United States Patent

Griot

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[45] ***Aug. 1, 1972**

[54] **DERIVATIVES OF ACETIC ACID**

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[*] Notice: The portion of the term of this patent subsequent to Dec. 8, 1987, has been disclaimed.

[22] Filed: **Oct. 18, 1968**

[21] Appl. No.: **768,881**

[52] **U.S. Cl.**....**260/293.82,** 260/239 D, 260/239 BF, 260/247.2 B, 260/268 R, 260/268 PH, 260/293.53, 260/293.64, 260/326.3, 260/465 D, 260/473 G, 424/244, 424/248, 424/250, 424/267, 424/274, 424/308

[51] **Int. Cl.**.....**C07d 29/24**

[58] **Field of Search**.....260/294.3 A

[56] **References Cited**

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[57] **ABSTRACT**

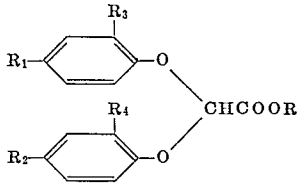
This disclosure relates to derivatives of acetic acid, e.g., (p-biphenylyloxy)-(p-chlorophenoxy)acetic acid methyl ester. These compounds are useful as hypocholesteremics/hypolipemics.

3 Claims, No Drawings

DERIVATIVES OF ACETIC ACID

This invention relates to derivatives of acetic acid. In particular, the invention pertains to bis-(substituted phenoxy) acetic acids and derivatives thereof which possess hypocholesteremic/hypolipemic activity. The invention further relates to pharmaceutical compositions containing the above compounds as an active ingredient thereof and the use of such compositions for the treatment of hypercholesteremia/hyperlipemia.

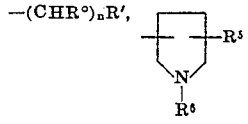
The compounds of the present invention are of the structural formula



(I)

wherein R represents hydrogen or the residue of a monohydric alcohol capable of forming an ester by reaction with an acid,

e.g. a saturated aliphatic alcohol, preferably a saturated lower aliphatic alcohol such as aliphatic alcohol having 1–5 carbon atoms, e.g. methanol, ethanol, propanol, isopropanol, butanol and the like; an unsaturated aliphatic alcohol such as alkyl alcohol; a substituted aliphatic alcohol such as ethanolamine; an aromatic alcohol other than a phenol such as benzyl or phenylethylalcohol; an alicyclic alcohol such as cyclohexanol; a heterocyclic alcohol such as furfuryl alcohol an alcohol of the formula B—OH where B represents piperidino, cyanomethyl or di[carb(lower)alkoxymethyl, where "lower" qualifies the alkoxy moiety to mean one containing 1–5 carbon atoms, an alcohol of the formula A—OH wherein A



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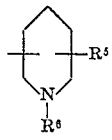

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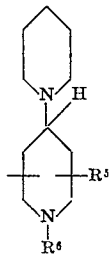

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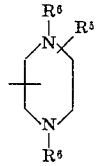

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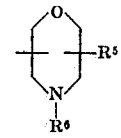

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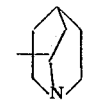

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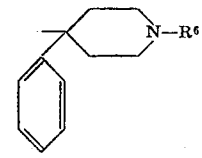
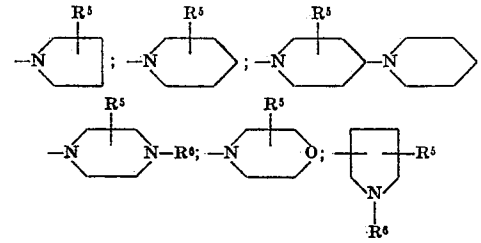


or 2-dimethylamine-2-methyl propyl; represents



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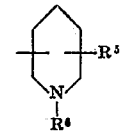

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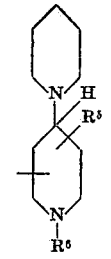

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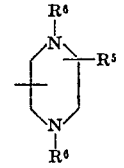

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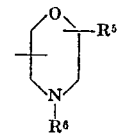

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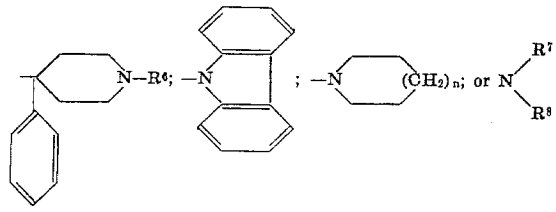


n represents a whole number from 1 to 4, inclusive;

each R°, independently, represents hydrogen or lower alkyl, preferably containing from one to four carbon atoms, e.g., methyl, ethyl, propyl and butyl;

n' represents **2**, **3** 2,3 4;

R^5 represents hydrogen; halo, preferably bromo or chloro; or lower alkyl, preferably containing from one to four carbon atoms, e.g., methyl, ethyl, propyl and butyl; R_6 represents lower alkyl, preferably containing from one to four carbon atoms, e.g., methyl, ethyl, propyl and butyl; propargyl; phenyl; halophenyl, the halo substitutent preferably being bromo or chloro; or phenyl(lower)alkyl, the lower alkyl substituent preferably containing from one to four carbon atoms, e.g., benzyl and phenethyl;

R^7 represents hydrogen; lower alkyl, preferably containing from one to four carbon atoms, e.g., methyl, ethyl, propyl and butyl; cycloalkyl containing from five to seven ring carbon atoms, e.g., cyclopentyl, cyclohexyl and cycloheptyl; phenyl; phenyl(lower)alkyl, the lower alkyl substituent preferably containing from one to four carbon atoms, e.g., benzyl and phenethyl; 1-naphthyl; or 2-naphthyl; and R^8 represents lower alkyl, preferably containing from one to four carbon atoms, e.g., methyl, ethyl, propyl and butyl; cycloalkyl containing from five to seven ring carbon atoms, e.g., cyclopentyl, cyclohexyl and cycloheptyl; phenyl; or phenyl(lower)alkyl, the lower alkyl substituent preferably containing from one to four carbon atoms, e.g., benzyl and phenethyl; provided that when R^7 is hydrogen R^8 is phenyl,

R^1, R_2, R_3 and R_4 each independently, represents hydrogen, chloro, iodo or bromo, and

R_1 and R_2 each additionally, independently, represents trifluoromethyl or phenyl (which term for purposes of the definition of the compounds of formula (I) in the specification and in the claims is also intended to include p-chlorophenyl, p-iodophenyl and p-bromophenyl), provided

1. at least one of the R_1 and r_2 is other than hydrogen,

2, R_1, R_2, R_3 and R_4 each, independently, may represent only chloro or hydrogen only when R represents other than hydrogen, a residue of a saturated aliphatic alcohol, the basic radical A defined above, piperidino, cyanomethyl or di[carb(lower)alkoxy]methyl,

3. R_1, R_2, R_3 and R_4 each, independently, represents only hydrogen, chloro, iodo or bromo, provided at least one represents other than chloro, only when R represents other than hydrogen or a residue of a saturated aliphatic alcohol,

4. R_1 and R_2 each, independently, represents trifluoromethyl or phenyl only

a. when at least one of R_1, R_2, R_3 and R_4 represents chloro, fluoro or iodo,

b. when one of R_1 and R_2 represents a trifluoromethyl or phenyl group and the other of R_1 and R_2 represents the second group, or

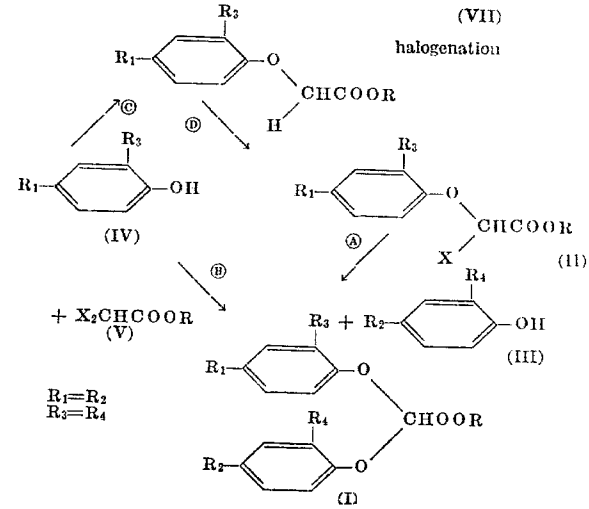
c. when R represents other than hydrogen, A as defined above, or the residue of a saturated aliphatic alcohol.

It will be clear that the term "residue of a monohydric alcohol" is meant that moiety of the alcohol other than the —OH portion.

As illustrative of the substituents represented by A there may be mentioned the following:

1-lower alkyl-4-piperidyl, e.g., 1-methyl-4-piperidyl and 1-ethyl-4-piperidyl; 1-lower alkyl-3-piperidyl, e.g., --methyl-3-piperidyl and 1-ethyl-3-piperidyl; 1-lower alkyl-2-piperidyl, e.g., 1-methyl-2-piperidyl and 1-ethyl-2-piperidyl; 1-phenyl-4-piperidyl; 1-phenyl-3-piperidyl; 1-phenyl-2-piperidyl; 1-benzyl-4-piperidyl; 1-benzyl-3-piperidyl; 1phenethyl-4-piperidyl; 1-phenethyl-3-piperidyl; 1-propargyl- 4-piperidyl; 1-propargyl-3-piperidyl; 1-[β-(p-chlorophenoxy)ethyl]-4-piperidyl; 3-quinuclidinyl; 2-quinuclidinyl; β-pyrrolidinoethyl; γ-pyrrolidinopropyl; β-piperidinoethyl; γ-piperidinopropyl; β-morpholinoethyl; γ-morpholinopropyl; β-dimethylaminoethyl; γ-diethylaminopropyl; β-anilinoethyl; γ-anilinopropyl; β-(N-methylanilino)ethyl; β(1-lower alkyl-2-pyrrolidinyl)ethyl, e.g., β-(1-methyl-2-pyrrolidinyl)ethyl; γ-(1-lower alkyl-2-pyrrolidinyl)propyl, e.g., γ-(1-methyl-2-pyrrolidinyl)propyl, β-(1-phenyl-3-pyrrolidinyl)ethyl; β-(1-phenyl-2-pyrrolidinyl)ethyl; β-(1-beyzyl-3-pyrrolidinyl)ethyl; β-(1-benzyl-2-pyrrolidinyl)ethyl; β-(1-phenethyl-3-pyrrolidinyl)ethyl; β -(1-phenethyl-2-pyrrolidinyl)ethyl; β-(1-propargyl-3-pyrrolidinyl)ethyl; β-(1-propargyl-2-pyrrolidinyl)ethyl; and β-[1-[β-(p-chlorophenoxy)ethyl]-3-pyrrolidinyl]ethyl.

The compounds of formula (I) may be prepared according to the processes indicated below.



where R, R_1, R_2, R_3 and R_4 are as defined above, and X represents halo, preferably chloro or bromo.

Method A pertains to the reaction of a substituted phenoxy halo acetic acid derivative (II) and an appropriately substituted phenol (III) as the phenolate. This reaction is conveniently effected in a suitable inert

organic solvent such as dimethylacetamide; diethylacetamide; dimethylformamide; and tetramethylurea. Preferably, the reaction is initially carried out at room temperature and then allowed to continue at elevated temperatures up to about 80°C. The particular solvent employed is not critical, nor is the temperature employed critical provided it does not exceed about 80°C. The resulting acetic acid derivative (I) is readily recovered employing conventional techniques. The substituted phenol (III) is converted to the phenolate using standard techniques, such as treating the phenol with either a strong alkali metal hydroxide, e.g., KOH or NaOH, and water or sodium hydride in dimethylacetamide.

Method B involves the reaction of the substituted phenol (IV) as a phenolate and a dihalocarboxylic acid or derivative thereof (V) and the solvents and temperatures which may be used are substantially as discussed with respect to method A.

The compounds (I) where R represents the basic radical A earlier described may be preferably obtained by treating the compounds of formula (I) where R = H or lower alkyl with an alcohol A — OH, where A is as earlier defined, under conventional transesterification conditions. For instance, this procedure may be performed in an inert organic solvent such as benzene, toluene or xylene, in the presence of an alkali metal alkoxide, preferably sodium methoxide or ethoxide, at a temperature of about 50°–150°C, preferably at reflux temperature.

The compounds of formula (I) where R represents piperidino are preferably prepared from the acid halide of the compounds (I) by treatment with 1-hydroxypiperidine or an appropriate salt thereof in inert solvent, e.g., benzene or toluene, at about room temperature. Preferably also, when R represents cyanomethyl or di[carb(lower)alkoxy] methyl, the free acid is treated with a haloacetonitrile or a dialkylhalomalonate, respectively, in inert solvent such as tetrahydrofuran or ethyl acetate in the presence of a tertiary amine such as triethylamine, preferably at the reflux temperature of the system.

The substituted phenoxy haloacetic acid ester starting materials (II) used for process A described above may be prepared as indicated according to processes C and D. Method C concerns treatment of the phenolate of compound (IV) with a monohaloacetic acid (VI), e.g., chloro acetic acid, to obtain the substituted phenoxy acetic acid of formula (VII). The same solvents and reaction conditions discussed respecting processes A and B apply here as well. The compounds of formula (VII) are then halogenated to provide the compounds of formula (II) (method D). Conventional halogenating agents such as bromine or chlorine may be employed. The halogenation is conveniently carried out in a suitable inert organic solvent such as a halocarbon, for instance a chloralkane, e.g., dichloromethane, chloroform, carbontetrachloride, and the like. Preferably, the reaction is initially carried out at room temperature and then allowed to continue at reflux temperature. However, neither the choice of solvent nor the temperature used is critical.

Certain of the compounds of formula I have asymmetric centers and therefore exist as optical isomers. The respective isomers can be readily separated by conventional techniques or they can be selectively prepared employing the desired isomeric form of the alcohol reactant and accordingly are included within the scope of this invention.

Various of the phenolates and alcohols employed as reactants above are known and are prepared according to methods disclosed in the literature. Those others not specifically described in the literature are prepared by analogous methods from known materials.

As previously indicated, the compounds of formula (I) are useful because they possess pharmacological properties in animals. In particular these compounds are useful as hypocholesteremics/hypolipemics, as indicated by activity in sodium hexobarbital anesthetized rat tested by extracting serum or plasma with isopropanol and noting the cholesterol content. For such usage, the compounds may be administered orally as such or admixed with conventional pharmaceutical carriers or administered orally in such forms as tablets, dispersible powders, granules, capsules, syrups and elixirs. Such compositions may be prepared according to any method known in the art for the manufacture of pharmaceutical compositions, and such compositions may contain one or more conventional adjuvants, such as sweetening agents, flavoring agents, coloring agents and preserving agents, in order to provide an elegant and palatable preparation. Tablets may contain the active ingredient in admixture with conventional pharmaceutical excipients, e.g., inert diluents, such as calcium carbonate, sodium carbonate, lactose and talc, granulating and disintegrating agents, e.g., starch and alginic acid, binding agents, e.g., starch, gelatin and acacia, and lubricating agents, e.g., magnesium stearate, stearic acid and talc. The tablets may be uncoated or coated by known techniques to delay disintegration and adsorption in the gastro-intestinal tract and thereby provide a sustained action over a longer period. Similarly, suspensions, syrups and elixirs may contain the active ingredient in admixture with any of the conventional excipients utilized for the preparation of such compositions, e.g., suspending agents (methylcellulose, tragacanth and sodium alginate), wetting agents (lecithin, polyoxyethylene stearate and polyoxyethylene sorbitan monooleate) and preservatives (ethyl-p-hydroxybenzoate). Capsules may contain the active ingredient alone or admixed with an inert solid diluent, e.g., calcium carbonate, calcium phosphate and kaolin.

The compounds of formula (I) where R = H may also be utilized as hypocholesteremics/hypolipemics in the form of non-toxic pharmaceutically acceptable salts thereof. As illustrative of such salts there may be included the aluminum salt, more specifically, that aluminum salt wherein two hydroxyl groups of $Al(OH)_3$ have been replaced by the acid radical; non-toxic alkali metal salts, e.g., potassium and sodium salts; non-toxic alkaline earth metal salts, e.g., magnesium and calcium salts; salts with N-containing bases such as ammonium salts and pharmaceutically acceptable primary, secondary and tertiary amine salts, e.g., ethanol amine salts, diethanol amine salts, and the like.

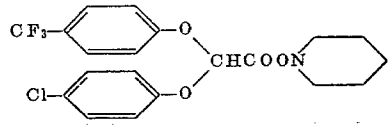
When the compounds (I) are basic esters, such as when R represents A as defined above, the compounds may also be used as the non-toxic acid addition salt thereof or quaternary salts. The salts are prepared using conventional techniques.

The dosage of active ingredient employed for the alleviation of hyperlipemia (hypercholesteremia) may vary depending on the particular compound employed and the severity of the condition being treated. In general, satisfactory results are obtained when these compounds are administered at a daily dosage of from about 0.5 milligrams to about 50 milligrams per kilogram of animal body weight. This daily dosage is preferably given in divided doses and administered two to four times a day, or in sustained release form. For most large mammals, the total daily dosage is from about 50–2000 mg., and dosage forms suitable for internal use comprise from about 12.5 milligrams to about 500 milligrams of active compound in intimate admixture with a solid or liquid pharmaceutically acceptable carrier or diluent. The preferred pharmaceutical compositions from the standpoint of preparation and ease of administration are solid compositions, particularly hard-filled capsules and tablets containing from 25 milligrams to about 250 milligrams of the active ingredient.

The following examples serve to further illustrate the present invention. However, it is to be understood that the examples are for purposes of illustration only and are not intended as in any way limiting the scope of the invention which is defined in the appended claims.

EXAMPLE 1

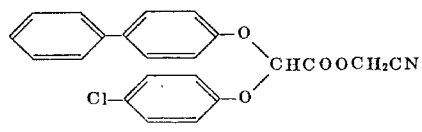
(p-trifluoromethylphenoxy)-(p-chlorophenoxy)acetic acid, ester with 1-hydroxypiperidine



A mixture of 20.2 g. of 1-hydroxypiperidine and 800 ml. of absolute diethyl ether is stirred and cooled to about 0°C. in an ice-salt bath. To the cooled mixture is then added dropwise with stirring a solution of 33 g. of (p-trifluoromethylphenoxy-(p-chlorophenoxy) acetyl chloride in 400 ml. of absolute diethyl ether, while maintaining the temperature of the reaction mixture between −5° to 0°C. with external cooling. After the addition is completed, the mixture is stirred for an additional 20 minutes and then, while cooling, 400 ml. of a cold saturated solution of sodium carbonate is added and the phases separated. The aqueous phase is extracted with 500 ml. of absolute diethyl ether. The combined organic phases are then washed twice with 400 ml. (each) of cold water, dried over anhydrous potassium carbonate and evaporated to dryness. The residue is recrystallized from absolute diethyl ether, using some charcoal as a decolorizing agent, to obtain (p-trifluoromethylphenoxy)-(p-chlorophenoxy)acetic acid, ester with 1-hydroxypiperidine.

EXAMPLE 2

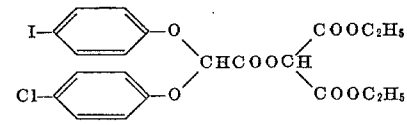
(p-biphenylyloxy)-(p-chlorophenoxy)acetic acid cyanomethyl ester



A mixture of 50 g. of (p-biphenylyloxy)-(p-chlorophenoxy) acetic acid, 24.2 g. of triethylamine and 18 g. of chloroacetonitrile and 240 ml. of ethyl acetate is refluxed on a steam bath for 24 hours, then filtered and the ethyl acetate solution extracted once with 500 ml. of water and then twice with 500 ml. (each) of 2N hydrochloric acid. The ethyl acetate layer is then dried over sodium carbonate, filtered with charcoal and then evaporated. The residue is crystallized and recrystallized from diethyl ether-petroleum ether (1:1) and washed with isopropyl ether to obtain (p-biphenylyloxy)-(p-chlorophenoxy)acetic acid cyanomethyl ester.

EXAMPLE 3

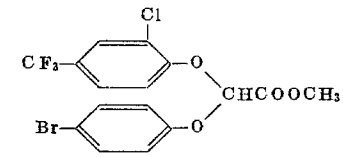
(p-iodophenoxy)-(p-chlorophenoxy)acetic acid dicarbethoxymethyl ester



A mixture of 50 g. of (p-iodophenoxy)-(p-chlorophenoxy) acetic acid, 24.2 g. of triethylamine, 57.3 g. of diethylbromomalonate and 240 ml. of ethyl acetate is refluxed on a steam bath for 24 hours, then filtered and the ethyl acetate solution extracted once with 500 ml. of water and then twice with 500 ml. of 2N hydrochloric acid. The ethyl acetate layer is then dried over sodium carbonate, filtered with charcoal and then evaporated. The residue is distilled using a high vacuum diffusion pump and a maximum oil bath temperature of 250°C. to obtain (p-iodophenoxy)-(p-chlorophenoxy) acetic acid dicarbethoxymethyl ester.

EXAMPLE 4

(p-bromophenoxy)-(2-chloro-4-trifluoromethylphenoxy) acetic acid methyl ester



Step 1. (p-bromophenoxy)-(acetic acid methyl ester

Sodium hydride (56.7 percent in mineral oil) (47 g.) is washed free from the mineral oil with low boiling petroleum either and suspended in 750 ml. of dimethylacetamide. To the suspension is added 130 g. of p-bromophenol in 500 ml. of dimethylacetamide as the temperature is maintained at 10°–20°C. The mixture is stirred for 2 hours and methyl chloro acetate is added. The resulting mixture is stirred for 5 hours at 80 °C. and then at room temperature for 72 hours. The resulting mixture is then poured over 2 liters of ice water, extracted with 750 ml. of isopropyl ether. The organic layer is separated, extracted with cold 1N sodium hydroxide, dried over anhydrous sodium sulfate, filtered and evaporated to provide (p-bromohenoxy)-(acetic acid methyl ester.

Step 2. α-bromophenoxy acetic acid methyl ester

To 1 liter of carbon tetrachloride is added 180 g. of (p-bromophenoxy)acetic acid methyl ester. With stirring at room temperature bromine (160 g.) is added dropwise and the mixture is stirred for 17 hours at

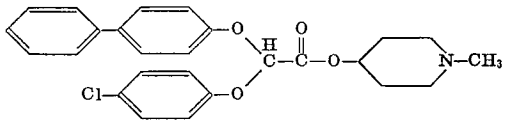
room temperature. The mixture is washed with 1,500 ml. of water and then 500 ml. of cold 10percent aqueous sodium bicarbonate. The organic layer is separated, dried over anhydrous sodium sulfate and evaporated to provide α-bromo-p-bromophenoxy acetic acid methyl ester.

Step 3. (p-bromophenoxy)-(2-chloro-4-trifluoromethylphenoxy acetic acid methyl ester

To 200 ml. of dimethylacetamide is added 15 g. of 2-chloro-4-trifluoromethylphenol and the resulting mixture is added dropwise, with stirring, to a suspension of 4.6 g. of 56.7 percent sodium hydride (which had been washed free of mineral oil with petroleum ether) in 100 ml. of dimethylacetamide. The resulting mixture is stirred at room temperature for 90 minutes and 26 g. of α-bromo-p-bromophenoxy acetic acid methyl ester in 50 ml. of dimethylacetamide is added in several portions. The mixture is stirred at room temperature for 72 hours, then at 50 °C. for 30 minutes, poured over 1,500 ml. of ice water and extracted with 500 ml. of isopropylether. The ether layer is extracted with 100 ml. of cold 1N sodium hydroxide, dried over anhydrous sodium sulfate, filtered and evaporated to yield (p-bromophenoxy)-(2-chloro-4-trifluoromethylphenoxy) acetic acid methyl ester.

EXAMPLE 5

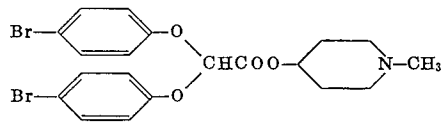
(p-biphenylyloxy)-(p-chlorophenoxy) acetic acid 1-methyl-4-piperidyl ester



A mixture of 15 g. of (p-biphenylyloxy)-(p-chlorophenoxy) acetic acid methyl ester, 3.2 g. of 1-methyl-4-hydroxypiperidine, 100 ml. of toluene and 0.2 g. of sodium methoxide is atmospherically distilled until the sump temperature reaches 150 °C. (approximately 30 minutes). The sump temperature is maintained at 150 °C. for an additional 15 minutes and then with the heat off water-aspirator vacuum is carefully applied until distillation ceases. The resulting mixture is cooled to 50 °C. and 200 ml. of benzene is added thereto. The resulting mixture is further cooled to 20°C. and then 200 ml. of water is added thereto. The top oily layer is separated, washed first with 200 ml. of water, then with 100 ml. of a saturated solution of sodium chloride and then dried over magnesium sulfate and evaporated on a rotary evaporator at approximately 100 mm vacuum. The residue is crystallized from 50 ml. of isopropanol to obtain (p-biphenylyloxy)-(p-chlorophenoxy) acetic acid 1-methyl-4piperidyl ester.

EXAMPLE 6

Bis-(p-bromophenoxy)acetic acid 1-methyl-4-piperidyl ester



Step A. Preparation of bis-(p-bromophenoxy)acetic acid methyl ester

A solution of 25 grams of 4-bromophenol in 200 ml. of dimethylacetamide is slowly added to a stirring slurry of 9.5 grams of sodium hydride (56 percent in mineral oil) in 250 ml. of dimethylacetamide and the mixture stirred at 20 °C. for 1 hour.

To the resulting clear solution is added 14 grams of methyldichloroacetate in 200 ml. of dimethylacetamide and a catalytic amount of potassium iodide. The reaction mixture is stirred at 20°C. for 17 hours and then poured over 1 liter of ice water. The mixture is then extracted with isopropyl ether. The separated ether layer is extracted with cold 1N sodium hydroxide and the organic phase separated, dried over magnesium sulfate and evaporated to obtain a brown oil which crystallizes upon standing. Recrystallization of the resulting produce from methanol yields bis-(p-bromophenoxy)acetic acid methyl ester; m.p. 79.5°–80.5°C.

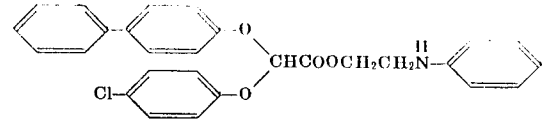
Step B. Preparation of bis-(p-bromophenoxy)acetic acid 1-methyl-4-piperidyl ester

Bis-(p-bromophenoxy)acetic acid methyl ester, 10 grams, is mixed with 10 grams of β-hydropyethyl-piperidine, 50 mg. of sodium methoxide and 10 ml. of toluene. The resulting mixture is then slowly heated to distill very slowly through a Vigreux column. When the temperature at the distilling head reaches 110°C., the reaction mixture is cooled to 65°C. and then evaporated on a rotary evaporator employing 12 mm. vacuum and maintaining the temperature between 65°–70C. The crude product thus obtained is treated with an excess of a 20 percent aqueous solution of tartaric acid to yield the tartrate salt of bis-(p-bromophenoxy)acetic acid β-piperidinoethyl ester. The free base is obtained by treating the washed tartrate salt with 2N sodium hydroxide and extracting the base with dichloromethane.

To obtain the hydrochloride salt, the dichloromethane extract is dried over magnesium sulfate, the solvent evaporated and the residue neutralized with an isopropanolic solution of hydrogen chloride (10 percent hydrogen chloride gas in isopropyl alcohol).

EXAMPLE 7

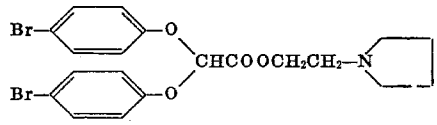
(p-biphenylyloxy)-(p-chlorophenoxy)acetic acid β-anilinoethyl ester



(p-biphenylyloxy)-(p-chlorophenoxy)acetic acid methyl ester, 10 grams, is mixed with 10 grams of β-anilinoethanol, 50 mg. of sodium methoxide and 10 ml. of toluene. The resulting mixture is slowly heated to distill very slowly through a Vigreux Column. When the temperature at the distilling head reaches 110°C., the reaction mixture is cooled to 65°C. and then evaporated on a rotary evaporator employing 12 mm. vacuum and maintaining the temperature between 65°–70C. The crude product is chromatographed on a Silica Gel Column and the product recovered by washing the column with benzene. The benzene is then evaporated off to obtain (p-biphenylyloxy)-(p-chlorophenoxy)acetic acid β-anilinoethyl ester.

EXAMPLE 8

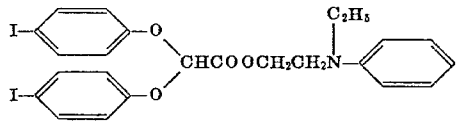
Bis-(p-bromophenoxy)acetic acid β-pyrrolidinoethyl ester



To a mixture of 120 g. of bis-(p-bromophenoxy)acetic acid methyl ester, 50 g. of 1-(β-hydroxyethyl) pyrrolidine and 200 ml. of benzene is added with stirring 1 g. of sodium methoxide. The resulting mixture is heated at 100°C. for 1 hour and then cooled to about 15°–20C. To the cooled mixture is added 500 ml. of benzene and 500 ml. of water. The aqueous phase is then extracted with 500 ml. of benzene and the combined organic layers washed twice with 500 ml. (each) of water and then evaporated on a rotary evaporator. The residue is dissolved in 200 ml. of isopropanol. To the cooled alcohol solution (5°C.) is added, with stirring, a solution of 11 percent hydrochloric acid in isopropanol until the pH thereof is 1. The resulting mixture is filtered, the filtrate cooled overnight at −5°C. The resulting solid material is filtered off and then slurried at reflux with 50 ml. Ligroin. The solids are recovered by filtration, then slurried at 20°C. with 100 g. of carbon tetrachloride and filtered off to obtain bis-(p-bromophenoxy)acetic acid β-pyrrolidinoethyl ester.

EXAMPLE 9

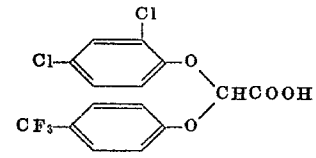
Bis-(p-iodophenoxy)acetic acid β-(N-ethylanilino)ethyl ester



To a mixture of 160 g. of bis-(p-iodophenoxy)acetic acid methyl ester, 80 g. of N-ethyl-N-phenylethanolamine and 1,000 ml. of toluene is added, with stirring 2 g. of sodium methoxide. The resulting mixture is heated at 120°C. for 1 hour and then cooled to about 20°C. To the cooled mixture is added 500 ml. of benzene and 500 ml. of water. The resulting mixture is stirred for 15 minutes, the organic phase separated and washed twice with 500 ml. (each) of water and then evaporated on a rotary evaporator at 100 mm. vacuum. The residue is dissolved in 500 ml. of isopropanol and the resulting solution cooled to 5°C., filtered and the solids washed with 200 ml. of cold isopropanol. The washed solids are dissolved in 500 ml. of isopropanol and the resulting solution treated at reflux with 10 g. of charcoal, then cooled and filtered. The filtrate is allowed to stand for 2 weeks at room temperature. The resulting crystalline material is recovered by decanting off the solvent, then ground in a mortar and slurried at room temperature with 500 ml. of isopropanol. The resulting mixture is filtered and the solids washed with 200 ml. of isopropanol to obtain bis-(p-iodophenoxy)acetic acid β-(N-ethylanilino) ethyl ester.

EXAMPLE 10

(p-trifluoromethylphenoxy)-(2,4-dichlorophenoxy)acetic acid



Step 1. (p-trifluoromethylphenoxy)acetic acid

Sodium hydride (56.7 percent in mineral oil) (47 g.) is washed free from the mineral oil with low boiling petroleum ether and suspended in 750 ml. of dimethylacetamide. To the suspension is added 81 g. of trifluoromethylphenol in 500 ml. of dimethylacetamide as the temperature is maintained at 10°–20°C. The mixture is stirred for 1 hour and 38 g. of chloroacetic acid is added. The resulting mixture is stirred for 5 hours at 80°C. and then at room temperature for 72 hours. The resulting mixture is then poured over 2 liters of ice water, made acidic with a slight excess of hydrochloric acid and is extracted with 750 ml. of isopropyl ether. The organic layer is separated, washed with water, dried over anhydrous sodium sulfate, filtered and evaporated to provide (p-trifluoromethylphenoxy)-acetic acid.

Step 2. α-bromo-p-trifluoromethylphenoxy acetic acid.

To 1 liter of carbon tetrachloride is added 10 g. of (p-trifluoromethylohenoxy)acetic acid. With stirring at room temperature bromine (160 g.) is added dropwise and the mixture is stirred for 17 hours at room temperature. The mixture poured onto 2 kilograms of crushed ice, stirred for 30 minutes and then separated. The organic layer is washed repeatedly with water and then dried over anhydrous sodium sulfate and evaporated to provide α-bromo-p-trifluoromethylphenoxy acetic acid.

Step 3. (p-trifluoromethylphenoxy)-(2,4-dichlorophenoxy)acetic acid

To 200 ml. of dimethylacetamide is added 16.3 g. of 2,4-dichlorophenol and the resulting mixture is added dropwise, with stirring, to a suspension of 9.2 g. of 56.7 percent sodium hydride (which had been washed free of mineral oil with petroleum ether) in 100 ml. of dimethylacetamide. The resulting mixture is stirred at room temperature for 90 minutes and 22 g. of α-bromo-p-trifluoromethylphenoxy acetic acid in 50 ml. of dimethylacetamide is added gradually. The mixture is stirred at room temperature for 72 hours, then at 50°C. for 30 minutes, poured over 1,500 ml. of ice water, acidified with hydrochloric acid, and extracted with 500 ml. of isopropylether. The ether layer is extracted with 100 ml. of water, dried over anhydrous sodium sulfate, filtered and evaporated to yield (p-trifluoro-methylphenoxy 2,4-dichlorophenoxy)acetic acid.

When the above procedure is carried out and p-chlorophenyl, p-iodophenol, p-bromophenol, p-phenylphenol, p-(p-chlorophenyl phenol or 2,4-dibromophenol is used in place of 2,4-dichlorophenol, there is obtained

(p-trifluoromethylphenoxy)-(p-chlorophenoxy)acetic acid,

(p-trifluoromethylphenoxy acetic acid,

(p-trifloromethylphenoxy acetic acid,

(p-triflouromethylphenoxy acetic acid,

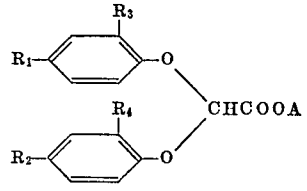
(p-triflouromethylphenoxy)-[p-(p-chlorophenyl)phenoxy] acetic acid, or

(p-trifluoromethylphenoxy)-(2,4-dibromophenoxy) acetic acid,

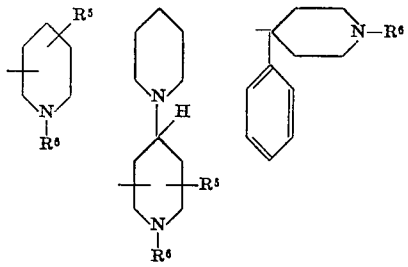
respectively.

What is claimed is:

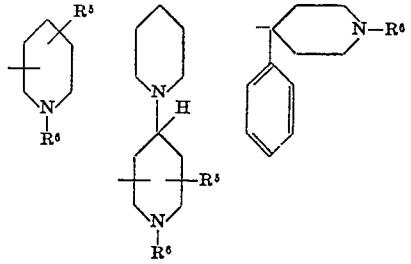
1. A compound of the formula



wherein A represents $-(CHR^\circ)_nR'$,



R′ represents



n represents a whole number of from 1 to 4, inclusive;

each R°, independently, represents hydrogen or lower alkyl;

R^5 represents hydrogen, halo or loweralkyl; and

R^6 represents lower alkyl, propargyl, phenyl, halophenyl or phenyl(lower)alkyl;

R_1, R_2, R_3 and R_4 each independently represents hydrogen, chloro, iodo or bromo, and R_1 and R_2 additionally each, independently, represents trifluoromethyl or phenyl, provided

1. at least one of R_1 and R_2 is other than hydrogen,
2. R_2, R_2, R_3 and R_4 each, independently, may not represent only chloro or hydrogen,
3. R_1 and R_2 each, independently, represents trifluoromethyl or phenyl only
   a. when at least one of R_1, R_2, a R_3 and R_4 represents chloro, bromo or iodo, or
   b. when one of R_1 and R_2 represents a trifluoromethyl or phenyl group and the other of R_1 and R_2 represents the second group;

or a non-toxic acid addition or quaternary salt thereof.

2. The compound of claim 1 which is bis-(p-bromophenoxy) acetic acid 1-methyl-4-piperidyl ester.

3. The compound of claim 1 which is (p-biphenylyloxy)-(p-chlorophenoxy) acetic acid 1-methyl-4-piperidyl ester.

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