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TRIGLYCERIDE-LOWERING COMPOSITIONS AND METHODS

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No Drawing. Continuation-in-part of abandoned application Ser. No. 854,756, Sept. 2, 1969. This application Oct. 27, 1971, Ser. No. 193,170
Int. Cl. A61k 27/00
U.S. Cl. 424—318 6 Claims

ABSTRACT OF THE DISCLOSURE

Pharmaceutical compositions comprising a pharmaceutical carrier and an α,α,α',α'-tetramethylalkanedioic acid having a total of 14 to 18 carbon atoms, or a salt or alkyl ester of such an alkanedioic acid. Methods for the lowering of serum triglyceride levels by administering an α,α,α',α'-tetramethylalkanedioic acid having a total of 14 to 18 carbon atoms, or a salt or alkyl ester of such an alkanedioic acid.

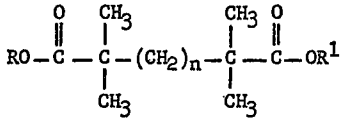
CROSS REFERENCE TO RELATED APPLICATION

This is a continuation-in-part of co-pending application Ser. No. 854,756, filed Sept. 2, 1969, now abandoned.

SUMMARY AND DETAILED DESCRIPTION

The present invention relates to pharmaceutical compositions possessing serum triglyceride-lowering activity, and to methods for lowering serum triglyceride levels, said compositions and methods employing certain alkanedioic acids and salts and alkyl esters thereof.

More particularly, the invention relates to pharmaceutical compositions and methods employing compounds which can be represented by the formula



in which *n* represents 6, 7, 8, 9, or 10; and each of R and R^1 represents hydrogen, a salt-forming cation, or a lower alkyl radical. The lower alkyl radicals are those containing not more than 8 carbon atoms. The salt-forming cations are preferably the pharmaceutically-acceptable cations of alkali metals, alkaline earth metals, ammonium, and substituted ammonium.

In accordance with the invention, pharmaceutical compositions are produced by formulating a compound of the foregoing formula (as an active ingredient) in dosage unit form with a pharmaceutical carrier. Some examples of dosage unit forms are tablets, capsules, lozenges, and pills; as well as powders and aqueous and non-aqueous solutions and suspensions packaged in containers containing either one or some larger number of dosage units and capable of being subdivided into individual doses by such means as measurement into a teaspoon or other standard container. Some examples of suitable pharmaceutical carriers, including pharmaceutical diluents, are gelatin capsules; sugars such as lactose and sucrose; starches such as corn starch and potato starch; cellulose derivatives such as sodium carboxymethyl cellulose, ethyl cellulose, methyl cellulose, and cellulose acetate phthalate; gelatin; talc; stearic acid; magnesium stearate; vegetable oils such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil, and oil of theobroma; propylene glycol; glycerine, sorbitol; polyethylene glycol; water; agar; alginic acid; isotonic saline; and phosphate buffer solutions; as well as other compatible substances normally used in pharmaceutical formulations. The compositions

of the invention can also contain other components such as coloring agents, flavoring agents, and/or preservatives. These materials, if present, are usually used in relatively small amounts. The compositions can, if desired, also contain other therapeutic agents.

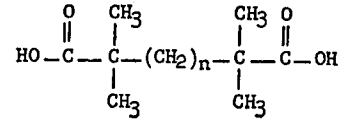
The percentage of the active ingredient in the foregoing compositions can be varied within wide limits but for practical purposes it is preferably present in a concentration of at least 10% in a solid composition and at least 2% in a primarily liquid composition. The most satisfactory compositions are those in which a much higher proportion of the active ingredient is present. The compositions of the invention preferably contain from 20 to 1,000 mg. of the active ingredient per dosage unit so that the entire amount to be administered during a day can be made up from a reasonable number of dosage units.

Also in accordance with the invention, the compounds of the foregoing formula are administered for the purpose of lowering serum triglyceride levels. The aforementioned compounds and compositions containing the same can be administered either orally or parenterally, in dosage unit form, with the dose adjusted to the needs and tolerances of the individual patient. Oral administration is preferred. The usual human dosage range is from 50 to 2,000 mg. per day, preferably 100 to 500 mg. per day, optionally in divided portions. Treatment is continued while satisfactory control of the serum triglyceride level is maintained without undesired side-effects.

The methods of the invention, as explained above, produce a lowering of the serum triglyceride level. In many cases the aforementioned compounds and compositions, especially when they are administered at a relatively high dosage, also produce a lowering of the serum cholesterol level. The lowering of serum triglycerides is a characteristic feature of the invention and the lowering of serum cholesterol is an incidental feature.

The effectiveness of the aforementioned compounds and compositions in lowering serum triglycerides can be demonstrated by standard methods. For example, male rats weighing 200–250 g. are maintained on a normal pellet diet. Each animal in a treatment group is given a daily oral dose of a test compound for 7 days. An untreated control group is also maintained. At the end of the 7-day test period the animals are weighed and sacrificed, and the serum cholesterol and serum triglycerides are determined from blood samples taken from the vena cava. The methods used are described in "Journal of Laboratory and Clinical Medicine," 50, 318 (1957) and "Journal of Laboratory and Clinical Medicine," 50, 152 (1957). The test compound is considered to exhibit a side effect if the weight of the animals in the treatment group is significantly less than the weight of the animals in the control group. In a representative determination, 2,2,9,9-tetramethyldecanedioic acid at 5 mg./kg. per day for 7 days produced a 44% reduction of serum triglycerides with no effect on serum cholesterol or weight of the animals, relative to the untreated control group. 2,2,9,9-tetramethyldecanedioic acid, diethyl ester at 75 mg./kg. per day for 7 days produced a 74% reduction of serum triglycerides with no effect on serum cholesterol or weight of the animals, relative to the untreated control group.

The preferred pharmaceutical compositions and methods of the invention are those employing an α,α,α',α'-tetramethylalkanedioic acid of the formula



or a cationic salt thereof; where *n* is as defined before and consequently represents 6, 7, 8, 9, or 10.

Many of the compounds employed in the compositions and methods of the invention are old. They can all be prepared in a number of different ways. The alkanedioic acids and a method of preparation have been described in "Journal of the American Chemical Society," 73, 136 (1951). The alkanedioic acids, their salts and esters can also be prepared by reacting isobutyric acid or an ester thereof with a polymethylene dihalide in the presence of a strong base in an anhydrous medium, optionally followed by acidification, as illustrated in greater detail hereinafter. The alkanedioic acid esters can also be prepared by esterifying the alkanedioic acids, typically by reaction with a lower alkanol in the presence of a mineral acid or strong organic acid. The alkanedioic acid salts can be prepared from the alkanedioic acids by reaction with any of a large number of bases.

The invention is illustrated by the following examples.

Example 1

Ingredient:	Quantity, g.
2,2,9,9-tetramethyldecanedioic acid	1,000
Lactose	960
Magnesium stearate	40

The mixture is blended in a twin-shell blender and filled into No. 4 hard gelatin capsules. Each capsule is filled with 200 mg. of the powder mixture and contains 100 mg. of 2,2,9,9-tetramethyldecanedioic acid. Yield equals approximately 10,000 capsules.

Example 2

Ingredient:	Quantity, g.
2,2,11,11-tetramethyldodecanedioic acid	1,000
Lactose	960
Magnesium stearate	40

The mixture is blended and filled into No. 4 hard gelatin capsules, filling each capsule with 200 mg. of the powder mixture. Yield equals approximately 10,000 capsules, each containing 100 mg. of 2,2,11,11-tetramethyldodecanedioic acid.

Similarly, filled gelatin capsules are obtained by substituting 1,000 g. of any of the following substances for the 2,2,11,11-tetramethyldodecanedioic acid in the foregoing procedure:

2,2,9,9-tetramethyldecanedioic acid, disodium salt.
2,2,9,9-tetramethyldecanedioic acid, dipotassium salt.
2,2,9,9-tetramethyldecanedioic acid, dicholine salt.
2,2,12,12-tetramethyltridecanedioic acid.
2,2,13,13-tetramethyltetradecanedioic acid.

Example 3

Ingredient:	Quantity, g.
2,2,9,9-tetramethyldecanedioic acid	1,000
Lactose	800
Magnesium stearate	35

The mixture is blended and filled into No. 3 hard gelatin capsules, filling each capsule with 367 mg. of the powder mixture. Yield equals approximately 5,000 capsules, each containing 200 mg. of 2,2,9,9-tetramethyldecanedioic acid.

Example 4

Ingredient:	Quantity, g.
2,2,9,9-tetramethyldecanedioic acid	1,000
Propylene glycol	1,000

The above ingredients are blended and filled into soft gelatin capsules, filling each capsule with 400 mg. of the mixture. Yield equals approximately 5,000 capsules, each containing 200 mg. of 2,2,9,9-tetramethyldecanedioic acid.

Similarly, filled gelatin capsules are obtained by substituting 1,000 g. of either of the following substances for the 2,2,9,9-tetramethyldecanedioic acid in the foregoing procedure:

2,2,9,9-tetramethyldecanedioic acid, diethyl ester.
2,2,9,9-tetramethyldecanedioic acid, diisopropyl ester.
2,2,9,9-tetramethyldecanedioic acid, dibutyl ester.
2,2,9,9-tetramethyldecanedioic acid, dioctyl ester.

Example 5

Ingredient:	Quantity
2,2,9,9-tetramethyldecanedioic acid	g. 3,000
Lactose	g. 750
Corn starch	g. 300
Gelatin	g. 120
Water	cc. 1,000
Magnesium stearate	g. 20

The 2,2,9,9-tetramethyldecanedioic acid, lactose, and 150 g. of the corn starch are blended and granulated with a solution of the gelatin in the water. The wet granulation is screened, dried, and re-screened. The resulting dried granulation is blended with the magnesium stearate and the remaining 150 g. of corn starch, and the mixture is compressed into 698 mg. tablets using $\frac{15}{32}$ inch standard concave punches. Yield equals approximately 6,000 tablets, each containing 500 mg. of 2,2,9,9-tetramethyldecanedioic acid.

Example 6

Ingredient:	Quantity
2,2,9,9-tetramethyldecanedioic acid (micronized)	g. 4
Polyoxyethylene sorbitan monostearate	cc. 0.1
Sodium carboxymethyl cellulose	g. 0.3
Complex magnesium-aluminum silicate	g. 0.5
Sugar	g. 10
Glycerin	cc. 2
Sodium benzoate	g. 0.5
Sodium citrate	g. 0.2
Approved red dye	mg. 1
Imitation cherry flavor	cc. 0.02
Citric acid, to make pH 4.0.	
Distilled water, to make 100 cc.	

The polyoxyethylene sorbitan monostearate can be a product such as polysorbate 60 or Tween 60. The complex magnesium-aluminum silicate is a gel-forming agent. A product such as Veegum H.V. can be used. This substance is hydrated overnight in 10 cc. of distilled water. A mixture is prepared from the polyoxyethylene sorbitan monostearate, imitation cherry flavor, 30 cc. of distilled water, and the 2,2,9,9-tetramethyldecanedioic acid and passed through a homogenizer. With vigorous stirring, the sugar, glycerin, sodium citrate, sodium benzoate, and sodium carboxymethyl cellulose are added, followed by hydated complex magnesium-aluminum silicate and a solution of the red dye in 2 cc. of water. The resulting suspension is homogenized, adjusted to pH 4.0 with citric acid, and diluted to a final volume of 100 cc. with distilled water. A 5 cc. oral dosage unit of this suspension contains 200 mg. of 2,2,9,9-tetramethyldecanedioic acid. If desired, the red dye and imitation cherry flavor can be omitted or replaced by other coloring and flavoring agents.

By the foregoing procedure, with the substitution of 4 g. of micronized 2,2,10,10-tetramethylundecanedioic acid for the 2,2,9,9-tetramethyldecanedioic acid, a suspension containing 200 mg. of 2,2,10,10-tetramethylundecanedioic acid per 5 cc. oral dosage unit is obtained.

Example 7

Ingredient:	Quantity
2,2,9,9-tetramethyldecanedioic acid	g. 20
Polyethylene glycol	cc. 50
Benzyl alcohol	cc. 4
Sodium hydroxide 10% solution, to make pH 8.0.	
Hydrochloric acid 10% solution, to make pH 8.0.	
Sterile distilled water, to make 200 cc.	

The polyethylene glycol used in this formulation can be a material such as polyethylene glycol 400. A solution is prepared by dissolving 2,2,9,9-tetramethyldecanedioic acid in 100 cc. of 10% sodium hydroxide solution. The polyethylene glycol and the benzyl alcohol are added and the pH is adjusted to 8.0 using 10% sodium hydroxide and 10% hydrochloric acid. The solution is sterilized by filtration using a sterilized millipore filter membrane and a microfiber glass pre-filter disc. Equipment suitable for this purpose is a type SS (0.22 micron pore size) millipore filter membrane and a type AP–20 microfiber glass pre-filter disc. The filtrate is collected in a sterile receiving vessel and aseptically filled into round amber glass vials, filling each vial with 2 cc. of the solution and sealing the vial. The resulting solution for parenteral administration contains 100 mg. of 2,2,9,9-tetramethyldecanedioic acid per cc.

PREPARATION OF TETRAMETHYLALKANEDIOIC ACIDS, SALTS, AND ESTERS

At 0–10° C., 375 ml. of a solution of n-butyllithium in heptane (1.6 millimoles/ml.) is added with stirring to a solution of 61 g. of diisopropylamine in 300 ml. of anhydrous tetrahydrofuran. The cold mixture is stirred for 10 more minutes and then treated with a solution of 26.4 g. of isobutyric acid in 25 ml. of anhydrous tetrahydrofuran, added over a period of 20 minutes. The mixture is stirred for 10 minutes at 0–10° C., for 30 minutes at room temperature, again cooled to 0–10° C., and treated with a solution of 36.6 g. of 1,6-dibromohexane in 50 ml. of anhydrous tetrahydrofuran. It is then stirred overnight at room temperature, cooled to 0° C., and cautiously diluted with 500 ml. of water. The aqueous phase is separated, washed with ether, and acidified with hydrochloric acid. The acidified mixture is extracted with ether and the ether extract is washed with water, dried, and evaporated to give a residue of 2,2,9,9-tetramethyldecanedioic acid; M.P. 116–117.5° C. following crystallization from acetonitrile.

By the foregoing procedure, with the substitution of another polymethylene dihalide for the 1,6-dibromohexane, the following additional products are obtained.

From 40.8 g. of 1,8-dibromooctane, the product is 2,2,11,11-tetramethyldodecanedioic acid; M.P. 92.5–95° C.

From 42.9 g. of 1,9-dibromononane, the product is 2,2,12,12-tetramethyltridecanedioic acid; M.P. 70–72° C.

From 45.0 g. of 1,10-dibromodecane, the product is 2,2,13,13-tetramethyltetradecanedioic acid; M.P. 86–88° C.

With stirring, 12.7 g. of sodium hydride and then 27.8 g. of isobutyric acid are added to a solution of 42 ml. of diisopropylamine in 300 ml. of anhydrous tetrahydrofuran. The mixture is heated at reflux for 45 minutes, cooled to 0° C., and treated with 213.5 ml. of a solution of n-butyllithium in heptane (1.4 millimoles/ml.). The mixture is then stirred for 30 minutes at room temperature, cooled to 0° C., treated with 25.4 g. of 1,7-dichloroheptane, and stirred overnight at room temperature. It is then hydrolyzed and the product isolated as described above to give 2,2,10,10-tetramethylundecanedioic acid; M.P. 75–77° C. following crystallization from acetonitrile.

Salts with pharmaceutically-acceptable cations are obtained by reacting any of the alkanedioic acids with a base such as sodium hydroxide, potassium hydroxide, potassium carbonate, calcium hydroxide, ammonia, diethylamine, 2-aminoethanol, or choline. For example, a suspension of 5.2 g. of 2,2,9,9-tetramethyldecanedioic acid in 30 ml. of water is treated with 37 ml. of 1 N sodium hydroxide and then with 20 ml. of methanol. The mixture is concentrated to one-third its original volume, diluted with 100 ml. of water, concentrated to two-thirds volume, and freeze-dried to give a residue of 2,2,9,9-tetramethyldecanedioic acid, disodium salt. By substituting an equivalent amount of potassium hydroxide for the sodium hydroxide, the product is 2,2,9,9-tetramethyldecanedioic acid, dipotassium salt. By substituting an equivalent amount of choline for the sodium hydroxide, the product is 2,2,9,9-tetramethyldecanedioic acid, dicholine salt.

A mixture of 50 g. of 2,2,9,9-tetramethyldecanedioic acid, 1.2 g. of p-toluensulfonic acid monohydrate, 45 ml. of ethanol, and 300 ml. of toluene is heated at reflux for 36 hours, with continuous removal of the water formed in the reaction. The mixture is cooled, washed with dilute sodium hydroxide solution and with water, dried over magnesium sulfate, and concentrated to dryness under reduced pressure to give a residue of 2,2,9,9-tetramethyldecanedioic acid, diethyl ester. For purification the product is distilled in vacuo; B.P. 134–136° C. at 1 mm.

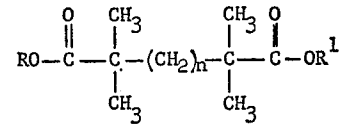
Similarly, with the substitution of 59 ml. of isopropyl alcohol for the ethanol, the product is 2,2,9,9-tetramethyldecanedioic acid, diisopropyl ester.

Similarly, with the substitution of 71 ml. of 1-butanol for the ethanol, the product is 2,2,9,9-tetramethyldecanedioic acid, dibutyl ester.

Similarly, with the substitution of 122 ml. of 1-octanol for the ethanol, the product is 2,2,9,9-tetramethyldecanedioic acid, dioctyl ester; B.P. higher than 180° C. at 0.05 mm.

I claim:

1. A pharmaceutical composition in dosage unit form possessing serum triglyceride-lowering activity and suitable for oral administration, comprising a solid pharmaceutical carrier and 20 to 1,000 mg. per dosage unit of a compound of the formula

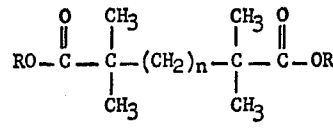


where *n* is 6, 7, 8, 9, or 10; and R and R^1 are selected from the group consisting of hydrogen, pharmaceutically-acceptable salt-forming cations, and lower alkyl.

2. The composition of claim **1** in the form of a capsule or tablet in which the compound of the indicated formula is 2,2,9,9-tetramethyldecanedioic acid.

3. The composition of claim **2** containing 100 mg. of 2,2,9,9-tetramethyldecanedioic acid.

4. A method for lowering serum triglyceride levels which comprises administering a compound of the formula



orally or parenterally in humans in need thereof in a dose of at least 50 mg. per day; where *n* is 6, 7, 8, 9, or 10; and R and R^1 are selected from the group consisting of hydrogen, pharmaceutically-acceptable salt-forming cations, and lower alkyl.

5. The method of claim **4** wherein 2,2,9,9-tetramethyldecanedioic acid is administered.

6. The method of claim **5** wherein the administration is oral.

References Cited

Journal of American Chemical Society, vol. 73 (1951), 136–141.

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