United States Patent Office 3,073,740 Patented Jan. 15, 1963

3,073,740

METHOD OF REDUCING CHOLESTEROL LEVELS WITH TRI - (DIALKYLAMINOALKYL) PHOSPHATES

Samuel M. Greenberg, Bala Cynwyd, and John F. Herndon, Sr., Levittown, Pa., assignors to Smith Kline & French Laboratories, Philadelphia, Pa., a corporation of Pennsylvania

No Drawing. Filed Oct. 6, 1958, Ser. No. 765,337
6 Claims. (Cl. 167—55)

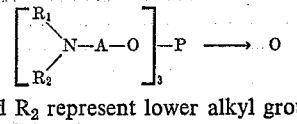
This invention relates to new tri-(dialkylaminoalkyl) phosphates and to antihypercholesterolemic preparations and a method of reducing cholesterol levels.

Prior to the present invention there has been an intense search for an antihypercholesterolemic agent which is effective in very low quantities, has very low toxicity and is relatively free of untoward side effects. This agent is needed to remove circulating blood cholesterol and to aid in the treatment of atherosclerosis. Previous known antihypercholesterolemic agents, such as the unsaturated fatty acids, achieve their results only by the utilization of inconvenient or unpleasant dosage forms. Extremely large doses of these materials are necessary for biological effect. Because of the bulk problem or unpleasant taste, they are undesirable forms of medicinal agents for patient consumption. The need for a safe, effective, low dosage medicament for use in this area of hypercholesterolemia has been great.

The new tri-(dialkylaminoalkyl) phosphates and the medicinal preparation of this invention are consistently effective in bringing about a rapid drop in plasma cholesterol levels using very much lower dosage regimens than previous agents require. This allows the administration of the effective medicament in a pharmaceutical form both convenient for administration as well as pleasant for patient consumption. The use of these novel tri-(dialkylaminoalkyl) phosphates gives a more dramatic fall in plasma cholesterol levels than the well known agents for lowering plasma cholesterol such as lipotropic agents and essential fatty acids. Furthermore, the compounds and preparations of this invention have a novel central nervous system stimulant activity which results in utility as an antidepressant agent with low toxicity.

The novel tri - (diloweralkylaminoloweralkyl) phosphates of this invention are represented by the general formula:

FORMULA 1

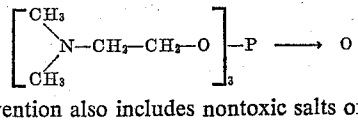


when: R_1 and R_2 represent lower alkyl groups containing a maximum of 4 carbon atoms.

A represents a divalent, straight or branched saturated alkylene chain containing 2 to 6 carbon atoms, preferably 2 to 4 carbon atoms, separating the nitrogen and oxygen atom by at least 2 carbon atoms.

The preferred and most advantageous compound of this invention is represented by the following structural formula:

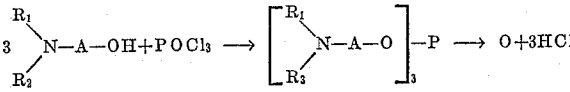
FORMULA 2



This invention also includes nontoxic salts of the above bases formed with nontoxic organic and inorganic acids. Such salts are easily prepared by methods known to the art. The base is reacted with either the stoichiometric

amount of organic or inorganic acid in aqueous miscible solvent, such as acetone or ethanol, with isolation of the salt by concentration and cooling, or reacted with an excess of the acid in aqueous immiscible solvent, such as ethyl ether or chloroform with the desired salt separating directly. Exemplary of organic salts are those formed with maleic, fumaric, benzoic, ethanedisulfonic, citric, lactic, benzene sulfonic, methane sulfonic, acetic, tartaric, and succinic acids. Exemplary of inorganic salts are those formed with hydrochloric, hydrobromic, sulfuric, nitric phosphoric, and sulfamic acids. Preferably the hydrochloride salt of the tri-(dialkylaminoalkyl) phosphate is used.

The novel tri-(dialkylaminoalkyl) phosphates of this invention are prepared by reacting the properly substituted alkanolamines with phosphorous oxychloride according to the following procedure:



A solution comprising of an excess of 6 molar equivalents of the desired alkanolamine in an organic solvent such as an aromatic solvent, for instance, benzene, xylene or toluene is reacted with phosphorus oxychloride. The reaction temperature is preferably maintained at about 0 to 10° C. The solution is then stirred at a temperature of about 20 to 50° C. and allowed to stand until reaction is complete. The resulting mixture is cooled and water added, separating the upper organic layer and concentrating in vacuo at a maximum temperature of about 50° C. The resultant viscous residue is the tri-(dialkylaminoalkyl) phosphate base. The trihydrochloride salt can be prepared from the base by reacting the base with the calculated amount of dilute isopropanolic hydrogen chloride in aqueous miscible solvents, such as acetone or ethanol, with isolation of the salt by cooling.

Advantageously the tri-(dialkylaminoalkyl) phosphates of this invention will be administered in a preparation in accordance with this invention comprising a pharmaceutical carrier and a tri-(dialkylaminoalkyl) phosphate of Formula 1 or a non-toxic pharmaceutical salt thereof in an amount to lower plasma cholesterol levels in human beings. Preferably the preparation will contain the tri-(dialkylaminoalkyl) phosphate ingredient in an amount of from about 5 mg. to about 300 mg., advantageously from about 15 mg. to about 75 mg. The dosage units will generally be administered from 2 to 5 times daily to provide advantageously a daily dosage regimen of from about 10 mg. to about 1000 mg. preferably about 40 mg. to about 250 mg. of the tri-(dialkylaminoalkyl) phosphate.

The pharmaceutical carrier may be, for example, either a solid or a liquid. Exemplary of solid carriers are lactose, magnesium stearate, terra alba, sucrose, talc, stearic acid, gelatin, agar, pectin or acacia. Exemplary of liquid carriers are peanut oil, olive oil, sesame oil and water.

A wide variety of pharmaceutical forms can be employed. Thus, if a solid carrier is used, the preparation can be tabletted, placed in a hard gelatin capsule or in the form of a troche or lozenge. The amount of solid carrier will vary widely but preferably will be from about 25 mg. to about 1 gm. If a liquid carrier is used the preparation may be in the form of a soft gelatin capsule, placed in an ampule or in a liquid suspension.

The method in accordance with this invention comprises administering internally tri-(dialkylaminoalkyl) phosphate, or a nontoxic salt thereof in an amount to lower plasma cholesterol levels in patients afflicted with

hypercholesterolemia. The administration may be parenterally or orally, the preferable route of administration. Advantageously equal doses will be administered three or four times daily. Preferably from about 10 mg. to about 1000 mg. and most advantageously from about 40 mg. to about 250 mg. of the tri-(dialkylaminoalkyl) phosphate will be administered daily. The dose may be individually determined by the physician.

When preparing the various pharmaceutical forms of this invention care should be taken because the tri-(dialkylaminoalkyl) phosphates are relatively hygroscopic. It is dseirable to include absorbable materials such as silica gel or Micro-Cel in the formulations. The preparations of this invention are made following the conventional techniques of the pharmaceutical chemist involving mixing, granulating and compressing when necessary or variously mixing and dissolving the ingredients as appropriate to the desired end product.

The following examples are not limiting but are illustrative of compounds and pharmaceutical preparations of this invention.

Example 1

A solution of 1376 g. of β-dimethylaminoethanol in 6 liters of dry toluene is stirred and cooled as 396 g. of phosphorous oxychloride is added. The rate of addition is so regulated that the reaction temperature remains at 0 to 10° C. This addition requires about three hours. After the addition is completed, the cooling bath is removed. The solution is stirred at room temperature for about three hours and is allowed to stand overnight. The resulting mixture is cooled to 20° C. and 800 mls. of water is added with stirring. The upper organic layer is separated and concentrated in vacuo at a temperature of 50° C. The resultant base as a viscous liquid is taken up in 3 liters of ethanol and made acidic with 1300 g. of 10% isopropanolic hydrogen chloride. The crystalline solid separates on cooling and recrystallized from 8.5 liters of hot ethanol. The melting point of the resultant tri-(dimethylaminoethyl) phosphate trihydrochloride is 169–170° C.

Example 2

Place 515 g. of β-dimethylaminoisopropanol in 1500 ml. of dry toluene and stir. Cool with an ice bath to 0 to 10° C. and add 122 g. of phosphorous oxychloride. Maintain the temperature at 0 to 10° C. by the rate of addition of the phosphorous oxychloride which requires three hours. When all the phosphorous oxychloride has been added, remove the cooling bath. The solution is stirred at room temperature for about three hours and is allowed to stand overnight. The resulting mixture is cooled to 20° C. and 200 mls. of water added with stirring. The upper organic layer is separated and concentrated in vacuo at a temperature of 50° C. The tri-dimethylaminoisopropyl phosphate and 348 g. of maleic acid are taken up in ethanol, and the crystalline solid is separated on cooling and recrystallized with hot ethanol. The resultant product is the maleate salt of tri-dimethylaminoisopropyl phosphate.

Example 3

A solution of 435 g. of β-dimethylaminohexanol in 2 liters of dry toluene is stirred and cooled as 77 g. of phosphorous oxychloride is added. The temperature is kept at 0 to 10° C. and the addition of the phosphorous oxychloride requires about three hours. After the addition was completed the cooling bath was removed. The solution is stirred at room temperature for about three hours and is allowed to stand overnight. The resulting mixture is cooled to 20° C. and 300 mls. of water are added with stirring. The upper organic layer is separated and concentrated in vacuo at a maximum temperature of 50° C. The resultant viscous liquid, which is the base, and 630 g. of citric acid are taken up in 2 liters of ethanol, and the crystalline solid is separated on cooling. The citrate salt of tri-β-dimethylaminohexyl phosphate is then recrystallized from hot ethanol.

Example 4

A solution of 1038 g. of β-dibutylaminoethanol in 4 liters of dry toluene is stirred and allowed to cool as 153 g. of phosphorous oxychloride is added. The reaction temperature is 0 to 10° C. and is regulated by the rate of addition of the phosphorous oxychloride. The addition requires about three hours. After the addition is completed, the cooling bath is removed. The solution is stirred at room temperature for three hours and is allowed to stand overnight. The resulting mixture is cooled to 20° C. and 600 ml. of water is added with stirring. The upper layer separated and concentrated in vacuo at a maximum temperature of 50° C. The tri-butylaminoethyl phosphate is taken up in 500 ml. of ethanol and made acidic with 1600 g. of 10% isopropanolic hydrogen bromide. The crystalline tri-butylaminoethyl phosphate trihydrobromide is separated on cooling.

Example 5

	Mg.
Tri-(dimethylaminoethyl) phosphate trihydrochloride	25
Micro-Cel (synthetic calcium silicates)	25
Calcium sulfate	225

The above powders are thoroughly mixed and filled into a #2 hard gelatin capsule.

Example 6

	Mg.
Tri-(dimethylaminoethyl) phosphate trihydrochloride	5
Silica gel (SiO_2)	5
Lactose	275

The ingredients are mixed and filled into a #2 hard gelatin capsule.

Example 7

	Mg.
Tri-(dimethylaminoethyl) phosphate tricitrate	200
Micro-Cel (synthetic calcium silicates)	150
Calcium sulfate	300

The ingredients are intimately mixed and filled into a #1 hard gelatin capsule.

Example 8

	Mg.
Tri-(dibutylaminohexyl) phosphate trihydrochloride	50
Silica gel (SiO_2)	50
Calcium sulfate, dihydrate	100
Sucrose	25
Starch	15
Talc	5
Stearic acid	3

The sucrose, calcium sulfate, silica gel and tri-(dibutylaminohexyl) phosphate trihydrochloride are thoroughly mixed and granulated with hot 10% gelatin solution. The wetted mass is passed through a #16 U.S. standard mesh screen directly onto drying trays. The granules are dried at 120° F. and passed through a #20 U.S. standard mesh screen. These granules are then mixed with the starch, talc and stearic acid, passed through a #60 U.S. standard mesh screen and then compressed into tablets.

Example 9

	Gms.
Tri-(dimethylaminoisopropyl) phosphate trisulfate	2.50
Sodium chloride	0.35
Water for injection, q.s. to 100.00 ml.	

The salts are dissolved in 60 ml. of the water and the volume is then brought to 100 ml. The solution is then filtered through a Selas filter, filled into ampuls and autoclaved.

Example 10

Tri-(dimethylaminoethyl) phosphate trihydrochloride	gms.	2.00
Vitamin B_6	gms.	0.04
Nicotinamide	gms.	0.14
Sorbitol	gms.	25.00
Imitation wild cherry	ml.	0.10

Water, q.s. to make volume 100.00 ml.

Example 11

Tri-diethylaminobutyl) phosphate triacetate	gms.	4.00
Vitamin B_6	gms.	0.04
Nicotinamide	gms.	0.14
Choline dihydrogen citrate	gms.	3.00
Betaine	gms.	4.00
Imitation wild cherry	ml.	0.10
Sorbitol	gms.	10.00

Water, q.s. to make volume 100.00 ml.

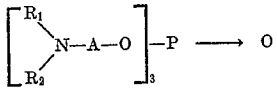
Example 12

	Mg.
Tri-(dimethylaminoethyl) phosphate trimaleate	75
Peanut oil	225

The ingredients are mixed to a thick slurry and filled into a soft gelatin capsule.

What is claimed is:

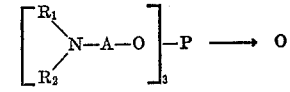
1. A method of lowering plasma cholesterol levels which comprises internally administering in an amount sufficient to lower the plasma cholesterol level compounds of the class consisting of a free base and its nontoxic pharmaceutically acceptable organic and inorganic acid addition salts, the free base having the formula:



in which R_1 and R_2 are alkyl groups containing a maximum of 4 carbon atoms and A represents a divalent saturated alkylene chain containing 2 to 6 carbon atoms separating the nitrogen and oxygen atoms attached thereto by at least 2 carbon atoms.

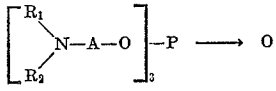
2. A method of lowering plasma cholesterol levels which comprises internally administering a dosage of about 5 mg. to about 300 mg. of a compound of the class consisting of a free base and its nontoxic pharmaceutically acceptable organic and inorganic acid addition salts,

the free base having the formula:



in which R_1 and R_2 are alkyl groups containing a maximum of 4 carbon atoms and A represents a divalent saturated alkylene chain containing 2 to 6 carbon atoms separating the nitrogen and oxygen atoms attached thereto by at least 2 carbon atoms.

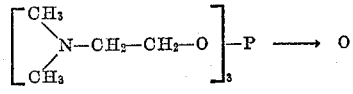
3. A method of lowering plasma cholesterol levels which comprises internally administering a daily dosage regimen of about 10 mg. to about 1000 mg. of a compound of the class consisting of a free base and its nontoxic pharmaceutically acceptable organic and inorganic acid addition salts, the free base having the formula:



in which R_1 and R_2 are alkyl groups containing a maximum of 4 carbon atoms and A represents a divalent saturated alkylene chain containing 2 to 6 carbon atoms separating the nitrogen and oxygen atoms attached thereto by at least 2 carbon atoms.

4. The method of claim 3 in which the administering is orally.

5. A method of lowering plasma cholesterol levels which comprises internally administering a dosage of about 5 mg. to about 300 mg. of a chemical compound and its nontoxic pharmaceutically acceptable organic and inorganic acid addition salts having the basic structural formula:



6. The method of claim 5 in which the administering is orally.

References Cited in the file of this patent

Bull. Soc. Chem. (France), 1957, pages 783–6, as cited in C.A., vol. 51, November 10, 1957, page 16331b.

Artom: Federation Procs., vol. 15, March 1956, page 213, No. 690.

Artom: J. Biol. Chem., vol. 180, 1949, pages 495–505.

Science, vol. 126, September 27, 1957, pages 610, 611.

Modern Drug Ency., Drug Publications, N.Y., 6th ed., 1955, pages 222, 223.

J.A.C.A., vol. 78, November 23, 1956, pages 5709 to 5730.