(2-dimethylaminoethoxy)benzoate hydrochloride.

Anal.—Calcd. for $C_{13}H_{18}N_2O_5 \cdot HCl$: N_D, 8.79; Cl, 11.12. Found: N_D, 8.56; Cl, 11.10.

Additional lower alkyl 4-nitro-2-(tertiary-aminoalkoxy)benzoates, in the form of their hydrochlorides, prepared according to the above described procedures are given in Table I.

TABLE I



n	NRR ₁	R ₂	M. P., °C. (cor.)	Formula	Analyses			
					N _D		Cl	
					Calcd.	Found	Calcd.	Found
2	NC ₇ H ₁₄ ^a	CH ₂ CH ₃	153.0-154.0	C ₁₈ H ₂₆ N ₂ O ₃ ·HCl	7.24	7.15	9.16	9.14
2	NC ₆ H ₉ O ^b	CH ₂ CH ₃	207.0-208.0	C ₁₅ H ₂₀ N ₂ O ₃ ·HCl	7.77	7.81	9.83	9.92
3	NC ₄ H ₉ O ^b	CH ₂ CH ₃	142.0-144.6	C ₁₆ H ₂₂ N ₂ O ₃ ·HCl	7.48	7.79	9.46	9.25
2	NC ₃ H ₁₀ ^c	CH ₂ CH ₃	191.0-191.5	C ₁₆ H ₂₂ N ₂ O ₃ ·HCl	7.81	7.82	9.88	9.90
2	NC ₄ H ₉ O ^b	CH ₃	206.0-206.4	C ₁₄ H ₁₈ N ₂ O ₃ ·HCl	* 4.04	* 4.05	10.22	10.21
2	NC ₆ H ₁₃ ^d	CH ₂ CH ₃	180.8-182.6	C ₁₇ H ₂₄ N ₂ O ₃ ·HCl	7.52	7.22	9.51	9.38
3	NC ₆ H ₁₃ ^d	CH ₂ CH ₃	158.2-159.6	C ₁₈ H ₂₆ N ₂ O ₃ ·HCl	7.24	7.03	9.16	8.92
3	N(C ₂ H ₅) ₂	CH ₂ CH ₃	164.8-165.6	C ₁₆ H ₂₄ N ₂ O ₃ ·HCl	7.77	7.87	9.83	9.72
2	N(C ₂ H ₅) ₂	CH ₂ CH ₂ CH ₃	153.4-155.4	C ₁₆ H ₂₄ N ₂ O ₃ ·HCl	7.77	7.95	9.83	9.83
2	N(C ₂ H ₅) ₂	CH ₃	156.9-159.2	C ₁₄ H ₂₀ N ₂ O ₃ ·HCl	8.42	8.38	10.65	10.50

^a NC₇H₁₄=2,6-dimethyl-1-piperidyl.

^b NC₆H₉O=4-morpholinyl.

^c NC₄H₉O=1-piperidyl.

^d NC₆H₁₃=2-methyl-1-piperidyl.

* Nitro nitrogen as determined by titration with standard titanous chloride in glacial acetic acid solution.

Additional lower alkyl 4-nitro-2-(tertiary-aminoalkoxy)benzoates which can be prepared according to the foregoing procedures include the following: ethyl 4-nitro-2-(2-dimethylamino-1-propoxy)benzoate; isobutyl 4-nitro-2-[3-(1-pyrrolidyl)propoxy]benzoate; ethyl 4-nitro-2-[2-(2,5-dimethyl-1-pyrrolidyl)ethoxy]benzoate; methyl 4-nitro-2-(4-dimethylaminobutoxy)benzoate; n-propyl 4-nitro-2-[2-(di-n-butylamino)ethoxy]benzoate; n-butyl 4-nitro-2-[3-(4-methyl-1-piperidyl)propoxy]benzoate; n-hexyl 4-nitro-2-[2-(3-ethyl-1-piperidyl)ethoxy]benzoate; n-amyl 4-nitro-2-[3-(2-methyl-1-pyrrolidyl)propoxy]benzoate; and the like.

(2). Lower alkyl 4-amino-2-(tertiary-aminoalkoxy)benzoates

These compounds were prepared by reduction of the corresponding lower alkyl 4-nitro-2-(tertiary-aminoalkoxy)benzoates, as described hereinabove. Illustrative of this reduction are the following examples.

Ethyl 4-amino-2-(2-diethylaminoethoxy)benzoate was prepared as follows: To a hot vigorously stirred mixture of 33.6 g. of powdered iron, 1 ml. of concentrated hydrochloric acid and 200 ml. of 50% aqueous ethanol was added slowly, over a period of about ten minutes, 35.7 g. of ethyl 4-nitro-2-(2-diethylaminoethoxy)benzoate hydrochloride. The resulting mixture was heated with stirring for another thirty minutes, after which time an excess of solid sodium bicarbonate (about 15 g.) was cautiously added. The mixture was stirred for an additional ten minutes and then filtered through a filter aid which was subsequently washed with hot ethanol. The combined filtrate and washings were concentrated by distilling in vacuo, thereby yielding an oily residue which was taken up with ethyl acetate. The ethyl acetate was dried over anhydrous calcium sulfate and taken to dryness in vacuo, yielding, as a pale orange, slightly viscous oil, 27.4 g. of the product, ethyl 4-amino-2-(2-diethylaminoethoxy)benzoate.

The preparation of ethyl 4-amino-2-(2-diethylaminoethoxy)benzoate in the form of its monohydrochloride salt was accomplished as follows: To a solution of 12.0 g. of ethyl 4-amino-2-(2-diethylaminoethoxy)benzoate dissolved in 50 ml. of absolute ethanol was added 8.50 ml. of an ethanolic solution of hydrogen chloride (0.1843 g./ml.; enough HCl to produce the monohydrochloride). The solution was mixed well, taken to dryness in vacuo, ethyl acetate added and removed in vacuo, and the remaining residue dissolved in a small amount of isopropanol. To

this solution was added a small amount of ethyl acetate and ether, just enough to produce turbidity, whereupon spontaneous crystallization resulted. The mixture was then diluted with ether, cooled in ice and the precipitate collected.

Two recrystallizations from this precipitate from acetone-ethyl acetate yielded, as rosettes of white prisms, ethyl 4-amino-2-(2-diethylaminoethoxy)benzoate monohydrochloride, M. P. 134-135° C.

Anal.—Calcd. for C₁₅H₂₄N₂O₃·HCl: Cl, 11.19.

Found: Cl, 11.20.

Alternatively, the foregoing preparation can be carried out using ethyl 4-nitro-2-(2-diethylaminoethoxy)benzoate in place of ethyl 4-nitro-2-(2-diethylaminoethoxy)benzoate hydrochloride.

The dihydrochloride salt of the above 4-amino benzoate was prepared by dissolving it in ethyl acetate and treating the solution with an excess of ethereal hydrogen chloride. The mobile colorless oil which separated crystallized readily when triturated. The solid was filtered, washed well with ethyl acetate and recrystallized twice from absolute ethanol-ethyl acetate. There was thus obtained ethyl 4-amino-2-(2-diethylaminoethoxy)benzoate dihydrochloride, M. P. 173.6-173.9° C. (cor.) [dried three days at 50° C.].

Anal.—Calcd. for C₁₅H₂₄N₂O₃·2HCl: C, 50.99; H, 7.42; Cl, 20.07. Found: C, 51.14; H, 7.36; Cl, 19.90.

Ethyl 4-amino-2-(2-diethylaminoethoxy)benzoate was converted into its phosphoric acid addition salts as follows: A solution of the ester in absolute ethanol was treated with a molar equivalent of 85% phosphoric acid in absolute ethanolic solution. The precipitated crystalline phosphate was collected and recrystallized four times from 95% ethanol, yielding ethyl 4-amino-2-(2-diethylaminoethoxy)benzoate phosphate, M. P. 168.7-169.6° C. (cor.).

Anal.—Calcd. for C₁₅H₂₇N₂O₇P: H₃PO₄, 25.91; N_D, 7.40. Found: H₃PO₄, 25.30; N_D, 7.41.

n-Butyl 4-amino-2-(2-diethylaminoethoxy)benzoate was prepared as follows: A stirred mixture of 71.5 g. of powdered iron, 300 ml. of ethanol, 75 ml. of water and 1 ml. of concentrated hydrochloric acid was brought to a boil. Heat was removed and 80.0 g. of n-butyl 4-nitro-2-(2-diethylaminoethoxy)benzoate hydrochloride was added portion-wise at such a rate as to maintain gentle boiling. After addition of the nitro compound had been completed, the reaction mixture was refluxed with stirring for thirty minutes. Then an excess of sodium bicarbonate (about 20 g.) was cautiously added and refluxing and stirring were continued for an additional

ten minutes. The reaction mixture was filtered hot and the filtrate was concentrated in vacuo to remove all the ethanol. The product, which separated as a distinct layer, was extracted with ethyl acetate. The ethyl acetate solution was dried over anhydrous calcium sulfate and concentrated in vacuo to yield, as a straw-colored oil, *n*-butyl 4-amino-2-(2-diethylaminoethoxy)-benzoate. This ester was converted into its phosphoric acid addition salt as follows: To a hot solution of 46 g. of *n*-butyl 4-amino-2-(2-diethylaminoethoxy)benzoate dissolved in a minimum quantity of hot absolute ethanol was added a hot ethanolic solution of 17.2 g. of 85% phosphoric acid. A white solid readily separated from the hot solution, which was diluted with ethyl acetate, cooled and filtered. The solid was recrystallized several times from absolute ethanol containing a small quantity of water, thereby yielding, as rosettes of white needles, *n*-butyl 4-amino-2-(2-diethylaminoethoxy)benzoate phosphate, M. P. 154.5–155.5° C. (cor.).

Anal.—Calcd. for $C_{17}H_{26}N_2O_3 \cdot H_3PO_4$: N_D , 6.88; H_3PO_4 , 24.12. Found: N_D , 7.10; H_3PO_4 , 24.15.

Ethyl 4-amino-2-[3-(1-piperidyl)propoxy]benzoate was prepared according to the procedure described above for the preparation of *n*-butyl 4-amino-2-(2-diethylaminoethoxy)benzoate, but using 67.2 g. of powdered iron, 400 ml. of ethanol, 100 ml. of water, 1 ml. of concentrated hydrochloric acid, 76 g. of ethyl 4-nitro-2-[3-(1-piperidyl)propoxy]benzoate hydrochloride and about 60 g. of sodium bicarbonate. Vacuum evaporation of the ethyl acetate extract yielded a solid product. This solid when recrystallized from ethanol yielded, as white needles, ethyl 4-amino-2-[3-(1-piperidyl)propoxy]benzoate, M. P. 109.2–110.1° C. (cor.).

Anal.—Calcd. for $C_{17}H_{26}N_2O_3$: N_D , 9.14. N_D , 8.90.

Ethyl 4-amino-2-[3-(1-piperidyl)propoxy]benzoate phosphate, prepared as above, melted at 160.2–161.6° C. (cor.) when recrystallized several times from absolute ethanol.

Anal.—Calcd. for $C_{17}H_{26}N_2O_3 \cdot H_3PO_4$: N_D , 6.93; H_3PO_4 , 24.22. Found: N_D , 6.83; H_3PO_4 , 24.37.

Methyl 4-amino-2-[2-(4-morpholinyl)ethoxy]benzoate was prepared according to the foregoing procedures but using 13.15 g. of powdered iron, 1 ml. of concentrated hydrochloric acid, 400 ml. of 75% aqueous methanol and 13.6 g. of methyl 4-nitro-2-[2-(4-morpholinyl)ethoxy]benzoate hydrochloride. The product, methyl 4-amino-2-[2-(4-morpholinyl)ethoxy]-

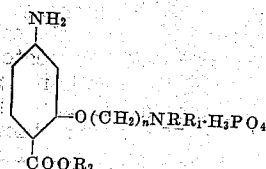
benzoate, was obtained as an oil. This ester was converted into its diphosphate as follows: A solution of 9.5 g. of methyl 4-amino-2-[2-(4-morpholinyl)ethoxy]benzoate in 25 ml. of methanol was treated with a solution of 3.19 g. of 85% phosphoric acid in 25 ml. of methanol, whereupon there separated immediately a gummy material. Ethyl acetate was added to the mixture and the precipitated material was triturated while warming. The supernatant liquid was decanted and the gummy material was triturated several times with warm absolute ethanol, whereupon solidification finally resulted. The solid was filtered and recrystallized by suspending it in hot absolute ethanol and adding hot water dropwise until the solution became clear, treating the solution with decolorizing charcoal, filtering and allowing the filtrate to cool. The finely divided white salt that separated was collected and dried in vacuo at 100° C., yielding 5.5 g. of methyl 4-amino-2-[2-(4-morpholinyl)ethoxy]benzoate diphosphate, M. P. 151.3–152.1° C. (cor.).

Anal.—Calcd. for $C_{14}H_{20}N_2O_4 \cdot 2H_3PO_4$: N_D , 5.83; $2H_3PO_4$, 41.16. Found: N_D , 5.96; $2H_3PO_4$, 40.85.

The foregoing reductions of the lower alkyl 4-nitro-2-(tertiaryaminoalkoxy)benzoates to yield the corresponding 4-amino benzoates can be carried out by catalytic hydrogenation as illustrated by the following general preparation: Ten grams of the lower alkyl 4-nitro-2-(tertiaryaminoalkoxy)benzoate in 150 ml. of ethanol is hydrogenated using 50 lbs. pressure of hydrogen at 25° C. in the presence of 2 g. of Raney nickel. After the rapid exothermic reaction, the catalyst is filtered off and the filtrate evaporated to dryness. The resulting residue is dissolved in absolute ethanol and is treated with a solution of 85% phosphoric acid in absolute ethanol to yield the corresponding lower alkyl 4-amino-2-(tertiaryaminoalkoxy)benzoate phosphate.

Additional lower alkyl 4-amino-2-(tertiaryaminoalkoxy)benzoates, in the form of their monophosphate salts, prepared according to the above procedures are given in Table II'.

TABLE II'



n	NRR ₁	R ₂	M. P., °C. (cor.)	Formula	Analyses			
					H ₃ PO ₄		N _D	
					Calcd.	Found	Calcd.	Found
2	N(C ₂ H ₅) ₂	n-C ₃ H ₇	153.0–154.0	C ₁₆ H ₂₄ N ₂ O ₇ P	24.98	25.23	7.14	7.15
3	N(C ₂ H ₅) ₂	C ₂ H ₅	151.5–153.2	C ₁₅ H ₂₂ N ₂ O ₇ P	24.98	25.00	7.14	7.05
2	N(C ₂ H ₅) ₂ ^a	C ₂ H ₅	220.8–221.4	C ₁₆ H ₂₄ N ₂ O ₇ P	25.11	25.41	7.18	7.17
2	N(C ₂ H ₅) ₂ ^b	C ₂ H ₅	211.0–211.8	C ₁₅ H ₂₂ N ₂ O ₇ P	23.43	23.60	6.70	6.67
3	N(C ₂ H ₅) ₂ ^c	C ₂ H ₅	136.4–138.3	C ₁₅ H ₂₂ N ₂ O ₇ P	23.43	23.12	6.70	6.56
2	N(C ₂ H ₅) ₂ ^d	C ₂ H ₅	196.3–196.9	C ₁₆ H ₂₄ N ₂ O ₇ P	24.99	24.50	7.14	7.16
3	N(C ₂ H ₅) ₂ ^e	C ₂ H ₅	143.3–144.4	C ₁₅ H ₂₂ N ₂ O ₇ P	24.12	24.00	6.89	6.65
2	N(CH ₃) ₂	C ₂ H ₅	176.3–177.3	C ₁₇ H ₂₄ N ₂ O ₇ P	27.98	28.10	8.00	7.98

^a N(C₂H₅)₂=1-piperidyl.

^b The crystalline base melted at 107.3–108.5° C. (cor.). Calcd. for C₁₆H₂₄N₂O₇: N_D , 9.58. Found: N_D , 9.40.

^c N(C₂H₅)₂=2-methyl-1-piperidyl.

^d The crystalline base melted at 91.2–92.4° C. (cor.). Calcd. for C₁₇H₂₆N₂O₇: N_D , 9.14. Found: N_D , 9.26.

^e N(C₂H₅)₂=2,6-dimethyl-1-piperidyl.

^f The crystalline base melted at 112.4–113.5° C. (cor.). Calcd. for C₁₅H₂₂N₂O₇: N_D , 8.74. Found: N_D , 8.54.

^g N(C₂H₅)₂=4-morpholinyl.

^h The crystalline base melted at 98.0–99.3° C. (cor.). Calcd. for C₁₅H₂₂N₂O₇: N_D , 9.52. Found: N_D , 9.42.

ⁱ The crystalline base melted at 106.8–108.0° C. (cor.). Calcd. for C₁₆H₂₄N₂O₇: N_D , 9.09. Found: N_D , 8.78.

^j The crystalline base melted at 94.2–95.6° C. (cor.). Calcd. for C₁₅H₂₂N₂O₇: N_D , 11.11. Found: N_D , 11.14.

Additional lower alkyl 4-amino-2-(tertiary-aminoalkoxy)benzoates which can be prepared according to the foregoing procedures include the following: ethyl 4-amino-2-(2-dimethylamino-1-propoxy)benzoate; isobutyl 4-amino-2-[3-(1-pyrrolidyl)propoxy]benzoate; ethyl 4-amino-2-[2-(2,5 - dimethyl-1-pyrrolidyl)ethoxy]benzoate; methyl 4-amino-2-(4-dimethylaminobutoxy)-benzoate; n-propyl 4-amino-2-[2-(di-n-butylamino)ethoxy]benzoate; n-butyl 4-amino-2-[3-(4-methyl - 1-piperidyl)propoxy]benzoate; n-hexyl 4-amino-2-[2-(3-ethyl-1-piperidyl)ethoxy]benzoate; n-amyl 4-amino-2-[3-(2-methyl-1-pyrrolidyl)propoxy]benzoate; and the like.

(3). *Lower alkyl 4-alkylamino- and 4-hydroxyalkylamino - 2-(tertiary - aminoalkoxy)benzoates*

These compounds were produced by alkylation of the corresponding lower alkyl 4-amino-2-(tertiary - aminoalkoxy)benzoates described above. This alkylation was run preferably by reductive alkylation procedures as illustrated in the following examples.

Ethyl 4-n-butylamino-2-(2-diethylaminoethoxy)benzoate was prepared as follows: To a hot stirred mixture of 26.0 g. of ethyl 4-amino-2-(2-diethylaminoethoxy)benzoate, 24.1 g. of zinc dust, 22.6 g. of glacial acetic acid and 450 ml. of dry benzene was added 8.0 g. of n-butanal (n-butyraldehyde) dissolved in 50 ml. of dry benzene over a fifteen minute period. After the mixture had been stirred for one hour, an additional 1 ml. of n-butanal was added and stirring continued for an additional fifteen minutes. The zinc acetate was filtered off and washed with hot dilute acetic acid and benzene. The cooled filtrate was made basic to litmus with concentrated ammonium hydroxide, the benzene layer was separated and the aqueous solution was extracted three times with benzene. After the combined benzene layer and extracts had been dried over anhydrous calcium sulfate, the benzene was removed by distilling in vacuo, yielding, as a straw colored oil, ethyl 4-n-butylamino-2-(2-diethylaminoethoxy)benzoate. This ester was converted into its monohydrochloride salt as follows: Eleven grams of the ester was dissolved in ethyl acetate and was treated with an excess of 20% by weight of ethanolic hydrogen chloride, whereupon a gummy material separated immediately. The supernatant liquid was decanted from the gum and the latter was triturated twice with warm ethyl acetate. The gummy material was then dissolved in a minimum amount of hot ethanol, 12 g. of ethyl 4-n-butylamino - 2 - (2-diethylaminoethoxy)benzoate was added and the solution was cooled. Absolute ether was then added to turbidity, whereupon a cream colored crystalline precipitate separated. The mixture was diluted to about 500 ml. with absolute ether. The precipitate was collected and recrystallized once from absolute ethanol-absolute ether with decolorization, using decolorizing charcoal, and a second time, with decolorization, from ethanol-ethyl acetate. There was thus obtained ethyl 4-n-butylamino-2-(2-diethylaminoethoxy)benzoate hydrochloride, M. P. 160.5-161.8° C. (cor.).

Anal.—Calcd. for $C_{19}H_{32}N_2O_3 \cdot HCl$: N_D , 7.51; Cl, 9.50. Found: N_D , 7.36; Cl, 9.45.

When the above procedure is followed but using n-propanol, n-pentanal and n-hexanal, in place of n-butanal, the resulting products, in the form

of their monohydrochlorides, are ethyl 4-n-propylamino-2 - (2 - diethylaminoethoxy)benzoate, ethyl 4-n-amylamino-2-(2-diethylaminoethoxy)-benzoate and ethyl 4-n-hexylamino-2-(2-diethylaminoethoxy)benzoate, respectively.

When the above procedure is followed but using, in place of ethyl 4-amino-2-(2-diethylaminoethoxy)benzoate, methyl 4-amino-2-[3-(1-piperidyl)-propoxy]benzoate, n-propyl 4-amino-2-[2-(2,6-dimethyl-1 - piperidyl)ethoxy]benzoate, n-butyl 4-amino-2-[2-2 - methyl-1-piperidyl)ethoxy]benzoate or ethyl 4-amino-2-[2-(4-morpholinyl)-ethoxy]benzoate, there is obtained, in the form of their monohydrochlorides, methyl 4-n-butylamino-2-[3 - (1 - piperidyl)propoxy]benzoate, n-propyl 4-n-butylamino-2-[2-(2,6-dimethyl-1-piperidyl)ethoxy]benzoate, n-butyl 4-n-butylamino-2-[2-(2-methyl-1 - piperidyl)ethoxy]benzoate or ethyl 4-n-butylamino-2-[2-(4-morpholinyl)ethoxy]benzoate, respectively.

Ethyl 4-(5-hydroxyamylamino)-2-(2-diethylaminoethoxy)benzoate was obtained, as an oil, following the above procedure but using 26.0 g. of ethyl 4-amino - 2-(2 - diethylaminoethoxy)-benzoate, 11.3 g. of 5-hydroxypentanal, 24.1 g. of zinc dust, 22.6 g. of glacial acetic acid and 500 ml. of dry benzene. Ethyl 4-(5-hydroxyamylamino)-2-(2-diethylaminoethoxy)benzoate monohydrochloride, M. P. 132.2-133.4° C. (cor.) was obtained following the procedure disclosed above for preparing ethyl 4-n-butylamino-2-(2-diethylaminoethoxy)benzoate monohydrochloride.

Anal.—Calcd. for $C_{20}H_{33}N_2O_4 \cdot HCl$: N_D , 6.95; Cl, 8.79. Found: N_D , 7.07; Cl, 9.05.

When the above procedure was followed but using, in place of ethyl 4-amino-2-(2-diethylaminoethoxy)benzoate, n-propyl 4-amino-2-(2-diethylaminoethoxy)benzoate and ethyl 4-amino-2-[2-(2,6-dimethyl - 1 - piperidyl)ethoxy]benzoate, there was obtained, as oils, n-propyl 4-(5-hydroxyamylamino)-2 - (2-diethylaminoethoxy)-benzoate and ethyl 4-(5-hydroxyamylamino)-2-[2-(2,6-dimethyl - 1-piperidyl)ethoxy]benzoate, respectively.

When the above procedure is followed but using, in place of 5-hydroxypentanal, 3-hydroxypropanal, 4-hydroxybutanal, 3-hydroxybutanal or 6-hydroxyhexanal, there is obtained, in the form of their monohydrochlorides, ethyl 4-(3-hydroxypropylamino) - 2 - (2 - diethylaminoethoxy)benzoate, ethyl 4-(4-hydroxybutylamino)-2-(2-diethylaminoethoxy)benzoate, ethyl 4-(3-hydroxybutylamino) - 2 - (2-diethylaminoethoxy)-benzoate or ethyl 4-(6-hydroxyhexylamino)-2-(2-diethylaminoethoxy)benzoate, respectively.

Ethyl 4-(3-hydroxy-2,2-dimethylpropylamino)-2-[2-(2,6-dimethyl-1-piperidyl)ethoxy]benzoate was prepared following the above procedures but using 19 g. of ethyl 4-amino-2-[2-(2,6-dimethyl-1-piperidyl)ethoxy]benzoate, 7.32 g. of 3-hydroxy-2,2-dimethylpropanal, 15.5 g. of zinc dust, 14.5 g. of glacial acetic acid and 500 ml. of dry benzene. The resulting product, a pale yellow mobile oil, crystallized when triturated. The crystalline material was recrystallized twice from benzene, with decolorization using decolorizing charcoal, yielding ethyl 4-(3-hydroxy-2,2-dimethylpropylamino) - 2 - [2 - (2,6 - dimethyl - 1 - piperidyl)ethoxy]benzoate, M. P. 90.0-91.0° C. (cor.) [dried in vacuo at 65° C.]

Anal.—Calcd. for $C_{23}H_{33}N_2O_4$: C, 67.94; H, 9.42; N_D , 6.89. Found: C, 68.06; H, 9.31; N_D , 6.81.

Alternatively, the foregoing reductive alkylations can be carried out using, in place of zinc dust and glacial acetic acid, hydrogen under

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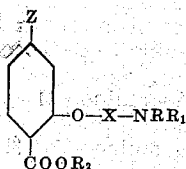
pressure in the presence of a hydrogenation catalyst such as platinum.

Other lower alkyl 4-alkylamino- or 4-hydroxy-alkylamino-2-(tertiary-aminoalkoxy)benzoates which can be prepared according to the above procedures using the appropriate alkanol or hydroxyalkanol and lower alkyl 4-amino-2-(tertiary-aminoalkoxy)benzoate include the following: ethyl 4-n-butylamino-2-(2-dimethylamino-1-propoxy)benzoate; isobutyl 4-n-propylamino-2-[3-(1-(1-pyrrolidyl)propoxy)]benzoate; ethyl 4-(3-hydroxypropylamino)-2-[2-(2,5-dimethyl-1-pyrrolidyl)ethoxy]benzoate; methyl 4-n-hexylamino-2-(4-dimethylaminobutoxy)benzoate; n-propyl 4-n-amylamino-2-[2-(di-n-butylamino)-ethoxy]benzoate; n-butyl 4-n-butylamino-2-[3-(4-methyl-1-piperidyl)propoxy]benzoate; n-hexyl 4-n-propylamino-2-[2-(3-ethyl-1-piperidyl)ethoxy]benzoate; n-amyl 4-(5-hydroxyamylamino)-2-[3-(2-methyl-1-pyrrolidyl)propoxy]benzoate; and the like.

Alternatively, the lower alkyl 4-alkylamino- and 4-hydroxyalkylamino-2-(tertiary-aminoalkoxy)benzoates of our invention can be prepared by direct alkylation of the corresponding 4-amino compounds. This mode of alkylation is illustrated by heating ethyl 4-amino-2-(2-diethylaminoethoxy)benzoate with methyl iodide, ethyl bromide, 2-hydroxyethyl bromide, n-propyl iodide, n-butyl bromide or 5-hydroxypentyl chloride in the presence of a hydrogen halide acceptor such as potassium carbonate to yield, respectively, ethyl 4-methylamino-2-(2-diethylaminoethoxy)benzoate, ethyl 4-ethylamino-2-(2-diethylaminoethoxy)benzoate, ethyl 4-(2-hydroxyethylamino)-2-(2-diethylaminoethoxy)benzoate, ethyl 4-n-propylamino-2-(2-diethylaminoethoxy)benzoate, ethyl 4-n-butylamino-2-(2-diethylaminoethoxy)benzoate and ethyl 4-(5-hydroxyamylamino)-2-(2-diethylaminoethoxy)benzoate.

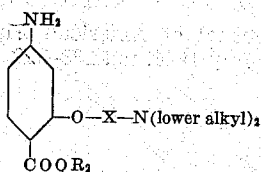
We claim:

1. A compound having the formula



where Z is a member of the group consisting of nitro, amino, lower alkylamino and lower hydroxyalkylamino, X is a lower alkylene radical whose two free valence bonds are on different carbon atoms, NRR_1 is a member of the group consisting of lower dialkylamino, 1-piperidyl, (lower alkylated)-1-piperidyl, 1-pyrrolidyl, (lower alkylated)-1-pyrrolidyl and 4-morpholinyl, and R_2 is a lower alkyl radical.

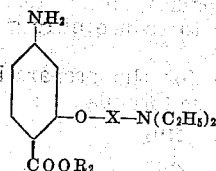
2. A compound having the formula



where X is a lower alkylene radical whose two free valence bonds are on different carbon atoms and R_2 is a lower alkyl radical.

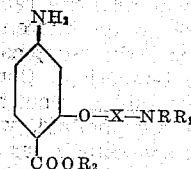
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3. A compound having the formula



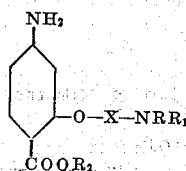
where X is a lower alkylene radical whose two free valence bonds are on different carbon atoms and R_2 is a lower alkyl radical.

4. A compound having the formula



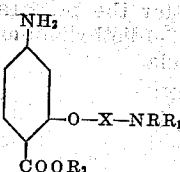
where X is a lower alkylene radical whose two free valence bonds are on different carbon atoms, NRR_1 is a 1-piperidyl radical and R_2 is a lower alkyl radical.

5. A compound having the formula



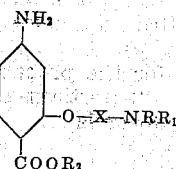
where X is a lower alkylene radical whose two free valence bonds are on different carbon atoms, NRR_1 is a (lower alkylated)-1-piperidyl radical and R_2 is a lower alkyl radical.

6. A compound having the formula



where X is a lower alkylene radical whose two free valence bonds are on different carbon atoms, NRR_1 is a 2-methyl-1-piperidyl radical and R_2 is a lower alkyl radical.

7. A process for the preparation of a compound having the formula

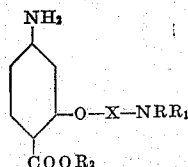


where X is a lower alkylene radical whose two free valence bonds are on different carbon atoms, NRR_1 is a member of the group consisting of lower dialkylamino, 1-piperidyl, (lower alkylated)-1-piperidyl, 1-pyrrolidyl, (lower alkylated)-1-pyrrolidyl and 4-morpholinyl, and R_2 is a lower alkyl radical, which comprises treating a member of the group consisting of a lower alkyl 4-nitro-2-hydroxybenzoate and a metal salt thereof with a tertiary-aminoalkyl halide of the formula, halogen-X-NRR₁, and

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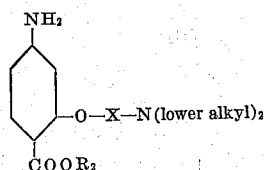
treating the resulting lower alkyl 4-nitro-2-(tertiary-aminoalkoxy)benzoate with a reducing agent effective to reduce nitro groups to amino groups.

8. A process for the preparation of a compound having the formula



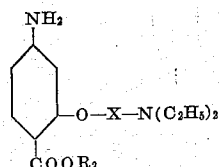
where X is a lower alkylene radical whose two free valence bonds are on different carbon atoms, NRR₁ is a member of the group consisting of lower dialkylamino, 1-piperidyl, (lower alkylated)-1-piperidyl, 1-pyrrolidyl, (lower alkylated)-1-pyrrolidyl and 4-morpholinyl, which comprises treating the corresponding lower alkyl 4-nitro-2-(tertiary-aminoalkoxy)benzoate with a reducing agent effective to reduce nitro groups to amino groups.

9. A process for the preparation of a lower alkyl 4-amino-2-(dialkylaminoalkoxy)benzoate having the formula



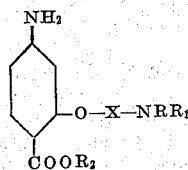
where X is a lower alkylene radical whose two free valence bonds are on different carbon atoms and R₂ is a lower alkyl radical, which comprises treating the corresponding lower alkyl-4-nitro-2-(dialkylaminoalkoxy)benzoate with a reducing agent effective to reduce nitro groups to amino groups.

10. A process for the preparation of a lower alkyl 4-amino-2-(diethylaminoalkoxy)benzoate having the formula



where X is a lower alkylene radical whose two free valence bonds are on different carbon atoms and R₂ is a lower alkyl radical, which comprises treating the corresponding lower alkyl 4-nitro-2-(diethylaminoalkoxy)benzoate with a reducing agent effective to reduce nitro groups to amino groups.

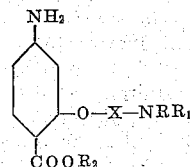
11. A process for the preparation of a lower alkyl 4-amino-2-(tertiary-aminoalkoxy)benzoate having the formula



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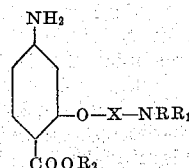
where X is a lower alkylene radical whose two free valence bonds are on different carbon atoms, NRR₁ is a 1-piperidyl radical and R₂ is a lower alkyl radical, which comprises treating the corresponding lower alkyl 4-nitro-2-(tertiary-aminoalkoxy)benzoate with a reducing agent effective to reduce nitro groups to amino groups.

12. A process for the preparation of a lower alkyl 4-amino-2-(tertiary-aminoalkoxy)benzoate having the formula



where X is a lower alkylene radical whose two free valence bonds are on different carbon atoms, NRR₁ is a (lower alkylated)-1-piperidyl radical and R₂ is a lower alkyl radical, which comprises treating the corresponding lower alkyl 4-nitro-2-(tertiary-aminoalkoxy)benzoate with a reducing agent effective to reduce nitro groups to amino groups.

13. A process for the preparation of a lower alkyl 4-amino-2-(tertiary-aminoalkoxy)benzoate having the formula



where X is a lower alkylene radical whose two free valence bonds are on different carbon atoms, NRR₁ is a 2-methyl-1-piperidyl radical and R₂ is a lower alkyl radical, which comprises treating the corresponding lower alkyl 4-nitro-2-(tertiary-aminoalkoxy)benzoate with a reducing agent effective to reduce nitro groups to amino groups.

14. Ethyl 4-amino-2-(2-diethylaminoethoxy)benzoate.

15. n-Propyl 4-amino-2-(2-diethylaminoethoxy)benzoate.

16. n-Butyl 4-amino-2-(2-diethylaminoethoxy)benzoate.

17. Ethyl 4-amino-2-[3-(1-piperidyl)propoxy]benzoate.

18. Ethyl 4-amino-2-[3-(2-methyl-1-piperidyl)propoxy]benzoate.

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