United States Patent Office

3,210,413
Patented Oct. 5, 1965

3,210,413

ANTIHYPERCHOLESTEROLEMIC AGENTS

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No Drawing. Filed May 17, 1962, Ser. No. 195,398
5 Claims. (Cl. 260—520)

This invention relates to certain novel organic compounds having useful biological and pharmacological properties and to processes for their preparation. More specifically, the invention described herein relates to specifically substituted phenoxyphenylacetic acid derivatives demonstrating certain properties which make them valuable hypocholesterolemic agents.

These compounds may be represented by the following structural formula:

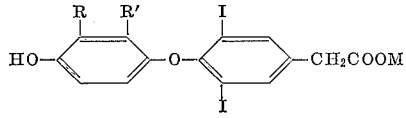


Figure I

wherein:

R and R' are each lower alkyl, and
M is a pharmaceutically acceptable non-toxic cation.

By the term "lower alkyl" is intended a straight or branched chain hydrocarbon of from 1 to 4 carbon atoms, as for example, methyl, ethyl, propyl, isopropyl, t-butyl and the like.

By the term "pharmaceutically acceptable non-toxic cation" is intended, in addition to hydrogen (whereby the above compounds are in the free acid form), metallic cations such as sodium, potassium, calcium, aluminum and the like, as well as unsubstituted and substituted amine cations such as lower alkylammonium; e.g., triethylammonium, cyclic amine cations such as N-ethylpiperidinium and the like. It is to be appreciated that the nature of this cation is relatively unimportant, the novel and highly specific properties of any particular salt being largely a function of the organic anion moiety.

By a virtue of their highly critical structural arrangement, the compounds of this invention possess the ability to normalize high lipid levels in the serum and tissues. This property can, for example, be demonstrated by gas chromatography of the lipid extracts of eggs laid by chickens to which the active compound has been administered.

Accordingly, these compounds are useful for reducing the level of cholesterol and other lipid materials when present in an animal organism to an abnormally high degree. Surprisingly, however, the calorigenic properties of these compounds are surprisingly low. Furthermore the hypertrophic properties of these compounds on myocardial tissue are practically negligible. This separation of hypocholesterolemic properties from calorigenisis and myocardial hypertrophy results in a high therapeutic ratio and permits the safe reduction of abnormally high cholesterol levels in the animal organism with a concurrent minimization of undesired cardiac manifestations such as angina, which are usually so prevalent in antihypercholesterolemic agents of this type.

While these compounds may be administered internally in many of the usual methods as for example, parenterally, the preferred route is orally. Accordingly a unit dosage is provided in which the active compound is present in quantity sufficient to supply from about 15 mcg./kg. to about 75 mcg./kg. of body weight per day. Within this range, the highly useful dosage consists of about 45 mcg./kg. per day. Thus for an animal of about 75 kg., a daily dosage would consist of from about 1 mg. to about 5 mg. of active compound and preferably about 3 mg. per day. While this dosage may be divided over several administrations, it can readily be administered only once a day. The active compound is combined with a pharmaceutical carrier with or without other therapeutic agents (such as inhibitors of cholesterol or lipid synthesis) and administered in the form of a pharmaceutical composition such as tablets, capsules, solutions, suspensions, powders, and the like. One particularly useful form consists of a sustained release composition which provides for a uniform dosage over an extended unit of time while requiring but a single administration.

The process for the preparation of these compounds involves the coupling of a 2,3-di(lower alkyl)-4-methoxyphenol with an ester, as for example a lower alkyl ester, of 3,5-dinitro-4-(p-toluenesulfonyloxy)-phenylacetic acid. Subsequent to coupling, the two nitro groups are reduced to amino groups as by catalytic hydrogenation. This 3,5-diamino compound is then "tetrazotized" (e.g., two diazonium cations are formed) so that treatment of the tetrazonium salt with iodine and sodium iodide will yield the 3,5-diiodo compound. Subsequent hydrolysis of the protective ester group and removal of the ether group affords the desired 3,5-diiodo-4-[2',3'-di(lower alkyl)-4'-hydroxyphenyl]-phenylacetic acid. This acid may be readily converted into a pharmaceutically acceptable non-toxic salt according to the standard methods known and recognized by the art. The corresponding 4'-methoxy compounds of our invention which may be obtained by saponifying the corresponding ester demonstrate a similar activity although generally at a lower level.

This synthetic route may be exemplified as follows:

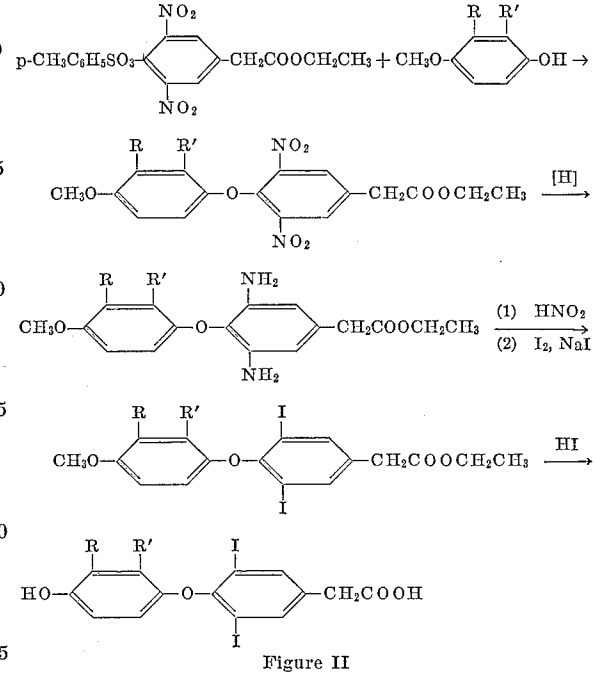


Figure II

The following examples will serve to further typify the nature of this invention but should not be construed as limiting the scope of this invention.

EXAMPLE 1

Ethyl 3,5-dinitro-4-(2',3'-dimethyl-4'-methoxyphenoxy)-phenylacetate

A solution of 5.4 g. (0.02 mole) of ethyl 3,5-dinitro-4-hydroxyphenylacetate and 3.8 g. (0.02 mole) of p-toluene sulfonyl chloride in 50 ml. of dry pyridine is heated for ten minutes on a steam bath with stirring. The steam bath is removed, 7.1 g. (0.046 mole) of 2,3-dimethyl-4-methoxyphenol are added and the solution is stirred under reflux for 1.5 hours. The solvent is then removed under reduced pressure and the residue dissolved in chloroform. This chloroform solution is washed twice with dilute hydrochloric acid, once with water, three times with 10% sodium hydroxide solution, and then again with water until the washings are neutral. (Acidification of the basic washes results in the recovery of unchanged 2,3-dimethyl-4-methoxyphenol suitable for use in succeeding reactions.) The chloroform solution is dried over magnesium sulfate and evaporated to dryness to yield a solid residue comprising ethyl 3,5-dinitro-4-(2',3'-dimethyl-4'-methoxyphenoxy)-phenylacetate which when recrystallized from ethanol, demonstrates a melting point of 122–124°.

EXAMPLE 2

Ethyl 3,5-diiodo-4-(2',3'-dimethyl-4'-methoxyphenoxy)-phenylacetate

A solution of 4.5 g. (0.011 mole) of the dinitro compound prepared in Example 1 in 150 ml. of acetic acid is reduced on a Parr shaker in the presence of 1.3 g. of 10% palladium on carbon under an initial pressure of 45 lbs./in.^{2} of hydrogen. The reduction is complete in about one hour. The catalyst is removed by filtration and the filtrate is added in a dropwise fashion to a cooled stirred solution of 3.5 g. of sodium nitrite in 75 ml. of concentrated sulfuric acid. This addition is executed at such a rate that the temperature does not exceed 5°. When the addition is complete, the mixture is stirred an additional hour with cooling. This reaction mixture is then added to a stirred mixture of 10.65 g. of iodine and 7.5 g. of sodium iodide in 190 ml. of water and 190 ml. of chloroform, and stirred one hour at room temperature. The layers are separated, the aqueous layer being extracted several times with chloroform. These combined chloroform layers are washed with 10% sodium bisulfite solution three times, with water twice, with 5% sodium bicarbonate solution twice, and again with water. After drying over calcium chloride, the solvent is removed by evaporation and the residue diluted with aqueous methanol and triturated until the residual gum solidified. The solid is filtered and dried. Recrystallization of the solid from acetonitrile then yields the product (containing some solvent), M.P. 124–125°. The unsolvated material is obtained by recrystallization from absolute ethanol, M.P. 126–127°.

EXAMPLE 3

3,5-diiodo-4-(2',3'-dimethyl-4'-hydroxyphenoxy)-phenylacetic acid

A solution of 2.1 g. (0.0037 mole) of ethyl 3,5-diiodo-4-(2',3'-dimethyl-4-methoxyphenoxy)-phenylacetic acid in 15 ml. of acetic acid and 15 ml. of 57% hydriodic acid is refluxed for three hours. The solution is diluted with an equal volume of water and cooled. The resulting solid is filtered, washed with water, and recrystallized from 50% aqueous alcohol to yield 3,5-diiodo-4-(2',3'-dimethyl-4'-hydroxyphenoxy)-phenylacetic acid, M.P. 194–196°.

EXAMPLE 4

3,5-diiodo-4-(2',3'-diethyl-4'-hydroxyphenoxy)-phenylacetic acid

2,3-diethyl-4-methoxyphenol (8.2 g.) is substituted for 2,3-dimethyl-4-methoxyphenol in the procedure of Example 1. By following sequentially the procedure therein described and those described in Examples 2 and 3, there is obtained the compound 3,5-diiodo-4-(2',3'-diethyl-4'-hydroxyphenoxy)-phenylacetic acid.

The requisite 2,3-diethyl-4-methoxy phenol may be prepared as follows:

To 50 g. of o-diethylbenzene is added slowly with stirring at a temperature between 0° to −10°, a mixture of 100 g. of sulfuric acid and 50 g. of nitric acid (d. 1.4). Stirring and cooling are continued for an additional 30 minutes and the mixture is then poured into ice-water. The resultant aqueous mixture is steam-distilled and the distillate extracted with ether. The ether extracts are dried and evaporated and the residue fractionally distilled to yield 2,3-diethylnitrobenzene.

A mixture of 50 g. of 2,3-diethylnitrobenzene, 5 g. of 10% palladium-on-carbon, and 1 l. of benzene are reduced with hydrogen at low pressure. When the reduction is complete, the catalyst is removed by filtration and washed with benzene. The filtrate is then evaporated to an oil and this oil is dissolved in hot dilute sulfuric acid. The acid solution may be filtered to remove any small amount of insoluble material.

The sulfuric acid solution of 2,3-diethylaniline is diluted to 1 l. with ice-water and cooled to 0° while 31.1 g. of sodium nitrite in 110 ml. of water are carefully added in several portions. The diazonium salt mixture is stirred an additional 30 minutes with cooling and then added in portions to a hot mixture of 700 ml. of sulfuric acid and 1400 ml. of water. Steam is allowed to pass through this mixture to remove the phenol as formed. Further additions of the diazonium solution are made only after no further phenol appears in the distillate. The distillate is extracted with benzene and the benzene in turn extracted with dilute aqueous sodium hydroxide. The basic extracts are acidified and extracted with benzene and these benzene extracts are washed with water and evaporated. The residue is recrystallized from petroleum ether to yield 2,3-diethylphenol.

A solution of 84 g. of 2,3-diethylphenol in 500 ml. of alcohol is diluted with 500 ml. of concentrated hydrochloric acid. The mixture is cooled with stirring and 72 g. of sodium nitrite are added at such a rate that the temperature is maintained below 5°. The solution is poured into 6 l. of ice-water and allowed to stand for 30 minutes. The resulting precipitate was filtered and the solid so obtained dissolved in a mixture of 900 ml. of 27% ammonium hydroxide and 1600 ml. of water. Any insoluble material is removed by filtration. Hydrogen sulfide is next passed through the stirred solution for two hours and the precipitated aminophenol is collected by filtration under nitrogen. The aminophenol is then immediately dissolved in a mixture of 110 ml. of sulfuric acid and 4 l. of water and filtered to remove any insoluble matter. To this solution is added with stirring, 150 g. of sodium nitrite in 5–10 g. portions. The solution is heated with stirring on a steam bath at 60° for 30 minutes and then steam distilled. The distillate is extracted with ether and the ether dried and evaporated to yield 2,3-diethyl-1,4-benzoquinone.

To a vigorously stirred solution of 82 g. of 2,3-diethyl-1,4-benzoquinone in 250 ml. of ether is gradually added a solution of 139 g. of sodium hydrosulfite in 300 ml. of water. The mixture is stirred three hours at room temperature and the layers separated. The aqueous phase is extracted twice with ether and the combined ether phases dried and evaporated. The solid residue so obtained is recrystallized from aqueous alcohol to yield 2,3-diethyl-1,4-hydroquinone.

To a well-stirred solution of 75 g. of 2,3-diethyl-1,4-hydroquinone in 450 ml. of 10% sodium hydroxide at 10° is added in small portions 68 g. of dimethylsulfate. Stir-

ring is continued an additional hour at 10° and the mixture is then extracted several times with ether. The aqueous phase is acidified with dilute hydrochloric acid and extracted with ether. The two ether fractions are evaporated separately. The first ether fraction yields the desired 2,3-diethyl-4-methoxyphenol. Additional material may be obtained by ligroin extraction of the residue obtained upon evaporation of the second ether fraction.

EXAMPLE 5

Ingredients:	Mg./tab.
3,5-diiodo-4-(2',3'-dimethyl - 4' - hydroxyphenyl)-phenylacetic acid (as the sodium salt)	5.00
Lactose	250.00
Starch	13.00
Talc	5.00
Magnesium stearate	2.50

The lactose and sodium 3,5-diiodo-4-(2',3'-dimethyl-4'-hydroxyphenoxy)-phenylacetate are mixed and granulated with hot 10% gelatin. The magnesium stearate, talc and starch are admixed and compressed into tablets.

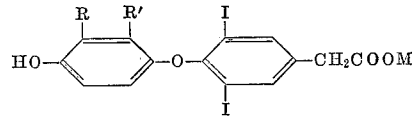
EXAMPLE 6

Ingredients:	Mg./capsule
3,5-diiodo-4-(2',3' - dimethyl-4' - hydroxyphenoxy)-phenylacetic acid (as the potassium salt)	3.00
Magnesium stearate	2.00
Lactose	130.00

The above powders are thoroughly mixed and filtered into #4 hard gelatin capsules.

What is claimed is:

1. A compound of the formula:



wherein R and R' are each lower alkyl and M is a non-toxic, pharmaceutically acceptable cation.

2. A compound according to claim 1 wherein R and R' are each methyl.

3. A compound according to claim 1 wherein R and R' are each ethyl.

4. 3,5-diiodo-4-(2',3'-dimethyl-4' - hydroxyphenoxy)-phenylacetic acid.

5. 3,5-diiodo-4-(2',3' - diethyl - 4' - hydroxyphenoxy)-phenylacetic acid.

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