983,661

PATENT SPECIFICATION

NO DRAWINGS

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COMPLETE SPECIFICATION

Benzyloxyamines and Compositions Containing Them

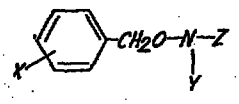
We, CARTER PRODUCTS, INC., a corporation organized under the laws of the State of Maryland, United States of America, of 2 Park Avenue, New York, State of New York, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to novel compositions of matter and methods for lowering blood cholesterol.

The invention consists in the novel steps, methods and compositions herein shown and described.

It is an object of this invention to provide novel compositions of matter which have the effect of lowering blood cholesterol upon administration of such compositions to warm-blooded animals, including humans. A further object of this invention is to provide novel compounds which are useful as active ingredients in compositions useful in lowering blood cholesterol in warm-blooded animals, including humans.

It has been found that some of the objects of this invention may be realized by employing as the active ingredient for reducing blood cholesterol a composition containing a dosage unit quantity as hereinafter defined of one or more benzyloxyamines of the general formula:



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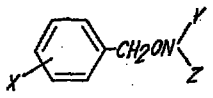
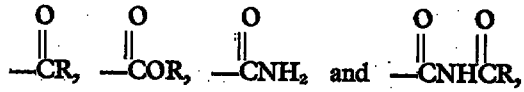
wherein X is hydrogen, one or two alkyls of 1 to 3 carbon atoms or halogen; Y is hydrogen, —C(=O)—R, —C(=O)—OR, —C(=O)—NH_2, or —C(=O)—NH—C(=O)—R and Z is hydrogen or aralkyl; or wherein X is alkoxy, Y is hydrogen, —C(=O)—R or —C(=O)—OR and Z is aralkyl; or wherein X is trifluoromethyl, Y is —C(=O)—R or —C(=O)—OR and Z is hydrogen or aralkyl; wherein in each case R is an alkyl, alkoxyalkyl or aryl group; and the acid addition salts of the above when Y and Z are hydrogen atoms or Z is an aralkyl group; wherein when Z is an aralkyl group it can be substituted by one or two alkyl groups, an alkoxy group, a halogen atom or a trifluoromethyl group on the aryl portion of the aralkyl group; and wherein the aralkyl groups hereinabove contain 7 to 12 carbon atoms and when R is alkyl it contains 1 to 20 carbon atoms and when R is aryl it contains 6 to 10 carbon atoms.

Some of the preferred benzyloxyamines have the formula:

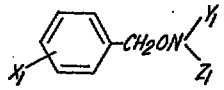


wherein X is hydrogen, short-chain alkyl of 1 to 3 carbons and halogen: Y is hydrogen,

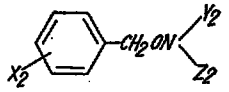
[*Price 4s. 6d.*]



wherein R is alkyl and aryl; and Z is hydrogen or arylalkyl; and, (2) compounds having the formula



wherein X_1 is a short-chain alkoxy group; Y_1 is hydrogen, $-\overset{O}{\overset{\|}{C}}R_1$ or $-\overset{O}{\overset{\|}{C}}OR_1$, wherein R_1 is alkyl or aryl; and Z_1 is an arylalkyl group; and (3) compounds having the formula:



wherein X_2 is a trifluoromethyl group, Y_2 is $-\overset{O}{\overset{\|}{C}}R_2$ or $-\overset{O}{\overset{\|}{C}}OR_2$, wherein R_2 is alkyl or aryl, and Z_2 is hydrogen or an arylalkyl group.

In the above compounds, when Y or Y_1 is hydrogen the compounds may also be employed in the form of their physiologically acceptable salts such as the hydrohalides (preferably the hydrochloride) salts with other readily tolerated inorganic acids such as sulphuric or phosphoric acid, and salts with the commonly used organic acids such as acetic, citric, maleic, and tartaric acid.

In the compounds of formula I hereinabove there is included some compounds which have been described in the prior art. For convenience sake, compounds having the aforedescribed chemical structures will be referred to hereinafter as "benzyloxyamine" compounds.

Examples of benzyloxyamine compounds which are the preferred active ingredients of the present invention are shown in Table A given hereinafter. Examples of different types of benzyloxyamine compounds useful as the active ingredients of this invention, including the preferred active ingredients of Table A, are given in Tables B to H given hereinafter.

As indicated hereinbefore, it has been found that the benzyloxyamine compounds used in accordance with this invention when taken internally have the effect of lowering the blood cholesterol content, e.g., the amount of cholesterol in the blood of the warm-blooded animal taking the active ingredients of the present invention. In forming the novel compositions of this invention, the active ingredient is incorporated in a suitable carrier such as, for example, a pharmaceutical carrier, beverage or foodstuff. Any suitable pharmaceutical carrier may be used for formulating the compositions of this invention, such as, for example, starch, lactose, glucose, sucrose, gelatin, powdered licorice, powdered marshmallow, powdered tragacanth, malt, rice flour, powdered althaea, magnesium carbonate or chalk. Among the liquid pharmaceutical carriers which may be utilized are ethyl alcohol, propylene glycol, polyethylene glycol, water, saline, glycerine and water mixtures, glucose syrup, honey, mucilage of acacia, syrup of acacia, mucilage of tragacanth, and glyceride of starch. Also, the active ingredient may be incorporated in a foodstuff such, for example, as incorporating it in butter or margarine. The preferred carrier for a given active ingredient depends upon the desired use and nature of the active ingredient. For example, a liquid active ingredient is preferably administered in the form of a soft gelatin capsule containing a therapeutic dose of the active ingredient. A crystalline solid active ingredient is preferably administered in the form of a capsule or tablet. When the composition of this invention is in the form of a solid, the active ingredient is generally in an amount from 25 to 95% by weight of the solid composition. When the composition of this invention is in the form of a solution, the active ingredient is generally in an amount of 0.1 gram to 90 grams per 100 grams of solution.

An *in vivo* technique which has been valuable in the determination of cholesterol lowering action of drugs is the procedure of Cuthbertson, *et al.*, 1959 (*Brit J. Nutrition*, Volume 13, page 227). Using the formulation given by these investigators, a stock diet (A) which is essentially normal rodent diet comparable to that available from commercial food dealers, and a special high fat diet (B) are prepared. The "B" diet features 2% cholesterol; 0.5% cholic acid; and specially prepared hydrogenated arachis oil, 22%; also corn starch, 45.5%; crude casein, 25%; choline chloride, 1%; and salt and vitamin mixtures. All percentages are by weight. The hydrogenated arachis oil specifies a 92°F. melting point with limits of 90—93°F. Drugs to be evaluated are added to Diet B at fixed graded concentrations in the diet, ranging from 0.125 to 2%. Male Charles River albino weanling rats weighing approximately 50 grams are placed in individual cages equipped with specially designed self-feeder devices which permit accurate determination of daily food intake. Groups of six animals, kept in individual cages, receive each of the concentrations of drugs. In addition, a group of six on the stock diet (A) serves as a negative control, and a high fat diet (B) group of six serves as a positive control. The rats are

placed on the special diets for fourteen consecutive days, after which time one to three millilitre blood samples are obtained by intracardiac puncture, and subjected to assay for their cholesterol content. The animals serving as the negative control group (Diet A) maintain a cholesterol level in the normal range which is less than 100 mg/100 ml. of serum, whereas the positive control group (Diet B) showed a marked elevated level of the order of 800 mg/100 ml.

The active ingredients used in accordance with this invention, when incorporated in Diet B following the above described Cuthbertson, *et al.* method, exhibit a cholesterol lowering activity. In general, when such active ingredients are in concentrations of about 0.5% in Diet B, the percent reduction in the blood cholesterol level is about 25% or more as compared to the positive control (Diet "B") without the active ingredient. Thus, if a positive control group given Diet B shows a blood cholesterol level of about 800 mg/100 ml, the active ingredients of this invention, if incorporated in such Diet B, in a concentration of about 0.5%, would generally reduce the blood cholesterol level of this positive group to about 600 mg/100 ml or lower. Effective drugs usually show a direct relationship between the concentration of drug in the diet, and the percent reduction in the blood cholesterol levels as compared to the positive control (Diet B without drug).

While the aforedescribed *in vivo* method of Cuthbertson, *et al* is the preferred procedure for determining the efficacy of an agent regarding its cholesterol lowering activity, the *in vitro* method based on the procedure described by N.P.L. Bucher in the Journal of the American Chemical Society, Vol. 75, p. 498 (1953), has also been found useful for this purpose. This *in vitro* procedure employs radioactive techniques and measures the ability of a compound to inhibit the conversion of acetate or other cholesterol precursors to cholesterol using liver homogenate as a source of the enzyme system. Compounds which are effective in preventing cholesterol formation under these conditions would presumably be effective in bringing about a lowering of the serum cholesterol content of the animal.

2 g. of liver from freshly killed Sprague-Dawley rats is homogenized at 0°C. in a medium containing 8.5 mgm. nicotinamide, 3.5 mgm. magnesium chloride, 3.2 mgm. glutathione, and 3.0 mgm. ethylenediaminetetraacetic acid tetrasodium salt in 2.5 ml. of 0.1 M. phosphate buffer, pH 7.4. The homogenate is centrifuged at 0° and 2 ml. of the supernatant liquid, free from hepatic cells, is combined with 1 mgm. adenosine triphosphate, 1 mgm. diphosphopyridine nucleotide, 0.5 mgm. of the compound under test, and 1 ml. of sodium acetate 1—C^{14} solution containing 0.2 mgm. of acetate with a count of about 2 microcuries of radioactivity. Controls are prepared in the same manner except that no compound is added. All compounds are run in triplicate.

The biosynthesis of cholesterol is effected by incubating the above mixture in a metabolic shaker for three hours at 37°C. under an oxygen-carbon dioxide mixture (95.5). After three hours the mixture is transferred to a glass ampoule where it is subjected to saponification along with 0.5 mg. of carrier cholesterol using 6 ml. of 15% alcoholic potassium hydroxide at 80° for 17 hours. After removal of the alcohol the cholesterol is isolated by extracting four times with petroleum ether. The extracts are combined, dried, and evaporated to dryness. The residue is dissolved in 1 ml. of hot 80% ethanol and treated with an excess of 1% digitonin, also in 80% ethanol, and heated for 5 minutes at 100°C. After standing for 12 to 18 hrs. at 5°C., the cholesterol digitonide is separated on a paper filter disc, washed in succession with 85% ethanol, an acetone-ether mixture (1:2), and anhydrous ether. After drying, the precipitate is counted in a thin window gas flow Geiger Counter and the results recorded as counts per minute per mgm. cholesterol. Comparison with the control gives the index of inhibition. When the active ingredients of this invention are tested by the aforedescribed procedure, a significant inhibition of cholesterol biosynthesis is usually effected.

A number of compositions found to exhibit outstanding activity in lowering blood cholesterol levels, when tested by the *in vivo* procedure of Cuthbertson, *et al.* method described hereinbefore in detail, are shown in Table A. In each instance, the carrier was Diet B containing the active ingredient in a concentration of 0.5%. The activity (% cholesterol lowering) was obtained in the manner described hereinbefore, i.e. determining the percent reduction in the blood cholesterol levels by incorporating the active ingredient in Diet B as compared to Diet B without the active ingredient.

By the term "dosage unit" as used herein is meant a physically discrete unit containing an individual quantity of the active material necessary for association with a pharmaceutical diluent or carrier, the quantity of active material being such that one or more units are required for a single therapeutic administration. It does not include solutions in water alone or other common solvents alone except when such are packaged in ingestible containers or have been prepared so as to be acceptable for parenteral injection.

TABLE A

Compound No.	Compound	% Reduction
4	*p*-chlorobenzyloxyamine	70
5	N-benzyl-N-benzyloxyamine hydrochloride	68
29	benzyl N-benzyl carbethoxyhydroxamate	77
53	N-benzyl-N-benzyloxy urea	75
71	benzyl N-benzyl benzhydroxamate	77
73	benzyl N-benzyl acethydroxamate	78
8	N-(*m*-methylbenzyl)-N-(*m*-methylbenzyloxy)amine	80
9	N-benzyl-N-(*m*-methylbenzyloxy)amine	81
10	N-(*o*-methylbenzyl)-N-benzyloxyamine	74
11	N-(*o*-methylbenzyl)-N-(*o*-methylbenzyloxy)amine hydrochloride	86
13	N-(*p*-methoxybenzyl)-N-(*p*-methoxybenzyloxy)amine	43
16	N(γ-phenylpropyl)-N-benzyloxyamine hydrochloride	89
26	*p*-chlorobenzyl N-*p*-chlorobenzyl carbethoxyhydroxamate	80
27	*m*-methylbenzyl N-*m*-methylbenzyl carbethoxyhydroxamate	73
30	benzyl N-benzyl carbophenoxyhydroxamate	80
31	*o*-methylbenzyl N-*o*-methylbenzyl carbethoxyhydroxamate	61
32	benzyl N-*m*-methylbenzyl carbethoxyhydroxamate	79
33	benzyl N-benzyl carbomethoxyhydroxamate	78
34	benzyl N-benzyl carbo(β-methoxyethoxy) hydroxamate	85
36	benzyl N-benzyl carbo-*n*-hexyloxyhydroxamate	68
37	benzyl N-*o*-methylbenzyl carbethoxyhydroxamate	59
41	*o*-ethylbenzyl N-*o*-ethylbenzyl carbethoxyhydroxamate	82
42	*p*-isopropylbenzyl N-*p*-isopropylbenzyl carbethoxy hydroxamate	62
45	*m*-trifluoromethylbenzyl N-*m*-trifluoromethylbenzyl carbethoxyhydroxamate	65
46	*p*-methoxybenzyl N-*p*-methoxybenzyl carbethoxy-hydroxamate	48
48	benzyl N-γ-phenylpropyl carbethoxyhydroxamate	84
61	benzyl N-benzyl isobutyrhydroxamate	82
64	benzyl N-benzyl propionhydroxamate	42
65	benzyl N-benzyl *n*-octanohydroxamate	82
66	benzyl N-*o*-methylbenzyl acethydroxamate	38

From the data shown in Table A, it is seen that the preferred active ingredients of this invention may be categorized as follows, reference being made to the general structural formulas given hereinbefore:

1. Those compounds wherein X is hydrogen, Y is —COR, and Z is arylalkyl, as exemplified by the compounds 29, 30, 32, 33, 34, 36, 37 and 48 shown in Table A;

2. Those compounds wherein X is hydrogen, Y is —CR and Z is arylalkyl, as exemplified by the compounds 61, 64, 65, 66, 71 and 73 shown in Table A;

3. Those compounds wherein X is alkyl, Y is —COR, and Z is arylalkyl as exemplified by the compounds 27, 31, 41 and 42 shown in Table A;

4. Those compounds wherein X is hydrogen, Y is hydrogen and Z is arylalkyl as exemplified by the compounds 5, 10 and 16 of Table A;

5. Those compounds wherein X is alkyl, Y is hydrogen and Z is arylalkyl, as exemplified by compounds 8, 9, and 11 shown in Table A;

6. Those compounds wherein X is halogen, Y is —COR and Z is arylalkyl, as exemplified by compound 26 shown in Table A;

7. Those compounds wherein X is hydrogen, Y is —CNH_2, and Z is arylalkyl, as exemplified by compounds 53 shown in Table A;

8. Those compounds wherein X is halogen, Y is hydrogen and Z is hydrogen, as exemplified by compound 4 shown in Table A;

9. Those compounds wherein X_1 is alkoxy, Y_1 is hydrogen and Z_1 is arylalkyl as exemplified by compound 13 in Table A;

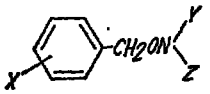
10. Those compounds wherein X_1 is alkoxy, Y_1 is —COR and Z_1 is arylalkyl as exemplified by compound 46 in Table A;

11. Those compounds wherein X_2 is trifluoromethyl, Y_2 is —COR and Z_2 is arylalkyl as exemplified by compound 45 of Table A.

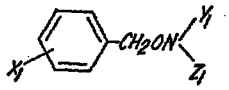
The active ingredients used in accordance with this invention are non-toxic in amounts required to effect significant reduction of blood cholesterol. In general, the daily dose for an average person (e.g., about 150 pounds in weight) is between 50—3000 mg., and, preferably, 200 to 1000 mg.

Of the preferred active ingredients, the first six compounds listed in Table A are previously described compounds, while the remaining listed compounds are new compounds.

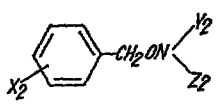
While a few of the active ingredients used in accordance with this invention are previously described compounds, e.g., N-benzyl-N-benzyloxyamine, for the most part, the active ingredients of this invention are novel compounds. The novel benzyloxyamines of formula IA of the present invention as distinguished from the novel compositions of this invention (containing a benzyloxyamine of formula I, which includes benzyloxyamines besides those defined by formula IA) may be defined as (1) compounds having the following formula:



wherein X is lower alkyl or halogen Y is hydrogen, —CR, —COR, —CNH_2, or —CNHCR, wherein R is selected from the group consisting of alkyl and aryl; and Z is hydrogen or arylalkyl with the proviso that when X is a halogen atom and Z is aralkyl then Y cannot be hydrogen) and wherein when X in the above formula is halogen, Y is hydrogen, —CR or —CNHCR and only one of the Y and Z groups may be hydrogen; and (2) compounds having the formula:



wherein X_1 is a short-chain alkoxy group; Y_1 is hydrogen, —CR_1 or —COR_1, wherein R_1 is alkyl or aryl; and Z_1 is an arylalkyl group, (3) compounds having the formula:

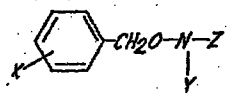


wherein X_2 is a trifluoromethyl group, Y_2 is —CR_2 or —COR_2, wherein R_2 is alkyl or

aryl, and Z_2 is hydrogen or an arylalkyl group.

In addition to the above-mentioned compounds, compounds which are novel and may be used as the active ingredient in accordance with this invention are given in Table I, given hereinafter, said compounds being included in Tables B to H.

In accordance with this invention there is provided novel benzyloxyamines of the general formula:

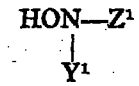


...IA

wherein X is hydrogen, one or two alkyls of 1 to 3 carbon atoms or halogen, Y is hydrogen, $-\overset{O}{\overset{\|}{C}}-R$, $-\overset{O}{\overset{\|}{C}}-OR$, $-\overset{O}{\overset{\|}{C}}-NH_2$ or $-\overset{O}{\overset{\|}{C}}-NH-\overset{O}{\overset{\|}{C}}-R$ and Z is hydrogen or aralkyl; or wherein X is alkoxy and Y is hydrogen, $-\overset{O}{\overset{\|}{C}}-R$ or $-\overset{O}{\overset{\|}{C}}-OR$ and Z is aralkyl; or wherein X is trifluoromethyl and Y is $-\overset{O}{\overset{\|}{C}}-R$ or $-\overset{O}{\overset{\|}{C}}-OR$ and Z is hydrogen or aralkyl wherein R in each case is an alkyl, alkoxyalkyl or aryl group and the acid addition salts of the above when Y and Z are hydrogen atoms or Z is an arylalkyl group wherein when Z is an aralkyl group it can be substituted by one or two alkyl groups, an alkoxy group, a halogen atom or a trifluoromethyl group on the aryl portion of the aralkyl group; and wherein the aralkyl groups hereinabove contain 7 to 12 carbon atoms and when R is alkyl it contains 1 to 20 carbon atoms and when R is aryl it contains 6 to 10 carbon atoms; with the proviso that (1) when X is a halogen atom and Z is a hydrogen atom then Y cannot be a hydrogen atom or a carbethoxy group $-\overset{O}{\overset{\|}{C}}-NH_2$, (2) when X is a halogen atom and Z is aralkyl, Y cannot be hydrogen and (3) when X is a hydrogen atom and Z is a hydrogen atom or a benzyl group, then Y cannot be a hydrogen atom or the group $-\overset{O}{\overset{\|}{C}}-A$, wherein A is $-NH_2$, $-OC_2H_5$, $-CH_3$ or phenyl.

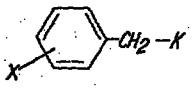
Also, in accordance with this invention there is provided a process for preparing the novel benzyloxyamines of formula IA which comprises:

(a) aralkylating a suitably protected hydroxylamine derivative of the formula



...IIA

wherein Z^1 and Y^1 are respectively Z and Y as previously defined or are hydrolyzable protective groups with one or two moles of a benzyl halide or sulfonate of the formula:



...IIIA

wherein K is a halogen atom or the residue of a sulfonic acid or ester and X is as defined hereinabove and then (1) if desired, when the protective group or the hydroxylamine derivative is $-\overset{O}{\overset{\|}{C}}-R$ or $-\overset{O}{\overset{\|}{C}}-OR$, hydrolyzing to form a product of formula IA in which Z is hydrogen, (2) if desired, when the protective group is $-\overset{O}{\overset{\|}{C}}-OR$ treating with ammonia to obtain a compound of formula IA wherein Y is $-\overset{O}{\overset{\|}{C}}-NH_2$, (3) hydrolyzing all other protective groups to form a product of formula IA in which Z is hydrogen, and

(b) if desired, when Y and Z in the product of step (a) are hydrogen atoms or one of them is an aralkyl group, then doing one of the following:

(1) acylating with an agent capable of providing the radical $R-\overset{O}{\overset{\|}{C}}-$ to convert Y into $-\overset{O}{\overset{\|}{C}}-R$

(2) reacting with cyanic acid to convert Y into $-\overset{O}{\overset{\|}{C}}-NH_2$

(3) reacting with a haloformate of the formula Halogen—C(=O)—OR; a carbonate of the formula RO—C(=O)—OR; or with phosgene followed by treatment of the resulting carbamoyl chloride with ROH or NH_3, to convert Y into —C(=O)—NH_2 or —C(=O)—OR

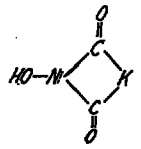
(4) forming the non-toxic acid addition salt wherein R is as defined hereinabove.

In the alkylation step the suitably protected hydroxylamine derivative (IIA) is one which makes for O-benzylation. The protective group is one which is readily hydrolyzed after benzylation. Typical examples of suitably protected hydroxylamines (IIA) are as follows

(1) HO—NH—C(=O)—R (hydroxamic acids)

(2) H—O—NH—C(=O)—OR (carboalkyl - (aryl)oxy hydroxamic acids)

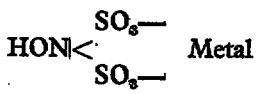
(3)



wherein K is an organic residue to form a cyclic imide, such as the phthalimido or succinimido group

(4) aldoximes or ketoximes

(5) a hydroxylamine disulfonic acid salt

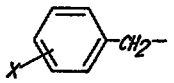


preferably the alkali metal salt.

When the hydroxamic acid (1) or the carboalkyl(aryl)oxyhydroxamic acids (2) are benzylated there is formed a product of formula IA. If desired, this product can be hydrolyzed so that a compound of formula IA is formed wherein Y and Z are both hydrogen or Y is hydrogen and Z arylalkyl. When any of the other suitably protected hydroxylamine derivatives (IIA), i.e., (3), (4) or (5) are benzylated the resulting product is treated in a known manner to remove the protective group and form a product of formula IA in which Y and Z are both hydrogen.

The benzylating agent of formula IIIA can be a benzyl halide, preferably a benzyl chloride or it can be a benzyl sulfonate such as a benzyl toluenesulfonate.

In one of the embodiments of the invention, one mole each of different benzylating agents of formula IIIA are used one after the other to form a product of formula IA in which Z and



are different.

Typical acylating agents capable of providing the radical R—C(=O)— are the acid chlorides, the acid anhydrides and the acid esters.

When forming the ureas by use of cyanic acid it is sometimes desirable to generate the cyanic acid *in situ*.

When carboalkyl(aryl)oxylating by treatment with a carbonate of the formula RO—C(=O)—OR it is preferable to effect the reaction by heating in the presence of a basic catalyst.

To form the carbamoyl chloride one treats the benzyloxyamine with equimolar amounts of phosgene and the product can then be reacted, with or without isolation, with alcohol to form the carboalkyl(aryl)oxy hydroxamates or with ammonia to form the benzyloxyureas.

In preparing the novel benzyl carbethoxyhydroxamate compounds of this invention, hydroxyurethane is reacted with the appropriate benzyl halide (e.g., parachlorobenzylchloride) under the influence of alkali in alcoholic solution. By varying the molar ratio of the benzyl halide to the hydroxyurethane employed one can obtain:

1. The benzyl carbethoxyhydroxamate substantially exclusively, or
2. A mixture of this compound and the corresponding benzyl N-benzyl carbethoxyhydroxamate, or
3. The benzyl N-benzyl carbethoxyhydroxamate substantially exclusively.

In general, an equimolar ratio of the reactants leads to the benzyl carbethoxyhydroxamate compound while the use of a 2:1 molar ratio of the benzyl halide to hydroxyurethane gives essentially the benzyl N-benzyl carbethoxyhydroxamate.

Alternatively, novel benzyl carboalkyl(aryl)oxyhydroxamates of this invention can be obtained by the reaction of an appropriate benzyloxyamine with an alkyl or aryl chloroformate in a suitable inert organic solvent

medium. Similarly, novel benzyl N-arylalkyl carboalkyl(aryl)oxyhydroxamates can be prepared from N-arylalkyl benzyloxyamines and the appropriate chloroformate.

Moreover, novel benzyl N-arylalkyl carboalkyl(aryl)oxyhydroxamates of this invention may be obtained by the reaction of the appropriate benzyl carboalkyl(aryl)oxyhydroxamate with a suitable arylalkyl halide in alcoholic solution in the presence of alkali.

The benzyloxyamine compounds and the N-arylalkyl benzyloxyamine compounds of this invention may be obtained by alkaline hydrolysis of the corresponding carbethoxyhydroxamate.

In preparing the novel benzyl acyl(aroyl)hydroxamates and benzyl N-arylalkyl acyl(aroyl)hydroxamates of this invention, the selected benzyloxamine or N-arylalkyl benzyloxyamine is reacted with the appropriate acyl or aroyl halide in a suitable aqueous or non-aqueous medium. An excess of the amine or other suitable base (e.g., pyridine, sodium hydroxide, trialkylamine) may be employed as acid acceptor to promote the reaction.

Substituted N-benzyloxy ureas or N-arylalkyl-N-benzyloxy ureas can be obtained by the reaction of suitable benzyloxyamines or N-arylalkyl benzyloxyamines with isocyanic acid esters or other derivatives of isocyanic acid in an inert solvent medium.

Some of the benzyl carboalkyl(aryl)oxyhydroxamates and benzyl N-arylalkyl carboalkyl(aryl)oxyhydroxamates comprising the active ingredients of this invention have also been referred to in the chemical literature as substituted N-benzyloxy urethanes and substituted N - benzyloxy - N - arylalkyl urethanes. The description of these compounds as used herein is consistent with Beilstein and other recognized authorities on organic chemical nomenclature.

The following are specific examples for the preparation of active ingredient compounds and therapeutic compositions formed in accordance with this invention.

Example I

Preparation of *o*-Chlorobenzyloxyamine hydrochloride

Compound 1

A solution of 11.7 grams of *o*-chlorobenzyl carbethoxyhydroxamate and 6.2 grams of sodium hydroxide in 50% aqueous ethanol was refluxed for two hours. The ethanol was removed by distillation and the residue extracted with ether. This extract was washed with water and dried over sodium sulfate. The addition of concentrated hydrochloric acid resulted in the precipitation of the desired compound. Recrystallization from methanol gave 3.5 grams of the pure hydrochloride, m.p. 143—145°C. Other compounds prepared using this procedure were benzyloxyamine hydrochloride, (Compound 2); *m*-methylbenzyloxyamine (Compound 3); and *p*-chlorobenzyloxyamine (Compound 4). The latter two compounds were isolated as the free amines and were purified by distillation under reduced pressure. These components had the physical constants and analytical values tabulated in Table B given hereinafter.

Example II

Preparation of N-Benzyl-N-benzyloxyamine hydrochloride

Compound 5

N-benzyl-N-benzyloxyamine is converted to its hydrochloride salt by the addition of an excess of concentrated hydrochloric acid to an ether solution of the amine. The product, which separates in the form of a slightly water-soluble crystalline solid, is purified by crystallization from methanol.

Example III

Preparation of N-(*p*-Methylbenzyl)-N-(*p*-methylbenzyloxy) amine

Compound 6

A solution of 14.6 grams of *p*-methylbenzyl N-*p*-methylbenzyl carbethoxyhydroxamate prepared by the method described in Example VI and 6.8 grams of sodium hydroxide in 300 ml. of 95% ethanol and 100 ml. of water was refluxed for one and one-half hours. The reaction mixture was then concentrated under vacuo and then poured into water. N-(*p*-methylbenzyl)-N-(*p*-methylbenzyloxy) amine in the form of a water-insoluble material was filtered off, thoroughly washed with water, and then crystallized from methanol. Yield 8.3 grams. N-(*p*-methylbenzyl)-N-(*p*-methylbenzyloxy) amine is converted to its hydrochloride salt by the addition of an excess of concentrated hydrochloric acid to an ether solution of the amine. The product, which separates in the form of a slightly water-soluble crystalline solid, is purified by crystallization from methanol, m.p. 188—190°C.

Example IV

Preparation of N-(*p*-Isopropylbenzyl)-N-(*p*-isopropylbenzyloxy) amine hydrogen sulfate

Compound 7

A solution of 63 grams of *p*-isopropylbenzyl N - *p* - isopropylbenzyl carbethoxyhydroxamate prepared by the method of Example VI and 20 grams of sodium hydroxide in 400 ml. of 50% aqueous ethanol was refluxed for two hours. The mixture was distilled at atmospheric pressure until the head temperature was 100°C. The residue was extracted with ether. This extract was washed with water until neutral and was dried over sodium sulfate. The resulting solution was added slowly to a cool solution of 17 grams of sulfuric acid in 200 ml. of anhydrous ether. The desired compound precipitated in

the form of colorless crystals. The yield was 39 grams.

EXAMPLE V

Preparation of N-(*m*-Methylbenzyl)-N-(*m*-methylbenzyloxy) amine

Compound 8

A solution of 13.0 grams of *m*-methylbenzyl N - *m* - methylbenzyl carbethoxyhydroxamate prepared as described in Example VI and of 4.8 grams of sodium hydroxide in 150 ml. of 65% aqueous ethanol was refluxed for one hour. The ethanol was removed by vacuum distillation and the residue was diluted with 100 ml. of water. The oily precipitate was extracted with ether and the extract was washed with water and dried over sodium sulfate. The ether was removed and the residue distilled in vacuo. The fraction boiling at 118—120°C./0.07 mm. consisted of the desired compound. Yield 7.8 grams.

The physical properties and analytical values for the compounds prepared by the methods of these examples and of compounds 9—17 which may be prepared by the same methods are summarized in Table C given hereinafter.

EXAMPLE VI

Preparation of *p*-Chlorobenzyl N-*p*-chlorobenzyl carbethoxyhydroxamate

(Compound 26) and

p-Chlorobenzyl carbethoxyhydroxamate

(Compound 18)

52.5 grams of hydroxyurethane in 500 ml. of 95% ethanol are combined with stirring at 25°C. with a solution of 56 grams potassium hydroxide in 100 ml. of 95% ethanol. 121 grams of *p*-chlorobenzylchloride is added at once and the temperature maintained at about 30°C. using external cooling. The mixture is stirred overnight and the potassium chloride removed by filtration. The filtrate is concentrated in vacuo and dissolved in 400 ml. of ether. The ether solution is extracted thoroughly with cold 10% aqueous sodium hydroxide. The resulting ether solution is dried, the solvent removed and the residue distilled under reduced pressure. 45 grams (25% theoretical) of *p*-chlorobenzyl N-*p*-chlorobenzyl carbethoxyhydroxamate is obtained.

The aforedescribed sodium hydroxide extract is acidified with hydrochloric acid while cooling. The mixture is then extracted with ether, the ether solution dried, the solvent evaporated, and a solid residue obtained. This product is purified by crystallization from ethanol. 34.5 grams (30% theoretical) of *p*-chlorobenzyl carbethoxyhydroxamate is obtained in the form of white crystals.

EXAMPLE VII

Preparation of *m*-Methylbenzyl carbethoxyhydroxamate

(Compound) 19 and

m-Methylbenzyl N-*m*-methylbenzyl carbethoxyhydroxamate

(Compound 27)

38 grams of hydroxyurethane in 150 ml. of 95% ethanol, 36 grams of potassium hydroxide in 200 ml. of 95% ethanol, and 100 grams of alpha-bromo-*m*-xylene were reacted as described in Example VI above. The ether extract was dried, freed from solvent by distillation, and the residue fractionated under reduced pressure. 17 grams (22%) of pure *m*-methylbenzyl carbethoxyhydroxamate was obtained distilling at 100—103°C. at 0.05 mm.

Further distillation of the aforedescribed residue yielded 38.5 grams (34%) of *m*-methylbenzyl N-*m*-methylbenzyl carbethoxyhydroxamate. b.p. 144—146°C. at 0.05 mm. Hg.

EXAMPLE VIII

Using the method described in Example VI, hydroxyurethane and *p*-methylbenzyl chloride were reacted to give *p*-methylbenzyl N - *p* - methylbenzyl carbethoxyhydroxamate (Compound 28). The purified product was obtained as a colorless liquid distilling at 137°C. at 0.1 mm. Hg.

EXAMPLE IX

Preparation of Benzyl carboisobutoxyhydroxamate

(Compound 20)

Solutions of 27.3 grams of isobutyl chloroformate in 1 liter of anhydrous ether and of 49.2 grams of benzyloxyamine in 250 ml. of anhydrous ether were combined with stirring and cooling. The reaction was allowed to go to completion by standing at room temperature overnight. The precipitate of benzyloxyamine hydrochloride was removed by filtration and was washed with ether. The combined ether solutions were evaporated in vacuo. The residue solidified upon cooling. Recrystallization from 150 ml. of 70% aqueous methanol furnished 33.5 grams of the desired compound, m.p. 37—38°C.

EXAMPLE X

Preparation of *m*-Trifluoromethylbenzyl carbethoxyhydroxamate

(Compound 21)

A solution of sodium ethylate was prepared by dissolving 6.8 grams of sodium metal in 500 ml. of anhydrous ethanol. To this was added with cooling 31.2 grams of hydroxyurethane and subsequently with continued

cooling 71 grams of *m*-trifluoromethylbenzyl bromide. The temperature did not exceed 30°C. during these operations. The mixture was stirred for 30 minutes at room temperature and for two hours at reflux temperature. The mixture was diluted with 250 ml. of water and neutralized by the addition of hydrochloric acid. The ethanol was removed by distillation and the residue was extracted with ether. This extract was washed with dilute hydrochloric acid and with water and was dried over sodium sulfate. Evaporation of the ether furnished a solid residue which afforded, upon recrystallization from carbon tetrachloride, 38 grams of the pure compound, m.p. 78—80°C.

The *m*-trifluoromethylbenzylbromide used in this example as well as other benzylhalides can be prepared by halogenation of the corresponding benzyl alcohols or toluenes using well-known reactions.

The physical constants and analytical values for the compounds of these examples and for compounds 22—25 inclusive, which may be prepared using these methods, are summarized in Table D given hereinafter, and in part in Table E given hereinafter.

Example XI

Preparation of Benzyl N-benzyl carbethoxyhydroxamate
(Compound 29)

A solution of 210 grams of hydroxyurethane and of 460 ml. of benzyl chloride in 1 liter of ethanol was heated to reflux. One liter of a 4-N solution of potassium hydroxide in ethanol was added within four hours. Subsequently, 1.5 liters of ethanol was removed by distillation and the residue was diluted with 1 liter of ether. The solution was decanted from the inorganic salts which were washed with three portions of ether. The combined solution was stirred while 30 ml. of concentrated hydrochloric acid was added. The mixture was filtered and the filtrate was washed with dilute bicarbonate solution and water until neutral. The resulting ether solution was dried over sodium sulfate and the ether was removed by distillation. Fractionation of the residue *in vacuo* furnished 382 grams of the desired compound distilling at 142—145°C./0.3 mm.

Example XII

Preparation of Benzyl N-benzyl carbophenoxyhydroxamate
(Compound 30)

A solution of 42.6 grams of N-benzyl-N-benzyloxyamine in 100 ml. of anhydrous ether was added dropwise to a cooled solution of 15.7 grams of phenyl chloroformate in 500 ml. of anhydrous ether. The resulting mixture was stirred for three hours at room temperature. The solid precipitate was removed by filtration and the filtrate was evaporated *in vacuo*. The residue solidified upon standing at room temperature. Recrystallization from methanol furnished 26.6 grams of the desired compound, m.p. 59—61°C.

Example XIII

Preparation of *o*-Methylbenzyl N-*o*-methylbenyzl carbethoxyhydroxamate
(Compound 31)

Solutions of 28.4 grams of hydroxyurethane in 150 ml. of ethanol and of 35.7 grams of potassium hydroxide in 250 ml. of ethanol were combined at room temperature. 100 grams of alpha-bromo-*o*-xylene was added dropwise with stirring while the temperature was maintained at 25—30°C. by external cooling. Subsequently, the mixture was heated to reflux and the ethanol was removed by distillation until the vessel temperature had reached 85°C. The residue was diluted with ether and was filtered from the inorganic salts. The resulting solution was washed with water and dried over sodium sulfate. The ether was removed by distillation and the residue was fractionated under vacuum. The fraction boiling at 143°C./0.04 consisted of the desired compound. Yield 59.4 grams.

Example XIV

Preparation of Benzyl N-*m*-methylbenzyl carbethoxyhydroxamate
(Compound 32)

A solution of sodium ethylate was prepared from 2.3 grams of sodium metal and 200 ml. of anhydrous ethanol. To this was added 19.5 grams of benzyl carbethoxyhydroxamate and subsequently there was added with cooling and stirring 18.5 grams of alpha-bromo-*m*-xylene over a period of 15 minutes. The mixture was heated to reflux for two hours and the ethanol was removed by distillation until the vessel temperature reached 85°C. The residue was diluted with water and was extracted with ether. This extract was washed with water and was dried over sodium sulfate. The ether was removed by distillation. Fractionation of the residue *in vacuo* furnished 18.3 grams of product, b.p. 136°C./0.02 mm.

The physical constants of the compounds prepared as described in these examples, and of compounds 33—49 inclusive, which may be prepared by these methods, are summarized in Table E given hereinafter.

Example XV

Preparation of N-Benzyloxy urea
(Compound 50)

A solution of 4.5 grams of potassium cyanate in 50 ml. of water was added to a stirred slurry of 8.0 grams of benzyloxyamine hydrochloride in 150 ml. of water. Stirring was continued for 15 minutes and the colorless solid was filtered and washed

with water. Recrystallization from ethanol furnished 4.9 grams of the desired product, m.p. 139—141°C.

EXAMPLE XVI

Preparation of N-Benzyl-N-benzyloxy-N¹-acetyl urea

(Compound 51)

Solutions of 21.3 grams of N-benzyl-N-benzyloxyamine in 300 ml. of anhydrous ether and of 8.5 grams of acetyl isocyanate in 200 ml. of anhydrous ether were combined at room temperature. The mixture was allowed to stand overnight and the ether was removed by distillation. The solid residue was extracted exhaustively with pentane. The extract yielded 22.4 grams of the desired compound, m.p. 61—62°C.

The physical constants and analytical values for these compounds, and for compounds 52 and 53, prepared using the same methods, are tabulated in Table F given hereinafter.

EXAMPLE XVII

Preparation of Benzyl acethydroxamate

(Compound 54)

A solution of 31.7 grams of acetyl chloride in 50 ml. of anhydrous ether was added dropwise with stirring to a solution of 98.7 grams of benzyloxyamine in 400 ml. of anhydrous ether. The mixture was stirred for two hours at room temperature. The precipitate of benzyloxyamine hydrochloride was removed by filtration and was washed with ether. The combined filtrates were evaporated at atmospheric pressure and the residue was fractionated *in vacuo*. The fraction distilling at 109°C./0.2 mm. consisted of the desired compound. Yield 42.4 grams.

Other compounds prepared by this method using the appropriate acid chloride were compounds 55—60. Analytical data and physical constants for these compounds appear in Table G given hereinafter.

EXAMPLE XVIII

Preparation of Benzyl N-benzyl isobutyrhydroxamate

(Compound 61)

A solution of 32 grams of N-benzyl-N-benzyloxyamine in 50 ml. of anhydrous ether was added with stirring and cooling to a solution of 8 grams of isobutyrl chloride in 150 ml. of anhydrous ether. The mixture was stirred for two hours and the precipitate was filtered and washed with ether. The combined filtrate was evaporated and the residue was fractionated *in vacuo*. The fraction distilling at 133—136°C./0.1 mm. consisted of the desired compound. The yield was 14.6 grams.

EXAMPLE XIX

Preparation of *m*-Trifluoromethylbenzyl N-*m*-trifluoromethylbenzyl acethydroxamate

(Compound 62)

1.10 parts by weight of N-(*m*-trifluoromethylbenzyl) - N - (*m* - trifluoromethylbenzyloxy) amine hydrochloride was dissolved in 25 parts by weight of pyridine and 0.9 parts by weight of acetyl chloride was added with cooling. The mixture was kept overnight at room temperature and was poured into an excess of cold water. The oily precipitate was extracted with ether and the extract washed with dilute hydrochloric acid and water. The extract was dried over sodium sulfate and the solvent evaporated. The oily residue was distilled under reduced pressure in a short path unit at 90°C./0.002 mm. The distillate consisted of the pure title compound. The yield was 0.8 parts of pure product.

EXAMPLE XX

Preparation of *p*-Chlorobenzyl N-*p*-chlorobenzyl benzhydroxamate

(Compound 63)

A mixture of 25.4 grams of N-(*p*-chlorobenzyl)-N-(*p*-chlorobenzyloxy) amine hydrochloride, 200 ml. of water, 14 ml. of 50% sodium hydroxide, 250 ml. of ether, and 12.3 grams of benzoyl chloride was stirred vigorously for two hours. The ether layer was separated and was washed with dilute sodium hydroxide, water, dilute hydrochloric acid and again with water until neutral. The ether was dried over sodium sulfate and the solvent was removed by distillation. The residue solidified upon cooling. Recrystallization from ethanol furnished 22.5 grams of the desired compound.

Physical constants and analytical values for the above-described compounds, and for compounds 64—75 inclusive, are presented in Table H given hereinafter.

The following are examples of compositions formed in accordance with this invention which have the effect of lowering blood cholesterol upon administration of such compositions in warm-blooded animals, including humans.

EXAMPLE XXI

A tablet is compressed from a composition having the following formula:

N - (*p* - methylbenzyl) - N - (*p*-methylbenzyloxy) amine	200 mgm.
Corn Starch	20 „
Lactose	20 „
Magnesium Stearate	2 „
Alginic Acid	4 „

EXAMPLE XXII

A tablet is compressed from a composition having the following formula:

N - (*p* - methylbenzyl) - N - (*p*-methylbenzyloxy) amine hydrochloride	200 mgm.
Corn Starch	20 „
Lactose	20 „
Magnesium Stearate	2 „
Alginic Acid	4 „

EXAMPLE XXIII

A table is compressed from a composition having the following formula:

N - benzyl - N - benzyloxy urea	200 mgm.
Corn Starch	20 „
Lactose	20 „
Magnesium Stearate	2 „
Alginic Acid	4 „

EXAMPLE XXIV

A tablet is compressed from a composition having the following formula:

p - chlorobenzyl carbethoxyhydroxamate	200 mgm.
Corn Starch	20 „
Lactose	20 „
Magnesium Stearate	2 „
Alginic Acid	4 „

EXAMPLE XXV

100 mg. of *m*-methylbenzyl N-*m*-methylbenzyl carbethoxyhydroxamate is mixed with 1.5 cc. of cottonseed oil and the resulting solution is encapsulated in a soft gelatin capsule.

EXAMPLE XXVI

200 mg. of benzyl N-benzyl carbethoxyhydroxamate is mixed with 0.5 cc. of cottonseed oil and the resulting solution is encapsulated in a soft gelatin capsule.

EXAMPLE XXVII

200 mg. of N-benzyl-N-benzyloxyamine is mixed with an equal volume of polyethylene glycol 400 and the resulting solution is encapsulated in a soft gelatin capsule.

EXAMPLE XXVIII

200 mg. of N-benzyl-N-benzyloxyamine hydrochloride is mixed with an equal volume of polyethylene glycol 400 and the resulting mixture is encapsulated in a soft gelatin capsule.

EXAMPLE XXIX

200 mg. of benzyl carbethoxyhydroxamate is mixed with an equal volume of polyethylene glycol 400 and the resulting solution is encapsulated in a soft gelatin capsule.

EXAMPLE XXX

200 mg. of *m*-methylbenzyl carbethoxyhydroxamate is mixed with an equal volume of propylene glycol and the resulting solution is encapsulated in a soft gelatin capsule.

EXAMPLE XXXI

200 mg. of *p*-chlorobenzyl N-*p*-chlorobenzyl carbethoxyhydroxamate is mixed with 0.5 cc. of cottonseed oil and the resulting solution is encapsulated in a soft gelatin capsule.

EXAMPLE XXXII

100 mg. of *p*-methylbenzyl N-*p*-methylbenzyl carbethoxyhydroxamate is mixed with 1.5 cc. of cottonseed oil and the resulting solution is encapsulated in a soft gelatin capsule.

EXAMPLE XXXIII

A tablet is compressed from a composition having the following formula:

benzyl N - benzyl carbophenoxyhydroxamate	360 mgm.
Corn Starch	20 „
Lactose	70 „
Magnesium Stearate	40 „
Dicalcium Phosphate	40 „

EXAMPLE XXXIV

A tablet is compressed from a composition having the following formula:

benzyl N-benzyl benzhydroxamate	300 mgm.
Corn Starch	20 „
Powdered Sugar	170 „
Stearic Acid	5 „
Talc	5 „
Magnesium Carbonate	40 „
Ethyl Cellulose	5 „
Alginic Acid	10 „

EXAMPLE XXXV

A tablet is compressed from a composition having the following formula:

benzyl N-benzyl acethydroxamate	400 mgm.
Corn Starch	25 „
Lactose	25 „
Magnesium Stearate	4 „
Alginic Acid	10 „

EXAMPLE XXXVI

250 mgm. of benzyl N-benzyl isobutyrhydroxamate is mixed with an equal weight of polyethylene glycol 400 and the resulting solution is encapsulated in a soft gelatin capsule.

EXAMPLE XXXVII

A table is compressed from a composition having the following formula:

	N-(*v*-phenylpropyl)-N-benzyloxyamine hydrochloride	250 mgm.
	Corn Starch	20 „
	Lactose	70 „
5	Magnesium Stearate	2 „
	Dicalcium Phosphate	50 „

EXAMPLE XXXVIII

200 mgm. of N - benzyl - N - (*m* - methylbenzyloxy) amine is mixed with 0.25 cc. of corn oil and the resulting solution is encapsulated in a soft gelatin capsule.

EXAMPLE XXXIX

200 mgm. of *p*-chlorobenzyloxyamine is mixed with 0.25 cc. of corn oil and the resulting solution is encapsulated in a soft gelatin capsule.

EXAMPLE XL

150 mgm. of *p*-methoxybenzyl N-*p*-methoxybenzyl carbethoxyhydroxamate is mixed with 0.5 cc. of corn oil and the resulting solution is encapsulated in a soft gelatin capsule.

EXAMPLE XLI

300 mgm. of *m*-trifluoromethylbenzyl N-*m*-trifluoromethylbenzyl carbethoxyhydroxamate is mixed with an equal volume of propylene glycol and the resulting mixture is encapsulated in a soft gelatin capsule.

The following tables B to I, mentioned hereinbefore, are now given:

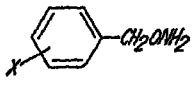


TABLE B

No.	X	Formula	M.p., °C.	Analysis					
				Calculated			Found		
				C	H	N	C	H	N
1	*o*-Cl	$C_7H_9Cl_2NO$*	143—145	43.32	4.68	7.22	43.52	5.26	7.49
2	H	$C_7H_{10}ClNO$*	232	52.67	6.32	8.78	53.13	6.51	8.60
3	*m*-CH_3	$C_8H_{11}NO$	**	70.04	8.08	10.21	70.07	8.19	10.07
4	*p*-Cl	C_7H_8ClNO	40	53.34	5.12	8.89	53.17	5.10	8.88

* Hydrochloride Salt

** Distillation Temp. 52°C./0.4 mm.; n^{28}_D 1.5344

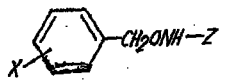


TABLE C

No.	X	Z	M.p. or B.p./mm.	$n^{23}D$	Formula	Analysis					
						Calculated			Found		
						C	H	N	C	H	N
5	H	benzyl	174—176	—	$C_{14}C_{16}ClNO$*	—	—	—	—	—	—
6	*p*-CH_3	*p*-methylbenzyl	58—60	—	$C_{16}H_{19}NO$	79.63	7.94	5.80	80.00	7.86	5.96
7	*p*-$CH(CH_3)_2$	*p*-isopropyl-benzyl	151—152	—	$C_{20}H_{29}NO_5S$**	60.73	7.39	3.54	60.64	7.40	3.56
8	*m*-CH_3	*m*-methylbenzyl	118—120/0.05	1.5582	$C_{16}H_{19}NO$	79.63	7.94	5.80	79.68	7.72	5.84
9	*m*-CH_3	benzyl	110/0.09	1.5593	$C_{15}H_{17}NO$	79.26	7.54	6.16	79.16	7.66	6.10
10	H	*o*-methylbenzyl	113/0.1	1.5618	$C_{15}H_{17}NO$	79.26	7.54	6.16	78.87	7.65	6.40
11	*o*-CH_3	*o*-methylbenzyl	161—163	—	$C_{16}H_{20}ClNO$*	69.17	7.26	5.04	68.98	7.82	5.16
12	*p*-OCH_3	*p*-methoxy-benzyl	56—57	—	$C_{16}H_{19}NO_3$	70.30	7.01	5.13	70.06	6.90	5.01
13	*o*-CH_3	benzyl	116/0.1	1.5630	$C_{15}H_{17}NO$	79.26	7.54	6.16	79.30	7.55	6.38
14	H	β-phenylethyl	99—100	—	$C_{15}H_{18}ClNO$*	68.30	6.88	5.31	68.53	6.66	5.32
15	H	γ-phenylpropyl	134—135	—	$C_{16}H_{20}ClNO$*	69.18	7.26	5.04	69.52	7.26	5.33
16	3,4-diCH_3	3,4-dimethyl-benzyl	164—166	—	$C_{18}H_{24}ClNO$*	70.68	7.91	4.58	70.82	7.71	4.39

* Hydrochloride

** Hydrogen Sulfate

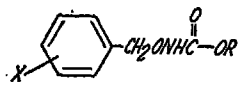


TABLE D

No.	X	R	Formula	M.p. or B.p./mm.	n^{23}_D	Analysis					
						Calculated			Found		
						C	H	N	C	H	N
17	*p*-Cl	C_2H_5	$C_{10}H_{12}ClNO_3$	83—84	—	52.59	5.27	6.10	52.44	5.51	6.18
18	*m*-CH_3	C_2H_5	$C_{11}H_{15}NO_3$	100—103/0.05	1.5138	63.14	7.23	6.70	63.47	7.39	6.83
19	H	$CH_2CH(CH_3)_2$	$C_{12}H_{17}NO_3$	37—38	—	64.55	7.68	6.28	64.94	8.01	6.27
20	*m*-CF_3	C_2H_5	$C_{11}H_{12}F_3NO_3$	78—80	—	50.19	4.60	5.32	50.05	4.69	5.21
21	H	CH_3	$C_9H_{11}NO_3$	108—109/0.2	1.5215	59.66	6.12	7.73	59.86	6.09	7.90
22	H	C_2H_5	$C_{10}H_{13}NO_3$	108—111/0.3	1.5125	61.53	6.71	7.18	61.79	6.55	6.97
23	H	$(CH_2)_3CH_3$	$C_{12}H_{17}NO_3$	123/0.8	1.5023	64.55	7.68	6.28	64.27	7.75	6.58
24	H	C_6H_5	$C_{14}H_{13}NO_3$	45	—	69.12	5.39	5.76	69.22	5.50	5.85

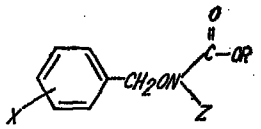


TABLE E

No.	X	R	Z	Formula	M.p. or B.p./mm.	n^{23}_D	Analysis					
							Calculated			Found		
							C	H	N	C	H	N
25	*p*-Cl	C_2H_5	*p*-chlorobenzyl	$C_{17}H_{17}Cl_2NO_3$	168—171/0.07	1.5538	57.64	4.84	3.95	57.71	5.08	4.00
26	*m*-CH_3	C_2H_5	*m*-methylbenzyl	$C_{19}H_{23}NO_3$	144—146/0.05	1.5361	72.82	7.40	4.47	73.48	7.54	4.72
27	*p*-CH_3	C_2H_5	*p*-methylbenzyl	$C_{19}H_{23}NO_3$	137/0.1	1.5340	72.82	7.40	4.47	72.90	7.68	4.72
28	H	C_2H_5	benzyl	$C_{17}H_{19}NO_3$	142—145/0.3	1.5390	71.55	6.71	4.91	71.37	6.78	5.04
29	H	C_6H_5	benzyl	$C_{21}H_{19}NO_3$	59—61	—	75.65	5.72	4.21	75.62	5.84	4.11
30	*o*-CH_3	C_2H_5	*o*-methylbenzyl	$C_{19}H_{23}NO_3$	143/0.04	1.5401	72.82	7.40	4.47	72.97	7.72	4.96
31	H	C_2H_5	*m*-methylbenzyl	$C_{18}H_{21}NO_3$	136/0.02	1.5362	72.22	7.07	4.68	72.36	7.24	4.75
32	H	CH_3	benzyl	$C_{16}H_{17}NO_3$	141/0.2	1.5490	70.83	6.32	5.16	71.05	6.40	5.35
33	H	$CH_2CH_2OCH_3$	benzyl	$C_{18}H_{21}NO_4$	173/0.3	1.5362	68.55	6.71	4.44	68.93	6.68	4.56
34	H	$CH_2CH(CH_3)_2$	benzyl	$C_{19}H_{23}NO_3$	144/0.1	1.5281	73.00	7.36	4.47	73.11	7.07	4.72
35	H	$(CH_2)_5CH_3$	benzyl	$C_{21}H_{27}NO_3$	169—170/0.2	1.5232	73.87	7.97	4.10	73.30	8.30	4.21
36	H	C_2H_5	*o*-methylbenzyl	$C_{18}H_{21}NO_3$	>124/0.1	1.5375	72.22	7.07	4.68	71.96	7.25	4.95
37	*o*-CH_3	C_2H_5	benzyl	$C_{18}H_{21}NO_3$	142/0.1	1.5405	72.22	7.07	4.68	72.07	6.97	4.87
38	*o*-CH_3	CH_3	*o*-methylbenzyl	$C_{18}H_{21}NO_3$	>140/0.2	1.5483	72.22	7.07	4.68	71.99	6.98	4.99
39	*o*-CH_3	C_6H_5	*o*-methylbenzyl	$C_{23}H_{23}NO_3$	51—53	—	76.43	6.41	3.88	76.25	6.63	3.93
40	*o*-C_2H_5	C_2H_5	*o*-ethylbenzyl	$C_{21}H_{27}NO_3$	>150/0.002	1.5305	73.87	7.97	4.10	73.65	7.81	4.32
41	*p*-$CH(CH_3)_2$	C_2H_5	*p*-isopropylbenzyl	$C_{23}H_{31}NO_3$	>140/0.2	1.5229	74.76	8.46	3.79	74.39	8.51	4.06
42	*p*-Cl	CH_3	*p*-chlorobenzyl	$C_{16}H_{15}Cl_2NO_3$	>120/0.001	1.6533	56.50	4.45	20.84*	56.52	4.66	20.96*
43	*p*-Cl	C_6H_5	*p*-chlorobenzyl	$C_{21}H_{17}Cl_2NO_3$	84—87	—	62.70	4.26	17.63*	62.90	4.31	18.23*
44	*m*-CF_3	C_2H_5	*m*-trifluoromethylbenzyl	$C_{19}H_{17}F_6NO_3$	126/0.15	1.4707	54.16	4.07	3.33	54.40	4.20	3.60
45	*p*-OCH_3	C_2H_5	*p*-methoxybenzyl	$C_{19}H_{23}NO_5$	>160/0.3	1.5436	66.07	6.71	4.06	66.17	6.94	4.61
46	H	C_2H_5	β-phenethyl	$C_{18}H_{21}NO_3$	146/0.07	1.5354	72.21	7.07	4.68	72.13	7.11	4.71
47	H	C_2H_5	γ-phenylpropyl	$C_{19}H_{23}NO_3$	157/0.08	1.5324	72.82	7.40	4.47	72.36	6.96	4.80
48	3,4-diCH_3	C_2H_5	3,4-dimethylbenzyl	$C_{21}H_{27}NO_3$	171—175/0.05	1.5399	73.87	7.97	4.10	73.94	7.75	

*Chlorine

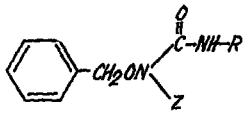


TABLE F

No.	R	Z	Formula	M.p. °C.	Analysis					
					Calculated			Found		
					C	H	N	C	H	N
49	H	H	$C_8H_{10}N_2O_2$	139—141	57.81	6.07	16.88	57.56	6.08	16.64
50	$COCH_3$	Benzyl	$C_{17}H_{18}N_2O_3$	61—62	68.44	6.08	9.39	68.18	6.03	9.37
51	$COCH_3$	H	$C_{10}H_{12}N_2O_3$	139—140	57.68	5.81	13.46	57.89	5.68	13.20
52	H	Benzyl	$C_{15}H_{16}N_2O_2$	98—100	70.29	6.29	10.93	69.60	6.27	11.05

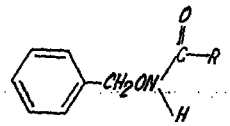


TABLE G

No.	R	Formula	M.p. or B.p./mm.	n^{25}_D	Analysis					
					Calculated			Found		
					C	H	N	C	H	N
53	CH_3	$C_9H_{11}NO_2$	109/0.2	1.5381	65.43	6.71	8.48	65.24	7.01	8.37
54	$CH(CH_3)_2$	$C_{11}H_{15}NO_2$	63—64	—	68.40	7.82	7.27	68.22	7.93	7.34
55	$(CH_2)_7CH_3$	$C_{16}H_{25}NO_2$	34—35	—	72.95	9.57	5.32	72.56	9.47	5.54
56	$(CH_2)_{12}CH_3$	$C_{21}H_{35}NO_2$	72—73	—	75.60	10.58	4.20	75.59	10.62	4.19
57	$(CH_2)_{14}CH_3$	$C_{23}H_{39}NO_2$	81—83	—	76.40	10.87	3.87	76.67	10.85	4.08
58	C_6H_5	$C_{14}H_{13}NO_2$	102—103	—	73.99	5.77	6.17	74.19	5.85	6.08
59	$(CH_2)_2CH_3$	$C_{11}H_{15}NO_2$	56—58	—	68.40	7.82	7.27	68.08	7.98	7.35

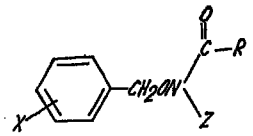


TABLE H

No.	X	R	Z	Formula	M.p. or B.p./mm.	$n^{25}D$	Analysis					
							Calculated			Found		
							C	H	N	C	H	N
60	H	$CH(CH_3)_2$	benzyl	$C_{18}H_{21}NO_2$	133—136/0.1	1.5470	76.29	7.47	4.94	76.50	7.45	5.02
61	*m*-CF_3	CH_3	*m*-trifluoro-methylbenzyl	$C_{18}H_{15}F_6NO_2$	90/0.002	1.4845	55.25	3.86	3.58	55.19	3.68	3.65
62	*p*-Cl	C_6H_5	*p*-chlorobenzyl	$C_{21}H_{17}Cl_2NO_2$	79—82	—	65.30	4.44	18.35*	65.07	4.56	18.51*
63	H	C_2H_5	benzyl	$C_{17}H_{19}NO_2$	146/0.1	1.5535	75.81	7.11	5.20	75.87	7.00	5.41
64	H	$(CH_2)_6CH_3$	benzyl	$C_{22}H_{29}NO_2$	167/0.2	1.5306	78.00	8.63	4.13	78.06	8.53	4.19
65	H	CH_3	*o*-methyl-benzyl	$C_{17}H_{19}NO_2$	66—68	—	75.81	7.11	5.20	75.33	7.01	5.31
66	*o*-CH_3	CH_3	benzyl	$C_{17}H_{19}NO_2$	38—40	—	75.81	7.11	5.20	75.86	6.99	5.14
67	*o*-CH_3	$CH(CH_3)_2$	*o*-methyl-benzyl	$C_{20}H_{25}NO_2$	147/0.03	1.5471	77.13	8.09	4.50	76.95	8.15	4.28
68	*o*-CH_3	C_6H_5	*o*-methyl-benzyl	$C_{23}H_{23}NO_2$	93—95	—	79.97	6.71	4.06	79.44	6.60	4.28
69	*p*-Cl	CH_3	*p*-chlorobenzyl	$C_{16}H_{15}Cl_2NO_2$	41—44	—	59.28	4.66	21.87*	59.14	4.61	22.19*
70	H	C_6H_5	benzyl	$C_{21}H_{19}NO_2$	65—67	—	79.47	6.04	4.41	79.22	6.23	4.59
71	*p*-OCH_3	$CH(CH_3)_2$	*p*-methoxy-benzyl	$C_{20}H_{25}NO_4$	>150/0.1	1.5499	69.94	7.34	4.08	70.11	7.31	4.25
72	H	CH_3	benzyl	$C_{16}H_{17}NO_2$	57—58	1.5629	75.27	6.71	5.49	75.29	7.25	5.61
73	3,4-diCH_3	CH_3	3,4-dimethyl-benzyl	$C_{20}H_{25}NO_2$	110/0.001	1.5554	77.13	8.09	4.50			
74	H	C_6H_5	γ-phenyl-propyl	$C_{23}H_{23}NO_2$	>130/0.2	1.5812	79.97	6.71	4.06	79.39	7.16	4.23

* Chlorine

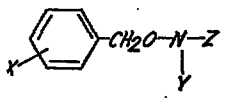
TABLE I

Compound No.	Compound
10	N-(*o*-methylbenzyl)-N-benzyloxyamine
14	N-(β-phenethyl)-N-benzyloxyamine
15	N-(γ-phenylpropyl)-N-benzyloxyamine hydrochloride
19	benzyl carboisobutoxyhydroxamate
21	benzyl carbomethoxyhydroxamate
23	benzyl carbo-*n*-butoxyhydroxamate
24	benzyl carbophenoxyhydroxamate
25	*p*-chlorobenzyl N-*p*-chlorobenzyl carbethoxyhydroxamate
29	benzyl N-benzyl carbophenoxyhydroxamate
31	benzyl N-*m*-methylbenzyl carbethoxyhydroxamate
32	benzyl N-benzyl carbomethoxyhydroxamate
33	benzyl N-benzyl carbo(β-methoxyethoxy)hydroxamate
34	benzyl N-benzyl carboisobutyoxyhydroxamate
35	benzyl N-benzyl carbo-*n*-hexyloxyhydroxamate
36	benzyl N-*o*-methylbenzyl carbethoxyhydroxamate
42	*p*-chlorobenzyl N-*p*-chlorobenzyl carbomethoxyhydroxamate
43	*p*-chlorobenzyl N-*p*-chlorobenzyl carbophenoxyhydroxamate
46	benzyl N-β-phenethyl carbethoxyhydroxamate
47	benzyl N-γ-phenylpropyl carbethoxyhydroxamate
50	N-benzyl-N-benzyloxy-N^1-acetyl urea
51	N-benzyloxy-N^1-acetyl urea
54	benzyl isobutyrhydroxamate
55	benzyl *n*-nonanohydroxamate
56	benzyl *n*-tetradecanohydroxamate
57	benzyl *n*-hexadecanohydroxamate
58	benzyl benzhydroxamate
59	benzyl *n*-butyrhydroxamate
60	benzyl N-benzyl isobutyrhydroxamate
63	benzyl N-benzyl *n*-propionohydroxamate
64	benzyl N-benzyl *n*-octanohydroxamate
65	benzyl N-*o*-methylbenzyl acethydroxamate
74	benzyl N-(γ-phenylpropyl)benzhydroxamate

The invention in its broader aspects is not limited to the specific steps, methods and compositions described but departures may be made therefrom within the scope of the accompanying claims without departing from the principles of the invention and without sacrificing its chief advantages.

WHAT WE CLAIM IS:—

1. A process for preparing a composition capable of reducing blood cholesterol in warm-blooded animals characterized by admixing, as an active ingredient, a dosage unit quantity as hereinbefore defined of one or more benzyloxyamines of the general formula:



...I

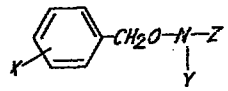
wherein X is hydrogen, one or two alkyls of 1 to 3 carbon atoms or halogen, Y is hydrogen, $-\overset{O}{\overset{\|}{C}}-R$, $-\overset{O}{\overset{\|}{C}}-OR$, $-\overset{O}{\overset{\|}{C}}-NH_2$, or $-\overset{O}{\overset{\|}{C}}-NH-\overset{O}{\overset{\|}{C}}-R$ and Z is hydrogen or aralkyl; or wherein X is alkoxy and Y is hydrogen, $-\overset{O}{\overset{\|}{C}}-R$ or $-\overset{O}{\overset{\|}{C}}-OR$ and Z is aralkyl; or wherein X is trifluoromethyl and Y is $-\overset{O}{\overset{\|}{C}}-R$ or $-\overset{O}{\overset{\|}{C}}-OR$ and Z is hydrogen or aralkyl, where when Z is an aralkyl group it can be substituted by one or two alykyl groups, an alkoxy group, a halogen atom or a trifluoromethyl group on the aryl portion of the aralkyl group; and wherein the aralkyl groups hereinabove contain 7 to 12 carbon atoms and when R is alkyl it contains 1 to 20 carbon atoms and when R is aryl it contains 6 to 10 carbon atoms; wherein in each case R is an alkyl, an alkoxyalkyl or aryl group; and the acid addition salts of the above when Y and Z are hydrogen atoms or Z is an arylalkyl group; with a non-toxic carrier.

2. A process according to claim 1, characterized by the fact that the carrier is a gelatin capsule.

3. A process according to claim 1, characterized by the fact that the composition is formed into a tablet or pill.

4. A process according to any one of the preceding claims, characterized by the fact that the composition contains a dosage unit capable of providing a daily dosage of substantially 50 to 300 mg., preferably 200 to 1000 mg., of active ingredient per 150 pounds of body weight.

5. A process for preparing benzyloxyamines of the general formula:



...IA

wherein X is hydrogen, one or two alkyls of 1 to 3 carbon atoms or halogen, Y is hydrogen, $-\overset{O}{\overset{\|}{C}}-R$, $-\overset{O}{\overset{\|}{C}}-OR$, $-\overset{O}{\overset{\|}{C}}-NH_2$ or $-\overset{O}{\overset{\|}{C}}-NH-\overset{O}{\overset{\|}{C}}-R$ and Z is hydrogen or aralkyl; or wherein X is alkoxy and Y is hydrogen, $-\overset{O}{\overset{\|}{C}}-R$ or $-\overset{O}{\overset{\|}{C}}-OR$ and Z is aralkyl; or wherein X is trifluoromethyl and Y is $-\overset{O}{\overset{\|}{C}}-R$ or $-\overset{O}{\overset{\|}{C}}-OR$ and Z is hydrogen or aralkyl; wherein when Z is an aralkyl group it can be substituted by one or two alkyl groups, an alkoxy group, a halogen atom or a trifluoromethyl group on the aryl portion of the aralkyl group; and wherein the aralkyl groups hereinabove contain 7 to 12 carbon atoms and when R is alkyl it contains 1 to 20 carbon atoms and when R is aryl it contains 6 to 10 carbon atoms; wherein R in each case is an alkyl, alkoxyalkyl or aryl group; and the acid addition salts of the above when Y and Z are hydrogen atoms or Z is an arylalkyl group with the proviso that (1) when X is a halogen atom and Z is a hydrogen atom then Y cannot be a hydrogen atom or a carbethoxy group or $\overset{O}{\overset{\|}{C}}NH_2$, (2) when X is a halogen atom and Z is aralkyl, Y cannot be hydrogen and (3) when X is a hydrogen atom and Z is a hydrogen atom or a benzyl group, then Y cannot be a hydrogen atom or the group $-\overset{O}{\overset{\|}{C}}-A$, wherein A is $-NH_2$, $-OC_2H_5$, $-CH_3$ or phenyl characterized by

(a) aralkylating a suitably protected hydroxylamine derivative of the formula

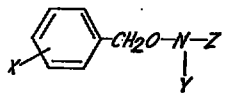
...IIA

wherein Z^1 and Y^1 are respectively Z and Y as previously defined or are hydrolyzable protective groups with one or two moles of a benzyl halide or sulfonate of the formula:

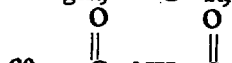
The invention in its broader aspects is not limited to the specific steps, methods and compositions described but departures may be made therefrom within the scope of the accompanying claims without departing from the principles of the invention and without sacrificing its chief advantages.

WHAT WE CLAIM IS:—

1. A process for preparing a composition capable of reducing blood cholesterol in warm-blooded animals characterized by admixing, as an active ingredient, a dosage unit quantity as hereinbefore defined of one or more benzyloxyamines of the general formula:



... I

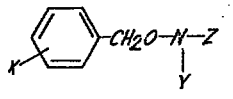
wherein X is hydrogen, one or two alkyls of 1 to 3 carbon atoms or halogen, Y is hydrogen, , , , or  and Z is hydrogen or aralkyl; or wherein X is alkoxy and Y is hydrogen, or and Z is aralkyl; or wherein X is trifluoromethyl and Y is or and Z is hydrogen or aralkyl, where when Z is an aralkyl group it can be substituted by one or two alykyl groups, an alkoxy group, a halogen atom or a trifluoromethyl group on the aryl portion of the aralkyl group; and wherein the aralkyl groups hereinabove contain 7 to 12 carbon atoms and when R is alkyl it contains 1 to 20 carbon atoms and when R is aryl it contains 6 to 10 carbon atoms; wherein in each case R is an alkyl, an alkoxyalkyl or aryl group; and the acid addition salts of the above when Y and Z are hydrogen atoms or Z is an arylalkyl group; with a non-toxic carrier.

2. A process according to claim 1, characterized by the fact that the carrier is a gelatin capsule.

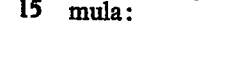
3. A process according to claim 1, characterized by the fact that the composition is formed into a tablet or pill.

4. A process according to any one of the preceding claims, characterized by the fact that the composition contains a dosage unit capable of providing a daily dosage of substantially 50 to 300 mg., preferably 200 to 1000 mg., of active ingredient per 150 pounds of body weight.

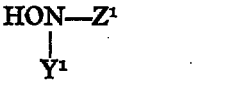
5. A process for preparing benzyloxyamines of the general formula:



... IA

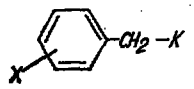
wherein X is hydrogen, one or two alkyls of 1 to 3 carbon atoms or halogen, Y is hydrogen, , , , or  and Z is hydrogen or aralkyl; or wherein X is alkoxy and Y is hydrogen, or and Z is aralkyl; or wherein X is trifluoromethyl and Y is or and Z is hydrogen or aralkyl; wherein when Z is an aralkyl group it can be substituted by one or two alkyl groups, an alkoxy group, a halogen atom or a trifluoromethyl group on the aryl portion of the aralkyl group; and wherein the aralkyl groups hereinabove contain 7 to 12 carbon atoms and when R is alkyl it contains 1 to 20 carbon atoms and when R is aryl it contains 6 to 10 carbon atoms; wherein R in each case is an alkyl, alkoxyalkyl or aryl group; and the acid addition salts of the above when Y and Z are hydrogen atoms or Z is an arylalkyl group with the proviso that (1) when X is a halogen atom and Z is a hydrogen atom then Y cannot be a hydrogen atom or a carbethoxy group or , (2) when X is a halogen atom and Z is aralkyl, Y cannot be hydrogen and (3) when X is a hydrogen atom and Z is a hydrogen atom or a benzyl group, then Y cannot be a hydrogen atom or the group , wherein A is $-NH_2$, $-OC_2H_5$, $-CH_3$ or phenyl characterized by

(a) aralkylating a suitably protected hydroxylamine derivative of the formula



... IIA

wherein Z^1 and Y^1 are respectively Z and Y as previously defined or are hydrolyzable protective groups with one or two moles of a benzyl halide or sulfonate of the formula:



... IIIA

wherein K is a halogen atom or the residue of a sulfonic acid or ester and X is as defined hereinabove and then (1) if desired, when the protective group on the hydroxylamine derivative is $-\overset{O}{\overset{\|}{C}}-R$ or $-\overset{O}{\overset{\|}{C}}-OR$, hydrolyzing to form a product of formula IA in which Z is hydrogen, (2) if desired, when the protective group is $-\overset{O}{\overset{\|}{C}}-OR$ treating with ammonia to obtain a compound of formula IA wherein Y is $-\overset{O}{\overset{\|}{C}}-NH_2$, (3) hydrolyzing all other protective groups to form a product of formula IA in which Z is hydrogen, and

(b) if desired, when Y and Z in the product of step (a) are hydrogen atoms or Z is an aralkyl group, then doing one of the following:

(1) acylating with an agent capable of providing the radical $R-\overset{O}{\overset{\|}{C}}-$ to convert Y into $-\overset{O}{\overset{\|}{C}}-R$

(2) reacting with cyanic acid to convert Y into $-\overset{O}{\overset{\|}{C}}-NH_2$

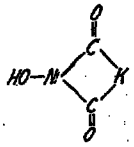
(3) reacting with a haloformate of the formula $Halogen-\overset{O}{\overset{\|}{C}}-OR$; a carbonate of the formula $RO-\overset{O}{\overset{\|}{C}}-OR$; or with phosgene followed by treatment of the resulting carbamoyl chloride with ROH or NH_3 to convert Y into $-CNH_2$ or $-\overset{O}{\overset{\|}{C}}-OR$

(4) forming the non-toxic acid addition salt wherein R is as defined hereinabove.

6. A process according to claim 5, characterized by the fact that the hydroxylamine derivative (IIA) has the formula:

$$HONH-\overset{O}{\overset{\|}{C}}-R \text{ or } HONH-\overset{O}{\overset{\|}{C}}-OR.$$

7. A process according to claim 5, characterized by the fact that the hydroxylamine derivative (IIA) has the formula:



wherein K is an organic residue to form a cyclic imide, such as the phthalimido or succinimido group.

8. A process according to claim 5, characterized by the fact that the hydroxylamine derivative (IIA) is an aldoxime or ketoxime.

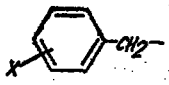
9. A process according to claim 5, characterized by the fact that the hydroxylamine derivative (IIA) is a salt of hydroxylamine disulfonic acid, having the formula:

$$H-O-N<\begin{matrix}SO_3-\\ \text{Metal}\\ SO_3-\end{matrix}$$

preferably the alkali metal salt.

10. A process according to any one of the preceding claims 5 to 9, characterized by the fact that the cyanic acid is generated *in situ*.

11. A process according to any one of the preceding claims 5 to 10, characterized by the fact that one mole each of different benzylating agent of formula IIIA are used one after the other to form a product of formula IA in which Z and



are different.

12. A process according to any one of claims 5 to 11, characterized by the fact that the sulfonate of formula IIIA is the tosyl or mesyl derivative.

13. A process according to any one of claims 5 to 12, characterized by the fact that the acylating agent capable of providing the radical $R-\overset{O}{\overset{\|}{C}}-$ is the acid chloride or the acid anhydride.

14. A process according to any one of claims 5 to 13, characterized by the fact that

the acid addition salt is the hydrochloride.

15. A process according to any one of claims 1 to 14, characterized by the fact that X is hydrogen, Y is —C(=O)—OR and Z is arylalkyl.

16. A process according to any one of claims 1 to 14, characterized by the fact that X is alkyl, Y is —C(=O)—OR and Z is arylalkyl.

17. A process according to any one of claims 1 to 14, characterized by the fact that X and Y are hydrogen and Z is arylalkyl.

18. A process according to any one of claims 1 to 14, characterized by the fact that X is alkyl, Y is hydrogen and Z is arylalkyl.

19. A process according to any one of claims 1 to 14, characterized by the fact that X is halogen, Y is —C(=O)—OR and Z is arylalkyl.

20. A process according to any one of claims 1 to 14, characterized by the fact that X is hydrogen, Y is —C(=O)—NH_2 and Z is arylalkyl.

21. A process according to any one of claims 1 to 4, characterized by the fact that X is halogen and Y and Z are hydrogen.

22. A process according to any one of claims 1 to 14, characterized by the fact that X is alkoxy, Y is hydrogen and Z is arylalkyl.

23. A process according to any one of claims 1 to 14, characterized by the fact that X is alkoxy, Y is —C(=O)—OR and Z is arylalkyl.

24. A process according to any one of claims 1 to 14, characterized by the fact that X is trifluoromethyl, Y is —C(=O)—OR and Z is arylalkyl.

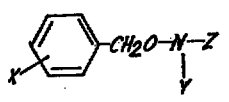
25. A process for preparing a cholesterol reducing composition substantially as described.

26. A cholesterol reducing composition whenever prepared substantially as described.

27. A process for producing benzyloxyamines of the general formula IA substantially as described.

28. Benzyloxyamines of the general formula IA whenever produced by the process substantially as described.

29. A composition capable of reducing blood cholesterol in warm-blooded animals characterized by the fact that it comprises a dosage unit quantity as hereinbefore defined of one or more benzyloxyamines of the general formula:



...I

wherein X is hydrogen, one or two alkyls of 1 to 3 carbon atoms or halogen, Y is hydrogen, —C(=O)—R, —C(=O)—OR, —C(=O)—NH_2 or —C(=O)—NH—C(=O)—R and Z is hydrogen or aralkyl; or wherein X is alkoxy and Y is hydrogen, —C(=O)—R or —C(=O)—OR and Z is aralkyl; or wherein X is trifluoromethyl, Y is —C(=O)—R or —C(=O)—OR and Z is hydrogen or aralkyl; wherein when Z is an aralkyl group it can be substituted by one or two alkyl groups, an alkoxy group, a halogen atom or a trifluoromethyl group on the aryl portion of the aralkyl group; and wherein the aralkyl groups hereinabove contain 7 to 12 carbon atoms and when R is alkyl it contains 1 to 20 carbon atoms and when R is aryl is contains 6 to 10 carbon atoms; wherein in each case R is an alkyl, alkoxyalkyl or aryl group and the acid addition salts of the above when Y and Z are hydrogen atoms or Z is an arylalkyl group, in a nontoxic carrier.

30. A composition according to claim 29, characterized by the fact that the carrier is a gelatine capsule.

31. A composition according to claim 29, characterized by the fact that the composition is in the form of a tablet or pill.

32. A composition according to any one of claims 29 to 31, characterized by the fact that the composition contains a dosage unit of 50 to 3000 mg., preferably 200 to 1000 mg. of active ingredient per 150 pounds of body weight.

33. A composition according to any one of claims 29 to 32, characterized by the fact that X is hydrogen, Y is —C(=O)—OR and Z is arylalkyl.

34. A composition according to any one of claims 29 to 32, characterized by the fact that X is lower alkyl, Y is —C(=O)—OR and Z is arylalkyl.

35. A composition according to any one of claims 29 to 32, characterized by the fact that X and Y are hydrogen and Z is arylalkyl.

36. A composition according to any one of claims 29 to 32, characterized by the fact that X is lower alkyl, Y is hydrogen and Z is arylalkyl.

37. A composition according to any one of claims 29 to 32, characterized by the fact that X is halogen, Y is $-\overset{O}{\overset{\|}{C}}-OR$ and Z is arylalkyl.

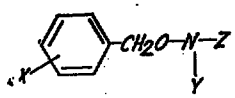
38. A composition according to any one of claims 29 to 32, characterized by the fact that X is hydrogen, Y is $-\overset{O}{\overset{\|}{C}}-NH_2$ and Z is arylalkyl.

39. A composition according to any one of claims 29 to 32, characterized by the fact that X is halogen and Y and Z are hydrogen.

40. A composition according to any one of claims 29 to 32, characterized by the fact that X is alkoxy, Y is hydrogen and Z is arylalkyl.

41. A composition according to any one of claims 29 to 32, characterized by the fact that X is alkoxy, Y is $-\overset{O}{\overset{\|}{C}}-OR$ and Z is arylalkyl.

42. Benzyloxyamines of the general formula:



... IA,

wherein X is hydrogen, one or two alkyls of 1 to 3 carbon atoms or halogen, Y is hydrogen, $-\overset{O}{\overset{\|}{C}}-R$, $-\overset{O}{\overset{\|}{C}}-OR$, $-\overset{O}{\overset{\|}{C}}-NH_2$ or $-\overset{O}{\overset{\|}{C}}-NH-\overset{O}{\overset{\|}{C}}-R$ and Z is hydrogen or aralkyl; or wherein X is alkoxy and Y is hydrogen, $-\overset{O}{\overset{\|}{C}}-R$ or $-\overset{O}{\overset{\|}{C}}-OR$ and Z is aralkyl; or wherein X is trifluoromethyl, Y is $-\overset{O}{\overset{\|}{C}}-R$ or $-\overset{O}{\overset{\|}{C}}-OR$ and Z is hydrogen or aralkyl; wherein in each case R is an alkyl, alkoxyalkyl or aryl group and the acid addition salts of the above when Y and Z are hydrogen atoms or Z is an arylalkyl group; wherein when Z is an aralkyl group it can be substituted by one or two alkyl groups, an alkoxy group, a halogen atom or a trifluoromethyl group on the aryl portion of the aralkyl group; and wherein the aralkyl groups hereinabove contain 7 to 12 carbon atoms and when R is alkyl it contains 1 to 20 carbon atoms and when R is aryl it contains 6 to 10 carbon atoms; with the proviso that (1) when X is a halogen atom and Z is a hydrogen atom then Y cannot be a hydrogen atom or a carbethoxy group or $\overset{O}{\overset{\|}{C}}NH_2$, (2) when X is a halogen atom and Z is aralkyl, Y cannot be hydrogen and (3) when X is a hydrogen atom and Z is a hydrogen atom or a benzyl group, then Y cannot be a hydrogen atom or the group $-\overset{O}{\overset{\|}{C}}-A$, wherein A is $-NH_2$, $-OC_2H_5$, $-CH_3$ or phenyl.

43. A benzyloxyamine of formula IA according to claim 42, characterized by the fact that X is lower alkyl, Y is $-\overset{O}{\overset{\|}{C}}-OR$ and Z is arylalkyl.

44. A benzyloxyamine of formula IA according to claim 42, characterized by the fact that X is lower alkyl, Y is hydrogen and Z is arylalkyl.

45. A benzyloxyamine of formula IA according to claim 42, characterized by the fact that X is alkoxy, Y is hydrogen and Z is arylalkyl.

46. A benzyloxyamine of formula IA according to claim 42, characterized by the fact that X is alkoxy, Y is $-\overset{O}{\overset{\|}{C}}-OR$ and Z is arylalkyl.

47. A benzyloxyamine of formula IA according to claim 42, characterized by the fact that X is trifluoromethyl, Y is $-\overset{O}{\overset{\|}{C}}-OR$ and Z is arylalkyl.

48. A capsule for use in lowering blood cholesterol which contains as the active ingredient benzyl N-benzyl carbethoxyhydroxamate.

49. A capsule according to claim 48, wherein the capsule is a soft gelatin capsule.

50. A capsule according to claim 48 or 49, wherein the active ingredient is incorporated in a liquid carrier miscible therewith.

* C L M S *

51. A capsule according to any of claims 48 to 50, wherein the active ingredient is present in an amount of 200 to 1000 mg.

STEVENS, LANGNER, PARRY & ROLLINSON,
Chartered Patent Agents.
Agents for the Applicants.

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