United States Patent Office 2,865,951 Patented Dec. 23, 1958

2,865,951

TERTIARY AMINOALCOHOL ESTERS OF 4-AMINO-2,6-DIMETHYLBENZOIC ACID

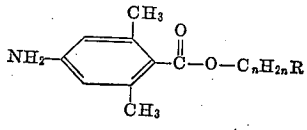
Robert D. Birkenmeyer and Richard V. Heinzelman, Kalamazoo Township, Kalamazoo County, Mich., assignors to The Upjohn Company, Kalamazoo, Mich., a corporation of Michigan

No Drawing. Application May 24, 1954
Serial No. 432,054

13 Claims. (Cl. 260—472)

The present invention relates to amines and to a process for the preparation thereof. More particularly, the invention relates to tertiary aminoalkyl esters of 2,6-dimethyl-4-aminobenzoic acid, acid addition and quaternary ammonium salts thereof, and to a process for the preparation of esters of 2,6-dimethyl-4-aminobenzoic acid.

The tertiary aminoalkyl esters of 2,6-dimethyl-4-aminobenzoic acid are represented by the following general formula:



wherein n is an integer from one to six inclusive and R is a secondary amino radical.

It is an object of the present invention to provide new and novel tertiary aminoalkyl esters of 2,6-dimethyl-4-aminobenzoic acid and acid addition and quaternary ammonium salts thereof. Another object of the invention is to provide a process for the preparation of these compounds. Other objects and features of the invention will be apparent to those skilled in the art to which this invention pertains.

The tertiary aminoalkyl esters of 2,6-dimethyl-4-aminobenzoic acid, including the acid addition and quaternary ammonium salts thereof, and especially the β-diethylaminoethyl ester of 2,6-dimethyl-4-aminobenzoic acid, are characterized by pharmacological activity, and more specifically, local anesthetic activity.

The β-diethylaminoethyl ester of 2,6-dimethyl-4-aminobenzoic acid is similar in chemical structure to procaine (β-diethylaminoethyl para-aminobenzoate) except for the presence of methyl groups in the two and six positions in the first mentioned compound. The presence of methyl groups in β-diethylaminoethyl 2,6-dimethyl-4-aminobenzoate, otherwise referred to as 2,6-dimethylprocaine, renders this compound, however, strikingly different from procaine itself. For example, a comparison of the hydrolysis rates of procaine and 2,6-dimethylprocaine shows that conditions under which procaine readily hydrolyzes, 2,6-dimethylprocaine, and acid addition and quaternary ammonium salts thereof are very stable and hydrolyze to no detectable extent. This is dramatically illustrated by a comparative enzymatic hydrolysis using three percent rat liver homogenate at a pH of 8.7, in which case, at the end of thirty minutes, procaine is found to have hydrolyzed to the extent of 52 percent whereas 2,6-dimethylprocaine is found to have undergone no hydrolysis. The stability of the tertiary aminoalkyl esters of 2,6-dimethyl-4-aminobenzoic acid is attributable to the presence of the two methyl groups in ortho position relative to the carboxyl group. Furthermore, it has been established (Brodie et al., Current Researches in Anesthesia and Analgesia, 29, 29–33, 1950) that procaine rapidly hydrolyzes in man to p-aminobenzoic acid and diethylaminoethanol and it appears that

the pharmacologic action of procaine is attributable to diethylaminoethanol. Since 2,6-dimethylprocaine does not hydrolyze readily, its pharmacologic activity can be considered as an inherent property of the compound per se as compared with procaine whose activity appears to be due to one of its hydrolysis products. This represents a further and highly important distinction between procaine and 2,6-dimethylprocaine. Thus, the novel local anesthetics of this invention, the tertiary aminoalkyl esters of 2,6-dimethyl-4-aminobenzoic acid and especially, the β-diethylaminoethyl ester of 2,6-dimethyl-4-aminobenzoic acid, have significantly superior and different properties as compared with the most closely analogous compounds of the prior art.

The process of the invention relating to the preparation of esters of 2,6-dimethyl-4-aminobenzoic acid comprises esterifying the starting 2,6-dimethyl-4-carbomethoxybenzoyl halide, ammonolyzing the resulting 2,6-dimethyl-4-carbomethoxybenzoate and then subjecting the resulting ester-amide to a Hofmann reaction to produce the corresponding 2,6-dimethyl-4-aminobenzoate.

In a more specific and preferred embodiment of this invention, a 2,6-dimethyl-4-carbomethoxybenzoyl halide is esterified with a tertiary alkanolamine such as, for example, dimethylaminoethanol, dimethylaminomethanol, diethylaminomethanol, diethylaminoethanol, diethylaminopropanol, diethylaminobutanol, diethylaminopentanol, diethylaminohexanol, dipropylaminoethanol, diisopropylaminoethanol, dipropylaminopropanol, dibutylaminoethanol, dibutylaminopropanol, methylethylaminoethanol, methyl-n-propylaminoethanol, methylhexylaminoethanol, and the like. Other tertiary alkanolamines which can be used include, dicycloalkylaminoalkanols such as, for example, dicyclobutylaminoethanol, dicyclohexylaminoethanol, and the like; alkyl-aralkylaminoalkanols such as, for example, methylbenzylaminomethanol, ethylbenzylaminoethanol, propylbenzylaminoethanol, and the like; diaralkylaminoalkanols such as, for example, dibenzylaminoethanol, diphenylethylaminoethanol, and the like; heterocyclic amino alkanols such as, for example, pyrrolidylmethanol, pyrrolidylethanol, pyrrolidylbutanol, piperidylethanol, morpholinylethanol, and the like; carbon-substituted pyrrolidylalkanols, piperidylalkanols, morpholinylalkanols, such as, for example 2-methylpyrrolidylethanol, 2,2-dimethylpyrrolidylethanol, 2-ethylpyrrolidylethanol, 2-, 3-, and 4-methylpiperidylethanols, 2-, 3-, and 4-ethylpiperidylethanols, 2- and 3-methylmorpholinylethanols, 2- and 3-ethylmorpholinylethanols, and the like. The resulting tertiary aminoalkyl 2,6-dimethyl-4-carbomethoxybenzoate is then ammonolyzed to form the corresponding tertiary aminoalkyl 2,6-dimethyl-4-carbamylbenzoate and the tertiary aminoalkyl 2,6-dimethyl-4-carbamylbenzoate thus obtained is then subjected to a Hofmann reaction to form the desired tertiary aminoalkyl 2,6-dimethyl-4-aminobenzoate.

The Hofmann reaction for the conversion of an amide to an amine is generally effected by dissolving the amide in a very slight excess of cold aqueous alkali-metal hypohalite solution followed by rapid warming. However, this procedure is advantageously modified in the invention by carrying out the reaction in an alcoholic (usually methanolic) solution, with subsequent hydrolysis of the intermediate so obtained to form the desired tertiary aminoalkyl 2,6-dimethyl-4-aminobenzoate.

Due to the presence of basic nitrogen in the molecule, the tertiary aminoalkyl 2,6-dimethyl-4-aminobenzoates react with suitable acids to form acid addition salts. Representative acids which may be used include mineral acids such as hydrogen chloride, hydrogen bromide, sulfuric acid, or the like; aliphatic carboxylic acids such as acetic acid, lactic acid, tartaric acid, succinic acid, or the like; aromatic acids such as benzoic acid, salicylic

acid, or the like; and strongly acidic phenols such as picric acid, or the like. The acid addition salts are stable and can be sterilized in aqueous solution by boiling without appreciable hydrolysis of the ester groups.

Various procedures can be used to prepare the acid addition salts of the tertiary aminoalkyl 2,6-dimethyl-4-aminozenzoates of the invention. A convenient or preferred method involves reacting the free basic material with a selected acid in a solvent such as alcohol or a mixture of alcohol and ethyl acetate. Upon distillation of the solvent, the acid salt remains as a residue which can then be purified by recrystallization from solvents such as alcohol, methyl ethyl ketone, ethyl acetate, and the like. Other methods for preparing the acid addition salts of the tertiary aminoalkyl 2,6-dimethyl-4-aminobenzoates of the invention may also be used and are known in the art.

Quaternary ammonium salts of the tertiary aminoalkyl 2,6-dimethyl-4-aminobenzoates of the invention may likewise be prepared by any convenient manner known in the art, such as, for example, by mixing a tertiary aminoalkyl 2,6-dimethyl-4-aminobenzoate with a selected ester, in stoichiometric proportions, in the presence of an organic solvent in which the resulting quaternary ammonium salt is insoluble so that precipitation occurs upon formation thereof. Representative esters which may be used to form quaternary ammonium salts of tertiary aminoalkyl 2,6-dimethyl-4-aminobenzoates, include alkyl halides, aralkyl halides, and alkyl esters of arylsulfonic acids such as, for example, methyl bromide, methyl iodide, cetyl bromide, myristyl iodide, lauryl bromide, benzyl chloride, allyl bromide, ethyl paratoluenesulfonate, or the like, in which cases the tertiary aminoalkyl 2,6-dimethyl-4-aminobenzoate and selected salt forming agent are mixed together, heated to complete the reaction and the solid quaternary ammonium salt of the tertiary aminoalkyl 2,6-dimethyl-4-aminobenzoate thereafter isolated.

The following examples illustrate the process and products of the present invention but are not to be construed as limiting.

Example 1

β-Diethylaminoethyl 2,6-dimethyl-4-carbomethoxybenzoate

In a 500-milliliter, three-necked flask fitted with a stirrer, reflux condenser and dropping funnel is placed 26.3 grams (0.116 mole) of 2,6-dimethyl-4-carbomethoxybenzoyl chloride (obtained by reacting 2,6-dimethyl-4-carbomethoxybenzoic acid, Amer. Chem. Journal, 20, 811, 1898, with thionyl chloride) and 200 milliliters of dry benzene. The solution is stirred, heated to reflux and a solution of thirty grams (0.256 mole) of diethylaminoethanol in fifty milliliters of dry benzene is added dropwise over a thirty minute period. Stirring and refluxing are continued overnight. The reaction mixture is then cooled to twenty degrees centigrade and made basic with a twenty percent sodium hydroxide solution. The organic layer is separated and the aqueous phase extracted three times with 100-milliliter portions of ether. The ether extracts are combined with the organic layer, the mixture is dried over anhydrous magnesium sulfate and then distilled. Twenty-seven grams (76 percent yield) of diethylaminoethyl 2,6-dimethyl-4-carbomethoxybenzoate is obtained characterized by a boiling point of 138 degrees centigrade at a pressure of 0.04 millimeter of mercury.

Analysis. — Calculated for $C_{17}H_{25}NO_4$: N, 4.56. Found: N, 4.63.

On replacing diethylaminoethanol by dimethylaminoethanol, dipropylaminoethanol, dimethylaminopropanol, diamylaminoethanol, and the like, the corresponding β-dimethylaminoethyl 2,6 - dimethyl - 4 - carbomethoxybenzoate, β-dipropylaminoethyl 2,6 - dimethyl - 4-carbomethoxybenzoate, γ-dimethylaminopropyl 2,6-dimethyl-4 - carbomethoxybenzoate, β-diamylaminoethyl 2,6-dimethyl-4-carbomethoxybenzoate, and the like, are obtained.

On treating an ether solution of β-diethylaminoethyl 2,6-dimethyl-4-carbomethoxybenzoate thus obtained with gaseous hydrogen chloride followed by recrystallization of the resulting material from isopropanol, substantially pure β-diethylaminoethyl 2,6-dimethyl-4-carbomethoxybenzoate hydrochloride is obtained melting between 168.5 and 169.5 degrees centigrade.

Analysis.—Calculated for $C_{17}H_{26}ClNO_4$: Cl, 10.31. Found: Cl, 10.33.

Example 2

β-Diethylaminoethyl 2,6-dimethyl-4-carbamylbenzoate

In a 250-milliliter, three-necked flask fitted with a stirrer, thermometer, and gas inlet tube is placed 21.5 grams (0.07 mole) of β-diethylaminoethyl 2,6-dimethyl-4-carbomethoxybenzoate (Example 1) and 100 milliliters of absolute methanol. Ammonia gas is bubbled into the agitated solution for twenty hours while the temperature is maintained between forty and fifty degrees centigrade. At the end of this period, an additional 100 milliliters of absolute methanol and 200 milliliters of dry ether are added to the reaction mixture. Ammonia gas is introduced for an additional 24 hour period. The temperature of the reaction mixture is raised to 100 degrees centigrade and ammonia gas is again bubbled into the solution for an additional 24 hour period. Upon cooling the reaction mixture, a white solid is obtained. On recrystallization of the white solid material from Skelly C, β-diethylaminoethyl 2,6-dimethyl-4-carbamylbenzoate is obtained in the form of white needles melting between 99 and 100 degrees centigrade.

Analysis. — Calculated for $C_{16}H_{24}N_2O_3$: N, 9.58. Found: N, 9.52.

Similarly, by replacing β-diethylaminoethyl 2,6-dimethyl-4-carbomethoxybenzoate by β-dimethylaminoethyl 2,6-dimethyl-4-carbomethoxybenzoate, γ-dimethylaminopropyl 2,6-dimethyl-4-carbomethoxybenzoate, β-diamylaminoethyl 2,6-dimethyl-4-carbomethoxybenzoate, β-dipropylaminoethyl 2,6-dimethyl-4-carbomethoxybenzoate, and the like, the corresponding β-dimethylaminoethyl 2,6-dimethyl-4-carbamylbenzoate, γ-dimethylaminopropyl 2,6-dimethyl - 4 - carbamylbenzoate, β - diamylaminoethyl 2,6 - dimethyl - 4 - carbamylbenzoate, β-dipropylaminoethyl 2,6-dimethyl-4-carbamylbenzoate, and the like, are obtained.

Example 3

β-Diethylaminoethyl 2,6-dimethyl-4-carbomethoxyaminobenzoate

In a fifty milliliter Erlenmeyer flask is placed 1.0 gram (0.00342 mole) of β-diethylaminoethyl 2,6-dimethyl-4-carbamylbenzoate (Example 2) and five milliliters of absolute methanol. In a second fifty milliliter flask, 0.161 gram (0.00686 mole) of sodium is dissolved in ten milliliters of absolute methanol. In a third fifty milliliter flask, 0.6 gram (0.00373 mole) of bromine is dissolved in ten milliliters of absolute methanol. The bromine and sodium methoxide solutions are cooled to zero degrees centigrade and mixed together. The resulting mixture is immediately poured onto the cold (zero degrees centigrade) β-diethylaminoethyl 2,6 - dimethyl - 4-carbamylbenzoate solution and the flask is placed on a shaker. After the flask has been agitated for thirty minutes, the reaction mixture is heated on a steam bath and evaporated to dryness in a stream of air. The viscous white material thus obtained is extracted with ether and the ether extracts are dried and evaporated. A clear, dark brown oil is obtained and is identified by infrared analysis as β-diethylaminoethyl 2,6-dimethyl-4-carbomethoxyaminobenzoate.

Similarly, by replacing β-diethylaminoethyl 2,6-dimethyl-4-carbamylbenzoate by β-dimethylaminoethyl 2,6-dimethyl - 4 - carbamylbenzoate, γ - dimethylamino-

propyl 2,6 - dimethyl - 4 - carbamylbenzoate, β-diamylaminoethyl 2,6 - dimethyl - 4 - carbamylbenzoate, β - dipropylaminoethyl 2,6 - dimethyl - 4 - carbamylbenzoate, or the like, the corresponding β-dimethylaminoethyl 2,6 - dimethyl - 4 - carbomethoxyaminobenzoate, γ-dimethylaminopropyl 2,6 - dimethyl - 4 - carbomethoxyaminobenzoate, β-diamylaminoethyl 2,6-dimethyl-4-carbomethoxyaminobenzoate, β-dipropylaminoethyl 2,6-dimethyl-4-carbomethoxyaminobenzoate, or the like, are obtained.

EXAMPLE 4

β-Diethylaminoethyl 2,6-dimethyl-4-aminobenzoate

To a fifty-milliliter distilling flask containing eight sodium hydroxide pellets and thirty milliliters of water is added 0.89 gram of β-diethylaminoethyl 2,6-dimethyl-4-carbomethoxyaminobenzoate (Example 3). Two hundred milliliters of liquid is distilled, additional quantities of water being added to the flask as necessary. The distillate is extracted with ether and the extracts dried and evaporated. A light brown oil is obtained which is identified by infrared analysis as β-diethylaminoethyl 2,6-dimethyl - 4 - aminobenzoate boiling between 155 and 157 degrees centigrade at a pressure of 0.04 millimeter of mercury and possessing an index of refraction n_D^{25}= 1.5477.

Analysis. — Calculated for $C_{15}H_{24}N_2O_2$: N, 10.60. Found: N, 10.49.

By heating a benzene solution of β-diethylaminoethyl 2,6 - dimethyl - 4 - aminobenzoate and methyl bromide and cooling and concentrating the resulting solution, β-diethylaminoethyl 2,6 - dimethyl - 4 - aminobenzoate methobromide is obtained.

Similarly, by reacting β-diethylaminoethyl 2,6-dimethyl-4-aminobenzoate with other esters such as, for example, ethyl chloride, benzyl chloride, and the like, the corresponding quaternary ammonium salts of β-diethylaminoethyl 2,6 - dimethyl - 4 - aminobenzoate are obtained such as, for example, β-diethylaminoethyl 2,6-dimethyl-4-aminobenzoate ethochloride, β-diethylaminoethyl 2,6-dimethyl-4-aminobenzoate benzyl chloride, and the like.

EXAMPLE 5

β-Diethylaminoethyl 2,6-dimethyl-4-aminobenzoate mono-hydrochloride

One gram of β-diethylaminoethyl 2,6-dimethyl-4-aminobenzoate (Example 4) is dissolved in thirty milliliters of diethyl ether and gaseous hydrogen chloride is bubbled into the solution until the precipitation of white solid ceases. The solid material is collected by filtration, immediately dissolved in isopropanol and then recrystallized therefrom. β - Diethylaminoethyl 2,6-dimethyl-4-aminobenzoate mono-hydrochloride is thus obtained melting between 129 and 130 degrees centigrade.

Analysis.—Calculated for $C_{15}H_{25}ClN_2O_2$: Cl, 11.79. Found: Cl, 11.67.

EXAMPLE 6

β-Diethylaminoethyl 2,6-dimethyl-4-aminobenzoate dihydrochloride

One gram of β - diethylaminoethyl 2,6 - dimethyl - 4-aminobenzoate (Example 4) is dissolved in thirty milliliters of diethyl ether and gaseous hydrogen chloride is bubbled into the solution until the precipitation of white solid ceases. The solid material is collected by filtration and exposed to the air. Over a period of eight hours, the white solid material becomes gummy, light tan in color and then resolidifies. Upon recrystallization from isopropanol, white crystalline β-diethylaminoethyl 2,6-dimethyl-4-aminobenzoate dihydrochloride is obtained melting between 194 and 194.5 degrees centigrade.

Analysis—Calculated for $C_{15}H_{26}Cl_2N_2O_2$: Cl, 21.07; N, 8.32. Found: Cl, 20.61; N, 8.28.

EXAMPLE 7

β-Diethylaminoethyl 2,6-dimethyl-4-aminobenzoate mono-acetate

On replacing the hydrochloric acid with 0.6 gram (0.01 mole) of glacial acetic acid and using the procedure set forth in Example 5, β-diethylaminoethyl 2,6-dimethyl-4-aminobenzoate mono-acetate is obtained in the form of colorless crystals.

EXAMPLE 8

β-Diethylaminoethyl 2,6-dimethyl-4-aminobenzoate benzoate

Following the procedure set forth in Example 5 except for the substitution of 1.22 grams (0.01 mole) of benzoic acid for the hydrochloric acid, β-diethylaminoethyl 2,6-dimethyl-4-aminobenzoate benzoate is obtained in the form of colorless crystals.

EXAMPLE 9

β-Diethylaminoethyl 2,6-dimethyl-4-aminobenzoate citrate

Following the procedure set forth in Example 5 except for the substitution of 1.92 grams (0.01 mole) of citric acid for the hydrochloric acid, β-diethylaminoethyl 2,6-dimethyl-4-aminobenzoate citrate is obtained in the form of colorless crystals.

EXAMPLE 10

β-Diethylaminoethyl 2,6-dimethyl-4-aminobenzoate sulfate

Following the procedure set forth in Example 5 except for the substitution of 0.52 gram (0.01 mole) of sulfuric acid for the hydrochloric acid, β-diethylaminoethyl 2,6-dimethyl-4-aminobenzoate sulfate is obtained in the form of colorless crystals.

EXAMPLE 11

β-Dimethylaminoethyl 2,6-dimethyl-4-aminobenzoate

Following the procedure set forth in Example 4 except for the substitution of β-diethylaminoethyl 2,6-dimethyl-4-carbomethoxyaminobenzoate by β-dimethylaminoethyl 2,6 - dimethyl - 4 - carbomethoxyaminobenzoate, β-dimethylaminoethyl 2,6 - dimethyl - 4 - aminobenzoate is obtained.

On reacting β - dimethylaminoethyl 2,6 - dimethyl-4-aminobenzoate with a suitable acid such as hydrochloric acid, acetic acid, benzoic acid, and the like, and using the procedure set forth supra for the preparation of acid addition salts, the corresponding β-dimethylaminoethyl 2,6 - dimethyl - 4 - aminobenzoate mono - hydrochloride, β - dimethylaminoethyl 2,6 - dimethyl - 4 - aminobenzoate mono-acetate, β-dimethylaminoethyl 2,6-dimethyl-4-aminobenzoate benzoate, and the like, are obtained.

Likewise, on reacting β - dimethylaminoethyl 2,6-dimethyl - 4 - aminobenzoate with selected esters such as, for example, ethyl chloride, benzyl chloride, and the like, and using the procedure set forth above, the corresponding quaternary ammonium salts of β-dimethylaminoethyl 2,6 - dimethyl - 4 - aminobenzoate are obtained such as, for example, β-dimethylaminoethyl 2,6 - dimethyl - 4 - aminobenzoate ethochloride, β-dimethylaminoethyl 2,6 - dimethyl - 4 - aminobenzoate benzyl chloride, and the like.

EXAMPLE 12

γ-Dimethylaminopropyl 2,6-dimethyl-4-aminobenzoate

Following the procedure set forth in Example 4 except for the substitution of β-diethylaminoethyl 2,6-dimethyl-4-carbomethoxyaminobenzoate by γ-dimethylaminopropyl 2,6-dimethyl-4-carbomethoxyaminobenzoate, γ-dimethylaminopropyl 2,6-dimethyl-4-aminobenzoate is obtained.

On reacting γ-dimethylaminopropyl 2,6-dimethyl-4-aminobenzoate with a suitable acid such as hydrochloric

acid, acetic acid, benzoic acid, and the like, and using the procedure set forth above for the preparation of acid addition salts, the corresponding γ-dimethylaminopropyl 2,6-dimethyl-4-aminobenzoate mono-hydrochloride, γ-dimethylaminopropyl 2,6 - dimethyl - 4 - aminobenzoate mono-acetate, γ-dimethylaminopropyl 2,6-dimethyl-4-aminobenzoate benzoate, and the like, are obtained.

Likewise, by reacting γ-dimethylaminopropyl 2,6-dimethyl-4-aminobenzoate with selected esters such as, for example, methyl bromide, ethyl chloride, or the like, the corresponding quaternary ammonium salts of γ-dimethylaminopropyl 2,6-dimethyl-4-aminobenzoate are obtained such as, for example, γ-dimethylaminopropyl 2,6-dimethyl-4-aminobenzoate methobromide, γ-dimethylaminopropyl 2,6-dimethyl-4-aminobenzoate ethochloride, or the like.

EXAMPLE 13

β-Diamylaminoethyl 2,6-dimethyl-4-aminobenzoate

Following the procedure set forth in Example 4 except for the substitution of β-diethylaminoethyl 2,6-dimethyl-4-carbomethoxyaminobenzoate by β-diamylaminoethyl 2,6-dimethyl-4-carbomethoxyaminobenzoate, β-diamylaminoethyl 2,6-dimethyl-4-aminobenzoate is obtained.

On reacting β-diamylaminoethyl 2,6-dimethyl-4-aminobenzoate with a suitable acid such as hydrochloric acid, acetic acid, benzoic acid, and the like, and using the procedure set forth supra for the preparation of acid addition salts, the corresponding β-diamylaminoethyl 2,6-dimethyl-4-aminobenzoate mono-hydrochloride, β-diamylaminoethyl 2,6-dimethyl-4-aminobenzoate mono-acetate, β-diamylaminoethyl 2,6-dimethyl-4-aminobenzoate benzoate, and the like are obtained.

Likewise, on reacting β-diamylaminoethyl 2,6-dimethyl-4-aminobenzoate with selected esters such as, for example, ethyl chloride, benzyl chloride, or the like, the corresponding quaternary ammonium salts of β-diamylaminoethyl 2,6-dimethyl-4-aminobenzoate are obtained such, as for example, β-diamylaminoethyl 2,6-dimethyl-4-aminobenzoate ethochloride, β-diamylaminoethyl 2,6-dimethyl-4-aminobenzoate benzyl chloride, or the like.

EXAMPLE 14

β-Dipropylaminoethyl 2,6-dimethyl-4-aminobenzoate

Following the procedure set forth in Example 4 except for the substitution of β-diethylaminoethyl 2,6-dimethyl-4-carbomethoxyaminobenzoate by β-dipropylaminoethyl 2,6-dimethyl-4-carbomethoxyaminobenzoate, β-dipropylaminoethyl 2,6-dimethyl-4-aminobenzoate is obtained.

On reacting β-dipropylaminoethyl 2,6-dimethyl-4-aminobenzoate with a suitable acid such as hydrochloric acid, acetic acid, benzoic acid, and the like, and using the procedure set forth supra for the preparation of acid addition salts, the corresponding β-dipropylaminoethyl 2,6-dimethyl-4-aminobenzoate mono-hydrochloride, β-dipropylaminoethyl 2,6-dimethyl-4-aminobenzoate mono-acetate, β-dipropylaminoethyl 2,6-dimethyl-4-aminobenzoate benzoate, and the like, are obtained.

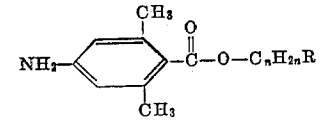
Likewise, on reacting β-dipropylaminoethyl 2,6-dimethyl-4-aminobenzoate with selected esters such as, for example, methyl bromide, ethyl chloride, or the like, the corresponding quaternary ammonium salts of β-dipropylaminoethyl 2,6-dimethyl-4-aminobenzoate are obtained such as, for example, β-dipropylaminoethyl 2,6-dimethyl-4-aminobenzoate methobromide, β-dipropylaminoethyl 2,6-dimethyl-4-aminobenzoate ethochloride, or the like.

Similarly, by following the procedure set forth supra except for the substitution of β-diethylaminoethyl 2,6-dimethyl-4-carbomethoxyaminobenzoate by other aminoalkyl 2,6-dimethyl-4-carbomethoxyaminobenzoates, aminoalkyl esters of 2,6-dimethyl-4-aminobenzoic acid are prepared analogous to those obtained by the procedures of Examples 4 and 11 to 14 inclusive. Such aminoalkyl esters of 2,6-dimethyl-4-aminobenzoic acid include β-diisopropylaminoethyl 2,6-dimethyl-4-aminobenzoate, β-di-n-butylaminoethyl 2,6 - dimethyl - 4 - aminobenzoate, β-methylhexylaminoethyl 2,6 - dimethyl-4-aminobenzoate, β-1-pyrrolidylethyl 2,6-dimethyl-4-aminobenzoate, β-1-(2,2-dimethylpiperidyl)ethyl 2,6-dimethyl-4-aminobenzoate, β-4-morpholinylethyl 2,6-dimethyl-4-aminobenzoate, β-methylethylaminoethyl 2,6-dimethyl-4-aminobenzoate, β-methylcyclohexylaminoethyl 2,6-dimethyl-4-aminobenzoate, β-methylbenzylaminoethyl 2,6-dimethyl-4-aminobenzoate, β-diethylaminopropyl 2,6-dimethyl-4-aminobenzoate, γ-diethylaminopropyl 2,6-dimethyl-4-aminobenzoate, δ-diethylaminobutyl 2,6-dimethyl-4-aminobenzoate, γ-dimethylaminopropyl 2,6-dimethyl-4-aminobenzoate, δ-dimethylaminobutyl 2,6-dimethyl-4-aminobenzoate, β-diisopropylaminopropyl 2,6-dimethyl-4-aminobenzoate, γ-diisopropylaminopropyl 2,6-dimethyl-4-aminobenzoate, δ-diisopropylaminobutyl 2,6-dimethyl-4-aminobenzoate, γ-di-n-butylaminopropyl 2,6 - dimethyl-4-aminobenzoate, δ-di-n-butylaminobutyl 2,6-dimethyl-4-aminobenzoate, γ-methylhexylaminopropyl 2,6-dimethyl-4-aminobenzoate, δ-pyrrolidylbutyl 2,6-dimethyl-4-aminobenzoate, β-1-(2,2-dimethylpiperidyl)propyl 2,6-dimethyl-4-aminobenzoate, γ - 1 - (2,2-dimethylpiperidyl) propyl 2,6-dimethyl-4-aminobenzoate, γ-morpholinylpropyl 2,6-dimethyl-4-aminobenzoate, δ-methylethylaminobutyl 2,6-dimethyl-4-aminobenzoate, γ-dicyclohexylaminopropyl 2,6-dimethyl-4-aminobenzoate, δ-methylbenzylaminobutyl 2,6-dimethyl-4-aminobenzoate, and the like, and acid addition and quaternary ammonium salts thereof.

It is to be understood that the invention is not to be limited to the exact details of operation or exact compounds shown and described as obvious modifications and equivalents will be apparent to one skilled in the art. The invention is therefore to be limited only by the scope of the appended claims.

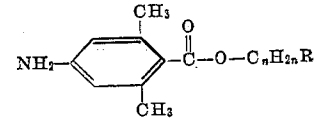
We claim:

1. Amines represented by the following formula:



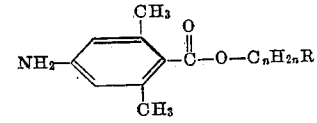
wherein *n* is an integer from one to six inclusive, R is a secondary amino radical and acid addition salts thereof.

2. Amines represented by the following formula:



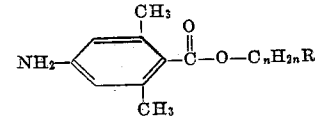
wherein *n* is an integer from one to six inclusive and R is a secondary amino radical.

3. Acid addition salts of amines represented by the formula:



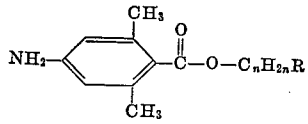
wherein *n* is an integer from one to six inclusive and R is a secondary amino radical.

4. Amines represented by the formula:



wherein R is a secondary amino radical and acid addition salts thereof.

5. Amines represented by the formula:



wherein n is an integer from one to six inclusive, R is a di-lower-alkylamino radical and acid addition salts thereof.

6. A compound selected from the group consisting of β-diethylaminoethyl 2,6-dimethyl-4-aminobenzoate and acid addition salts thereof.

7. β-Diethylaminoethyl 2,6-dimethyl-4-aminobenzoate.

8. Acid addition salts of β-diethylaminoethyl 2,6-dimethyl-4-aminobenzoate.

9. A β-diethylaminoethyl 2,6-dimethyl-4-aminobenzoate hydrochloride.

10. β-Diethylaminoethyl 2,6-dimethyl-4-aminobenzoate monohydrochloride.

11. β-Diethylaminoethyl 2,6-dimethyl-4-aminobenzoate di-hydrochloride.

12. β-Diethylaminoethyl 2,6-dimethyl-4-aminobenzoate monoacetate.

13. β-Dimethylaminoethyl 2,6-dimethyl-4-aminobenzoate.

References Cited in the file of this patent

UNITED STATES PATENTS

1,765,621 Schoeller ---------- June 24, 1930

FOREIGN PATENTS

349,640 Great Britain ---------- June 4, 1931

OTHER REFERENCES

Hickinbottom: "Reactions of Organic Compounds," 1948, page 254.

Dovoretzky et al.: J. Org. Chem., 615 to 619 (1953), vol. 18.

UNITED STATES PATENT OFFICE

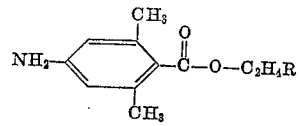
Certificate of Correction

Patent No. 2,865,951 December 23, 1958

Robert D. Birkenmeyer et al.

It is hereby certified that error appears in the printed specification of the above numbered patent requiring correction and that the said Letters Patent should read as corrected below.

Column 8, lines 68 to 73, claim 4, the structural formula should appear as shown below instead of as in the patent—



Signed and sealed this 30th day of June 1959.

[SEAL]

Attest:
KARL H. AXLINE,
Attesting Officer.

ROBERT C. WATSON,
Commissioner of Patents.