HYPOLIPIDEMIC 4-(MONOALKYLAMINO)BENZOIC ACID DERIVATIVES

Inventors: Jay Donald Albright, Nanuet; Stephen Joseph Riggi, Suffern; Robert Gordon Shepherd, South Nyack, all of N.Y.

Assignee: American Cyanamid Company, Stamford, Conn.

Filed: Oct. 1, 1973

Appl. No.: 402,212


Int. Cl............................................ C07C 101/60


References Cited
UNITED STATES PATENTS

Primary Examiner—Lorraine A. Weinberger
Assistant Examiner—L. A. Thaxton
Attorney, Agent, or Firm—Jack W. Richards

ABSTRACT
4-(Monoalkylamino)benzoic acids and esters, pharmaceutically acceptable salts thereof, and a method for lowering serum lipids in mammals by administration of said acids, esters and salts; and pharmaceutical compositions thereof.

7 Claims, No Drawings
This invention relates to organic compounds and more particularly it is concerned with 4-(monoalkylamino)benzoic acids and 4-(monoalkylamino)benzoic acid esters which may be represented by the following structural formula:

\[
\text{R}^1\text{-N-H-CO}_{2}\text{R}^2
\]

wherein \(\text{R}^1\) is an unbranched or branched alkyl group, \(\text{C}_n\text{H}_{2n+1}\), wherein \(n\) is 4 to 19; and \(\text{R}^2\) is hydrogen, lower alkyl, benzyl, dialkyl alkylaminoetyl, lower alkoxyethyl, 1-methyl-4-piperidyl, 2-pyrlydylmethyl, 4-pyridylmethyl, and the pharmaceutically acceptable salts thereof. Suitable lower alkyl groups contemplated by the present invention are those having up to six carbon atoms such as, for example, methyl, isopropyl, n-propyl, ethyl, sec-butyl, tert-amyl and n-hexyl.

With reference to the above formula, the invention contemplates as novel compounds per se only those acids, esters and pharmaceutically acceptable salts thereof wherein \(n\) is 8 to 19. Compounds wherein \(n\) is 4 to 7 are known in the art. However, the invention contemplates a method for lowering serum lipids in mammals by administration of said acids and esters wherein \(n\) is 4 to 19, and the use of pharmaceutically acceptable salts and pharmaceutical compositions employing said acids, esters and salts to lower serum lipids.

Compounds of the present invention were shown to possess hypolipidemic activity as determined by animal experiments. Compounds represented by the above formula wherein \(n\) is 4 to 19 have been found to possess hypolipidemic activity in animals, namely, serum triglyceride lowering, with cholesterol lowering when \(n\) is 14 to 17. Of the active compounds, the preferred compound comprises those compounds wherein \(n\) is 14 to 17, i.e., wherein the straight-chain alkyl group contains 14 to 17 carbon atoms and \(\text{R}^2\) in the above formula is hydrogen. The compounds of the present invention may be utilized either as the free acids or in the form of a pharmaceutically acceptable salt. Since the compounds are amphoteric, the salts can involve either the acidic or the basic moiety. The salts may be either of an inorganic nature, such as the ammonium salt, sodium salt, potassium salt, etc., of the carboxyl group or the hydrochloric or sulfuric acid salts of the amino group, or of an organic type, such as an organic amine salt of the carboxyl group or a trifluoroacetic or citric acid salt of the amino group.

BACKGROUND OF THE INVENTION

Considerable effort has been directed in recent years to obtain substances which are useful in the treatment of hyperlipidemia, a condition associated with elevated cholesterol, phospholipid and/or triglyceride blood levels. This condition is associated with a number of diseases, one of the most serious being atherosclerosis. Medicaments used to lower cholesterol, phospholipid and triglyceride blood levels are termed hypolipidemic drugs. Presently three major lipid-lowering agents are available; clofibrate, D-thyroxine, and nicotinic acid. [R.I. Levy and D.S. Fredrickson, Postgraduate Medicine, Vol. 47, pgs. 130-136 (1970).] These compounds encompassed by the present invention may be termed 4-(monoalkylamino)benzoic acids, esters and salts thereof.

As pointed out heretofore, 4-(monoalkyl)benzoic acids and/or esters wherein \(n\) in the above formula is 4 to 7 are known. Also known are such acids and/or esters wherein \(n\) in the above formula is 1 to 3. Moreover, certain 4-(monoalkylamino)benzoic acid esters, i.e., those wherein \(n\) in the above formula is 3 to 7, have been disclosed as having local anesthetic activity. However, there is no known disclosure of even local anesthetic activity for the acids or esters of this invention.


No disclosure is known reporting on, or concerned with, hypolipidemic activity for any of the known \(n = 1-7\) compounds. It has now, unexpectedly, been found that both the known \(n = 4-7\) and the heretofore unknown \(n = 8-19\) compounds all possess hypolipidemic activity. No pharmaceutical activity has been reported for any of the \(n = 8-19\) compounds herein.

DETAILED DESCRIPTION OF THE INVENTION

The 4-(monoalkylamino)benzoic acids and esters of the present invention are, in general, colorless or tan crystalline solids (some being colorless or tan oils) having characteristic melting points and spectral properties. They are soluble in organic solvents such as chloroform, benzene, dichloromethane, N,N-dimethylformamide, dimethylsulfoxide and lower alkanols. They are, however, generally insoluble in water.

The 4-(monoalkylamino)benzoic acids and esters of the present invention are bases and may be converted to their non-toxic acid-addition salts by treatment with acids such as sulfuric, hydrochloric, phosphoric, sulfuric, citric, and the like. The latter compounds wherein \(\text{R}^2\) is hydrogen may be reacted with alkali bases such as sodium hydroxide, potassium hydroxide and calcium hydroxide.
droxide or with organic bases such as ammonium hydroxide or lower mono-, di- or tri(lower alkyl)amines such as methylamine, diethylamine, trimethylamine, dibutylamine, N,N′-dimethylethylendiamine, and the like to obtain the corresponding carboxylic acid salts.

The lower alkyl 4-(monoalkylamino)benzoates of this invention are prepared by reaction of lower alkyl p-aminobenzoates with suitable alkylating agents such as alkyl halides, sulfates, tosylates or trifluoromethylsulfonates with or without solvent at 50°C to 150°C. Suitable solvents are lower alkanols, chloroform, N,N-dimethylformamide, N,N-dimethylacetamid, diglyme, dimethylsulfoxide, acetonitrile, toluene, benzene, hexamethylphosphoramide and the like. The reaction may be carried out with or without a catalytic amount of copper powder when alkyl halides are used as the alkylating agent. Alternatively, the lower alkyl 4-(monoalkylamino)benzoates are prepared by reaction of a lower alkyl aminobenzoate with an alkyl halide of 4 to 19 carbon atoms in the presence of an equivalent of sodium hydride in an inert solvent such as N,N-dimethylformamide, N,N-dimethylacetamide, and diglyme at 50°C to 150°C.

Alternative methods of preparation are by reductive alkylation of a 4-aminoanabzoate ester or by a metal hydride reduction of a 4-(acylamino)benzoate ester or acid. For example, n-hexadeccanol and methyl 4-aminoanbzoate are reduced under 1-10 atmospheres of hydrogen using an activated metal catalyst, forming 4-(n-hexadecylamino)benzoic acid methyl ester. The aldehyde appears to be formed in small amounts in situ in the synthetic procedure comprising heating at an elevated temperature and pressure n-hexadeccanol and methyl 4-aminoanbzoate in the presence of an activated Raney nickel catalyst to give methyl 4-(n-hexadecylamino)benzoate. Diborane reduction of ethyl 4-(n-hexadecanoylamino)benzoate at room temperature or above for 1-6 hours yields the ethyl analog of the above ester.

Two types of substitution reactions also yield the desired 4-(alkylamino)benzoic acids or esters, namely, reaction of ethyl 3,4-didehydrobenzoate with an alkyamine (or its alkali metal salt) and Friedel-Crafts acylation of an N-alkylamine or N-acyl-N-alkylaniline. The former type of reaction is carried out by treating a 4-haloanbzoate ester such as ethyl 4-bromobenzoate with the lithium, potassium, or sodium salt of an alkyamine (in excess) such as n-hexadecylamine in ether or other apotropic solvent. The latter type comprises reacting N-n-hexadecylamine and the like or its N-acytethyl derivative with oxalyl chloride and anhydrous aluminum chloride in dry ether, halocarbon or hydrocarbon medium.

The 4-(alkylamino)benzoic acids of this invention are prepared by hydrolysis of the corresponding benzoate esters by reacting with an alkali hydroxide such as sodium or potassium hydroxide in a lower alkanol, water or an aqueous lower alkanol at 25°C to 150°C. Alternatively, the 4-(alkylamino)benzoic acids may be prepared by hydrolysis of the lower alkyl 4-(monoalkylamino)benzoates with mineral acids such as hydrochloric, hydrobromic and sulfuric acid in water or aqueous lower alkanoils.

Of lower activity than the compounds of the present invention are the lower alkyl 4-(dialkylamino)benzoates or the 4-(dialkylamino)benzoic acids, which can be prepared by reaction of a lower alkyl 4-(monoalkylamino)benzoate with an appropriate alkylating agent to give the lower alkyl esters with subsequent hydrolysis to give the acids. Suitable alkylating agents are lower alkylsubstituted, lower dialkylsulfates (such as dimethyl sulfate, diethyl sulfate and dipropyl sulfate), tri-(lower alkyl)oxonium trifluoroborates (such as trimethylxonium and triethylxonium tetrafluoroborates), lower alkyl halides, methyl fluorosulfonate and ethyl fluorosulfonate. The alkylation reactions may be carried out with or without a solvent at 20°C to 150°C. Suitable solvents are chloroform, dichloromethane, carbon tetracloride, benzene, xylene and the like. For example, methylations are conveniently carried out with methyl fluorosulfonate in dichloromethane at 25°C. For 2-20 hours while ethylations are conveniently carried out with excess diethyl sulfate at 100°C to 150°C without solvent. Alkyulations with alkyl halides may be carried out by first reacting the lower alkyl monoalkylaminoanbzoate in a suitable solvent with sodium hydride or butyl lithium to give the amine anion and then reacting with the alkyl halide. The lower alkylamino benzoic acid derivatives may be converted to their potassium, sodium or lithium salts and alkylated to give dialkylaminoanbzoate esters —alkylation occurring on both the amino group and on the oxygen of the acid salt. Representative dialkylaminoanbzoic acids and esters which have been prepared are ethyl 4-(dodecylamino)benzoate, 4-(dodecylamino)benzoic acid, 4-(dodecylamino)benzoic acid, 4-(methyltetradecylamino)benzoic acid, 4-(ethyloctadecylamino)benzoic acid, 4-(ethylpentadecylamino)benzoate, 4-(ethylpentadecylamino)benzoi acid, 4-(ethylhexadecylamino)benzoate, 4-(ethylhexadecylamino)benzoic acid, 4-(methylheptadecylamino)benzoic acid, 4-(ethylheptadecylamino)benzoic acid, 4-(methylheptadecylamino)benzoic acid, and 4-(methyloc-tadecylamino)benzoic acid. In animal tests these compounds have shown inferior hypolipidemic activity.

Lower alkyl acylmonoalkylaminoanbzoates can be prepared by acylation of the lower alkyl monoalkylaminoanbzoates with acyl halides or anhydrides such as acetyl chloride, acetic anhydride, benzoyl chloride, benzoic anhydride, succinic anhydride, etc. in the presence of a suitable base as pyridine, triethylamine and the like with or without an organic solvent. Acylation of monoalkylaminoanbzoic acids under similar conditions gives the acylmonoalkylaminoanbzoic acid derivatives. The N-acyl derivatives were prepared for testing for their activity per se and for the activity generated by their de-acylation. The compounds studied were N-benzoyl, N-acetyl, and N-succinyl derivatives, for example, ethyl 4-(N-acetyl-3-n-tetradecylamino)benzoate, 4-(N-acetyl-3-n-tetradecylamino)benzoic acid, 4-(N-benzoyl-3-n-hexadecylamino)benzoic acid, 4-(N-acetyl-3-n-hexadecylamino)benzoic acid. Such compounds have been prepared by acylation of ethyl 4-(tetradecylamino)benzoate with acetyl chloride or acetic anhydride in presence of a suitable base such as pyridine or 4-dimethylaminopyridine or by the acylation of 4-(tetradecylamino)benzoic acid and 4-(hexadecylamino)benzoic acid with acetyl chloride, benzoyl chloride, acetic anhydride or succinic anhydride in the presence of a suitable base such as pyri-
In animal tests these compounds showed hypolipidemic activity inferior to the compounds of the present invention. The mechanism of action of the 4-(monoalkylamino)-benzoic acid compounds of this invention is not known and the inventors do not wish to be limited to any particular mechanism. However, the compounds of the present invention were shown to possess hypolipidemic activity as determined by animal experiments as follows: the compounds studied were administered orally admixed with the diet to groups of 4–6 male rats, CFE strain from Carworth Farms, New City, N.Y. A control group of 6–8 rats was maintained on the diet alone; test groups were maintained on the diet plus the indicated percentage of compound by weight. After 6 days or 2–4 weeks treatment, serum sterol concentrations were determined either (1) according to the saponification and extraction method of P. Trinder, Analyst 77, 321 (1952) and the colorimetric determination of Zlatkis, et al., J. Lab. Clin. Med. 44, 486 (1953) or (2) by the extraction method of H. H. Leffler, Amer. J. Clin. Path. 31, 310 (1959), and the colorimetric determination of Zlatkis (vide supra), the overall method appropriately modified for use with an automatic mechanical analyzer. Serum triglycerides were estimated by the automated procedure of Kessler and Lederer (“Automation in Analytical Chemistry” Skeggs, L. T. (Ed.), Mediad Inc. New York, 1965, p. 341). The phospholipids were determined by standard methods [G. R. Bartlett, J. Biol. Chem. 234, 466 (1959)]. Changes in serum lipids are expressed as percent lowering from control. In these tests, a compound is considered to have hypolipidemic activity if it depresses serum sterol levels 15% or more below that of the controls, and/or depresses triglyceride levels by 25% or more below controls. Table I shows several of the compounds of the present invention and the degree to which they depress serum sterols and triglyceride levels after a 1-week and 4-week dosing period and phospholipids after a 4-week dosing period.

### TABLE I

<table>
<thead>
<tr>
<th>Compound</th>
<th>1-Week % Lowering of Serum</th>
<th>4-Week % Lowering of Serum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sterol</td>
<td>Triglyceride</td>
<td>Sterol</td>
</tr>
<tr>
<td>4-(Butylamino-benzoic Acid)</td>
<td>0.1</td>
<td>16</td>
</tr>
<tr>
<td>4-(n-Hexylamino)benzoic Acid</td>
<td>0.1</td>
<td>16</td>
</tr>
<tr>
<td>4-(n-Octylamino)benzoic Acid</td>
<td>0.1</td>
<td>11</td>
</tr>
<tr>
<td>4-(n-Dodecylamino)benzoic Acid</td>
<td>0.1</td>
<td>10</td>
</tr>
<tr>
<td>4-(n-Undecylamino)benzoic Acid</td>
<td>0.1</td>
<td>16</td>
</tr>
<tr>
<td>4-(n-Undecylamino)benzoic Acid</td>
<td>0.1</td>
<td>10</td>
</tr>
<tr>
<td>Dimethylaminoethyl 4-(n-hexadecylamino)benzoate</td>
<td>0.1</td>
<td>19</td>
</tr>
<tr>
<td>4-(n-Hexadecylamino)benzoic Acid</td>
<td>0.1</td>
<td>1</td>
</tr>
<tr>
<td>4-(n-Heptadecylamino)benzoic Acid</td>
<td>0.1</td>
<td>30</td>
</tr>
<tr>
<td>4-(n-Octadecylamino)benzoic Acid</td>
<td>0.1</td>
<td>12</td>
</tr>
<tr>
<td>4-(n-Nonadecylamino)benzoic Acid</td>
<td>0.1</td>
<td>18</td>
</tr>
<tr>
<td>4-(n-Hexadecylamino)benzoate hydrochloride</td>
<td>0.1</td>
<td>0</td>
</tr>
</tbody>
</table>

The data in Table I indicate that the 4-(monoalkylamino)benzoic acids and derivatives tested are all effective hypolipidemic agents, i.e., they reduce serum triglyceride and/or sterol levels. Reduction of serum sterol is highly desirable clinically since essentially all major studies reported in the literature indicate that elevated serum sterol concentration is directly related to the development of other atherosclerosis. Of the clinical types of hyperlipoproteinemias described to date, the major lipids found in abnormal levels are sterol and triglycerides. The preferred compounds of this invention are capable of decreasing both of these blood lipid fractions as well as phospholipids, the third major lipid moiety in blood.

The effects of one of the compounds [4-(n-hexadecylamino)benzoic acid] of this invention on serum lipid levels were determined in mice and gerbils (Table II) after 1 week of treatment. Mice (CF-1 strain) were obtained from Carworth Farms, New City, N.Y. and gerbils were purchased from Chick Line Co., Vineland, N.J. The methods used for lipid analysis were the same as those indicated above for Table I.

### TABLE II

<table>
<thead>
<tr>
<th>Compound</th>
<th>Gerbils</th>
<th>Mice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose, percent of diet</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Serum Sterol, % Lowering</td>
<td>20</td>
<td>22</td>
</tr>
</tbody>
</table>
The 4-(monoalkylamino)benzoic acids and derivatives of this invention have potencies similar to or greater than 1-methyl-4-piperidyl bis(p-chlorophenoxy)acetate and clofibrate, and thus are useful as hypolipidemic compounds in mammals when administered in amounts ranging from about 0.5 mg. per kg. to about 40 mg. per kg. of body weight per day. A preferred dosage regimen for optimum results would be from about 2 mg. per kg. to about 29 mg. per kg. Thus the daily dosage employed for a subject of about 70 kg. of body weight is about 35 mg. to about 2.8 g., and preferably about 140 mg. to about 2.0 g.

The active compounds of the present invention may be orally administered, for example, with an inert diluent or with an assimilable edible carrier, or they may be enclosed in hard or soft gelatin capsules, or they may be compressed into tablets, or they may be incorporated directly with the food of the diet. For oral therapeutic administration, the active compounds of this invention may be incorporated with excipients and used in the form of tablets, troches, capsules, elixirs, suspensions, syrups, wafers, chewing gum, and the like. Such compositions and preparations should contain at least 0.1% of active compound. The percentage in the compositions and preparations may, of course, be varied and may conveniently be between about 5% to about 75% or more of the weight of the unit. The amount of active compound in such therapeutically useful compositions or preparations is such that a suitable dosage will be obtained. Preferred compositions or preparations according to the present invention are prepared so that an oral dosage unit form contains between about 10 and 500 milligrams of active compound.

The tablets, troches, pills, capsules and the like may also contain the following: a binder such as gum tragacanth, acacia, corn starch or gelatin; an excipient such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose or saccharin may be added or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring. When the dosage unit form is a capsule, it may contain in addition to materials of the above type a liquid carrier such as a fatty oil. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit, for instance, tablets, pills or capsules may be coated with shellac, sugar, or both. A syrup or elixir may contain the active compounds, sucrose as a sweetening agent, methyl and propyl parabens as preservatives, a dye and a flavoring such as cherry or orange flavor. Of course, any material used in preparing any dosage unit form should be pharmaceutically pure and substantially nontoxic in the amounts employed.

In addition, the active ingredients may be incorporated into sustained release preparations. Preparations of this type would contain greater quantities of the active ingredients.

**TABLE II-Continued**

<table>
<thead>
<tr>
<th>HYPOLIPIDEMIC ACTIVITY OF 4-(n-Hexadecylamino)-benzoic Acid in Mice and Gerbils</th>
<th>Gerbils</th>
<th>Mice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Phospholipid, % Lowering</td>
<td>10</td>
<td>15</td>
</tr>
</tbody>
</table>

EXAMPLE 1

4-(n-Dodecylamino)benzoic Acid

A solution of 10.4 g. of potassium hydroxide in 200 ml. of 90% aqueous ethanol was added to a solution of 25.4 g. of 4-amino benzoic acid in 200 ml. of 90% ethanol. After all the solid material had dissolved, 44.3 ml. of 1-bromododecane and 25.5 g. of potassium carbonate were added and the mixture refluxed for 24 hrs. An additional 44 ml. of 1-bromododecane was then added and heating was continued for 30 hrs. The crude product was freed of ester by adding 31.2 g. of potassium hydroxide in 100 ml. of water and refluxing for 24 hrs. The acid was precipitated by adding 160 ml. of concentrated hydrochloric acid followed by 200 ml. of water and chilling. The filtered material was slurried in chloroform to give a white solid which was recrystallized from 95% aqueous ethanol to give the 2.95 g. of 4-(n-dodecylamino)benzoic acid as white crystals, m.p. 111.5°-113°C, 125°-125.5°C.

The chloroform filtrate was taken to dryness and the resulting solid washed with pentane. The insoluble material was recrystallized from 95% aqueous ethanol to give 3.10 g. of 4-(n-dodecylamino)benzoic acid as off-white flakes, m.p. same as above. The pentane filtrate was taken to dryness and the resulting solid recrystallized from benzene to give the 4.90 g. of 4-(n-dodecylamino)benzoic acid, m.p. same as above.

EXAMPLE 2

Ethyl 4-(n-Tridecylamino)benzoate

A mixture of 47.0 g. of ethyl 4-amino benzoate, 72.8 ml. of 1-bromotridecane, and 39.3 g. of potassium carbonate in 500 ml. of dry N,N-dimethylacetamide was heated (110°C.) under nitrogen for 24 hours. The reaction mixture was then chilled, filtered, and the solid product washed once with cold absolute ethanol and water. Additional product was obtained by adding water to the filtrate and washing it twice with absolute ethanol. The total yield of ethyl 4-(n-tridecylamino)benzoate was 66.5 g. of white crystals.

EXAMPLE 3

4-(n-Tridecylylamino)benzoic acid

A mixture of 27.7 g. of ethyl 4-(n-tridecylamino)benzoate, and 44.7 g. of potassium hydroxide in 450 ml. of water-ethanol (1:1) was refluxed for 6 hours. Concentrated hydrochloric acid (80 ml.) was added to the hot mixture, which was then cooled, diluted with water and filtered. Recrystallization from absolute ethanol and from ethanol-benzene (1:1) gave 16.5 g. of 4-(n-tridecylamino)benzoic acid as white crystals, m.p. 106°-109°C: 112°-113°C.

EXAMPLE 4

Ethyl 4-(n-Tetradecylamino)benzoate

A mixture of 16.5 g. of ethyl 4-amino benzoate and 30 g. of 1-bromotetradecane was heated on a steam bath for 19 hours. Ethanol was added and the mixture filtered. The solid was washed with ethanol, water, 0.1 N sodium hydroxide and with water to give 9.0 g. of white crystals. The filtrate was basified, filtered and the solid was washed with ethanol to give 1.7 g. of crystals. The two crops were recrystallized from ethanol to give 8.75 g. of white ethyl 4-(n-tetradecylamino)benzoate, m.p. 81°-82°C.
EXAMPLE 5

4-(n-Tetradecylamino)benzoic acid

To a solution of 16.5 g. of ethyl 4-aminobenzoate in 150 ml. of dry N,N-dimethylformamide was added 4.12 g. of sodium hydride (56% in oil) and 27.7 g. of 1-bromotetradecane. The mixture was heated on a steam bath until hydrogen evolution began and then chilled briefly to control the reaction. After the sodium hydride had reacted, the mixture was heated on a steam bath under nitrogen for 6 hours. The mixture was chilled, filtered and the solid washed with ethanol and with water to give 21.75 g. (59%) of ethyl 4-(n-tetradecylamino)benzoate, m.p. 81°-82°C.

A mixture of 29 g. of ethyl 4-(n-tetradecylamino)benzoate, 28 g. of potassium hydroxide and 500 ml. of 50% ethanol was refluxed for 6 hours. The mixture was acidified with concentrated hydrochloric acid, chilled and filtered to give tan crystals. Recrystallization from ethanol gave 15.1 g. of white 4-(n-tetradecylamino)benzoic acid, m.p. 108°-111°C.

EXAMPLE 6

Ethyl 4-(n-pentadecylamino)benzoate

A mixture of 49.5 g. of ethyl 4-aminobenzoate, 87.3 g. of 1-bromopentadecane and 41.4 g. of potassium carbonate in 550 ml. of N,N-dimethylacetamide was heated (135°C.) under nitrogen for 24 hours. The reaction mixture was chilled, filtered and the solid washed with cold absolute ethanol, with water and dried in air. Recrystallization from absolute ethanol gave 58.8 g. of white ethyl 4-(n-pentadecylamino)benzoate, m.p. 73°-74.5°C.

EXAMPLE 7

4-(n-Pentadecylamino)benzoic acid

A mixture of 58.8 g. of ethyl 4-(n-pentadecylamino)benzoate and 87.5 g. of potassium hydroxide in 900 ml. of water-ethanol (1:1) was refluxed for 6 hours. Concentrated hydrochloric acid (140 ml.) was added to the hot solution followed by 600 ml. of water and the mixture was chilled. The product was collected, washed well with water, and recrystallized from benzene-ethanol (1:1) to give 42.5 g. of white 4-(n-pentadecylamino)benzoic acid, m.p. 107°-108°C., 126°-126.5°C.

EXAMPLE 8

Ethyl 4-(n-hexadecylamino)benzoate

A solution of 49.5 g. of ethyl 4-aminobenzoate and 45.8 ml. of 1-bromohexadecane in 525 ml. of absolute ethanol was refluxed overnight. The reaction mixture was chilled and the filtered product recrystallized from 750 ml. of absolute ethanol to give 16.5 g. of ethyl 4-(n-hexadecylamino)benzoate as white crystals, m.p. 84°-86.5°C.

EXAMPLE 9

Ethyl 4-(n-hexadecylamino)benzoate

A mixture of 33.0 g. of ethyl 4-aminobenzoate, 61.0 g. of 1-bromohexadecane, 21.2 g. of sodium carbonate and 300 ml. of ethanol was refluxed for 24 hours. The mixture was chilled and filtered. The solid was washed with 250 ml. of cold ethanol and with one liter of water to give 20 g. of white ethyl 4-(n-hexadecylamino)benzoate, m.p. 81°-84°C.

EXAMPLE 10

Ethyl 4-(n-hexadecylamino)benzoate

A mixture of 33.0 g. of ethyl 4-aminobenzoate, 61.0 g. of 1-bromohexadecane, 27.6 g. of potassium carbonate and 400 ml. of dry ethanol was refluxed for 24 hours. An additional 61 g. of 1-bromohexadecane was added and the mixture refluxed for an additional 32 hours. The mixture was chilled, filtered and the solid washed with 250 ml. of cold ethanol and with 1 liter of water to give 30.6 g. of white ethyl 4-(n-hexadecylamino)benzoate, m.p. 80°-83°C.

EXAMPLE 11

4-(n-Hexadecylamino)benzoic acid

A mixture of 5.85 g. of ethyl 4-(n-hexadecylamino)benzoate and 4.21 g. of potassium hydroxide in 150 ml. of water-ethanol (1:1) was refluxed for 6.5 hours. Concentrated hydrochloric acid (40 ml.) was added to the hot solution followed by cooling, adding 100 ml. of water and chilling gave the hydrochloride salt of the product. It was recrystallized from ethanol-water (9:1) to yield 5.0 g. (m.p. 107°-110°C., 124°-127.5°C.) of white 4-(n-hexadecylamino)benzoic acid.

EXAMPLE 12

4-(n-Hexadecylamino)benzoic acid

A mixture of 13.7 g. of 4-aminobenzoic acid and 5.61 g. of potassium hydroxide in 150 ml. of 90% aqueous ethanol was added 33.6 ml. of 1-bromohexadecane and the mixture was refluxed for 25 hours. A solution of 28 g. of potassium hydroxide in 150 ml. of 90% aqueous ethanol and 100 ml. of water was added. The mixture was refluxed for 24 hours and 35 ml of concentrated hydrochloric acid was added to the hot solution. Chilling and filtering gave product which was washed with water and dried. Recrystallization from benzene yielded 10.7 g. of 4-(n-hexadecylamino)benzoic acid, m.p. 106°-108°C., complete melt 125°-127°C.

EXAMPLE 13

Ethyl 4-(n-heptadecylamino)benzoate

A mixture of 48.3 g. of ethyl 4-aminobenzoate, 93.4 g. of 1-bromohexadecane and 40.4 g. of potassium carbonate in 700 ml. of absolute ethanol was refluxed for 24 hours. The reaction was then chilled, filtered and the solid washed with cold absolute ethanol, and then with water until it was neutral. The product was pure ethyl 4-(n-heptadecylamino)benzoate.

EXAMPLE 14

4-(n-Heptadecylamino)benzoic acid

A mixture of 48.3 g. of ethyl 4-aminobenzoate, 93.4 g. of 1-bromohexadecane, and 40.4 g. of potassium carbonate in 700 ml. of absolute ethanol was refluxed for 24 hours. The reaction mixture was chilled, filtered and the solid washed with cold absolute ethanol and with water to give 27.9 g. of ethyl 4-(n-heptadecylamino)benzoate as white flakes. A mixture of 27.9 g. of this ester, 38.8 g. of potassium hydroxide and 400 ml. of ethanol-water (1:1) was refluxed for 6.5 hours. To the hot solution was added 65 ml. of concen-
trated hydrochloric acid. The mixture was diluted with 400 ml. of water, chilled and filtered to give 25.2 g. of white crystals. Recrystallization from 300 ml. of benzene-ethanol (1:1) gave 21.7 g. of 4-(n-heptadecylamino)benzoic acid, m.p. 105°-108°C.; 128°-128.5°C.

EXAMPLE 15
Ethyl 4-(n-octadecylamino)benzoate
A mixture of 66 g. of ethyl 4-aminobenzoate, 133.4 g. of 1-bromoacteconade, 55 g. of potassium carbonate and 550 ml. of N,N-dimethylacetamide was heated at 135°C. for 20 hours. The mixture was chilled, filtered and the solid washed with cold ethanol. Recrystallized from ethanol to give 98 g. of product. Recrystallization from benzene-ethanol (1:1) gave 67 g. of ethyl 4-(n-octadecylamino)benzoate as white crystals m.p. 88°-89°C.

EXAMPLE 16
4-(n-Octadecylamino)benzoic acid
A mixture of 33 g. of ethyl 4-aminobenzoate, 67 g. of 1-bromoacteconade, 27.6 g. of potassium carbonate and 400 ml. of N,N-dimethylacetamide was heated at 130°-135°C. for 18 hours. The mixture was chilled, filtered and the solid washed with water and shurred in 100 ml. of ethanol to give 38 g. of white crystals.

The crystals were combined with 56 g. of potassium hydroxide, 1000 ml. of ethanol-water (1:1) and the mixture was refluxed for 7 hours. While hot, 100 ml. of concentrated hydrochloric acid was slowly added to the mixture followed by adding 200 ml. of water, cooling and filtering to give 40 g. of white crystals. Recrystallization from benzene and then from ethanol gave 22.6 g. of 4-(n-octadecylamino)benzoic acid, m.p. 103°-106°C., complete melt 123°-126°C.

EXAMPLE 17
Ethyl 4-(n-nondecyldiamino)benzoate
A mixture of 40.4 g. of ethyl 4-aminobenzoate, 85.2 g. of 1-bromonondecanale, and 33.8 g. of potassium carbonate in 400 ml. of dry N,N-dimethylacetamide was heated under nitrogen at 130°C. for 24 hours. The mixture was chilled, filtered, and the solid washed with cold absolute ethanol and then with water. The product was recrystallized from absolute ethanol to give 791 g. of white ethyl 4-(n-nondecyldiamino)benzoate.

EXAMPLE 18
4-(n-Nonadecylamino)benzoic acid
A mixture of 79.1 g. of ethyl 4-(n-nonadecylamino)benzoate and 103 g. of potassium hydroxide in 1200 ml. of 50% ethanol was refluxed for 6 hours. Hydrochloric acid (170 ml) was then added to the hot solution and the mixture was diluted with 300 ml. of water, chilled and filtered. Recrystallization from benzene-ethanol (1:1) gave 67.4 g. of white 4-(n-nonadecylamino)benzoic acid, m.p. 104°-106°C., 120°-124°C.

EXAMPLE 19
Ethyl 4-[[1-methylundecylamino]benzoate
A mixture of 49.6 g. of ethyl 4-aminobenzoate, 74.9 g. of 2-bromododecane, and 41.5 g. of potassium carbonate in 550 ml. of N,N-dimethylacetamide was heated at 130°C. for 24 hours. The reaction mixture was taken to a small volume by distillation under high vacuum. Water and ethanol were added and the mixture was chilled. The product was collected, washed with water and recrystallized from absolute ethanol followed by chromatography on silica gel in chloroform solution. The fractions containing the product were combined and the solvent was removed under vacuum. The yield was 15.0 g. of ethyl 4-[[1-Methylundecylamino]benzoate.

EXAMPLE 20
4-[[1-methylundecylamino]benzoic acid
A mixture of 15.0 g. of ethyl 4-[[1-methylundecylamino]benzoate and 25.2 g. of potassium hydroxide in 175 ml. of 50% aqueous ethanol was refluxed for 6 hours. Concentrated hydrochloric acid (37 ml.) was added to the hot reaction mixture and the product precipitated upon chilling. The filtered product was recrystallized from absolute ethanol to give 7.70 g. of 4-[[1-methylundecylamino]benzoic acid, m.p. 76.5°-78.5°C.

EXAMPLE 21
Ethyl 3-(n-hexadecylamino)benzoate
A mixture of 24.8 g. of ethyl 3-aminobenzoate, 45.8 ml. of 1-bromohexadecane and 20.7 g. of potassium carbonate in 250 ml. of N,N-dimethylacetamide was heated at 125°-135°C. for 24 hours. The mixture was then chilled, filtered, and the solid washed with water and dried. The yield was 49.7 g. of ethyl 3-(n-hexadecylamino)benzoate.

EXAMPLE 22
3-(n-Hexadecylamino)benzoic acid
A mixture of 49.7 g. of ethyl 3-(n-hexadecylamino)benzoate and 71.3 g. of potassium hydroxide in 700 ml. of water-ethanol (1:1) was refluxed for 6 hours. Concentrated hydrochloric acid was added to the hot solution followed by 500 ml. of water and chilling. The product was recrystallized from ethanol-benzene (3:1) yielding 28.4 g. of white 3-(n-hexadecylamino)benzoic acid, m.p. 107.5°-109.5°C.

EXAMPLE 23
Dimethylaminoethyl 4-[[1-hexadecylamino]benzoate hydrochloride
To 90 ml. of thionyl chloride cooled to 0°C. was added portionwise, 21.7 g. (0.060 mole) of 4-[[1-hexadecylamino]benzoic acid. To the viscous mass was added 100 ml. of toluene. After stirring overnight (16.5 hour), the solvent was removed in vacuo. Toluene (50 ml.) was added the solvent removed in vacuo. Nitrogen was bubbled through the residual oil, 100 ml. of toluene added and the solution cooled. To the mixture was added 6.24 g. (0.070 mole) of 2-dimethylaminoo ethanol. The mixture was stirred at room temperature for 4.5 hours, diluted with ether, stirred 1.0 hour. Chilling and filtering gave solid which was washed with ether and with water to give 7.0 g. of tan crystals. Recrystallization (twice) from ethanol gave 5.2 g. of tan crystals, m.p. 162°-165°C. with previous sintering.
EXAMPLE 24
Ethyl 4-(n-octylamino)benzoate

A mixture of 33 g. (0.20 mole) of ethyl 4-amino- benzoate, 44 ml. of 1-bromooctane and 0.50 g. of cooper powder was heated on a steam bath for 19 hours. The mixture was chilled, diluted with ethanol, filtered and the solid washed with cold ethanol and with water to give tan crystals. The filtrate was neutralized with 10 N potassium hydroxide, chilled and filtered and the solid washed with water and with ethanol to give tan crystals. The two crops of crystals were combined to give 16 g. of product. The mother liquors from the two crops of crystals were combined, diluted with water and extracted with ether. The ether extracts were washed with water, with 1 N hydrochloric acid and with water. The ether extracts were dried over magnesium sulfate and concentrated under reduced pressure. The residue was diluted with ethanol, chilled and filtered to give 3.7 g. of product. The two crops of product (19.7 g.) were combined and recrystallized from ethanol to give 15.1 g. of white crystals, m.p. 79°-80°C.

EXAMPLE 25
4-(n-Octylamino)benzoic acid

A mixture of 3.0 g. of ethyl 4-(n-octylamino)benzoate, 3 g. of potassium hydroxide and 50 ml. of ethanol-water (9:1) was refluxed for 3 hours. The mixture was acidified with concentrated hydrochloric acid, diluted with water and filtered. The solid was washed thoroughly with water and recrystallized from ethanol to give 2.1 g. of 4-(n-octylamino)benzoic acid as white crystals, m.p. 117°-118°C.

EXAMPLE 26
4-(n-Hexadecylamino)benzoic acid

A mixture of 4.98 g. of ethyl 4-(n-hexadecylamino)benzoate, 11.2 g. of potassium hydroxide and 50 ml. of ethanol-water (1:1) was refluxed for 6 hours. To the hot solution was added 16.6 ml. of concentrated hydrochloric acid. The mixture was diluted with 100 ml. of water, chilled, filtered and the solid washed with water. The solid was recrystallized from ethanol-water (3:1) to give 3.85 g. of 4-(n-hexadecylamino)benzoic acid, m.p. 121.5°-123.5°C. and 127°-128°C.

EXAMPLE 27
Ethyl 4-(n-hexadecylamino)benzoate

A mixture of 54.4 g. of ethyl 4-aminobenzoate, 54.4 g. of 1-bromohexane and 45.6 g. of potassium carbonate in 660 ml. of hexamethylphosphoramide was stirred and heated at 120°C. for 24 hours. The mixture was chilled, diluted with 60 ml. of water, chilled and filtered. An additional 140 ml. of water was added and the mixture chilled and filtered to give solid which was washed with cold ethanol and with water to give 44 g. of pale yellow crystals. A sample was recrystallized from ethanol-benzene (95:5) to give ethyl 4-hexadecylaminobenzoate, m.p. 91°-94°C.

EXAMPLE 28

The present compounds can be dispensed in dosage unit form such as hard shell capsules or soft shell capsules. A representative formulation of such capsules is as follows:

<table>
<thead>
<tr>
<th>Example 29 Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Component</td>
</tr>
<tr>
<td>4-(n-Hexadecylamino)-</td>
</tr>
<tr>
<td>benzoic acid</td>
</tr>
<tr>
<td>Corn starch</td>
</tr>
<tr>
<td>Methylcellulose 400</td>
</tr>
<tr>
<td>Magnesium stearate %</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

The active ingredient, corn starch and methylcellulose are to be blended together. The mixture, after drying, is to be lubricated with 1% magnesium stearate and compressed into tablets in a suitable tableting machine.

EXAMPLE 30
The following example represents a formulation for preparing an oral syrup.

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>dimethylaminoethyl</td>
<td>5000 mg.</td>
</tr>
<tr>
<td>4-(n-hexadecylamino)-benzoate</td>
<td>40 ml.</td>
</tr>
<tr>
<td>hydrochloride Sorbitol solution</td>
<td>150 mg.</td>
</tr>
<tr>
<td>(70% N.F.)</td>
<td>10 mg.</td>
</tr>
<tr>
<td>Sodium benzoate</td>
<td>10 mg.</td>
</tr>
<tr>
<td>Saccharin</td>
<td>10 mg.</td>
</tr>
<tr>
<td>Red dye (F.D. &amp; C. No. 2)</td>
<td></td>
</tr>
<tr>
<td>Distilled water, q.s. ad</td>
<td>100 ml.</td>
</tr>
</tbody>
</table>

The sorbitol solution is to be added to 40 ml. of distilled water and the active ingredient is suspended therein. The saccharin, sodium benzoate, flavor and dye are to be added and dissolved in the above solution. The volume is adjusted to 100 ml. with distilled water. Each ml. of syrup contains 50 mg. of drug.

What is claimed is:

1. 4-(Monoalkylamino)benzoic acid derivatives of the formula:
wherein \( R^1 \) is an unbranched or branched alkyl group, 
\( \text{C}_n\text{H}_{2n+1} \) wherein \( n \) is 8 to 19; and \( R^2 \) is hydrogen, lower alkyl, benzyl, dilower alkylaminoethyl, or lower alkoxyethyl; and the pharmaceutically acceptable salts thereof.

2. 4-(n-Tetradecylamino)benzoic acid.
3. 4-(n-Pentadecylamino)benzoic acid.
4. 4-(n-Hexadecylamino)benzoic acid.
5. 4-(n-Heptadecylamino)benzoic acid.
6. Pharmaceutically acceptable salts of 4-(n-Hexadecylamino)benzoic acid.
7. Sodium salt of 4-(n-Hexadecylamino)benzoic acid.