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3,716,644

HYPOLIPIDEMIC AGENTS

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No Drawing. Filed July 15, 1971, Ser. No. 163,083

Int. Cl. A61k 27/00

U.S. Cl. 424—308

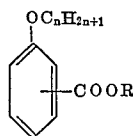
5 Claims

ABSTRACT OF THE DISCLOSURE

A method for the lowering of serum lipids in mammals by the administration of meta and para alkoxybenzoic acids, esters and pharmaceutically acceptable salts of said benzoic acids and dimethylaminoethyl esters, wherein the alkoxy group comprises from 12 to 20 carbon atoms; and pharmaceutical compositions thereof.

SUMMARY OF THE INVENTION

This invention relates to a method for lowering serum lipids in mammals by the administration of compounds of the following formula:



wherein the COOR group is meta or para to the $\text{OC}_n\text{H}_{2n+1}$ group, n is 12–20, R is hydrogen, lower alkyl having 1–5 carbon atoms, phenyl, benzyl, 3-pyridyl and 2-dimethylaminoethyl. In addition, wherein R is hydrogen and 2-dimethylaminoethyl, pharmaceutically acceptable salts may be utilized. The invention also relates to useful pharmaceutical compositions employing said compounds to lower serum lipids.

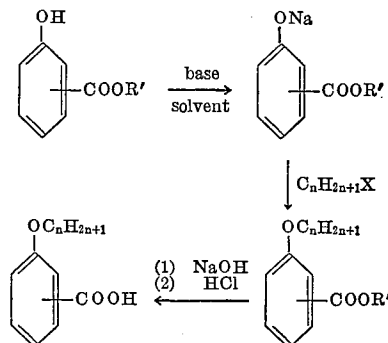
BACKGROUND OF THE INVENTION

Considerable effort has been directed in recent years to obtain substances which are useful in the treatment of hyperlipidemia, a condition associated with elevated cholesterol, phospholipid and/or triglyceride blood levels. This condition is associated with a number of diseases, one of the most serious being atherosclerosis. Medicaments used to lower blood cholesterol, phospholipid and triglyceride blood levels are termed hypolipidemic drugs. Presently four major lipid lowering agents are available; clofibrate, D-thyroxine, nicotinic acid, and cholestyramine; [R. I. Levy and D. S. Fredrickson, Postgraduate Medicine, vol. 47, pps. 130–136 (1979)]. It has now been found that another class of compounds also exhibits marked hypolipidemic activity. The class of compounds encompassed by the present invention may be termed alkoxybenzoic acids and esters thereof.

SPECIFIC DISCLOSURE

The compounds of this invention are generally prepared by the following reaction sequence:

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R' is a lower alkyl having 1 to 5 carbon atoms, phenyl, benzyl or 3-pyridyl; n is 12–20 and the alkoxy group may be meta or para to the carboxyl or carboxylate group. While it is preferred that the alkoxy group be composed of a straight chain alkyl group, some branching is permissible, such as the presence of one or two methyl groups or an ethyl group as part of the chain.

Of the active compounds, the preferred group comprises those compounds which are alkoxy benzoic acids wherein the alkyl group consists of 12 to 20 carbon atoms. These compounds may be utilized either as the free acids or in the form of a pharmaceutically acceptable salt. The salts may be either of an inorganic nature, such as the ammonium salt, sodium salt, potassium salt, etc., or of an organic type, such as an organic amine salt.

The 2-dimethylaminoethyl alkoxybenzoic acid esters may also be utilized either in the form of the free base or as a pharmaceutically acceptable acid addition salt, thereof. These salts may be prepared by reacting the free base with an inorganic acid, such as hydrochloric, sulfuric, phosphoric, etc. or an organic acid, such as acetic, citric, tartaric, etc.

While the invention encompasses groupings comprising 12 to 20 carbon atoms as the alkyl portion of the ether function, the preferred groupings are straight chain alkyls with a length of about 16 carbon atoms. Of the two possible positions that the alkoxy group may be in relation to the carboxyl or carboxylate group, the preferred one is when the groups are para to each other.

The mechanism of action of the compounds of this invention is not known and the inventors do not wish to be limited to any particular mechanism. However, it is believed that the hypolipidemic activity results from the free acid, or ester of the above general formula which are readily converted in mammals to the acid or its metabolites (e.g. glycerol or cholesterol esters of the parent acid).

In preparing compounds of this invention, the appropriate ester of a hydroxybenzoic acid is employed. The esters are converted to the corresponding phenolate salts which may be used directly without isolation or isolated and purified prior to formation of the ether linkage. Numerous strong bases may be employed, such as sodium hydride, sodamide, sodium methoxide, sodium ethoxide, etc., and solvents which are compatible with the base being employed, such as sodium hydride or sodamide in dimethylformamide, dimethylacetamide, toluene and dimethylsulfoxide or sodium methoxide in methanol. Where the phenolate salt is to be isolated, an aqueous or alcoholic sodium hydroxide solution may be used provided calculated quantities are used so as not to cleave the

ester portion of the intermediate to be prepared. Other salts could be utilized with an equal degree of success such as potassium or magnesium. The phenolate salt is converted to the hypolipidemic ether by reaction with a compound having the general formula $C_nH_{2n+1}X$, where X represents a group which is chemically termed an efficient leaving group, such as bromo, iodo and benzene-sulfonyloxy. The esters are converted to the corresponding acids by hydrolysis with a base, such as sodium hydroxide, potassium hydroxide, etc. and acidification.

Occasionally special procedures are employed in the preparation of a particular ester. The 2-dimethylaminoethyl esters are prepared by converting the alkoxybenzoic acid to the corresponding acid chloride and interacting said acid chloride with 2-dimethylaminoethanol. The ethyl and phenyl esters are conveniently prepared by esterifying the corresponding alkoxybenzoic acids with ethanol and phenol, respectively. In the case of ethanol, sulfuric acid is utilized to facilitate esterification, while the pheno-

TABLE I

Compound	Percent in diet	Percent sterol lowering from control	Percent triglyceride lowering from control
P-Tridecyloxybenzoic acid.....	0.1	24	34
	0.03	1	28
Methyl p-tridecyloxybenzoate.....	0.1	5	57
	0.03	0	33
Methyl p-tetradecyloxybenzoate.....	0.1	29	29
Ethyl p-tetradecyloxybenzoate.....	0.1	16	59
Methyl m-tetradecyloxybenzoate.....	0.1	14	36
m-Tetradecyloxybenzoic acid.....	0.1	27	42
p-Pentadecyloxybenzoic acid.....	0.1	30	28
Methyl p-pentadecyloxybenzoate.....	0.1	26	51
Methyl p-octadecyloxybenzoate.....	0.1	0	56
Benzyl p-tetradecyloxybenzoate.....	0.1	20	47
Sodium p-tetradecyloxybenzoate.....	0.1	18	58
15 Methyl p-(1-methylundecyloxy) benzoate.....	0.1	14	53
2-dimethylaminoethyl p-hexadecyloxybenzoate.....	0.1	14	54

TABLE II

Compounds	Percent in diet	Percent serum sterol lowering from control	Percent triglyceride lowering from control	Percent phospholipid lowering from control
p-Dodecyloxybenzoic acid.....	0.1	37	62	43
p-Hexadecyloxybenzoic acid.....	0.1	33	53	32
p-Pentadecyloxybenzoic acid.....	0.1	38	45	33
p-Tetradecyloxybenzoic acid.....	0.1	33	40	40
p-Tridecyloxybenzoic acid.....	0.1	34	60	43
p-Heptadecyloxybenzoic acid.....	0.1	1	66	7
p-Octadecyloxybenzoic acid.....	0.1	14	59	13
p-Nonadecyloxybenzoic acid.....	0.1	130	51	13
p-Eicosyloxybenzoic acid.....	0.1	114	54	10
Clofibrate.....	0.3	10	31	16
	0.1	4	22	13
2 0.1	31	48	25	
2 0.03	10	35	18	

¹ These values are increases from control.

² Tested for two weeks.

late esters are formed with the aid of carbonyldiimidazole. In addition, numerous other standard esterification techniques are available to prepare the compounds of this invention.

The compounds of the present invention were shown to possess hypolipidemic activity as determined by animal experiments as follows: the compounds studied were administered orally admixed with the diet to groups of 4-6 male rats, CFE strain from Carworth Farms. A control group of 6-8 rats was maintained on the diet alone; test groups were maintained on the diet plus the indicated percentage of compound by weight. After 6 days or 2-4 weeks treatment, serum sterol concentrations were determined either (1) according to the saponification and extraction method of P. Trinder, Analyst 77, 321 (1952) and the colorimetric determination of Zlatkis, et al., J. Lab. Clin. Med. 44, 486 (1953) or (2) by the extraction method of H. H. Leffler, Amer. J. Clin. Path. 31, 310 (1959), and the colorimetric determination of Zlatkis (vide supra), the overall method appropriately modified for use with an automatic mechanical analyzer. Serum triglycerides were estimated by the automated procedure of Kessler and Lederer ["Automation in Analytical Chemistry," Skeggs, L. T. (Ed.), Mediad Inc., New York, 1965, p. 341]. The phospholipids were determined by standard methods [G. R. Bartlett, J. Biol. Chem. 234, 466 (1959)]. Concentrations of serum lipids are expressed as milligrams per 100 milliliters.

In these tests, a compound is considered to have hypolipidemic activity if it depresses serum sterol levels 15% or more below that of the controls, and/or depresses triglyceride levels by 25% or more below controls. Table I shows several of the compounds of the present invention and the degree to which they depress serum sterols and triglyceride levels after a 6 day dosing period.

Table II gives the results of a 4 week dosing period using several compounds from this invention and clofibrate. Clofibrate and SaH 42-348 [1-methyl-4-piperidylbis-(p-chlorophenoxy)acetate] which were administered to animals for two weeks are included for comparison.

The effect of one of the compounds in this series on serum sterol levels was also determined in mice (Table III). C3H mice from the Roscoe B. Jackson Memorial Labs., Bar Harbor, Maine were used. The methods used for lipid analysis were the same as those disclosed above. The results obtained in two tests using p-tetradecyloxybenzoic acid are presented.

TABLE III

Treatment	Experiment 1		Experiment 2	
	Control	Drug	Control	Drug
Dose, percent of diet.....	0	0.1	0	0.1
Food intake, g./day.....	3.2	3.0	2.9	2.4
Body weight change, grams.....	0.8	0.8	-0.3	-1.7
50 Serum sterol, percent lowering.....		21		16

The compounds of this invention, that is the alkoxybenzoic acids, esters or pharmaceutically acceptable salts, have potencies similar to 1-methyl-4-piperidyl bis-(p-chlorophenoxy)acetate and clofibrate; and thus have been found to be highly useful as hypolipidemic compounds in mammals when administered in amounts ranging from about .5 mg. per kg. to about 40 mg. per kg. of body weight per day. A preferred dosage regimen for optimum results would be from about 2 mg. per kg. to about 29 mg. per kg. Thus the daily dosage employed for a subject of about 70 kg. of body weight is about 35 mg. to about 2.8 g., and preferably about 140 mg. to about 2.0 g.

The active compounds of the present invention may be orally administered, for example, with an inert diluent or with an assimilable edible carrier, or they may be enclosed in hard or soft gelatin capsules, or they may be compressed into tablets, or they may be incorporated directly with the food of the diet. For oral therapeutic administration, the active compounds of this invention may be incorporated with excipients and used in the form of tablets, troches, capsules, elixirs, suspensions, syrups, wafers, chewing gum, and the like. Such com-

positions and preparations should contain at least 0.1% of active compound. The percentage in the compositions and preparations may, of course, be varied and may conveniently be between about 5% to about 75% or more of the weight of the unit. The amount of active compound in such therapeutically useful compositions or preparations is such that a suitable dosage will be obtained. Preferred compositions or preparations according to the present invention are prepared so that an oral dosage unit form contains between about 10 and 500 milligrams of active compound.

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

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

EXAMPLE 1

Methyl p-tridecyloxybenzoate

A 4.8 gram (0.1 mole) (50% in oil) portion of sodium hydride was added to 15.2 grams (0.1 mole) of methyl p-hydroxybenzoate in 150 ml. of dimethylformamide, followed by 26.3 grams (0.1 mole) of 1-bromotridecane. The reaction was heated at 90–100° (steam bath) for 4 hours, and then it was poured into about 1000 ml. of water. The resulting mixture was extracted with four 250 ml. portions of chloroform. The combined extracts were dried over magnesium sulfate, then taken to an oil using the rotary evaporator. Upon crystallization, the compound was crystallized from ethanol to give 23.49 g. (70%) of methyl p-tridecyloxybenzoate. An analytical sample was obtained by recrystallization from methanol; M.P. 60–63°.

Analysis.—Calcd. for $C_{21}H_{34}O_3$ (percent): C, 75.40; H, 10.25. Found (percent): C, 75.65; H, 10.03.

EXAMPLE 2

p-Tridecyloxybenzoic acid

Methyl p-tridecyloxybenzoate 13.49 grams (0.403 mole) was refluxed in 100 ml. of 1 N sodium hydroxide and 100 ml. of ethanol for 3 hours. The hot solution was acidified with 10 ml. of 12 N hydrochloric acid. On cooling the precipitate was filtered and recrystallized from ethanol to give 10.72 g. (80%) of p-tridecyloxybenzoic acid; M.P. 132–4°.

Analysis.—Calcd. for $C_{20}H_{32}O_3$ (percent): C, 74.96; H, 10.06. Found (percent): C, 74.87; H, 9.79.

EXAMPLE 3

Methyl p-tetradecyloxybenzoate

Method I.—1-bromotetradecane 27.7 grams (0.1 mole) dissolved in 50 ml. of methanol was added to 15.2 grams (0.1 mole) of methyl p-hydroxybenzoate and 5.4 g. (0.1

mole) of sodium methoxide in 50 ml. of methanol. After refluxing for 17 hours, 0.5 gram of sodium hydroxide was added, and the solvent was removed in vacuo, and the solid was extracted with ether. The ethereal extracts were taken in vacuo to a solid, which was recrystallized from hexane to give 14 g. (40.3%) of methyl p-tetradecyloxybenzoate; M.P. 52–57°.

Method II.—To 15.2 grams (0.1 mole) of methyl p-hydroxybenzoate in 50 ml. of dimethylformamide was added 4.8 grams (0.1 mole) (50% in oil) of sodium hydride, followed by 27.7 g. (0.1 mole) of 1-bromotetradecane. The reaction was heated at 90–100° (steam bath) for 4 hours, and then poured into about 600 ml. of water. The resulting crystals were filtered and recrystallized from hexane to give 21.1 g. (60.7%) of methyl p-tetradecyloxybenzoate, M.P. 50–54°.

Method III.—In a manner analogous to Example 1, 45.6 grams (0.3 mole) of methyl p-hydroxybenzoate, 14.4 grams (0.3 mole) (50% in oil) of sodium hydride, and 83.1 grams (0.3 mole) of 1-bromotetradecane gave 74.87 g. (70%) of methyl p-tetradecyloxybenzoate.

Analysis.—Calcd. for $C_{22}H_{36}O_3$ (percent): C, 75.81; H, 10.41. Found (percent): C, 75.42; H, 10.21.

EXAMPLE 4

p-Tetradecyloxybenzoic acid

In a manner analogous to Example 2, 39.61 g. (0.112 mole) of methyl p-tetradecyloxybenzoate, gave, after refluxing for 3 hours, 34.62 g. (90%) of p-tetradecyloxybenzoic acid, M.P. 129–132°.

Analysis.—Calcd. for $C_{21}H_{34}O_3$ (percent): C, 75.40; H, 10.25. Found (percent): C, 75.27; H, 10.15.

EXAMPLE 5

Methyl p-pentadecyloxybenzoate

In a manner analogous to Example 1, 30.66 g. (84.8%) of methyl p-pentadecyloxybenzoate was prepared from 15.2 grams (0.1 mole) of methyl p-hydroxybenzoate, 4.8 grams (0.1 mole) (50% in oil) of sodium hydride, and 29.1 grams (0.1 mole) of 1-bromopentadecane. The analytical sample melted at 63–66°.

Analysis.—Calcd. for $C_{23}H_{38}O_3$ (percent): C, 76.19; H, 10.57. Found (percent): C, 76.57; H, 10.50.

EXAMPLE 6

p-Pentadecyloxybenzoic acid

In a manner analogous to Example 2, 24.66 grams (0.068 mole) of methyl p-pentadecyloxybenzoate gave 22.11 grams (90%) of p-pentadecyloxybenzoic acid; M.P. 124–130° (softens at 100°).

Analysis.—Calcd. for $C_{22}H_{36}O_3$ (percent): C, 75.81; H, 10.41. Found (percent): C, 75.81; H, 10.29.

EXAMPLE 7

Methyl hexadecyloxybenzoate

In a manner analogous to Example 1, 175.92 grams (93.5%) of methyl hexadecyloxybenzoate was prepared from 76 grams (0.5 mole) of methyl p-hydroxybenzoate, 21.1 grams (0.5 mole) (57% in oil) of sodium hydride, and 157.5 grams (0.5 mole) of 1-bromohexadecane. The product melted at 62–65°.

Analysis.—Calcd. for $C_{24}H_{40}O_3$ (percent): C, 76.55; H, 10.71. Found (percent): C, 76.34; H, 10.59.

EXAMPLE 8

p-Hexadecyloxybenzoic acid

In a manner analogous to Example 2, 170.92 grams (0.455 mole) of methyl p-hexadecyloxybenzoate gave, after refluxing for 16 hours, 118.09 grams (70%) of p-hexadecyloxybenzoic acid; M.P. 128–131° (softens 97°).

Analysis.—Calcd. for $C_{23}H_{38}O_3$ (percent): C, 76.19; H, 10.57. Found (percent): C, 75.89; H, 10.28.

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EXAMPLE 9

Methyl p-heptadecyloxybenzoate

In a manner analogous to Example 1, 24.13 g. (61.8%) of methyl p-heptadecyloxybenzoate was prepared from 15.2 grams (0.1 mole) of methyl p-hydroxybenzoate, 4.8 grams (0.1 mole) (50% in oil) of sodium hydride, and 31.9 g. (0.1 mole) of 1-bromoheptadecane. The product melted at 68–71°.

Analysis.—Calcd. for $C_{25}H_{42}O_3$ (percent): C, 76.87; H, 10.84. Found (percent): C, 77.05; H, 10.77.

EXAMPLE 10

p-Heptadecyloxybenzoic acid

In a manner analogous to Example 2, 7.48 g. (42.8%) of p-heptadecyloxybenzoic acid was obtained from 18.13 g. (0.0464 mole) of methyl p-heptadecyloxybenzoate; M.P. 130–131° (softens 103°).

Analysis.—Calcd. for $C_{24}H_{40}O_3$ (percent): C, 76.55; H, 10.71. Found (percent): C, 76.70; H, 10.56.

EXAMPLE 11

Methyl octadecyloxybenzoate

In a manner analogous to Example 1, 32.58 g. (80.0%) of methyl octadecyloxybenzoate was prepared from 15.2 grams (0.1 mole) of methyl p-hydroxybenzoate, 4.8 grams (0.1 mole) (50% in oil) of sodium hydride, and 33.3 g. (0.1 mole) of 1-bromooctadecane. The product melted at 69–72°.

EXAMPLE 12

p-Octadecyloxybenzoic acid

In a manner analogous to Example 2, 26.58 grams (0.0654 mole) of methyl p-octadecyloxybenzoate gave, after refluxing for 16 hours, 16.40 grams (61.9%) of p-octadecyloxybenzoic acid; M.P. 124–127° (softens 97°).

Analysis.—Calcd. for $C_{25}H_{40}O_3$ (percent): C, 76.87; H, 10.84. Found (percent): C, 76.50; H, 10.60.

EXAMPLE 13

Methyl p-nonadecyloxybenzoate

In a manner analogous to Example 1, 15.35 grams (73.5%) of methyl p-nonadecyloxybenzoate was prepared from 7.6 grams (0.05 mole) of methyl p-hydroxybenzoate, 2.4 grams (0.05 mole) (50% in oil) of sodium hydride, and 17.37 grams (0.05 mole) of 1-bromononadecane. The product melted at 73–75°.

Analysis.—Calcd. for $C_{27}H_{46}O_3$ (percent): C, 77.46; H, 11.08. Found (percent): C, 77.57; H, 10.92.

EXAMPLE 14

p-Nonadecyloxybenzoic acid

In a manner analogous to Example 2, 9.35 grams (0.0222 mole) of methyl p-nonadecyloxybenzoate, after refluxing for 16 hours, gave 6.66 grams (74.2%) of p-nonadecyloxybenzoic acid; M.P. 123–126° (softens 105°).

Analysis.—Calcd. for $C_{27}H_{44}O_3$ (percent): C, 77.17; H, 10.96. Found (percent): C, 77.43; H, 10.85.

EXAMPLE 15

Methyl p-eicosyloxybenzoate

A solution consisting of 15.2 grams (0.1 mole) of the methyl ester of p-hydroxybenzoic acid and 36.1 grams (0.1 mole) of 1-bromoeicosane were dissolved in 200 ml. of dry DMF and treated with 2.4 grams (0.1 mole) of NaH added portionwise. After addition of the NaH the dark-brown colored suspension was heated at 95–100° for 3 hours and then poured into 3 liters of cold H_2O . The organic material was collected by filtration and recrystallized three times from benzene to afford the desired methyl p-eicosyloxybenzoate; M.P. 76–78° C.

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Analysis.—Calcd. for $C_{28}H_{48}O_3$ (percent): C, 77.66; H, 11.17. Found (percent): C, 77.26; H, 11.05.

EXAMPLE 16

p-Eicosyloxybenzoic acid

Forty three grams (0.1 mole) of the methyl ester of p-eicosyloxybenzoic acid was dissolved in 750 ml. of hot EtOH. When solution was complete 15 ml. of 10 N NaOH was added all at once. The sodium salt of the desired product formed in quantitative yield after 20 minutes. Filtration afforded the solid salt which was triturated with two 100-ml. portions of ether and two 100 ml. portions of acetone. After this treatment the salt of the p-eicosyloxybenzoic acid was suspended in water (300 ml.) and warmed with 50 ml. of conc. HCl. The desired product p-eicosyloxybenzoic acid was collected by filtration, air-dried, and recrystallized from benzene; transition point temperature 126–127°.

Analysis.—Calcd. for $C_{27}H_{46}O_3$ (percent): C, 77.46; H, 11.08; O, 11.47. Found (percent): C, 76.41; H, 10.76; O, 12.83 (diff.).

EXAMPLE 17

Phenyl p-tetradecyloxybenzoate

p-Tetradecyloxybenzoic acid 6.7 grams (0.02 mole) and 3.3 grams (0.02 mole) of 1,1'-carbonyldiimidazole were dissolved in 50 ml. of tetrahydrofuran for two hours. Then, 2 grams (0.021 mole) of phenol, and a trace of sodium hydride were added, and the reaction was refluxed for 3 hours. The reaction mixture was filtered, and the filtrate was taken to an oil in vacuo. The compound solidified and was recrystallized from isopropanol to give 6.59 grams (80%) of phenyl p-tetradecyloxybenzoate, M.P. at 78–81°.

Analysis.—Calcd. for $C_{27}H_{38}O_3$ (percent): C, 78.98; H, 9.33. Found (percent): C, 78.70; H, 9.20.

EXAMPLE 18

Ethyl p-tetradecyloxybenzoate

Ten grams (0.03 mole) of p-tetradecyloxybenzoic acid was dissolved in ca. 175 ml. of absolute EtOH and 3 drops of concentrated H_2SO_4 . The clear solution was refluxed for 8 hours and then concentrated to a crude solid which was recrystallized from hot EtOH to afford 8.5 grams (70%) of the desired ethyl p-tetradecyloxybenzoate; M.P. 80–82°.

Analysis.—Calcd. for $C_{23}H_{38}O_3$ (percent): C, 76.19; H, 10.57. Found (percent): C, 75.80; H, 10.42.

EXAMPLE 19

Methyl m-tetradecyloxybenzoate

A solution consisting of 3.2 grams (0.02 mole) of the methyl ester of m-hydroxybenzoic acid and 5.7 g. (0.02 mole) of 1-bromotetradecane in 50 ml. of DMF was treated with 1.0 gram (0.02 mole) of NaH (51.2% active) suspended in mineral oil. When addition of NaH was complete the reaction mixture was heated at steam cone temperature for ca. 3 hours. At the end of this period the reaction mixture was poured into approximately 2 liters of H_2O and the crude product was separated by filtration. Two recrystallizations from hot ethanol afforded the desired methyl ester of m-tetradecyloxybenzoic acid; M.P. 40–42.5°.

Analysis.—Calcd. for $C_{22}H_{36}O_3$ (percent): C, 75.82; H, 10.41. Found (percent): C, 75.54; H, 10.24.

EXAMPLE 20

m-Tetradecyloxybenzoic acid

Three grams (0.009 mole) of the methyl ester of m-tetradecyloxybenzoic acid were dissolved in 50 ml. of 3A ethanol by heating the solution to reflux temperature. To the refluxing solution was added 3 ml. of 10 N sodium hydroxide solution which caused a precipitation of the sodium salt of the desired product. The suspension

was allowed to cool to room temperature and then acidified with an excess of concentrated hydrochloric acid. Following this procedure 2.8 grams of m-tetradecyloxybenzoic acid was isolated; M.P. 95–97°.

Analysis.—Calcd. for $C_{21}H_{34}O_3$ (percent): C, 75.40; H, 10.25. Found (percent): C, 75.33; H, 10.14.

EXAMPLE 21

Benzyl p-tetradecyloxybenzoate

In a manner analogous to Example 1, 11.4 grams (0.05 mole) of benzyl p-hydroxybenzoate, 2.4 grams (0.05 mole) (50% in oil) of sodium hydride, and 13.85 grams (0.05 mole) of 1-bromotetradecane gave 12.39 grams (0.0293 mole) (60%) of benzyl p-tetradecyloxybenzoate; M.P. 49–52°.

Analysis.—Calcd. for $C_{28}H_{40}O_3$ (percent): C, 79.20; H, 9.50. Found (percent): C, 79.53; H, 9.44.

EXAMPLE 22

Sodium p-tetradecyloxybenzoate

A 6.7 grams (0.02 mole) portion of p-tetradecyloxybenzoic acid was heated in 25 ml. of ethanol and 25 ml. of 1 N sodium hydroxide (0.025 mole) until a solution formed. On cooling the crystals were filtered, and then suspended in 125 ml. of boiling ethanol. When was added until a solution formed, and cooling gave 6.55 g. (90%) of sodium p-tetradecyloxybenzoate; M.P. >310°.

Analysis.—Calcd. for $C_{21}H_{33}O_3Na$ (percent): C, 70.75; H, 9.33; Na, 6.45. Found (percent): C, 71.04; H, 8.98; Na, 6.02.

EXAMPLE 23

3-pyridyl p-tetradecyloxybenzoate

In a manner analogous to Example 17, 5.8 g. (0.0173 mole) of p-tetradecyloxybenzoic acid and 0.82 g. (0.0173 mole) of 1,1'-carbonyldiimidazole followed by 1.65 g. (0.0173 mole) of 3-hydroxypyridine and a trace of sodium hydride gave 5.44 g. (80%) of 3-pyridyl p-tetradecyloxybenzoate; M.P. 61–64°.

Analysis.—Calcd. for $C_{26}H_{37}NO_3$ (percent): C, 75.87; H, 9.06; N, 3.40. Found (percent): C, 75.56; H, 9.14; N, 3.39.

EXAMPLE 24

Methyl p-(1-methylundecyloxy)benzoate

In a manner analogous to Example 1, methyl p-(2-dodecyloxy)benzoate was prepared from 25.0 g. (0.1 mole) of 2-bromododecane, 15.2 g. (0.1 mole) of methyl p-hydroxybenzoate and 4.8 g. (0.1 mole) of sodium hydride (50% active; dispersed in mineral oil). The product melted at 68–70°.

Analysis.—Calcd. for $C_{20}H_{32}O_3$ (percent): C, 74.95; H, 10.07. Found (percent): C, 74.24; H, 9.73.

EXAMPLE 25

2-dimethylaminoethyl p-(p-hexadecyloxy)benzoate hydrochloride

A solution of 4.1 g. (0.012 mole) of 4-(n-hexadecyloxy)benzoic acid and 6.0 ml. (0.083 mole) of thionyl chloride in 50 ml. of benzene is stirred under reflux for one hour and then concentrated under reduced pressure. Crystallization of the residue from petroleum ether (B.P. 30–60°) affords 4-(n-hexadecyloxy)benzoyl chloride as a white solid. A solution of this material and 1.0 ml. (0.010 mole) of 2-dimethylaminoethanol in 50 ml. of benzene is stirred under reflux for 90 minutes, allowed to cool, and filtered. Recrystallization of the solid from acetone affords 2-dimethylaminoethyl p-(n-hexadecyloxybenzoate hydrochloride, M.P. 130–133°.

EXAMPLE 26

Methyl p-dodecyloxybenzoate

In a manner analogous to Example 1, 30.4 grams of methyl p-hydroxybenzoate, 9.6 g. (50% in oil) of so-

dium hydride, and 49.8 g. of 1-bromododecane gave about 65 grams of crude methyl p-dodecyloxy benzoate. Careful purification of 10 g. of this gave 4.39 grams of pure material; M.P. 52–54°.

Analysis.—Calcd. for $C_{20}H_{32}O_3$ (percent): C, 74.96; H, 10.06. Found (percent): C, 74.96; H, 9.99.

EXAMPLE 27

p-Dodecyloxy benzoic acid

In a manner analogous to Example 2, about 55 grams of crude methyl p-dodecyloxy benzoate gave after careful purification, 6.42 grams of p-dodecyloxy benzoic acid; M.P. 130–133°.

Analysis.—Calcd. for $C_{19}H_{30}O_3$ (percent): C, 74.47; H, 9.87. Found (percent): C, 74.54; H, 9.71.

EXAMPLE 28

The present compounds can be dispersed in dosage unit form such as hard shell capsules or soft shell capsules. A formulation found useful in the preparation of such capsules is as follows:

p-Hexadecyloxybenzoic:	Per 100 capsules, grams
Acid	50.0
Lactose, USP	300.0
Magnesium stearate (0.5%)	3.1
Total	353.1

The above formulation is thoroughly mixed and placed in equal quantities in 100 capsules.

EXAMPLE 29

The following example represents a formulation useful in preparing tablets. Larger tablets can be scored and divided in halves to be given once or twice a day. Obviously smaller tablets can be used in multiple doses to obtain the daily amount of active material. The following formulation has been found useful.

p-Hexadecyloxybenzoic acid	Per tablet, mg.
Corn starch	210
Methylcellulose 400	350
Magnesium stearate 1%	182
Total	1242

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

EXAMPLE 30

The following example represents a formulation useful in preparing an oral syrup.

Ingredient:	Amount
2-dimethylaminoethyl p-hexadecyloxybenzoate hydrochloride	mg. 5000
Sorbitol solution (70% N.F.)	ml. 40
Sodium benzoate	mg. 150
Saccharin	mg. 10
Red dye (F.D. & C. No. 2)	mg. 10
Cherry flavor	mg. 50
Distilled water, q.s. ad 100 ml.	

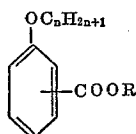
The sorbitol solution is added to 40 ml. of distilled water and the active ingredient is suspended therein. The saccharin, sodium benzoate, flavor and dye are added and dissolved in the above solution. The volume is adjusted to 100 ml. with distilled water. Each ml. of syrup contains 50 mg. of drug.

We claim:

1. A method of lowering elevated serum lipid levels in mammals which comprises orally administering to said

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mammals an effective lipid-lowering amount of a compound of the formula:



wherein the position of the —COOR group is meta or para to the $\text{OC}_n\text{H}_{2n+1}$ group, n is an integer from 12 to 20 inclusive, and R is selected from the group consisting of hydrogen, lower alkyl having 1 to 5 carbon atoms, phenyl, benzyl, 3-pyridyl, 2-dimethylaminoethyl and where R is hydrogen or 2-dimethylaminoethyl the pharmaceutically acceptable salts thereof.

2. The method of claim 1 wherein said compound is administered to provide a daily dosage of from about .5 mg. to about 40 mg. per kg. of body weight of said mammal.

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3. The method of claim 2 wherein said daily dosage is about 2 mg. to about 29 mg. per kg. of body weight of said mammal.

4. The method of claim 1 wherein the compound is $\text{p}-(\text{n-C}_{16}\text{H}_{33}\text{O})\text{C}_6\text{H}_4\text{CO}_2\text{H}$.

5. The method of claim 1 wherein the compound is $\text{p}-(\text{n-C}_{16}\text{H}_{33}\text{O})\text{C}_6\text{H}_4\text{CO}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$ and pharmaceutically acceptable salts thereof.

References Cited

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Chemical Abstracts, vol. 48, 6218.

ALBERT T. MEYERS, Primary Examiner

15 F. E. WADDELL, Assistant Examiner

U.S. Cl. X.R.

424—263, 317

UNITED STATES PATENT OFFICE
CERTIFICATE OF CORRECTION

Patent No. 3,716,644 Dated February 13, 1973

Inventor(s) HENRY JOHN ALBERS, STEPHEN JOSEPH RIGGI,
FREDERICK LOUIS BACH, ELLIOTT COHEN

It is certified that error appears in the above-identified patent
and that said Letters Patent are hereby corrected as shown below:

Column 1, line 58, "1979" should read -- 1970 - ;

Column 4, line 11, "methy" should read -- methyl ---;

Column 7, line 60, "C₂" should read -- C₂₆ -- ;

Column 9, line 26, "When" should read -- Water -- .

Signed and sealed this 10th day of July 1973.

(SEAL)

Attest:

EDWARD M. FLETCHER, JR.
Attesting Officer

Rene Tegtmeyer
Acting Commissioner of Patents