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ETHER ACIDS AND DERIVATIVES THEREOF

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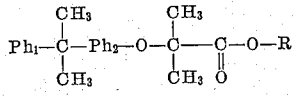
10 Claims. (Cl. 167—65.5)

This is a continuation-in-part of application Ser. No. 305,819, filed Aug. 30, 1963, which in turn is a continuation-in-part of application Ser. No. 238,742, filed Nov. 19, 1962, now abandoned.

The present invention concerns and has for its object the provision of 2-phenoxy-isobutyric acids and their esters and salts, as well as methods for their preparation.

More particularly it relates to compounds having the formula



in which Ph_1 is phenyl or (halogeno)-phenyl, Ph_2 is 1,4-phenylene or (halogeno)-1,4-phenylene, and R is hydrogen or lower alkyl, and the salts of the compounds in which R is hydrogen.

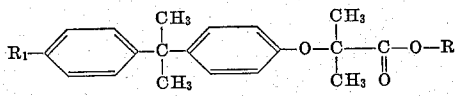
(Halogeno)-phenyl and/or (halogeno)-1,4-phenylene, representing Ph_1 and Ph_2, respectively, are substituted by one or more than one halogeno atom substituting any position available for substitution; halogeno has preferably an atomic weight between 19 and 80, both inclusive, and is above all chloro, as well as fluoro or bromo.

In the above formula, R is hydrogen or lower alkyl, having preferably from one to four carbon atoms, e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl and the like.

Also included within the scope of the invention are the salts of the compounds having a salt-forming carboxy group; these are primarily pharmaceutically acceptable, one-toxic salts, for example, the ammonium salts, or, more especially, metal salts, such as salts of alkali metals, e.g. sodium or potassium, or of alkaline earth metals, e.g. magnesium or calcium, as well as salts of organic bases, such as amines, e.g. piperidine, diethylamine, triethylamine, pyridine and the like.

The compounds of the invention exhibit valuable pharmacological properties. Apart from their activity to shorten the duration of the pharmacological effects caused by barbiturates, they show primarily hypochloesterolemic effects, as can be demonstrated in animal tests, using, for examples, rats as test objects. Furthermore they cause in rats and chickens an enlargement of the liver, an increase of its growth after subtotal hepatectomy and its protection against carbon tetrachloride damage in reducing the amount of centrolobular necrosis and fatty infiltration in the liver. The compounds of the invention are, therefore, useful in limiting barbiturate-induced sleep, in lowering the cholesterol level in the body and thus bringing about an amelioration of the syndromes connected with arteriosclerosis, e.g. atherosclerosis, and as liver protecting agents, for example, in liver cirrhosis or liver poisoning caused by chemicals. Furthermore, they can be used as intermediates for the preparation of other valuable products, particularly of pharmacologically active compounds, such as those disclosed in co-pending application Ser. No. 394,049, filed Sept. 2, 1964.

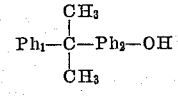
Particularly useful are compounds of the formula



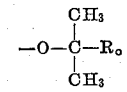
in which R is hydrogen or lower alkyl and R_1 is hydrogen or chloro, and the alkali metal salts of compounds in which R is hydrogen, which, when given to rats orally between

about 20 and 100 mg./kg./day or subcutaneously at about 50 mg./kg./day show outstanding activity in lowering serum cholesterol levels.

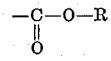
The compounds of this invention are prepared according to methods known per se. Thus, they are obtained, for example, by converting in a compound of the formula



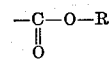
in which Ph_1 and Ph_2 have the previously-given meaning, or a salt thereof, the hydroxyl group into the group of the formula



in which R_o is above all the group of the formula

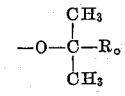


in which R has the above-given meaning, of a functionally converted carboxy group capable of being converted into a group of the formula



and, if desired, converting a resulting salt into the free compound, and/or, if desired, converting in a resulting compound with a carboxy group or a functionally converted carboxy group capable of being converted into a carbo-lower alkoxy group, such group into a carbo-lower alkoxy group, and/or, if desired, converting in a resulting compound with a carbo-lower alkoxy group or another functionally converted carboxy group capable of being converted into a carboxy group, such group into a carboxy group, and/or, if desired, converting a resulting compound having a free carboxyl group into a salt thereof.

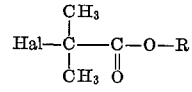
The conversion of a hydroxyl group into the group of the formula



in which R_o has the previously-given meaning, is carried out according to known methods. For example, the starting material having the phenolic hydroxyl group may be converted into a metal salt, particularly an alkali metal, e.g. lithium, sodium, potassium and the like, salt thereof. Formation of the latter may be achieved, for example, by reacting the starting material with a metal compound-forming reagent, such as an alkali metal hydride or amide, e.g. lithium hydride, sodium hydride, sodium amide, potassium amide and the like, or any other suitable reagent, such as an alkali metal lower alkanolate, e.g. lithium, sodium or potassium methanolate, ethanolate, tertiary butanolate and the like, an alkali metal compound of a hydrocarbon, e.g. butyl lithium, phenyl lithium, phenyl sodium and the like, or an alkali metal hydroxide, e.g. sodium hydroxide, potassium hydroxide and the like. The preparation of the metal salts is carried out in the presence of a solvent, which is selected on the basis of the solubility of the starting material and the reactivity of the metal compound-forming reagent; suitable solvents are, for example, hexane, benzene, toluene, xylene, diethyl ether, p-dioxane, tetrahydrofuran, diethyleneglycol dimethylether, N,N-dimethylformamide and the like, or any other proper solvent, such as a lower alkanol, e.g. methanol, ethanol and the like.

The starting material, particularly the metal compound thereof, is then reacted with a compound of the formula

in which R_o has the previously-given meaning, whereby R is primarily a carboxy group or a carbo-lower alkoxy group, but may also represent cyano and the like, and X stands for a reactive esterified hydroxyl group. The latter is above all a hydroxyl group esterified with a strong mineral acid, such as a hydrohalic acid, e.g. hydrochloric, hydrobromic acid and the like; the group X represents, therefore, primarily halogeno, e.g. chloro, bromo and the like. Other suitable inorganic acids furnishing a reactive esterified hydroxyl group are, for example, sulfuric acid and the like. The group X may also be a hydroxyl group esterified with a strong organic sulfonic acid, such as a lower alkane sulfonic acid, e.g. methane sulfonic, ethane sulfonic acid and the like, or a monocyclic carbocyclic aryl-sulfonic acid, e.g. p-toluene sulfonic acid and the like; thus, the group X may also stand for lower alkyl-sulfonyloxy, e.g. methylsulfonyloxy, ethylsulfonyloxy and the like, or monocyclic carbocyclic aryl-sulfonyloxy, e.g. 4-methyl-phenyl-sulfonyloxy and the like. The preferred reactive esters used as the reagents in the above reaction are those having the following formula

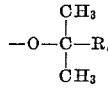


in which R has the previously-given meaning, but is primarily a lower alkyl group, and Hal is halogeno having preferably an atomic weight greater than 19, and representing above all chloro or bromo.

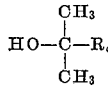
The reaction of the starting material, particularly a metal compound thereof, with the reactive ester reagent is carried out in a suitable diluent, for example, in the solvent used for the preparation of a metal compound, which, however, may be replaced by or diluted with another diluent or solvent mixture; if necessary, it is performed while cooling or at an elevated temperature, and/or, in the atmosphere of an inert gas, e.g. nitrogen.

The formation of the metal salt of the starting material may also be carried out in situ, i.e. the phenolic starting material and the reagent having a reactive esterifed hydroxyl group are reacted together in the presence of a salt-forming reagent, or of another suitable base.

The conversion of a free hydroxyl group of the above starting material into the group of the formula

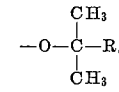


in which R_o has the previously-given meaning, may also be carried out by reacting the previously-described starting material with a compound of the formula



in which R_o has the previously-given meaning, in the presence of a di-substituted carbonate, for example, a di-aryl carbonate, e.g. diphenyl carbonate and the like, or especially a di-lower alkyl carbonate, e.g. dimethyl carbonate, diethyl carbonate and the like. The above reaction is carried out at an elevated temperature, ranging from about 100° to about 210°, preferably from about 180° to about 200°; if desired, it is performed in the presence of a transesterification catalyst, e.g. sodium carbonate, potassium carbonate, a sodium lower alkanolate and the like, and preferably in the absence, as well as in the presence of a diluent.

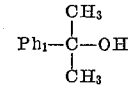
A modification of the conversion of a hydroxyl group in the starting material into the group of the formula



in which R_o is a carboxy group, comprises reacting the starting material of the above formula or a salt thereof with acetone in the presence of a trihalogenated methane derivative or a tetrahalogenated methane derivative and of a strong base.

Trihalogenated or tetrahalogenated methane derivatives used in the above reaction are, for example, chloroform, 1,1,1-trichloro-acetone, bromoform, 1,1,1-tribromo-acetone, iodoform, chloral, chloral hydrate, bromal, hydrate, carbon tetrachloride, carbon tetrabromide and the like. A strong base is more particularly an alkali metal hydroxide, e.g. sodium hydroxide, potassium hydroxide and the like, which is preferably used in solid form. The reaction is advantageously carried out in the presence of a diluent, which may be furnished by using an excess of the ketone reagent, and at an elevated temperature, if necessary, in a closed vessel and/or, in the atmosphere of an inert gas, e.g. nitrogen.

The starting materials used in the above reaction are known or may be prepared according to known methods. A compound having the formula

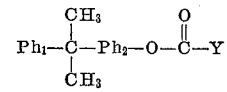


in which Ph_1 has the previously-given meaning, may be reacted with a phenolic compound of the formula

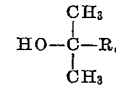
$$H—Ph_2—OH$$

in which Ph_2 has the previously-given meaning, in the presence of a suitable Lewis acid reagent, particularly of a Friedel-Crafts reagent, e.g. aluminum chloride and the like.

The compounds of this invention may also be prepared by reacting a compound of the formula



in which Ph_1 and Ph_2 have the previously-given meaning, and Y is halogeno or etherified hydroxyl, with a compound of the formula



in which R_o has the previously-given meaning, and, if desired, carrying out the optional steps.

In the above starting materials, halogeno, representing the group Y, is particularly chloro, as well as bromo and the like; etherified hydroxyl, representing Y, is primarily lower alkoxy, e.g. methoxy, ethoxy and the like, as well as phenyloxy and the like.

The reaction is carried out according to known methods, preferably at temperatures ranging from 100–210°, if desired, in the presence of a suitable transesterification catalyst, e.g. sodium carbonate, potassium carbonate and the like, and in the absence, as well as in the presence, of a suitable diluent.

The starting materials used in the above procedure are prepared according to known procedures used for the esterification of a phenolic hydroxyl group.

A resulting salt, such as a metal salt, an ammonium salt or a salt of an amine may be reconverted into the free carboxylic acid compound by treatment with an acid, e.g. hydrochloric, sulfuric, acetic acid and the like.

In a resulting compound with a free carboxy group, such group may be converted into a carbo-lower alkoxy

group according to any known esterification procedure, such as, for example, treatment with an alcohol, e.g. a lower alkanol, in the presence of an acid, e.g. hydrochloric, sulfuric acid and the like, or with a diazo-compound, e.g. a lower diazo-alkane, or by converting the carboxylic acid compound into a carboxylic acid halide, e.g. chloride and the like, derivative, and reacting the latter with an alkali metal lower alkoxide, e.g. sodium or potassium methoxide, ethoxide, or isopropoxide and the like, or any other suitable esterification procedure.

Furthermore, in a resulting compound having a functionally converted carboxy group capable of being converted into a carbo-lower alkoxy group. Thus, a carbo-lower alkoxy group in a resulting compound may be converted into another carbo-lower alkoxy group by transesterification, for example, by treatment with a lower alkanol in the presence of a transesterification reagent, such as a corresponding metal lower alkanolate, such as an alkali metal, e.g. sodium, potassium and the like, lower alkanolate or an aluminum lower alkanolate, an alkali metal cyanide, e.g. potassium cyanide, or benzyl trimethyl ammonium hydroxide and the like. Furthermore, other functionally converted carboxy groups are converted into carbo-lower alkoxy groups according to known methods. For example, in a resulting compound having a cyano group, such group is converted into carbo-lower alkoxy by treatment of the nitrile compound with an alcohol, e.g. a lower alkanol, in the presence of a suitable mineral acid, e.g. sulfuric, hydrochloric acid and the like.

A functionally converted carboxy group may be converted into carboxy according to known methods. For example, a carbo-lower alkoxy group may be converted into a carboxyl group by hydrolysis, for example, by treatment of a resulting compound having a carbo-lower alkoxy group with a base, e.g. sodium hydroxide, potassium hydroxide and the like, or any other suitable hydrolysis reagent. Other functionally converted carboxy groups, such as cyano or amido groups, in resulting compounds are converted into the carboxy groups according to known methods. For example, a nitrile or an amide compound is converted into a carboxy compound by hydrolysis with a strong base, e.g. sodium hydroxide, potassium hydroxide and the like, or a strong acid, e.g. sulfuric acid and the like.

A resulting compound having a free carboxy group may be converted into its salts according to conventional methods, for example, by reacting the free carboxylic acid compound with an about stoichiometric amount of a suitable salt-forming reagent, such as ammonium hydroxide, or a metal hydroxide, amide or hydride and the like, or an organic amine, if necessary, in the presence of a diluent, which may be partially or totally removed in order to isolate the desired salt.

The invention also comprises any modification of the process wherein a compound resulting as an intermediate at any stage of the process is used as starting material, and the remaining step(s) of the process is (are) carried out using such intermediate, as well as any new intermediates.

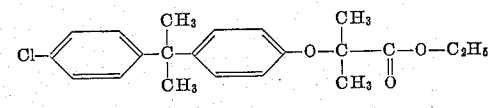
In the process of this invention, those starting materials are preferably used, which lead to final products indicated before as being the preferred embodiments of the invention.

The compounds of the invention can be used, for example, for the manufacture of pharmaceutical compositions containing them in conjunction or admixture with inorganic or organic, solid or liquid pharmaceutical excipients, suitable for enteral or parenteral administration. Suitable excipients are substances that do not react with the compounds of the invention, for example, water, gelatine, sugars, e.g. lactose, glucose or sucrose, starches, e.g. corn starch or arrowroot, stearic acid or salts thereof, e.g. magnesium or calcium stearate, talc, vegetable fats or oils, gums, alginic acid, benzyl alcohols, glycols and other known excipients. The compositions may be, for example, in solid form as tablets, dragees or capsules, or in liquid form as solutions, suspensions or emulsions. They may be sterilized and/or contain adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers. They may further contain other therapeutically valuable substances. Said pharmaceutical compositions, which are prepared by conventional methods, are also intended to be included within the scope of the present invention.

The following examples are intended to illustrate the invention and are not to be construed as being limitations thereon. Temperatures are given in degrees centigrade and all parts wherever given are parts by weight.

Example 1

To a solution of 12.3 g. of 2-(4-chloro-phenyl)-2-(4-hydroxy-phenyl)-propane in 50 ml. of N,N-dimethylformamide is added while stirring and cooling to 5°, 2.4 g. of a 53 percent suspension of sodium hydride in mineral oil. After the evolution of hydrogen ceases, 9.15 g. of ethyl 2-bromo-isobutyrate in 50 ml. of toluene is added. The reaction mixture is stirred for two hours at room temperature and then allowed to stand for 15 hours. The inorganic precipitate is filtered off, the filtrate is concentrated to a volume of about 25 ml. and is diluted with water. The organic material is extracted with diethyl ether, the organic extract is washed with saturated aqueous solutions of sodium hydrogen carbonate and sodium chloride, dried over sodium sulfate and evaporated to dryness. The oily residue is distilled, and the fraction collected at 135–145°/0.08 mm., yield: 12.0 g., is chromatographed on 480 g. of aluminum oxide (Woelm, neutral, activity III). The desired ethyl 2-{4-[2-(4-chloro-phenyl)-2-propyl]-phenyloxy}-isobutyrate of the formula



is eluted with a 4:1-mixture of hexane and benzene and obtained as a clear, colorless oil; yield: 5.0 g.

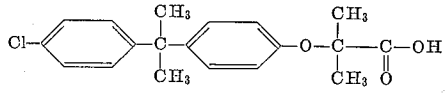
The starting material used in the above example is prepared as follows: To the ice-cooled Grignard reagent, prepared from 284.0 g. of methyl iodide and 48.6 g. of magnesium turnings in 550 ml. of diethyl ether, is added dropwise a solution of 154.6 g. of 4-chloro-acetophenone in 200 ml. of diethyl ether while stirring. The reaction mixture is allowed to stand at room temperature and is then heated to reflux for two hours. The Grignard complex is decomposed by slowly adding 300 ml. of a saturated aqueous solution of ammonium chloride and 300 ml. of water while stirring and cooling in an ice bath; 300 ml. of diethyl ether is added, and the organic layer is separated, washed and dried over sodium sulfate. The solvent is removed, and the 2-(4-chloro-phenyl)-2-propanol is obtained by distilling the residue, B.P. 92–96°/3 mm.

To a mixture of 28.2 g. of phenol and 6.7 g. of aluminum chloride (prepared by adding the latter in portions to the phenol while stirring) is given in portions a mixture of 17.1 g. of 2-(4-chloro-phenyl)-2-propanol and 9.4 g. of phenol while stirring and cooling with water. The reaction mixture is stirred at room temperature for two hours, allowed to stand for fifteen hours and is then heated for one hour to 40–50° while stirring. It is added to 100 ml. of 6 N aqueous hydrochloric acid while stirring; the organic layer is separated and the excess phenol is removed by distillation at temperatures up to 130°/13 mm. The oily residue is distilled to yield the 2-(4-chloro-phenyl)-2-(4-hydroxy-phenyl)-propane, which crystallizes from hexane, M.P. 72–74°.

Example 2

A total of 6.0 g. of ethyl 2-{4-[2-(4-chloro-phenyl)-2-propyl]-phenyloxy}-isobutyrate is stirred into 40 ml. of methanol containing 1.4 g. of potassium hydroxide and the reaction mixture is allowed to stand at room temperature for four days. The solvent is then removed to yield the crude crystalline potassium salt of 2-{4-[2-(4-chloro-phenyl)-2-propyl]-phenyloxy}-isobutyric acid; the solubility of this salt in water is greater than 10 percent. A small portion of the salt is recrystallized by dissolving the crude material in boiling acetone, adding a small amount of methanol and cooling; it melts at about 290° (decomposition).

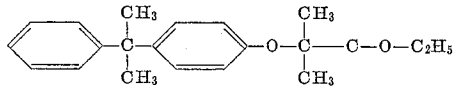
The above potassium salt is dissolved in 50 ml. of water; the solution is treated with 12 ml. of 2 N aqueous hydrochloric acid and the acidic solution is extracted three times with diethyl ether. The organic extracts are washed with a saturated solution of sodium chloride in water, dried over sodium sulfate, filtered, and evaporated to dryness. The 2-{4-[2-(4-chloro-phenyl)-2-propyl]-phenyloxy}-isobutyric acid of the formula



is recrystallized by dissolving it in diethyl ether, adding hexane evaporating the diethyl ether and diluting the solution with pentane, M.P. 91–92° C.; yield: 3.9 g.

Example 3

To a solution of 10.0 g. of 2-(4-hydroxy-phenyl)-2-phenyl-propane in a mixture of 50 ml. of N,N-dimethyl-formamide and 75 ml. of toluene is added in portions 5.0 g. of a 53 percent suspension of sodium hydride in mineral oil while cooling in an ice-bath and stirring. Upon cessation of the hydrogen evolution, 10.0 g. of ethyl 2-bromo-isobutyrate in 50 ml. of toluene is added, and the resulting mixture is stirred at room temperature for eighteen hours. Most of the solvents are removed under reduced pressure and the oily residue is taken up into water. The organic material is extracted three times with diethyl ether; the ether solutions are combined, washed three times with 100 ml. portions of water and a saturated solution of sodium chloride in water, dried over sodium sulfate, filtered and evaporated to dryness under reduced pressure. The crude product is chromatographed on 300 g. of aluminum oxide (Woelm, neutral, activity III), and the desired ethyl 2-[4-(2-phenyl-2-propyl)-phenyloxy]-isobutyrate of the formula

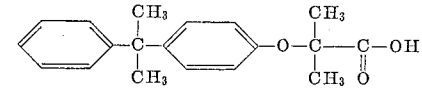


is eluted with benzene, containing 15 percent of hexane after washing the column with hexane to remove the mineral oil. The colorless oil boils at 129–133°/0.03 mm.; yield: 4.0 g.

Example 4

To a solution of 54.0 g. of crude ethyl 2-[4-(2-phenyl-2-propyl)-phenyloxy]-isobutyrate in 200 ml. of methanol is added a solution of 14.0 g. of potassium hydroxide pellets in 200 ml. of methanol; the clear solution is allowed to stand at room temperature for eighteen hours. The solvent is then removed under reduced pressure, and the resulting crude potassium salt of 2-[4-(2-phenyl-2-propyl)-phenyloxy]-isobutyric acid is dissolved in 300 ml. of water; the solution is extracted with diethyl ether and is then acidified with concentrated hydrochloric acid. The organic material is extracted twice with diethyl ether; the extracts are washed with water and a saturated aqueous solution of sodium chloride, dried over sodium sulfate, filtered and evaporated to dryness, to yield 42.0 g.

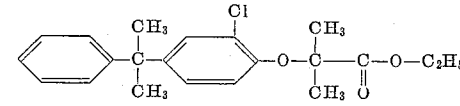
of the crystalline 2-[4-(2-phenyl-2-propyl)-phenyloxy]-isobutyric acid of the formula



which is recrystallized from a mixture of benzene and pentane, M.P. 117–118°.

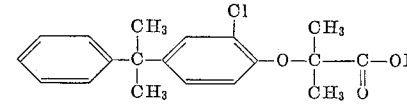
Example 5

To a solution of 4.1 g. of 2-(2-chloro-4-hydroxy-phenyl)-2-phenyl-propane in 20 ml. of N,N-dimethylformamide is added while stirring and cooling in an ice-bath, 0.8 g. of a 53 percent suspension of sodium hydride in mineral oil. After the evolution of hydrogen ceases, a solution of 3.03 g. of ethyl 2-bromo-isobutyrate in 20 ml. of toluene is added, and the reaction mixture is worked up as described in Example 1 to yield the ethyl 2-[2-chloro - 4 - (2 - phenyl - 2 - propyl) - phenyloxy] - isobutyrate of the formula



Example 6

A solution of 2.0 g. of ethyl 2-[2-chloro-4-(2-phenyl-2-propyl)-phenyloxy]-isobutyrate in 20 ml. of methanol containing 0.45 g. of potassium hydroxide is allowed to stand at room temperature for several days and is then worked up as described in Example 2 to yield the 2-[2-chloro - 4 - (2 - phenyl - 2 - propyl) - phenyloxy] - isobutyric acid of the formula



Other compounds, such as methyl 2-[4-(2-phenyl-2-propyl)-phenyloxy]-isobutyrate, ethyl 2-{4-[2-(4-bromo-phenyl)-2-propyl]-phenyloxy}-isobutyrate, ethyl 2-{4-[2-(4 - fluoro-phenyl) - 2 - propyl]-phenyloxy}-isobutyrate and the like are prepared as described in the above examples by converting the 2-(4-hydroxy-phenyl)-2-phenyl - propane, 2 - (4 - bromo - phenyl) - 2 - (4 - hydroxy-phenyl)-propane or 2-(4-fluoro-phenyl)-2-(4-hydroxy-phenyl)-propane into their alkali metal, particularly the sodium, salts with an alkali metal amide or an alkali metal hydride in the presence of an appropriate diluent, and reacting the salts with the appropriate lower alkyl 2-halogeno-isobutyrate, such as methyl 2-bromo-isobutyrate and ethyl 2-bromo-isobutyrate. If desired, the above esters are then converted into their free acids, such as the 2-[4 - (2 - phenyl - 2 - propyl) - phenyloxy] - isobutyric acid, the 2 - {4 - [2 - (4 - bromo-phenyl) - 2 - propyl]-phenyloxy}-isobutyric acid and the 2-{4-[2-(4-fluoro-phenyl)-2-propyl]-phenyloxy}-isobutyric acid, by treatment with an alkali metal hydroxide, e.g. potassium hydroxide and the like, according to the procedure described hereinbefore.

Example 7

A solution of 14.9 g. of 2-[4-(2-phenyl-2-propyl)-phenyloxy]-isobutyric acid in 100 ml. of anhydrous ethanol containing dry hydrogen chloride, is refluxed for six hours and then taken to dryness under reduced pressure. The residue is distilled to yield the desired ethyl 2-[4-(2-phenyl-2-propyl)-phenyloxy]-isobutyrate, B.P. 129–133°/0.03 mm.

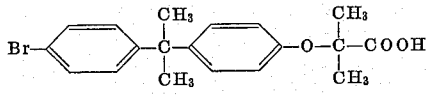
Example 8

10.0 g. of 2-(p-chlorophenyl)-2-(p-hydroxyphenyl)-propane are dissolved in 100 ml. of acetone and 9 g. of sodium hydroxide pellets are added. The reaction mixture is stirred and heated to reflux for about 10 min. Ex-

ternal heating is discontinued and 6 g. of chloroform are added dropwise at a rate to maintain reflux. After completed addition heating is resumed and the sodium salt of the product precipitates. 200 ml. more of acetone are added to facilitate stirring and refluxing which is continued for 2 more hours. The precipitated tan-colored sodium salt is collected on a Büchner funnel and washed with acetone. The salt is then dissolved in 200 ml. of water, made acidic with concentrated hydrochloric acid and extracted 3 times with ether. The extract is washed with water and saturated sodium chloride solution and dried. The oily product is recrystallized from hexane to give the 2-{4-[2-(4-chloro-phenyl)-2-propyl]-phenoxy}-isobutyric acid melting at 86–87°. The product is identical with that obtained according to Example 2.

Example 9

The mixture of 2.9 g. 2-(4-bromo-phenyl)-2-(4-hydroxyphenyl)-propane, 2.3 g. sodium hydroxide pellets and 50 ml. acetone is refluxed with stirring for 10 minutes and hereupon 1.5 g. chloroform in 50 ml. acetone are added dropwise. The mixture is again refluxed for 2 hours, then filtered, the precipitate washed with acetone and dissolved in 75 ml. warm water. The solution is acidified with concentrated hydrochloric acid, extracted with diethyl ether, the extract washed with water, dried and evaporated. The resulting 2-{4-[2-(4-bromo-phenyl)-2-propyl]-phenoxy}-isobutyric acid of the formula



is recrystallized from pentane, it melts at 91–92°.

Example 10

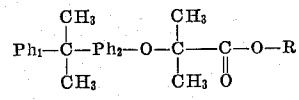
10,000 tablets each containing 50 mg. of the active ingredient.

Material:	G.
2-[4-(2-phenyl-2-propyl)-phenyloxy]-isobutyric acid	500.0
Lactose	1812.5
Tragacanth	50.0
Corn starch	125.0
Magnesium stearate	12.5

Procedure.—The acid is triturated with the starch and passed through a No. 40 screen, the other ingredients through a No. 20 screen. The powders are thoroughly mixed and the mix compressed into tablets each weighing 0.25 g. using $1\frac{1}{32}$" standard concave punches.

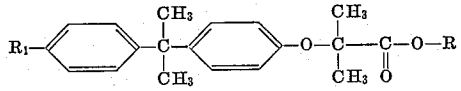
What is claimed is:

1. A member selected from the group consisting of a compound having the formula



in which Ph_1 is a member selected from the group consisting of phenyl and (halogeno)-phenyl, Ph_2 is a member selected from the group consisting of 1,4-phenylene and (halogeno)-1,4-phenylene, and R is a member selected from the group consisting of hydrogen and lower alkyl, and the salts of the compounds in which R is hydrogen.

2. A compound as claimed in claim **1** and having the formula



in which R_1 is a member selected from the group consisting of hydrogen and chloro, and R is a member selected from the group consisting of hydrogen and lower alkyl and of which acid the salt is an alkali metal salt.

3. A compound as claimed in claim **1** and being the ethyl 2-{4-[2-(4-chloro-phenyl)-2-propyl] - phenyloxy}-isobutyrate.

4. A compound as claimed in claim **1** and being the 2-{4-[2-(4-chloro-phenyl) - 2 - propyl]-phenyloxy}-isobutyric acid.

5. A compound as claimed in claim **1** and being the ethyl 2-[4-(2-phenyl-2-propyl)-phenyloxy]-isobutyrate.

6. A compound as claimed in claim **1** and being the 2-[4-(2-phenyl-2-propyl)-phenyloxy]-isobutyric acid.

7. A compound as claimed in claim **1** and being the ethyl 2-[2-chloro-4-(2-phenyl-2-propyl)-phenyloxy]-isobutyrate.

8. A compound as claimed in claim **1** and being the 2-[2-chloro - 4 - (2 - phenyl-2-propyl)-phenyloxy]-isobutyric acid.

9. A compound as claimed in claim **1** and being the 2-{4-[2-(4-bromo-phenyl) - 2 - propyl]-phenyloxy}-isobutyric acid.

10. A pharmaceutical composition comprising about 20% of a compound as claimed in claim **1** together with a pharmaceutical excipient.

References Cited

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