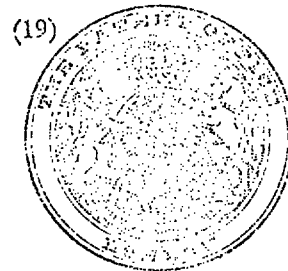


PATENT SPECIFICATION

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 533 534 537 538 552 584 60X 613 615 620 623
 624 625 628 62X 652 660 662 668 672 675 682
 694 697 699 69Y 761 762 775 776 778 790 79Y
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(54) SUBSTITUTED 5-SULFAMYL BENZOIC ACIDS

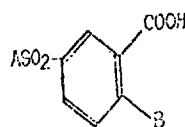
(71) We, PFIZER INC., a Corporation organized under the laws of the State of Delaware, United States of America, of 235 East 42nd Street, New York 17, State of New York, United States of America, do hereby declare the invention, for which we pray that a Patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

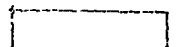
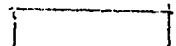
Atherosclerosis, a form of arteriosclerosis, is characterized by accumulation of lipids in the aorta and in the coronary, cerebral and peripheral arteries of the lower extremities. As these masses increase in size, the risk of thrombosis and occlusion arises.

It has been found that those suffering from the disease exhibit elevated levels of plasma lipoprotein, of which cholesterol and triglycerides comprise major constituents. While the etiology of the disease is not yet fully understood, it is believed that β -lipoproteins play an important role, and it has been recommended that dietary habits which promote low β -lipoprotein plasma levels be observed. In addition, various therapeutic agents such as estrogens, thyroxine analogues and simvastatin preparations have been used to lower plasma cholesterol levels in individuals prone to the condition.

It has now been found that certain 2-substituted-5-sulfamyl-benzoic acids are effective in reducing plasma lipid levels. These compounds can be expected to be useful in the treatment of atherosclerosis and related cardiovascular diseases associated with elevated lipid levels.

A number of 5-sulfamylbenzoic acids are found in the literature:



A	B	Reference
NH ₂	Cl	(1)
CH ₃ NH	Cl	(2)
(CH ₃) ₂ N	Cl	(2)
C ₂ H ₅ NH	Cl	(2)
(CH ₃)(C ₂ H ₅)N	Cl	(2)
(C ₂ H ₅) ₂ N	Cl	(2)
<i>i</i> -C ₃ H ₇ NH	Cl	(2)
(CH ₃)(<i>i</i> -C ₃ H ₇)N	Cl	(2)
NH ₂	Br	(3)
(CH ₃)NH	Br	(3)
(CH ₃) ₂ N	Br	(3)
(C ₂ H ₅) ₂ N	Br	(3)
 CH ₂ (CH ₂) ₃ -N	Br	(3)
(CH ₃)NH	NH ₂	(2)
(C ₂ H ₅)NH	NH ₂	(2)
(C ₂ H ₅) ₂ N	NH ₂	(2)
(CH ₃)(C ₂ H ₅)N	NH ₂	(2)
(<i>i</i> -C ₃ H ₇)NH	NH ₂	(2)
(CH ₃)(<i>i</i> -C ₃ H ₇)N	NH ₂	(2)
 CH ₂ (CH ₂) ₄ -N	NH ₂	(4)
(CH ₃) ₂ N	C ₂ H ₅ NH	(2)
(CH ₃) ₂ N	(<i>i</i> -C ₃ H ₇)NH	(2)
(CH ₃) ₂ N	C ₄ H ₉ NH	(2)

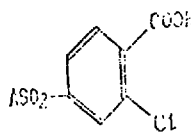
(1) Jackman et al, *J. Pharm. Pharmacol.* p 679 (1962)

(2) Belgian Pat. 620,741 (1963) (Chem. Abstr. 59, 11359)

(3) Kunzle et al, *Helvetica Chimica Acta* 52, 625 (1969)

(4) U.S. Pat. 2,453,164 (1948) (Chem. Abstr. 43, 7710)

In addition, 4-sulfamylbenzoic acids are found in the literature:



A	Reference
(C ₁ H ₃) ₂ N	(5)
(i-C ₃ H ₇) ₂ N	(5)
(C ₄ H ₉) ₂ N	(5)
C ₂ H ₅ CH ₂ NH	(5)
CH ₃ (CH ₂) ₄ N	(5)

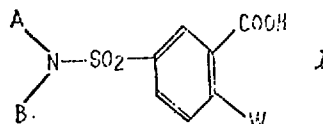
(5) British Pat. 795,937 (1958) (Chem. Abstr. 53, 297)

Although the foregoing summary has been disclosed by a diligent search of the literature, it does not of course purport to be an exhaustive listing of all known sulfamylbenzoic acids. Nevertheless, so far as can be determined, the ability of the 5-sulfamylbenzoic acids of the present invention to reduce plasma lipid levels has never before been recognized.

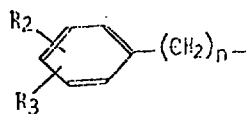
It has been discovered that blood lipid levels may be reduced by the method of administering to a hyperlipemic mammal a compound selected from 5-sulfamylbenzoic acids and the amides, C₁—C₆ alkyl esters and salts thereof with pharmacologically acceptable bases, said compound being substituted in the 2-position by chloro, bromo, hydroxy, lower alkoxy, amino, mono- and di-C₁—C₆ alkyl amino, benzylamino, phenethylamino, piperidino, mono- and di-C₁—C₆ alkyl-piperidino, pyrrolidinyl, hexamethyleneimino or morpholine.

The hypocholesteremic activity appears to be shared by all substances of this particular configuration, but one would obviously avoid any substituents known to be toxic at a level required for lipid-lowering effectiveness.

The compounds of the present invention are those of the formula



and the amides, C₁—C₆ alkyl esters and pharmaceutically acceptable salts thereof wherein A is hydrogen, C₁—C₆ alkyl, cycloalkyl of from 5 to 8 carbon atoms, benzyl or phenyl; B is



wherein

n has a value from zero to 3;

R² and R³ are each hydrogen, chloro, bromo, alkyl or alkoxy of from one to four carbon atoms, carboxy, trifluoromethyl, phenyl, benzyl or benzyloxy; and

W is, chloro, bromo, hydroxy, C₁—C₆ alkoxy, amino, mono- or di-C₁—C₆ alkyl amino, benzylamino, phenethylamino, piperidino, mono- or di-C₁—C₆ alkylpiperidino, pyrrolidinyl, hexamethyleneimino, or morpholino; and

when A is hydrogen or C₁—C₆ alkyl B is also cycloalkyl of from 5 to 8 carbon atoms; and

A and B when taken together with the nitrogen atom to which they are attached comprise a heterocyclic ring selected from morpholine, thiomorpholine, and the S-oxide thereof, piperazinyl, hexamethyleneimino, heptamethyleneimino, octamethyleneimino, 3-azabicyclo[3,2,2]nonanyl, tetrahydropyridyl or mono- and di-substituted derivatives of said heterocyclic rings;

said substituents being alkyl, alkyloxy or alkyloxyalkyl of one to four carbon atoms in each alkyl group, hydroxy, chloro, bromo, trifluoromethyl, phenyl, tolyl, benzyl, benzyloxy, chloromethyl or hydroxymethyl;

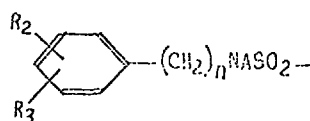
5 or the heterocyclic ring is unsubstituted-, mono- or di-substituted piperidino, said substituents being alkyl, alkyloxy or alkyloxyalkyl of one to four carbon atoms in each alkyl group, hydroxy, chloro, bromo, trifluoromethyl, oxo, methylene, phenyl, tolyl, benzyl, benzyloxy, benzyloxymethyl, chloromethyl or hydroxymethyl.

One preferred class of compounds of the aforementioned configuration is that wherein the sulfamyl group is piperidinosulfonyl or substituted piperidinosulfonyl having up to two substituents which are the same or different and are alkyl, alkyloxy or alkyloxyalkyl of one to four carbon atoms in each alkyl group, hydroxy, chloro, bromo, trifluoromethyl, phenyl, tolyl, benzyl, benzyloxy, benzyloxymethyl, chloromethyl or hydroxymethyl.

15 A second preferred class of compounds is that wherein the sulfamyl group is $RR'NSO_2-$, wherein R and R' together with the nitrogen to which they are attached comprise a heterocyclic ring which is morpholino, thiomorpholino, piperaziny, hexamethylenimine, heptamethylenimine, octamethylenimine, 3-azabicyclo[3,2,2]nonanyl or tetrahydropyridyl and mono- and di-substituted derivatives of said heterocyclic rings;

20 said substituents being alkyl, alkyloxy or alkyloxyalkyl or one to four carbon atoms in each alkyl group, hydroxy, chloro, bromo, trifluoromethyl, phenyl, tolyl, benzyl, benzyloxy, chloromethyl or hydroxymethyl.

A third preferred class of compounds is that wherein the sulfamyl group is



25 wherein

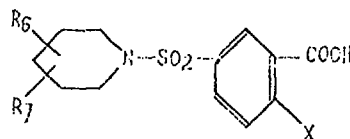
n has a value from 0 to 3;

A is hydrogen, C_1-C_6 alkyl, cycloalkyl of 5 to 8 carbon atoms, benzyl or phenyl; and

30 R^2 and R^3 are hydrogen, chloro, bromo, alkyl and alkoxy of from one to four carbon atoms, carboxy, trifluoromethyl, phenyl, benzyl or benzyloxy.

A fourth preferred class of compounds is that wherein the sulfamyl group is $R^4R^5NSO_2-$ wherein R^4 is hydrogen or lower alkyl and R^5 is C_1-C_6 alkyl or cycloalkyl of 5 to 8 carbon atoms.

35 One subclass of novel and particularly preferred compounds of the present invention embraces those of the formula



wherein

X is chloro, bromo, piperidino, mono- or di- C_1-C_6 -alkylpiperidino, hexamethylenimine or morpholino;

40 R^6 is alkyl, alkyloxy and alkyloxyalkyl of one to four carbon atoms in each alkyl group, hydroxy, chloro, bromo, trifluoromethyl, phenyl, tolyl, benzyl, benzyloxy, benzyloxymethyl, chloromethyl or hydroxymethyl; and

45 R^7 is hydrogen, alkyl, alkyloxy or alkyloxyalkyl of one to four carbon atoms in each alkyl group, hydroxy, chloro, bromo, trifluoromethyl, phenyl, tolyl, benzyl, benzyloxy, benzyloxymethyl, chloromethyl or hydroxymethyl (R^6 and R^7 taken together may also signify oxo or methylene).

Especially preferred are the compounds of the latter structure wherein X is chloro or bromo and R^6 and R^7 are each C_1-C_6 alkyl or benzyl.

50 A second and related subclass of novel and particularly preferred compounds of the present invention embraces those of the formula

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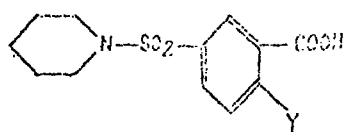
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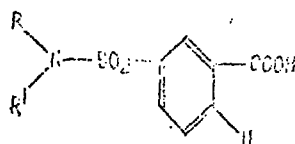
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wherein Y is piperidino or mono- or di- C_1-C_6 -alkyl piperidino.

A third subclass of novel and particularly preferred compounds of the present invention embraces those of the formula



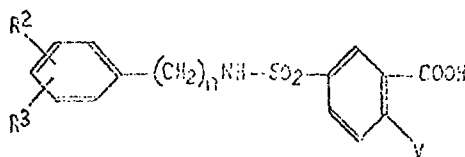
wherein

U is chloro, bromo, di- C_1-C_6 -alkylamino, piperidino, mono- or di- C_1-C_6 -alkylpiperidino, morpholino or hexamethylendiamino; and

R and R' together with the nitrogen to which they are attached comprise a heterocyclic ring which is morpholino, thiomorpholino, piperazino, hexamethylendiamino, heptamethylendiamino, octamethylendiamino, 3-azabicyclo[3.2.2]nonanyl or tetrahydropyridyl or mono- and di-substituted derivatives of said heterocyclic rings;

said substituents being alkyl, alkyloxy or alkyloxyalkyl of one to four carbon atoms in each alkyl group, hydroxy, chloro, bromo, trifluoromethyl, phenyl, tolyl, benzyl, benzoyloxy, chloromethyl or hydroxymethyl.

A fourth subclass of novel and particularly preferred compounds of the present invention embraces those of the formula



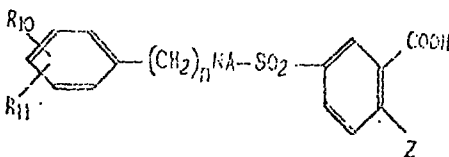
wherein

n has a value from 0 to 3;

V is bromo, piperidino or mono- or di- C_1-C_6 -alkylpiperidino; and

R² and R³ are hydrogen, chloro, bromo, alkyl or alkoxy of from one to four carbon atoms, carboxy, trifluoromethyl, phenyl, benzyl or benzyloxy.

A fifth and closely related subclass of novel and particularly preferred compounds of the present invention embraces those of the formula



wherein

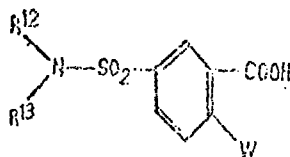
n has a value from 0 to 3;

A is C_1-C_6 alkyl, cycloalkyl of 5 to 8 carbon atoms, benzyl or phenyl;

Z is chloro or bromo; and

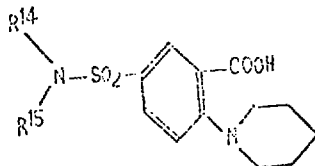
R¹⁰ and R¹¹ are each hydrogen, C_1-C_6 alkyl, chloro, bromo or phenyl.

A sixth subclass of novel and particularly preferred compounds of the present invention embraces those of the formula



wherein W is chloro, bromo, piperidino or mono- and di- C_1-C_6 -alkylpiperidino; R^{12} is hydrogen or C_1-C_6 alkyl; and R^{13} is cycloalkyl of 5 to 8 carbon atoms.

A seventh and closely related subclass of novel and particularly preferred compounds of the present invention embraces those of the formula



wherein R^{14} and R^{15} are each C_1-C_6 alkyl.

The sulfamylbenzoic acids of the present invention have been found to be well tolerated in the form of the free carboxylic acid. If desired, however, they may be administered in the form of an amide, C_1-C_6 alkyl ester or salt of a pharmacologically acceptable base.

The amides include not only the unsubstituted amides but amides of pharmacologically acceptable amines, for example, the amino acids, such as glycine or ϵ -aminobutyric acid. The amides are readily prepared by standard techniques, for example, by treating a corresponding sulfamyl benzoic acid ester in alcohol with ammonia, or by combining the corresponding sulfamyl benzoyl chloride with amine under basic conditions and precipitating the amide product with mineral acid.

Of the C_1-C_6 alkyl esters, the ethyl ester will generally be preferred. In addition, esters of complex alcohols such as acetauridoethyl alcohol may be employed. The esters may be prepared by condensation of the acid with the corresponding alcohol in the presence of acid catalyst.

The pharmacologically acceptable salts include the ammonium, sodium, potassium, calcium and magnesium salts, as well as salts with pharmacologically acceptable amines. The salts are prepared by conventional procedures, for example, by adding the acid to an aqueous solution containing an equivalent amount of the appropriate base, followed by concentration to obtain the desired product. Although salts formed from pharmacologically-unacceptable bases are not useful therapeutically, they may be used in the purification. For example, an impure acid can be purified by dissolving it in an aqueous solution containing a pharmacologically-unacceptable base and extracting the resulting salt solution with organic solvent to remove non-acidic impurities. The free, purified acid is then isolated by acidifying the aqueous solution and filtering.

Although parenteral modes of administration of the compounds of the present invention may be employed, oral administration is effective and preferred for its obvious convenience. The products of the invention are tested *in vivo* for hypolipemic activity in rats. Groups, each comprising 4 animals, of normal Sprague-Dawley (Charles River) male rats weighing from 160 to 220 grams are fed rat chow containing the compound under test for two overnight feeding periods. On the morning of the third day the animals are anesthetized and bled from the abdominal aorta. The total plasma cholesterol is then determined by the method of J. J. Carr and I. J. Drecker, reported in *Clin. Chem.*, 2, 353 (1956). Most of the tests are conducted at a feed concentration of 0.15 to 0.25 weight per cent of the compound under test, but lower levels, 0.01 to 0.10 weight per cent, are employed in some instances where particularly high potency is anticipated. The plasma cholesterol level of the treated animals is found to be significantly reduced when compared to animals not receiving the test compound.

This pharmacological test for measuring hypocholesteremic activity is a reasonably reliable indication that similar activity in humans can be expected. In fact, those compounds effective in the rat which have been tested in humans have demonstrated similar activity. *p*-Chlorophenoxisulbutyric acid, ethyl ester, marketed as Atromid-S, a well known and clinically effective hypocholesteremic agent, causes a 30-35% cholesterol fall in the rat test when administered at a level of 0.25% in the feed (Atromid is a Registered Trade Mark).

In humans, an individual having a plasma cholesterol level above 260 mg. per cent (mg per 100 ml) or a plasma triglyceride level above 150 mg per cent is regarded as hyperlipemic. The term "lipids" is used herein in the broad sense to include triglycerides, cholesterol, phospholipids and free fatty acids. Plasma lipids are carried in the body in the form of lipoproteins, i.e. protein complexes. These may be separated by electrophoresis into several fractions: high-density or α -lipoprotein, containing a high proportion of phospholipids; low-density or β -lipoprotein, containing a major proportion of cholesterol; very-low-density or pre- β -lipoprotein; and chylomicrons.

microas; the latter two fractions containing a major proportion of triglycerides. In a particular individual, one of the four fractions may be elevated. The agents of the present invention depress plasma lipoproteins, with associated cholesterol and triglyceride, and hence are expected to be of value in hyperlipoproteinemic individuals.

One of the novel compounds of the present invention, 2-chloro-5-(*cis*-3,5-dimethylpiperidinosulfonyl)benzoic acid, which exhibits higher potency than Atromid-S in the rat test, has produced significant depression in plasma cholesterol and triglycerides in human studies. Overall reductions compare closely with those produced by Atromid-S in similar populations. In these clinical studies, the compound was administered in three equally divided doses at daily levels of 0.5--1.5 grams. It is now being further evaluated in hyperlipemic humans in the form of capsules containing 250 mg. of active ingredient, at a dosage schedule of two capsules three times daily. Further testing at a level of one capsule three times daily, equivalent to 0.75 gram per day, is also planned.

Obviously, the optimum dosage level for a particular compound of the present invention will vary with the relative potency of the substance and with the age, weight and response of the particular patient. An approximation of suitable dosage levels for various compounds can be estimated from their potency in the rat test relative to a standard which has been tested in humans, such as Atromid-S or 2-chloro-5-(*cis*-3,5-dimethylpiperidinosulfonyl)benzoic acid. In determining relative potency, dose response curves are preferably constructed by rat testing at several dosage levels, for example, at seven levels. A compound which proves twice as potent as the standard in this test will generally be evaluated in toxicology as a candidate for use at half the level employed with the standard.

Having full regard for the foregoing factors, it is considered that an effective daily dosage of the compounds of the present invention in humans will generally range from 0.3 to 3 grams per day, in single or divided dosage, or at 5 to 50 mg. per kg. body weight. These values are illustrative, and there may of course be individual cases where higher or lower dosage ranges are merited.

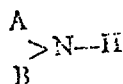
The sulfamylbenzoic acids of this invention can be administered either alone or, preferably, in combination with a pharmaceutically-acceptable carrier. They may be combined with various pharmaceutically-acceptable, inert carriers in the form of tablets, capsules, lozenges, troches, powders, aqueous suspensions or solutions, elixirs and syrups. Suitable carriers include solid diluents or aqueous media and non-toxic organic solvents. The oral pharmaceutical compositions of this invention may be suitably sweetened and flavored by means of various agents commonly employed for such a purpose.

For parenteral administration, solutions or suspensions of the herein described sulfamylbenzoic acids in sesame or peanut oil or in aqueous propylene glycol solutions can be employed, as well as sterile aqueous solutions of the corresponding water-soluble salts. Such solutions are suitable for intramuscular and subcutaneous administration. Sterile aqueous solutions are additionally useful for intravenous injection, provided that their pH is suitably adjusted and buffered, if necessary, and the liquid diluent rendered isotonic with saline or glucose.

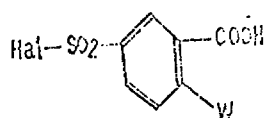
The herein disclosed compounds may also be useful in other aspects of abnormal metabolism, the latter possibly accounting for clinical problems in diabetes, pancreatitis, coronary heart disease, and cerebrovascular disease. Hence the ability of sulfamylbenzoic acids of this invention to regulate lipid metabolism might find utility in the treatment of the said diseases.

The present invention also provides a process for preparing a compound of formula 1 as defined in claim 1, which comprises

a) reacting an amine of the formula

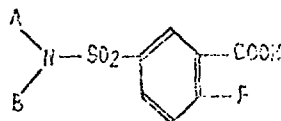


wherein A and B are as defined in claim 1 with a compound of the formula



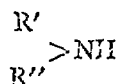
wherein Hal is halogen and W is as defined in claim 1;

b) reacting a compound of the formula



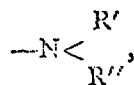
1) with an amine of the formula

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wherein R' and R'' are the same or different and are alkyl of up to 6 carbon atoms and when taken together comprise a piperidine ring to form a compound of Formula I wherein W is



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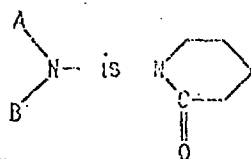
2) with a straight or branched chain lower alcohol of up to 6 carbon atoms in the presence of a base to form a compound of the Formula I wherein W is —O— lower alkyl, or

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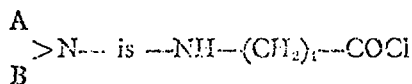
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3) with an alkali metal hydroxide to form a compound of Formula I wherein W is —OH and, if desired, subsequently reacting a compound of Formula I wherein A and B when taken together with the nitrogen to which they are attached form a hydroxymethylpiperidino group, with thionyl chloride to form the corresponding chloromethyl compound which may if desired be converted to the corresponding *exo*-methylene compound and when required, reducing a compound of Formula I wherein W is benzylamino to the corresponding amine and, when required subsequently forming a compound of Formula I wherein

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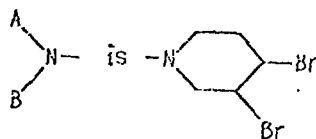


by cyclization of the corresponding precursor wherein



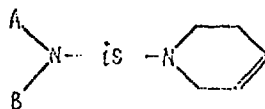
and when required forming a compound of Formula I wherein

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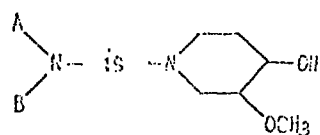


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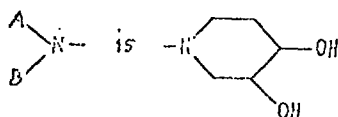
by bromination of a compound of Formula I wherein



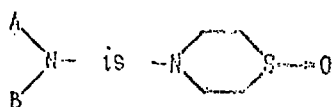
and when required forming a compound of the Formula I wherein



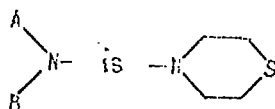
by O-alkylation of a compound of Formula I wherein



and when required forming a compound of Formula I wherein



by oxidation of a compound of Formula I wherein



and when required converting the COOH group of the compound of Formula I via the acid Chloride to a $\text{CONHCH}_2\text{COOH}$ or $\text{CONHC}_2\text{H}_4\text{COH}$ group by reaction with the appropriate amino acid and, if desired subsequently converting a compound of Formula I wherein A is hydrogen to N-alkyl by N-alkylation.

The preparation of the compounds of this invention are summarized in the reaction schemes of Charts 1 and 2, wherein

I—II represents chlorosulfonation of a 2-halo benzoic acid, where X' is Cl, Br or I;

II—III represents reaction of the resulting 2-halo-5-chloro-sulfonyl benzoic acid with amine in the presence of alkali or in a non-aqueous medium such as methylene chloride;

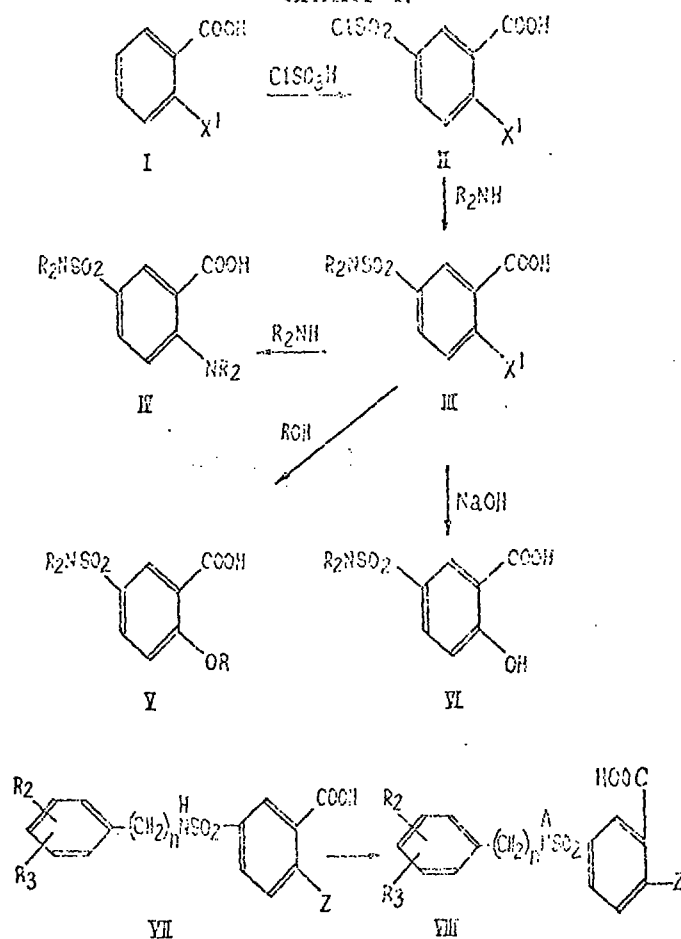
III—IV represents replacement of the 2-halo substituent by a 2-amino group, effected by refluxing the sulfamylbenzoic acid with the corresponding amine;

III—V represents replacement of the 2-halo substituent by a 2-alkoxy group (i.e. OR), effected by heating the sulfamylbenzoic acid with the corresponding alcohol in the presence of sodium hydride;

III—VI represents replacement of the 2-halo substituent by a 2-hydroxyl group, effected by heating the sulfamylbenzoic acid in the presence of strong alkali such as sodium hydroxide or potassium hydroxide; and

VII—VIII represents N-alkylation of a 2-halo-5-phenyl- or phenylalkyl-amino-sulfonyl benzoic acid, e.g. by treatment with the corresponding alkyl or aralkyl halide or dialkyl sulfate in the presence of aqueous alkali, wherein A, R₁, R₂, Z and n are as previously defined.

CHART 1.



The following examples 1 to 28 illustrate in greater detail the preparation of typical members of the compounds of the invention; preparations of certain of the known members are also given.

EXAMPLE 1.

2-chloro-5-chlorosulfonylbenzoic acid

A mixture of *o*-chlorobenzoic acid (2.0 kg.) and chlorosulfonic acid (10.5 kg.) is heated at 90–100° C. for 5 hours. The reaction mixture is cooled to 25° C. and then slowly poured into a 10 liter mixture of ice and water. The addition requires about 1 hour, and the temperature is maintained below 10° C. during this period by the addition of more ice. The final volume of slurry after the quench is about 40 liters. The solid material is collected and thoroughly washed on the funnel with fresh water. The crude wet cake is dissolved in 16 liters of diethyl ether. The ether layer is washed once with 2 liters of saturated aqueous sodium chloride solution and then dried over anhydrous magnesium sulfate. The filtered ether solution is concentrated *in vacuo* with the continual addition of hexane. The resulting hexane slurry is concentrated to a final volume of approximately 8 liters and filtered. The crystalline cake is washed with hexane and dried in the atmosphere to give 2.5 kg. of product (76.8% of theory) m.p. 149–151° C.

cis-3,5-dimethylpiperidine hydrochloride

3,5-Lutidine (6475.0 g.) is hydrogenated under 1000 psi hydrogen pressure in ethanol using 1665 g. of 5% rhodium on carbon catalyst (50% H₂O) at room temperature. The catalyst is filtered off and anhydrous hydrogen chloride bubbled into the filtrate at a temperature below 40° C. until the solution is strongly acidic. The solution is then concentrated *in vacuo* to a thick slurry which is diluted with 40 liters of hexane. The crystalline material is filtered off and dried in the atmosphere to give 8.9 kg. of crude product. The crude cis-3,5-dimethylpiperidine hydrochloride is dissolved in 14 liters of water and the pH of this solution adjusted to 7.0 with dilute sodium hydroxide solution. The mixture is washed with 7 l. and then with 3 l. of chloroform

to remove unreduced 3,5-lutidine. The aqueous solution is then adjusted to pH 12—13 by the addition of 40% sodium hydroxide solution and extracted with 6 l. and then with 3 l. of chloroform. The combined chloroform extract is dried over anhydrous magnesium sulfate and chilled to 5° C. in an ice bath. Anhydrous hydrogen chloride is then injected until the solution is strongly acidic. The chloroform solution is concentrated *in vacuo* as benzene is continuously added. When most of the chloroform has been replaced, the product is filtered from about 36 l. of benzene. The filter cake is washed with cold benzene and hexane, and air dried, to obtain 4.8 kg. of product, m.p. 222—224° C.

2-chloro-5-(cis-3,5-dimethylpiperidinesulfonyl)benzoic acid
2-Chloro-5-chlorosulfonylbenzoic acid (510.2 g.) and cis-3,5-dimethylpiperidine hydrochloride are slurried in 7.0 l. of water and stirred at 15° C. as a cold solution of 240.0 g. of sodium hydroxide in 6 l. of water is added in a steady stream. The hazy reaction mixture is stirred at 20—25° C. for 1 hour and then filtered by suction through a funnel precoated with diatomaceous earth filter aid. The filtrate is acidified with concentrated hydrochloric acid and the resulting precipitate collected. The cake is washed with methanol and ether, and air-dried to obtain 650.0 g. of crude product. This is dissolved in 6 l. of 1:1 isopropyl alcohol: chloroform and filtered. The filtrate is concentrated *in vacuo* to about 3 l. and the crystalline material filtered off. The filter cake is washed with isopropyl alcohol and ether. Air drying gives 471.0 g. of crystalline product, m.p. 250—251° C.

Anal. Calc'd. for $C_{14}H_{19}O_4NSCl$: C, 50.67; H, 5.47; N, 4.22
Found: C, 50.73; H, 5.46; N, 4.24

In the same way, 2-chloro-4-(cis-3,5-dimethylpiperidinesulfonyl)benzoic acid, m.p. 233—234° C., is prepared from 2-chloro-4-chlorosulfonylbenzoic acid.

EXAMPLE 2.

2-chloro-5-(trans-dl-3,5-dimethylpiperidinesulfonyl)benzoic acid

The mother liquors of the reduced 3,5-lutidine of Example 1 are evaporated to dryness. The residue contains approximately 75% trans and 22% cis isomers. A portion of this material is reacted with 2-chloro-5-chlorosulfonylbenzoic acid by the method of Example 1. Recrystallization from methylene chloride followed by benzene yields the desired product, m.p. 188—191.5° C.

EXAMPLE 3.

2-chloro-5-(β,β' -dichloro-diethylaminosulfonyl)benzoic acid

To a solution of 1.8 gram (10 mmoles) of β,β' -dichlorodiethylamine hydrochloride in 20 ml. water, 20 ml. acetone and 30 ml. 1N aqueous sodium hydroxide is added 2.55 gram (10 mmoles) of 2-chloro-5-chlorosulfonyl benzoic acid. After stirring at room temperature for one hour, the mixture is washed with 20 ml. ether and acidified with concentrated hydrochloric acid to obtain 0.7 gram crystalline product, m.p. 161—163° C. Recrystallization from benzene-hexane does not change the melting point.

Anal. Calc'd. for $C_{11}H_{12}O_4NSCl_2$ (MW 360.65): C, 36.64; H, 3.35; N, 3.88
Found: C, 36.66; H, 3.39; N, 3.71

EXAMPLE 4.

2-chloro-5-(4-chloropiperidinesulfonyl)benzoic acid

4-Chloropiperidine hydrochloride is prepared by refluxing 4-hydroxypiperidine hydrochloride, 4.2 g., with 2 ml. thionyl chloride for 10 minutes, and evaporating to dryness.

10 mmoles of this product is permitted to react with 10 mmoles of 2-chloro-5-chlorosulfonyl benzoic acid as described in the previous example. After washing with ether and acidifying, the reaction mixture is extracted with ethyl acetate and the extract is evaporated to dryness. The residue is then dissolved in a mixture of 3 ml. acetone and 10 ml. ethyl acetate and passed over 30 grams silica gel packed in a column in a solution of 5% acetic acid in 1:1 benzene-hexane. The column is eluted with the same solvent mixture and the product isolated by evaporation of first effluent fractions. The residue is purified by dissolving in 20 ml. acetone, adding an equal volume of hexane, and decanting the supernatant from the resulting precipitate. The

supernatant is then concentrated to half volume to crystallize 0.45 gram of product, m.p. 193—195° C.

Anal. Calc'd for $C_{12}H_{13}O_2NSCl_2$ (MW 338.2): C, 42.63; H, 3.87; N, 4.14
Found: C, 42.79; H, 3.99; N, 3.91

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EXAMPLE 5.

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2-chloro-5-(2-[*p*-chlorophenyl]ethylaminesulfonyl)benzoic acid

2-Chloro-5-chlorosulfonyl benzoic acid, 3.5 g. (0.014 mole), is added to a solution of 2-(*p*-chlorophenyl)ethylamine, 6.5 g. (0.042 mole) in 25 ml. methylene chloride. The resulting slurry is stirred overnight and filtered to recover 9.7 g. of residue. This is recrystallized three times from aqueous isopropanol, then dissolved in 1N aqueous sodium hydroxide, washed three times with ether, and then acidified with conc. hydrochloric acid. The resulting precipitate is recrystallized twice from aqueous isopropanol to yield the desired product, m.p. 176—178° C.

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Anal. Calc'd. for $C_{17}H_{15}O_2NSCl_2$: C, 48.14; H, 3.50; N, 3.72
Found: C, 48.19; H, 3.31; N, 3.42

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EXAMPLE 6.

2-Chloro-5-chlorosulfonylbenzoic acid is reacted by the method of Example 1 with each of the indicated amines to yield the corresponding sulfanybenzoic acid.

	Amine	Product, m.p. (°C.)	
20	2,5-dimethylpiperidine	128.5—131	20
	3,5-dimethylmorpholine	201—203	
	3-piperidylcarbinol	191—193	
	3,5-diethylpiperidine	182—184	
	2,2-dimethylthiomorpholine	181.5—183	
25	2-benzylpiperidine	164—166	25
	4-ethoxy-4-phenylpiperidine	200—201	
	3-hydroxypiperidine	175—177	
	cis-3,4-dibenzylexypyrrolidine	70—75	
	3,5-dipropylpiperidine	170—176	
30	3,4-dihydroxypiperidine	172—175	30
	1-[N-β hydroxyethyl-4-piperidyl]-3-[4-piperidyl]propane	187—190	
	4-benzylexymethylpiperidine	129—132	
	3-methoxypiperidine	191—193	
	1-octamethyleneimine	232—233	
35	dimethylamine	175—177.5	35
	17% aq. ammonia	209—212	
	3-benzylpiperidine	145—148	
	3,5-dibenzylpiperidine	175—179	
	3,4-dichloropiperidine	185.5—187	

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EXAMPLE 7.

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2-bromo-5-(2-methylpiperidinosulfonyl)benzoic acid

2-Bromo-5-chlorosulfonylbenzoic acid is prepared by reacting *o*-bromobenzoic acid with chlorosulfonic acid by the method of Example 1. This is reacted with 2-methylpiperidine by the procedure of Example 6. Recrystallization from acetone-hexane yields the product, m.p. 148—150° C.

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Anal. Calc'd. for $C_{13}H_{16}O_2NSBr$ (MW 362.2): C, 43.11; H, 4.45; N, 3.87
Found: C, 42.96; H, 4.55; N, 3.74

EXAMPLE 8.

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The method of Example 2 is repeated with 2-bromo-5-chloro-sulfonylbenzoic acid in place of 2-chloro-5-chlorosulfonylbenzoic acid to yield 2-bromo-5-(trans-di-3,5-dimethylpiperidinosulfonyl) benzoic acid, m.p. 188—190° C.

EXAMPLE 9.

The following compounds are prepared by reacting 2-bromo-5-chlorosulfonylbenzoic acid with the appropriate amine by the method of Example 7:

Compound	M.P. (°C.)
2-bromo-5-(cis-3,5-dimethylpiperidinosulfonyl)benzoic acid	237.5—239.5
2-bromo-5-(3-trifluoromethyl-4-chlorophenylsulfonyl)benzoic acid	199 —201
2-bromo-5-(3-phenylpropylsulfonyl)benzoic acid	160 —161
2-bromo-5-(4- <i>tert</i> -butyl-1-piperazylsulfonyl)benzoic acid	207 —208
2-bromo-5-(2-carboxyphenylsulfonyl)benzoic acid	236 —237
2-bromo-5-(<i>N</i> -phenyl- <i>N</i> -butylsulfonyl)benzoic acid	149 —151
2-bromo-5-(4-methoxybenzylsulfonyl)benzoic acid	176 —176.5
2-bromo-5-(4-phenylpiperidino-sulfonyl)benzoic acid	193.5—194.5
2-bromo-5-(3-azabicyclo[3,2,2]nonan-3-ylsulfonyl)benzoic acid	194.5—195.5
2-bromo-5-(1,2,5,6-tetrahydro-1-pyridylsulfonyl)benzoic acid	195 —187
2-bromo-5-(1-methyl-3-hydroxypropylsulfonyl)benzoic acid	121 —123
2-bromo-5-(3-hydroxymethylpiperidinosulfonyl)benzoic acid	181 —183
2-bromo-5-(2-carboxy-5-chlorophenylsulfonyl)benzoic acid	231.5—232
2-bromo-5-(<i>N</i> -methyl- <i>N</i> -cyclohexylsulfonyl)benzoic acid	141 —143
2-bromo-5-(3,5-dimethyl-1-piperazinylsulfonyl)benzoic acid	298 —300
2-bromo-5-(cyclohexylmethylsulfonyl)benzoic acid	200 —202
2-bromo-5-(1-hexamethylencininosulfonyl)benzoic acid	192 —193
2-bromo-5-(1-heptamethylencininosulfonyl)benzoic acid	216 —217.5
2-bromo-5-(4,4-dimethylpiperidinosulfonyl)benzoic acid	179 —180
2-bromo-5-octamethylencininosulfonylbenzoic acid	231 —232
2-bromo-5-cyclooctylsulfonylbenzoic acid	171 —173
2-bromo-5-(3-hydroxypiperidinosulfonyl)benzoic acid	194 —196
2-bromo-5-(1-pyrrolidinylsulfonyl)benzoic acid	213 —214.5
2-bromo-5-dimethylaminosulfonylbenzoic acid	173 —174
2-bromo-5-diethylaminosulfonylbenzoic acid	143 —143.5
2-bromo-5-cyclopentylsulfonylbenzoic acid	176 —177
2-bromo-5-sulfonylbenzoic acid	226 —228
2-bromo-5-(3,5-diethylpiperidinosulfonyl)benzoic acid	186 —188
2-bromo-5-(3-benzylpiperidinosulfonyl)benzoic acid	150 —154
2-bromo-5-(3,5-dibenzylpiperidinosulfonyl)benzoic acid	180 —185
2-bromo-5-(2-[<i>p</i> -chlorophenyl]ethylaminosulfonyl)benzoic acid	184 —185

EXAMPLE 10.

2-bromo-5-(*N*-propyl-*N*-2-[*p*-chlorophenyl]ethylaminesulfonyl)benzoic acid

2-Bromo-5-(2-[*p*-chlorophenyl]ethylaminesulfonyl)-benzoic acid, 4.2 grams (10 mmoles), is combined with 1-iodopropane, 3.4 grams (20 mmoles) in 20 ml. 1*N* aqueous sodium hydroxide and 30 ml. ethanol. This mixture is heated at reflux temperature for 8 hours, with addition of two further 20 mmole portions of iodopropane during the reflux period. Each time iodopropane is added, sufficient sodium hydroxide pellets to keep the reaction mixture basic are also introduced.

The reaction mixture is then evaporated at reduced pressure to remove the ethanol, diluted with water, and washed twice with diethyl ether. The reaction mixture is then acidified with concentrated hydrochloric acid and the oil which separates is extracted three times with diethyl ether. The combined extract is dried, concentrated, treated with hexane and filtered to recover 3.7 grams of solid product.

The product is purified by recrystallization from isopropyl ether-hexane and chromatography in benzene on 100 ml. silica gel in a column. The column is eluted with 5% acetic acid in 1:1 benzene:hexane and the effluent evaporated at reduced pressure to obtain 2.7 grams, m.p. 125—128° C. Recrystallization from diethyl ether replaced with hexane raises the melting point to 128—129° C.

Anal. Calc'd. for $C_{18}H_{19}O_4NSBrCl$ (MW 461): C, 46.92; H, 4.16; N, 3.04
Found: C, 47.11; H, 4.13; N, 2.88

EXAMPLE 11.

2-bromo-5-(*N*-methyl-*N*-2-[*p*-chlorophenyl]ethylaminesulfonyl)benzoic acid

This product is prepared by the procedure of the previous example, substituting 15 mmoles of dimethyl sulfate for the iodopropane and employing 40 ml. 1*N* aqueous sodium hydroxide as reaction medium, with no ethanol.

3.3 grams of white crystalline product, m.p. 122—123° C., is obtained.

Anal. Calc'd. for $C_{16}H_{15}O_4NSBrCl$: C, 44.40; H, 3.49; N, 3.24
 Found: C, 44.11; H, 3.42; N, 3.18

EXAMPLE 12

2-bromo-5-(N-benzyl-N-2-[p-chlorophenyl]ethylaminosulfonyl)benzoic acid

This product is prepared by the procedure of Example 10, substituting 20 mmoles of α -bromotoluene for iodopropane. 2.1 grams of product, m.p. 142–144° C., is recovered.

Anal. Calc'd. for $C_{22}H_{19}O_4NCIBr$ (MW 508): C, 51.94; H, 3.76; N, 2.75
 Found: C, 52.03; H, 3.87; N, 2.76

EXAMPLE 13.

1-acetyl-3-hydroxypiperidine

3-Hydroxypiperidine (0.4 mole) is dissolved in 150 ml. of methylene chloride. The solution is cooled to 10° C. and acetic anhydride (0.46 mole) is added dropwise, maintaining the temperature under 20° C. The reaction mixture is allowed to come to room temperature, and is then refluxed for 2 hours. The methylene chloride is evaporated off, and the remaining liquid is distilled under high vacuum. A thick yellow oil is collected at 122–126° C. (0.3 mm Hg).

1-acetyl-3-benzoyloxypiperidine

1-Acetyl-3-hydroxypiperidine (0.10 mole) is dissolved in 50 ml. of dimethylformamide. 0.12 mole of sodium hydride (56%) is added over a 10 minute period, and the reaction mixture is stirred for 30 minutes. Benzyl chloride (0.12 mole) is added dropwise over a 30 minute period, and the reaction mixture is then heated on a steam bath for 30 minutes. Water (3 volumes) is added, the solution extracted with ether, the ether extract washed with water and the ether removed by evaporation. A yellow oil is obtained on distillation at 136–140° C. (0.01 mm Hg).

Anal. Calc'd. for $C_{17}H_{19}O_2N$: C, 72.97; H, 8.21; N, 6.00
 Found: C, 72.18; H, 8.25; N, 5.98

3-benzoyloxypiperidine

1-Acetyl-3-benzoyloxypiperidine (0.043 mole), sodium hydroxide (0.086 mole) and water (30 ml.) are combined and refluxed for 24 hours. The reaction mixture is saturated with potassium carbonate and extracted three times with ether. The ether is removed by evaporation and the yellow oil is distilled at 92–94° C. (0.3 mm Hg).

2-bromo-5-(3-benzoyloxypiperidinosulfonyl) benzoic acid

2-bromo-5-chlorosulfonylbenzoic acid is reacted with 3-benzoyloxypiperidine by the method of Example 1. Recrystallization from ether-hexane yields the product, m.p. 177–178° C.

Anal. Calc'd. for $C_{17}H_{19}O_5NSBr$ (MW 454): C, 50.22; H, 4.44; N, 3.03
 Found: C, 50.51; H, 4.52; N, 3.41

2-chloro-5-(3-benzoyloxypiperidinosulfonyl)benzoic acid

2-Chloro-5-chlorosulfonylbenzoic acid is reacted with 3-benzoyloxypiperidine by the method of Example 1. Recrystallization from ether-hexane yields the product, m.p. 173–174° C.

Anal. Calc'd. for $C_{19}H_{20}O_5NSCl$: C, 55.67; H, 4.92; N, 3.42;
 Found: C, 55.93; H, 5.09; N, 3.41

EXAMPLE 14.

3,N,N-diethylamino-5-(3,5-dimethylpiperidinosulfonyl)benzoic acid

α -Fluorobenzoic acid is reacted with chlorosulfonic acid by the method of Example 1 to form 2-fluoro-5-chlorosulfonylbenzoic acid. This is reacted with 3,5-dimethylpiperidine by the method of Example 1 to form 2-fluoro-5-(3,5-dimethylpiperidinosulfonyl)benzoic acid. This product (0.0015 moles) is heated to 60° C. with diethylamine (10 ml.) and ethanol (3.0 ml.) to form a clear solution, and the reaction mixture is then heated at reflux temperature for 24 hours. The resulting brown solid is filtered

off, dissolved in 1N NaOH, washed twice with ether, and the product precipitated by the addition of concentrated HCl. Recrystallization from diethyl ether followed by isopropyl ether yields the product, m.p. 139.5--140° C.

Anal. Calc'd. for $C_{18}H_{28}O_4N_2S$: C, 58.67; H, 7.66; N, 7.60

Found: C, 58.67; H, 7.70; N, 7.53

EXAMPLE 15.

2-piperidino-5-(2-[*p*-chlorophenyl]ethylaminosulfonyl)benzoic acid

2-Fluoro-5-chlorosulfonyl benzoic acid, 7.1 grams (0.03 mole), is added to a solution of 2-*p*-chlorophenylethylamine, 9.3 grams (0.06 mole) in 40 ml. methylene chloride, while keeping the temperature below 15° C. The reaction mixture is stirred for 3 hours at room temperature and the precipitate is recovered by filtration and dissolved in 25 ml. 1N aqueous sodium hydroxide. The solution is washed twice with diethyl ether and acidified with concentrated hydrochloric acid. The resulting precipitate of 2-fluoro-5-(2-[*p*-chlorophenyl]ethylaminosulfonyl)benzoic acid, 3.3 grams, is recrystallized from ethyl acetate and melts at 206--208° C.

This product, 1.5 grams (0.04 mole) is stirred in 20 ml. chloroform and piperidine, 3.5 grams (0.04 mole) is added. The resulting clear yellow solution is heated at reflux temperature for one hour, evaporated in vacuum to a gum, and dissolved in 1N aqueous sodium hydroxide. The solution is washed twice with diethyl ether and acidified with concentrated hydrochloric acid. The resulting precipitate, 1.7 grams, m.p. 199--200° C., is recrystallized from ethyl acetate.

Anal. Calc'd. for $C_{20}H_{28}O_4N_2SCl$: C, 56.80; H, 5.48; N, 6.63

Found: C, 56.86; H, 5.50; N, 6.48

EXAMPLE 16.

The following compounds are prepared by the method of Example 14.

Compound	M.P. (°C.)
2-piperidino-5-(3,5-dipropylpiperidinosulfonyl)benzoic acid	135 —137
2-morpholino-5-(3-benzoyloxy-piperidinosulfonyl)benzoic acid	178 —178.5
2-piperidino-5-piperidinosulfonylbenzoic acid	161 —164
2-piperidino-5-(cis-3,5-dimethylpiperidino-sulfonyl)benzoic acid	172 —174
2-diethylamino-5-diethylaminosulfonylbenzoic acid	129 —131.5
2-(3,5-dimethylpiperidino)-5-(3,5-dimethylpiperidinosulfonyl)benzoic acid	181 —182
2-n-butylamino-5-(3,5-dimethylpiperidinosulfonyl)benzoic acid	207 —208
2-piperidino-5-diethylsulfamylbenzoic acid	154 —155.5
2-dibutylamino-5-piperidinosulfonylbenzoic acid	102 —104
2-dimethylamino-5-(3,5-dimethylpiperidinosulfonyl)benzoic acid	195 —196.5
2-piperidino-5-(1-hexamethylenciminosulfonyl)benzoic acid	136 —137.5
2-(4-methylpiperidino)-5-(4-methylpiperidinosulfonyl)benzoic acid	145 —147
2-(1-hexamethylencimino)-5-(3,5-dimethylpiperidinosulfonyl)benzoic acid	177 —179
2-piperidino-5-(1-heptamethylenciminosulfonyl)benzoic acid	117 —120
2-piperidino-5-(3-azabicyclo(3,2,2)nonan-3-yl-sulfonyl)benzoic acid	183 —189
2-(3,5-dimethylpiperidino)-5-dibutylsulfamylbenzoic acid	85 — 87.5
2-(3,5-dimethylpiperidino)-5-piperidinosulfonylbenzoic acid	191 —193
2-(di-n-butylamino)-5-(3,5-dimethylpiperidinosulfonyl)benzoic acid	134.5—136
2-(3-methylpiperidino)-5-(3-methylpiperidinosulfonyl)benzoic acid	142 —144
2-(3-methylpiperidino)-5-piperidinosulfonylbenzoic acid	173.5—175
2-pyrrolidinyl-5-(3,5-dimethylpiperidinosulfonyl)benzoic acid	202— 203.5

EXAMPLE 17.

2-amino-5-(3,5-dimethylpiperidinosulfonyl)benzoic acid

5 2-Fluoro-5-(3,5-dimethylpiperidinosulfonyl)benzoic acid is combined with 10ml. of benzylamine and heated at 110° C. for 15 minutes. The reaction mixture is concentrated *in vacuo* (10 mm Hg.) at 85° C. to a thick oil. After the addition of 75ml. of water, 2-benzylamino-5-(3,5-dimethylpiperidinosulfonyl)benzoic acid, m.p. 220—227° C., is precipitated by the addition of concentrated hydrochloric acid.

10 1.9 g. of this amine is dissolved in 50 ml. of acetic acid, and hydrogenated in the presence of 200 mg. of palladium on carbon on a Parr shaker overnight at 60° C. The filtered solution is concentrated to dryness, taken up in 40 ml. of isopropyl alcohol, and allowed to crystallize from 10 ml. of solution. Recrystallization from isopropyl alcohol yields the title product, m.p. 240—241° C.

Anal. Calc'd. for $C_{14}H_{20}O_3N_2S$: C, 53.82; H, 6.45; N, 8.97

Found: C, 53.78; H, 6.78; N, 8.64

EXAMPLE 18.

2-isopropoxy-5-(3-methylpiperidinosulfonyl)benzoic acid

2-Fluoro-5-chlorosulfonylbenzoic acid is reacted with 3-methylpiperidine by the method of Example 1, and the resulting 2-fluoro-5-(3-methylpiperidinosulfonyl)benzoic acid (5 millimoles) is heated on a steam bath for 3-1/2 hours in isopropyl alcohol (50 ml.) with 5 millimoles of sodium hydride (56.6% suspension in mineral oil). The reaction mixture is evaporated to dryness, and then dissolved in 50 ml. of water. After washing with ether, the aqueous solution is acidified with concentrated HCl. The acid solution is then extracted with ether, and the ether extract washed with water and evaporated to an oil. The oil crystallizes from isopropyl ether-hexane. Recrystallization from the same solvent mixture affords the product, m.p. 102—104° C.

Anal. Calc'd. for $C_{16}H_{23}O_5NS$ (MW 341.4): C, 56.29; H, 6.79; N, 4.10

Found: C, 56.13; H, 6.65; N, 3.66

EXAMPLE 19.

2-hydroxy-5-(2-methylpiperidinosulfonyl)benzoic acid

2-Fluoro-5-(3-methylpiperidinosulfonyl)benzoic acid (5 millimoles) and 25 ml. of 1N aqueous sodium hydroxide are heated overnight on a steam bath. The precipitate obtained on acidification of the alkaline solution is redissolved in 2.5 N sodium hydroxide and heating is continued on the steam bath for 3-1/2 hours to complete the reaction. Acidification with concentrated HCl yields the crystalline product, m.p. 189—190° C., which is purified by recrystallization from acetone-hexane.

Anal. Calc'd. for $C_{13}H_{17}O_5NS$ (MW 299.3): C, 52.17; H, 5.73; N, 4.68

Found: C, 52.19; H, 5.75; N, 4.52

EXAMPLE 20.

2-chloro-5-(2-oxopiperidinosulfonyl)benzoic acid

Delta-Amino-n-valeric acid (0.03 mole) is dissolved in 50 ml. of water and 30 ml. of 1 N aqueous sodium hydroxide. To this solution is added 2-chloro-5-chlorosulfonylbenzoic acid (0.03 mole) followed by 25 ml. of 2.5 N sodium hydroxide. After stirring at room temperature for about 25 minutes, the solution is acidified with concentrated hydrochloric acid. The precipitated 2-chloro-5-(4-carboxybutylsulfamyl)benzoic acid, on recrystallization from acetone-ethyl acetate, melts at 173—175° C.

Anal. Calc'd. for $C_{12}H_{13}O_6NSCl$ (MW 335.8): C, 42.92; H, 4.20; N, 4.17

Found: C, 43.06; H, 4.23; N, 3.90

2-Chloro-5-(4-carboxybutyl)sulfamylbenzoic acid (0.5 g.) is refluxed for two hours with 10 ml. of thionyl chloride, and then evaporated to dryness to obtain 2-chloro-5-(4-chloroformylbutylsulfamyl)benzoic acid. 0.4 g. is stirred at room temperature for about 15 minutes with 10 ml. of acetone and 2 ml. of water. The clear solution is evaporated to dryness. The residue is dissolved in hot methanol, and the 2-oxopiperidinosulfonyl product, m.p. 207.5—209.0° C., is obtained by addition of ether-hexane.

Anal. Calc'd. for $C_{12}H_{13}O_6NSCl$ (MW 317.75): C, 45.36; H, 3.81; N, 4.41

Found: C, 45.30; H, 3.83; N, 4.35

EXAMPLE 21.

2-chloro-5-(4-hydroxymethylpiperidinosulfonyl)benzoic acid

2-Chloro-5-chlorosulfonylbenzoic acid (5.0 g.) is added to a solution of 4-piperidyl carbinol (6.9 g.) in 40 ml. of methylene chloride. The solution is refluxed for 2 hours, cooled to room temperature and stirred overnight. The solution is evaporated to dryness, the gummy residue dissolved in 1 N sodium hydroxide, and the alkaline solution extracted twice with ether. The aqueous solution is acidified with concentrated hydrochloric acid, and the precipitate recovered by filtration. Recrystallization from ethyl acetate yields crystals, m.p. 185—187° C.

In the same way, the following products are prepared from the corresponding piperidyl carbinols:

		m.p.	
55	2-chloro-5-(2-hydroxymethylpiperidinosulfonyl)benzoic acid	136—138	55
	2-chloro-5-(3-hydroxymethylpiperidinosulfonyl)benzoic acid	191—193	

EXAMPLE 22.

2-chloro-5-(4-chloromethylpiperidinesulfonyl)benzoic acid

5 2-Chloro-5-(4-hydroxymethylpiperidinesulfonyl)benzoic acid (5.0 g.) is refluxed overnight with 50 ml. of thionyl chloride. After evaporation to dryness, the residue is dissolved in 70 ml. of acetone, 30 ml. of water added and the mixture is allowed to stand at room temperature for a half hour. The solution is then filtered and concentrated to half volume. On the addition of 20 ml. of water a precipitated oil is obtained which crystallizes on stirring. Recrystallization from acetone-benzene yields the product, m.p. 175—177° C.

10 *Anal.* Calc'd. for $C_{13}H_{15}O_3NSCl_2$ (MW 352.23): C, 44.33; H, 4.29; N, 3.98
Found: C, 44.85; H, 4.62; N, 3.82

In the same way, the following chloromethyl compounds are prepared from the products of the previous example:

		m.p.	
15	2-chloro-5-(2-chloromethylpiperidinesulfonyl)benzoic acid	134—136	15
	2-chloro-5-(3-chloromethylpiperidinesulfonyl)benzoic acid	190—192	

EXAMPLE 23.

2-chloro-5-(1,2,5,6-tetrahydropyridylsulfonyl)benzoic acid

20 2-Chloro-5-chlorosulfonylbenzoic acid (25.5 g.) is added in small portions over a 5 minute period with cooling to a solution of 1,2,5,6-tetrahydropyridine (25.0) in 200 ml. of water. After stirring at room temperature for a half hour, the reaction mixture is acidified with concentrated hydrochloric acid. The crystalline precipitate is filtered off and dissolved in 75 ml. of methylene chloride and 10 ml. of ether. After concentration to 50 ml., hexane is added to turbidity, affording crystals of the title compound, m.p. 180—182° C.

2-chloro-5-(3,4-dibromopiperidinesulfonyl)benzoic acid

25 2-Chloro-5-(1,2,5,6-tetrahydropyridylsulfonyl)benzoic acid (2.0 g.) is dissolved in 25 ml. of hot acetic acid. Bromine (3.0 ml.) is added dropwise while heating the acetic acid solution for 2 hours at 100° C. The solution is taken to dryness *in vacuo*. The residue is dissolved in 20 ml. of 1 N sodium hydroxide and then acidified with concentrated hydrochloric acid. The precipitated gum is dissolved in ether, which is then washed with water. The product crystallizes as the ether is replaced with benzene on a steam bath. Recrystallization from acetone-benzene yields the purified product, m.p. 176—178° C.

30 *Anal.* Calc'd. for $C_{12}H_{12}O_3NSBr_2Cl$ (MW 461.6): C, 31.22; H, 2.62; N, 3.03
Found: C, 31.44; H, 2.64; N, 3.01

EXAMPLE 24.

2-chloro-5-(3-methoxy-4-hydroxypiperidinesulfonyl)benzoic acid

40 2-Chloro-5-(3,4-dihydroxypiperidinesulfonyl)benzoic acid (4.0 g.) is heated for 16 hours at 90° C. with water (15 ml.), NaOH (1.0 g.) and dimethyl sulfate (0.5 ml.). Dimethyl sulfate and NaOH are added during the course of the reaction to maintain basicity. After cooling to room temperature, the reaction mixture is washed with ether and the aqueous phase is acidified with concentrated hydrochloric acid and decanted from the precipitated gum. The gum is dissolved in ethyl acetate and chromatographed on a silica gel column. The product fractions in the column effluent are identified by paper chromatography, with development in a solvent system of ethyl acetate-acetic acid. Concentration of the column fraction yields the product, m.p. 170—174° C.

50 *Anal.* Calc'd. for $C_{13}H_{16}O_5NSCl$ (MW 349.8): C, 44.63; H, 4.61; N, 4.04
Found: C, 44.14; H, 4.66; N, 3.74

EXAMPLE 25.

2-chloro-5-(4-methylpiperidinesulfonyl)benzoic acid

55 2-Chloro-5-(4-chloromethylpiperidinesulfonyl)benzoic acid (0.5 g.) is dissolved in 10 ml. of 5 N sodium hydroxide and refluxed for one hour. 10 ml. of water is then added and the mixture is acidified with concentrated hydrochloric acid. The precipitated

solid is chromatographed on a 10 g. silica gel column with a developing solvent system of 1:7 benzene:hexane containing 5% acetic acid. 2-Chloro-5-(4-methylenepiperidinosulfonyl)benzoic acid, m.p. 157—160° C., is isolated from the first fraction.

Anal. Calc'd. for $C_{13}H_{14}O_4NSCl$ (MW 316): C, 49.44; H, 4.47; N, 4.44
Found: C, 49.71; H, 4.44; N, 4.28

In the same way, the following compounds are prepared from the corresponding 5-chloromethylpiperidinosulfonyl benzoic acids:

		m.p.
2-chloro-5-(3-methylenepiperidinosulfonyl)benzoic acid		165—171° C.
2-bromo-5-(3-methylenepiperidinosulfonyl)benzoic acid		158—163° C.

EXAMPLE 26.

2-bromo-5-thiomorpholinosulfonylbenzoic acid

This product is prepared by the reaction of 2-bromo-5-chlorosulfonyl benzoic acid with excess thiomorpholine in methylene chloride. The product, m.p. 195.5—197.5° C., is purified by solution in aqueous sodium hydroxide, crystallization by acidifying the basic solution, and recrystallization from acetone-hexane.

Anal. Calc'd. for $C_{11}H_{12}O_4NS_2Br$ (MW 366.26): C, 36.07; H, 3.30; N, 3.82
Found: C, 36.24; H, 3.49; N, 3.96

2-bromo-5-thiomorpholinosulfonylbenzoic acid, 1'-oxide

The previous product, 1.8 grams (5 mmoles) is oxidized by treatment with 0.55 ml. (5.5 mmoles) 30% hydrogen peroxide in 20 ml. acetic acid. The reaction mixture is heated on the steam bath 40 minutes and cooled. The resulting crystalline product, 1.5 grams m.p. 237—239° C., is recovered by filtration and washed with acetic acid and methanol.

Anal. Calc'd. for $C_{11}H_{12}O_5NS_2Br$ (MW 382.26): C, 34.56; H, 3.16; N, 3.66
Found: C, 34.59; H, 3.20; N, 3.46

EXAMPLE 27.

2-chloro-5-(3,5-dimethylpiperidinosulfonyl)benzoyl chloride

2-Chloro-5-(3,5-dimethylpiperidinosulfonyl)benzoic acid (6.0 g.) is refluxed for 2-1/2 hours with 50 ml. of thionyl chloride, and then taken to dryness. The residue is triturated with 200 ml. of hot benzene-hexane (1:1), filtered and evaporated to obtain the dry product, m.p. 164—166.5° C.

N-[2-chloro-5-(cis-3,5-dimethylpiperidinosulfonyl)benzoyl]glycine

2-Chloro-5-(cis-3,5-dimethylpiperidinosulfonyl)benzoyl chloride (2.4 g.) and glycine (525 mg.) are dissolved in 30 ml. of water, 30 ml. of acetone and 14 ml. of 1 N sodium hydroxide. After stirring at room temperature for about 25 minutes, the reaction mixture is acidified with concentrated hydrochloric acid. The precipitated material is recrystallized from acetone (25 ml.)-hexane (40 ml.) to yield the product, m.p. 189.5—191.5° C.

Anal. Calc'd. for $C_{16}H_{21}O_5N_2SCl$ (MW 388.9): C, 49.41; H, 5.44; N, 7.20
Found: C, 49.55; H, 5.43; N, 7.19

EXAMPLE 28.

N-[2-chloro-5-(cis-3,5-dimethylpiperidinosulfonyl)benzoyl]-4-aminobutyric acid

2-Chloro-5-(cis-3,5-dimethylpiperidinosulfonyl)benzoyl chloride (1.75 g.) is added to a solution of 4-aminobutyric acid (0.54 g.) in water (30 ml.) acetone (30 ml.) and 1 N sodium hydroxide (10 ml.). After stirring at room temperature for a half hour, the acetone is removed by evaporation, and the aqueous solution is acidified with concentrated hydrochloric acid. The precipitate is dissolved in 50 ml. of hot acetone-methanol (1:1) and concentrated to half volume. Hexane is added to crystallize the product, m.p. 193—195° C.

Anal. Calc'd. for $C_{18}H_{23}O_5N_2SCl$ (MW 416.9): C, 51.85; H, 6.04; N, 6.72
Found: C, 51.43; H, 5.86; N, 6.47

Pharmaceutical Compositions

A dry solid pharmaceutical composition is prepared by blending the following materials together in the specified weight proportions:

5	2-chloro-5-(cis-3,5-dimethylpiperidinosulfonyl)benzoic acid	50	5
	sodium citrate	25	
	alginic acid	10	
	polyvinylpyrrolidone	10	
	magnesium stearate	5	

After the dried composition is thoroughly blended, tablets are punched from the mixture, each tablet being of such size as to contain 100 mg. of the active ingredient. Tablets are also prepared containing, respectively, 5, 10, 25 and 50 mg. of the active ingredient, by employing the appropriate proportions of 2-chloro-5-(cis-3,5-dimethylpiperidinosulfonyl)benzoic acid and excipient blend in each case.

A dry solid pharmaceutical composition is prepared by combining the following materials in the indicated weight proportions:

2-chloro-5-(cis-3,5-dimethylpiperidinosulfonyl)benzoic acid	50
calcium carbonate	20
polyethylene glycol, average molecular weight 4000	30

The dry mixture is thoroughly agitated to obtain a completely uniform blend. Soft elastic and hard gelatin capsules containing this composition are then prepared, employing sufficient material to provide each capsule with 100 mg. of active ingredient.

Test

Groups, each comprising 4 animals, of normal Sprague-Dawley (Charles River) male rats weighing from 160 to 220 grams are fed rat chow containing the test compounds for two overnight feeding periods. On the morning of the third day the animals are anaesthetized and bled from the abdominal aorta. The total plasma cholesterol is then determined by the method of J. J. Carr and I. J. Draker reported in Clin. Chem., 2, 353 (1956). Most of the tests are conducted at a concentration in the feed of 0.15 to 0.25 weight % of the compound under test, but lower levels are employed in some instances. The total quantity of test compound consumed is computed from feed consumption over the two-day period and is tabulated, in milligrams per kilogram body weight per day, along with the associated per cent cholesterol fall measured:

	Compound	% Cholesterol Fall	Daily Dosage mg/kg
5	2-chloro-5-(trans-dl-3,5-dimethylpiperidinosulfonyl)benzoic acid	35	126
	2-chloro-5-(cis-3,5-dimethylpiperidinosulfonyl)benzoic acid	44	112
	2-chloro-4-(cis-3,5-dimethylpiperidinosulfonyl)benzoic acid	inactive	182
10	2-bromo-5-(cis-3,5-dimethylpiperidinosulfonyl)benzoic acid	40	120
	2-bromo-5-(3-benzyloxypiperidinosulfonyl)benzoic acid	25	114
	2-chloro-5-(3-benzyloxypiperidinosulfonyl)benzoic acid	26	129
15	2-chloro-5-(2,5-dimethylpiperidinosulfonyl)benzoic acid	35	110
	2-bromo-5-(3-trifluoromethyl-4-chlorophenylsulfamyl)benzoic acid	38	174
	2-chloro-5-(3,5-dimethylmorpholinosulfonyl)benzoic acid	29	156
20	2-isopropoxy-5-(3-methylpiperidinosulfonyl)benzoic acid	22	149
	2-hydroxy-5-(3-methylpiperidinosulfonyl)benzoic acid	35	134
	2-piperidino-5-(piperidinosulfonyl)benzoic acid	35	129
25	2-bromo-5-(1-methyl-4-hydroxypropylsulfamyl)benzoic acid	16	279
	2-bromo-5-(3-phenylpropylaminosulfonyl)benzoic acid	26	131
	2-bromo-5-(4- <i>m</i> -tolyl-1-piperazinylsulfonyl)benzoic acid	20	123
30	2-bromo-5-(2-carboxyphenylsulfamyl)benzoic acid	37	273
	2-chloro-5-(2-oxopiperidinosulfonyl)benzoic acid	30	136
	2-pyrrolidinyl-5-(3,5-dimethylpiperidinosulfonyl)benzoic acid	31	215
	N-[2-chloro-5-(cis-3,5-dimethylpiperidinosulfonyl)benzoyl]glycine	35	180
	N-[2-chloro-5-(cis-3,5-dimethylpiperidinosulfonyl)benzoyl]-4-aminobutyric acid	44	129
	2-amino-5-(cis-3,5-dimethylpiperidinosulfonyl)benzoic acid	26	143
	2-morpholino-5-(3-benzyloxypiperidinosulfonyl)benzoic acid	29	139
	2-chloro-5-(3,5-dipropylpiperidinosulfonyl)benzoic acid	39	47
	2-diethylamino-5-(diethylaminosulfonyl)benzoic acid	21	44
	2-bromo-5-[2-(<i>p</i> -chlorophenyl)ethylaminosulfonyl]benzoic acid	21	22
	2-bromo-5-(N-phenyl-N-butylsulfamyl)benzoic acid	17	236
	2-bromo-5-(4-methoxybenzylsulfamyl)benzoic acid	20	363
	2-bromo-5-(4-phenylpiperidinosulfonyl)benzoic acid	28	226
	2-bromo-5-(3-azabicyclo[3,2,2]nonan-3-ylsulfonyl)benzoic acid	32	228

Compound	% Cholesterol Fall	Daily Dosage mg/kg
2-bromo-5-(1,2,5,6-tetrahydro-1-pyridylsulfonyl)benzoic acid	22	149
2-chloro-5-(2,2-dimethylthiomorpholinosulfonyl)benzoic acid	35	139
2-chloro-5-(2-benzylpiperidinosulfonyl)benzoic acid	32	124
2-chloro-5-(4-phenyl-4-ethoxypiperidinosulfonyl)benzoic acid	13	136
2-chloro-5-(3-hydroxypiperidinosulfonyl)benzoic acid	23	135
2-bromo-5-(3-hydroxymethylpiperidinosulfonyl)benzoic acid	20	23
2-chloro-5-(3,4-dibromopiperidinosulfonyl)benzoic acid	21	46
2-chloro-5-(cis-3,4-dibenzoyloxy-1-pyrrolidinylsulfonyl)benzoic acid	25	126
2-chloro-5-(3-methoxy-4-hydroxypiperidinosulfonyl)benzoic acid	15	141
2-bromo-5-(thiomorpholinosulfonyl)benzoic acid, 1'-oxide	20	270
2-bromo-5-cyclooctylsulfamylbenzoic acid	25	181
2-bromo-5-cyclohexylmethylsulfamylbenzoic acid	27	126
2-chloro-5-(3,5-dibenzylpiperidinosulfonyl)benzoic acid	24	131
2-bromo-5-(3,5-dibenzylpiperidinosulfonyl)benzoic acid	38	118
2-bromo-5-(3-hydroxypiperidinosulfonyl)benzoic acid	26	126
2-(4-methylpiperidino)-5-(4-methylpiperidinosulfonyl)benzoic acid	35	140
2-chloro-5-(3-methoxypiperidinosulfonyl)benzoic acid	20	152
2-(1-hexanemethylencimino)-5-(3,5-dimethylpiperidinosulfonyl)-benzoic acid	14	45
2-bromo-5-(1-hexamethyleneiminosulfonyl)benzoic acid	28	212
2-bromo-5-(1-heptamethyleneiminosulfonyl)benzoic acid	23	218
2-chloro-5-(1-octamethyleneiminosulfonyl)benzoic acid	31	133
2-piperidino-5-(1-heptamethyleneiminosulfonyl)benzoic acid	20	24
2-piperidino-5-(1-hexamethyleneiminosulfonyl)benzoic acid	23	44
2-chloro-5-(2-[p-chlorophenyl]ethylaminosulfonyl)benzoic acid	30	49
2-diethylamino-5-(3,5-dimethylpiperidinosulfonyl)benzoic acid	41	77

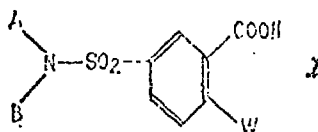
Dosage /kg	Compound	% Cholesterol Fall	Daily Dosage mg/kg
49	2-n-butylamino-5-(3,5-dimethylpiperidinosulfonyl)benzoic acid	14	130
39	2-di-n-butylamino-5-(3,5-dimethylpiperidinosulfonyl)benzoic acid	22	9
24	2-(3,5-dimethylpiperidino)-5-(piperidinosulfonyl)benzoic acid	21	49
36	2-(3,5-dimethylpiperidino)-5-dibutylsulfonylbenzoic acid	12	22
35	2-chloro-5-(4-chloromethylpiperidinosulfonyl)benzoic acid	21	127
23	2-chloro-5-(4-benzyloxymethylpiperidinosulfonyl)benzoic acid	23	20
46	2-chloro-5-(4-chloropiperidinosulfonyl)benzoic acid	16	48
26	2-chloro-5-(3,4-dichloropiperidinosulfonyl)benzoic acid	40	104
41	2-chloro-5-(3-benzylpiperidinosulfonyl)benzoic acid	31	25
70	2-chloro-5-(3-methylenepiperidinosulfonyl)benzoic acid	30	21
81	2-bromo-5-(3-hydroxypiperidinosulfonyl)benzoic acid	26	126
26	2-bromo-5-(3-benzylpiperidinosulfonyl)benzoic acid	35	23
31	2-bromo-5-(3-methylenepiperidinosulfonyl)benzoic acid	31	39
18	2-(3-methylpiperidino)-5-(3-methylpiperidinosulfonyl)benzoic acid	22	136
26	2-(cis-3,5-dimethylpiperidino)-5-(cis-3,5-dimethylpiperidino-sulfonyl)benzoic acid	37	195
10	2-(3-methylpiperidino)-5-piperidinosulfonylbenzoic acid	12	23
32	2-chloro-5-(3,5'-dichloro-diethylaminosulfonyl)benzoic acid	23	125
45	2-bromo-5-(N-ethyl, N-[2-p-chlorophenylethyl]aminosulfonyl)-benzoic acid	39	32
12	2-bromo-5-(N-methyl, N-[2-p-chlorophenylethyl]aminosulfonyl)-benzoic acid	31	21
18	2-piperidino-5-diethylaminosulfonylbenzoic acid	22	47
24	2-bromo-5-(N-propyl, N-[2-p-chlorophenylethyl]aminosulfonyl)-benzoic acid	34	21
14	2-bromo-5-(N-isobutyl, N-[2-p-chlorophenylethyl]aminosulfonyl)-benzoic acid	34	22
19	2-bromo-5-(N-benzyl, N-[2-p-chlorophenylethyl]aminosulfonyl)-benzoic acid	34	23
77	2-bromo-5-(1-pyrrolidinylsulfonyl)benzoic acid	19	169
	2-bromo-5-(diethylaminosulfonyl)benzoic acid	33	267

24	1,353,357	24	2.
Compound	% Cholesterol Fall	Daily Dosage mg/kg	
2-bromo-5-(dimethylaminosulfonyl)benzoic acid	10	247	
2-chloro-5-(dimethylaminosulfonyl)benzoic acid	27	253	
2-piperidino-5-(3-azabicyclo[3,2,2]nonan-3-ylsulfonyl)benzoic acid	35	153	
2-bromo-5-(cyclopentylsulfamyl)benzoic acid	12	229	5
2-bromo-5-sulfamyl benzoic acid	10	185	
2-chloro-5-sulfamyl benzoic acid	10	265	
2-chloro-5-(3-hydroxymethylpiperidinosulfonyl)benzoic acid	14	131	
2-chloro-5-(3,5-diethylpiperidinosulfonyl)benzoic acid	42	5	
2-bromo-5-(3,5-diethylpiperidinosulfonyl)benzoic acid	36	273	10
2-chloro-5-(4-hydroxymethylpiperidinosulfonyl)benzoic acid	15	222	
2-bromo-5-(2-methylpiperidinosulfonyl)benzoic acid	29	72	15
2-bromo-5-(2-carboxy-5-chlorophenylsulfamyl)benzoic acid	13	282	
2-bromo-5-(4,4-dimethylpiperidinosulfonyl)benzoic acid	30	122	
2-bromo-5-(octamethylenciminosulfonyl)benzoic acid	37	158	2
2-piperidino-5-(3,4-dipropylpiperidinosulfonyl)benzoic acid	18	23	
2-piperidino-5-(cis-3,5-dimethylpiperidinosulfonyl)benzoic acid	32	37	
2-dibutylamino-5-(piperidinosulfonyl)benzoic acid	14	5	
2-dimethylamino-5-(3,5-dimethylpiperidinosulfonyl)benzoic acid	11	22	
2-chloro-5-(2-hydroxymethylpiperidinosulfonyl)benzoic acid	14	124	
2-chloro-5-(3-hydroxymethylpiperidinosulfonyl)benzoic acid	14	131	
2-chloro-5-(2-chloromethylpiperidinosulfonyl)benzoic acid	38	95	
2-chloro-5-(3-chloromethylpiperidinosulfonyl)benzoic acid	18	5	
2-chloro-5-(4-methylenepiperidinosulfonyl)benzoic acid	29	39	
2-bromo-5-[N-isopropyl-N-2-(p-chlorophenyl)ethylamino-sulfonyl]benzoic acid	27	24	
2-piperidino-5-[2-(p-chlorophenyl)ethylaminosulfonyl]benzoic acid	33	251	
2-chloro-5-(3,4-dihydroxypiperidinosulfonyl)benzoic acid	11	225	
2-bromo-5-(N-methyl-N-cyclohexylsulfamyl)benzoic acid	13	226	
2-bromo-5-(3,5-dimethyl-1-piperazinylsulfonyl)benzoic acid	11	226	

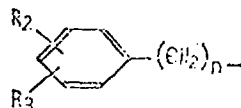
Dosage
/kg

WHAT WE CLAIM IS:—

1. Compounds of the formula



and the amides, C_1-C_6 alkyl esters and pharmaceutically acceptable salts thereof wherein A is hydrogen, C_1-C_6 alkyl, cycloalkyl of from 5 to 8 carbon atoms, benzyl or phenyl; B is



wherein

n has a value from zero to 3;

R^2 and R^3 are each hydrogen, chloro, bromo, alkyl or alkoxy of from one to four carbon atoms, carboxy, trifluoromethyl, phenyl, benzyl or benzyloxy; and

W is, chloro, bromo, hydroxy, C_1-C_6 alkoxy, amino, mono- or di- C_1-C_6 alkyl amino, benzylamino, phenethylamino, piperidino, mono- or di- C_1-C_6 alkylpiperidino, pyrrolidinyl, hexamethylenimine, or morpholino; and

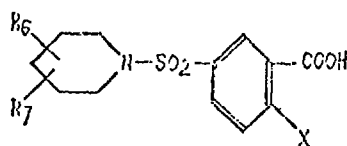
when A is hydrogen or C_1-C_6 alkyl B is also cycloalkyl of from 5 to 8 carbon atoms; and

A and B when taken together with the nitrogen atom to which they are attached comprise a heterocyclic ring selected from morpholino, thiomorpholino, and the S-oxide thereof, piperazinyl, hexamethylenimine, heptamethylenimine, octamethylenimine, 3-azabicyclo[3,2,2]nonanyl, tetrahydropyridyl or mono- and di-substituted derivatives of said heterocyclic rings;

said substituents being alkyl, alkyloxy or alkyloxyalkyl of one to four carbon atoms in each alkyl group, hydroxy, chloro, bromo, trifluoromethyl, phenyl, tolyl, benzyl, benzyloxy, chloromethyl or hydroxymethyl;

or the heterocyclic ring is unsubstituted-, mono- or di-substituted piperidino, said substituents being alkyl, alkyloxy or alkyloxyalkyl of one to four carbon atoms in each alkyl group, hydroxy, chloro, bromo, trifluoromethyl, oxo, methylene, phenyl, tolyl, benzyl, benzyloxy, benzyloxymethyl, chloromethyl or hydroxymethyl.

2. A compound of the formula



and the amides, C_1-C_6 alkyl esters and salts thereof with pharmacologically acceptable bases, wherein

X is chloro, bromo, piperidino, mono- or di-lower-alkylpiperidino, hexamethylenimine or morpholino;

R^5 is alkyl, alkyloxy or alkyloxyalkyl of one to four carbon atoms in each alkyl group, hydroxy, chloro, bromo, trifluoromethyl, phenyl, tolyl, benzyl, benzyloxy, benzyloxymethyl, chloromethyl or hydroxymethyl; and

R^6 is hydrogen, alkyl, alkoxy or alkyloxyalkyl of one to four carbon atoms in each alkyl group, hydroxy, chloro, bromo, trifluoromethyl, phenyl, tolyl, benzyl, benzyloxy, benzyloxymethyl, chloromethyl or hydroxymethyl or R_6 and R_7 taken together may also signify oxo or methylene.

3. The compound according to claim 2 wherein X is chloro, bromo or morpholino, R^6 is 3-benzyloxy and R^7 is hydrogen.

4. The compound according to claim 2 wherein X is bromo, R^6 is 4-phenyl and R^7 is hydrogen.

5. The compound according to claim 2 wherein X is chloro, R^6 is 2-benzyl and R^7 is hydrogen.



6. The compound according to claim 2 wherein X is chloro, R⁶ is 4-phenyl and R⁷ is 4-ethoxy.

7. The compound according to claim 2 wherein X is chloro, R⁶ is 3-hydroxy and R⁷ is hydrogen.

8. The compound according to claim 2 wherein X is chloro, R⁶ is 3-bromo and R⁷ is 4-bromo.

9. The compound according to claim 2 wherein X is chloro, R⁶ is 3-methoxy and R⁷ is 4-hydroxy.

10. The compound according to claim 2 wherein X is chloro, R⁶ is 4-chloromethyl and R⁷ is hydrogen.

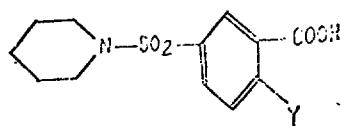
11. The compound according to claim 2 wherein X is bromo, R⁶ is 3-hydroxy-methyl and R⁷ is hydrogen.

12. The compound according to claim 2 wherein X is 4-methylpiperidino, R⁶ is 4-methyl and R⁷ is hydrogen.

13. The compound of claim 2 wherein X is chloro, R⁶ is 3-methoxy and R⁷ is hydrogen.

14. The compound of claim 2 wherein X is 1-hexamethyleneimino, R⁶ is 3-methyl and R⁷ is 5-methyl.

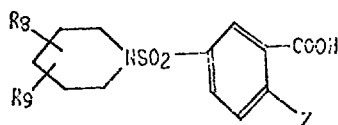
15. A compound of the formula



and the amides, C₁-C₆ alkyl esters and salts thereof with pharmacologically acceptable bases, wherein Y is piperidino or mono- or di-C₁-C₆-alkyl piperidino.

16. The compound of claim 15 wherein Y is 3,5-dimethylpiperidino.

17. A compound of the formula



wherein Z is chloro or bromo and R⁸ and R⁹ are each C₁-C₆ alkyl or benzyl.

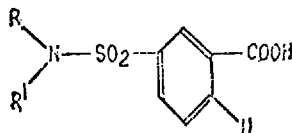
18. The compound of claim 17 wherein Z is chloro or bromo, R⁸ is 3-methyl and R⁹ is 5-methyl.

19. The compound of claim 17 wherein Z is chloro, R⁸ is 2-methyl and R⁹ is 5-methyl.

20. The compound of claim 17 wherein Z is chloro, R⁸ is 3-propyl and R⁹ is 5-propyl.

21. The compound according to claim 17 wherein Z is chloro or bromo, R⁸ is 3-benzyl and R⁹ is 5-benzyl.

22. A compound of the formula



and the amides, C₁-C₆ alkyl esters and salts thereof with pharmacologically acceptable bases, wherein

U is chloro, bromo, di-lower-alkylamino, piperidino, mono- or di-lower-alkyl-piperidino, morpholine, or hexamethyleneimino; and

R and R' together with the nitrogen to which they are attached comprise a heterocyclic ring selected from morpholine, thiomorpholine, piperazine, hexamethyleneimino, heptamethyleneimino, octamethyleneimino, 3-azabicyclo[3,2,2]nonan-yl, tetrahydropyridyl or mono- and di-substituted derivatives of said heterocyclic rings;

said substituents being alkyl, alkyloxy or alkyloxyalkyl of one to four carbon atoms in each alkyl group, hydroxy, chloro, bromo, trifluoromethyl, phenyl, tolyl, benzyl, benzyloxy, chloromethyl or hydroxymethyl.



23. The compound of claim 22 wherein U is chloro and R and R' together with the nitrogen form a 3,5-dimethylmorpholino ring.

24. The compound according to claim 22 wherein U is bromo and R and R' together with the nitrogen form a 4-*m*-tolyl-1-piperazinyl ring.

25. The compound of claim 22 wherein U is bromo and R and R' together with the nitrogen form a 1,2,5,6-tetrahydro-1-pyridyl ring.

26. The compound of claim 22 wherein U is chloro and R and R' together with the nitrogen form a 2,2-dimethylthiomorpholino ring.

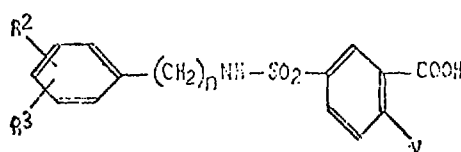
27. The compound of claim 22 wherein U is bromo or piperidino and R and R' together with the nitrogen form a 3-azabicyclo(3,2,2)nonan-3-yl ring.

28. The compound of claim 22 wherein U is bromo and R and R' together with the nitrogen form a 1-hexamethyleneimino ring.

29. The compound of claim 22 wherein U is bromo or piperidino and R and R' together with the nitrogen form a 1-heptamethyleneimino ring.

30. The compound of claim 22 wherein U is chloro and R and R' together with the nitrogen form a 1-octamethyleneimino ring.

31. A compound of the formula



and the amides, C_1-C_6 alkyl esters and salts thereof with pharmacologically acceptable bases, wherein

n has a value from 0 to 3;

V is bromo, piperidino or mono- or di- C_1-C_6 -alkylpiperidino; and

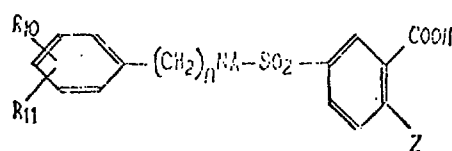
R^2 and R^3 are each hydrogen, chloro, bromo, alkyl and alkoxy of from one to four carbon atoms, carboxy, trifluoromethyl, phenyl, benzyl or benzyloxy.

32. The compound according to claim 31 wherein V is bromo, n is 0, R^2 is 3-trifluoromethyl and R^3 is 4-chloro.

33. The compound according to claim 31 wherein V is bromo, n is 0, R^2 is 2-carboxy and R^3 is hydrogen.

34. The compound according to claim 31 wherein V is bromo, n is 2, R^2 is *p*-chloro and R^3 is hydrogen.

35. A compound of the formula



and the amides, C_1-C_6 alkyl esters and salts thereof with pharmacologically acceptable bases, wherein

n has a value from 0 to 3;

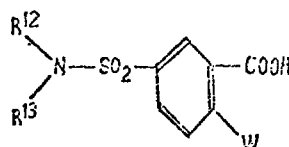
A is C_1-C_6 alkyl, cycloalkyl of 5 to 8 carbon atoms, benzyl or phenyl;

Z is chloro or bromo; and

R^{10} and R^{11} are each hydrogen, C_1-C_6 alkyl, chloro, bromo or phenyl.

36. The compound according to claim 35 wherein Z is bromo, n is 2, A is methyl, ethyl, propyl, isobutyl or benzyl, R^{10} is *p*-chloro and R^{11} is hydrogen.

37. A compound of the formula

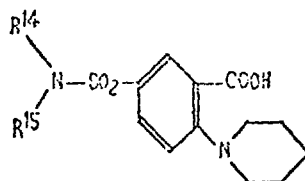


wherein W is chloro, bromo, piperidino or mono- and di-lower-alkylpiperidino; R^{12} is hydrogen or C_1-C_6 alkyl; and R^{13} is cycloalkyl of 5 to 8 carbon atoms.

38. The compound according to claim 37 wherein W is bromo, R^{12} is hydrogen and R^{13} is cyclooctyl or cyclohexylmethyl.



39. A compound of the formula



wherein R^{14} and R^{15} are each C_1-C_6 alkyl.

40. The compound of claim 39 wherein R^{14} and R^{15} are each ethyl.

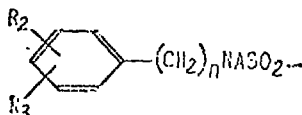
41. The method for reducing blood lipid levels which comprises administering to a hyperlipemic mammal other than human a compound selected from 5-sulfamylbenzoic acids of formula I in claim 1 and the amides, C_1-C_6 alkyl esters and salts thereof with pharmacologically acceptable bases, said compound being substituted in the 2-position by chloro, bromo, hydroxy, C_1-C_6 alkoxy, amino, mono or di- C_1-C_6 -alkyl amino, benzylamino, phenethylamino, piperidino, mono- or di- C_1-C_6 -alkyl-piperidino, pyrrolidinyl, hexamethylenimine or morpholino.

42. The method according to claim 41 wherein the sulfamyl group is piperidino-sulfonyl or substituted piperidinosulfonyl having up to two substituents each being alkyl, alkyloxy or alkyloxyalkyl of one to four carbon atoms in each alkyl group, hydroxy, chloro, bromo, trifluoromethyl, phenyl, tolyl, benzyl, benzyloxy, benzyloxy-methyl, chloromethyl or hydroxymethyl.

43. The method of claim 41 wherein the sulfamyl group is $RR'NSO_2-$, wherein R and R' together with the nitrogen to which they are attached comprise a heterocyclic ring selected from morpholino, thiomorpholino, and the S-oxide thereof, piperazinyl, hexamethylenimine, heptamethylenimine, octamethylenimine, 3-azabicyclo[3,2,2]-nonanyl or tetrahydropyridyl or mono- and di-substituted derivatives of said heterocyclic rings;

said substituents being alkyl, alkyloxy or alkyloxyalkyl of one to four carbon atoms in each alkyl group, hydroxy, chloro, bromo, trifluoromethyl, phenyl, tolyl, benzyl, benzyloxy, chloromethyl or hydroxymethyl.

44. The method of claim 41 wherein the sulfamyl group is



wherein

n has a value from 0 to 3;

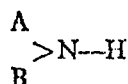
A is hydrogen, C_1-C_6 alkyl, cycloalkyl of 5 to 8 carbon atoms, benzyl or phenyl; and

R^2 and R^3 are each hydrogen, chloro, bromo, alkyl or alkoxy of from one to four carbon atoms, carboxy, trifluoromethyl, phenyl, benzyl or benzyloxy.

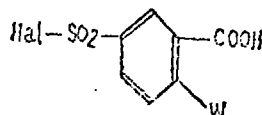
45. The method of claim 41 wherein the sulfamyl group is $R^4R^5NSO_2-$ wherein R^4 is hydrogen or C_1-C_6 alkyl and R^5 is C_1-C_6 alkyl or cycloalkyl of 5 to 8 carbon atoms.

46. A process for preparing a compound of the formula I as defined in claim 1, which comprises

a) reacting an amine of the formula



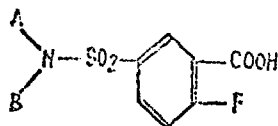
wherein A and B are as defined in claim 1, with a compound of the formula



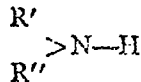
wherein Hal is halogen and W is as defined in claim 1;



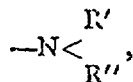
b) reacting a compound of the formula



1) with an amine of the formula



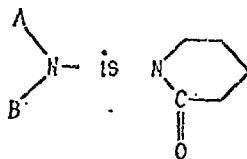
wherein R' and R'' are the same or different and are alkyl of up to 6 carbon atoms and when taken together comprise a piperidine ring to form a compound of Formula I wherein W is



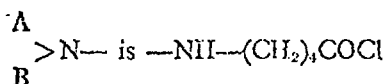
2) with a straight or branched chain lower alkanol of up to 6 carbon atoms in the presence of a base to form a compound of the Formula I wherein W is $-\text{O}-$ lower alkyl, or

3) with an alkali metal hydroxide to form a compound of Formula I wherein W is $-\text{OH}$ and, if desired, subsequently reacting a compound of Formula I wherein A and B when taken together with the nitrogen to which they are attached form a hydroxy-

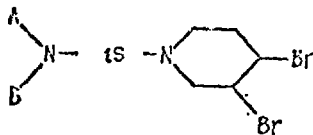
compound which may if desired be converted to the corresponding *exo*-methylene compound and when required, reducing a compound of Formula I wherein W is methylpiperidino group, with thionyl chloride to form the corresponding chloromethyl benzylamino to the corresponding amine and, when required subsequently forming



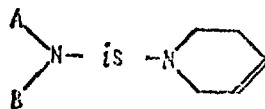
by cyclization of the corresponding precursor wherein



and when required forming a compound of Formula I wherein

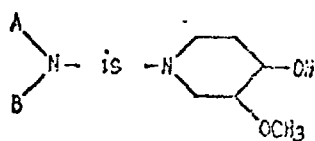


by bromination of a compound of Formula I wherein

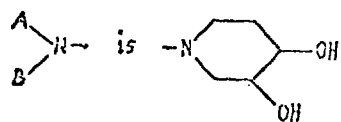


and when required forming a compound of the Formula I wherein

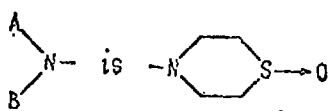




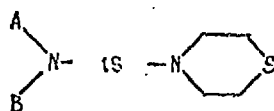
by O-alkylation of a compound of Formula I wherein



and when required forming a compound of Formula I wherein



by oxidation of a compound of Formula I wherein



and when required converting the COOH group of the compound of Formula I via the acid chloride to a CONHCH₂COOH or CONHC₂H₅COOH group by reaction with the appropriate amino acid and, if desired subsequently converting a compound of Formula I wherein A is hydrogen to N-alkyl by N-alkylation.

47. A compound of Formula I according to claim 1, prepared by a process substantially as herein described.

48. A process for preparing a compound of Formula I according to claim 1 substantially as herein described.

STEVENS, HEWLETT & PERKINS,
Chartered Patent Agents,
5, Quality Court, Chancery Lane, London, W.C.2.

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