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[54] SUBSTITUTED BIPHENYL ACETIC ACIDS AND ESTER DERIVATIVES THEREOF

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[51] **Int. Cl.**.....**C07c 65/14**

[58] **Field of Search**.....260/520, 473 R, 473 S, 479 R

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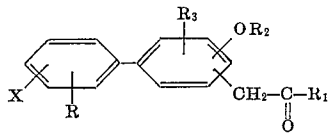
[57] **ABSTRACT**

New 4(and 5)-substituted phenylacetic acids useful as anti-inflammatory, analgesic and anti-pyretic agents.

4 Claims, No Drawings

SUBSTITUTED BIPHENYL ACETIC ACIDS AND ESTER DERIVATIVES THEREOF

This invention relates to new biphenyl compounds, to a method of treating inflammation using these compounds and to processes for producing the same. More specifically, this invention relates to substituted 4(or 5)-(phenyl)-phenylacetic acids, esters, amides, anhydrides and non-toxic pharmaceutically acceptable salts thereof. Still more specifically, this invention relates to compounds having the following formula:



(1-5) I

wherein:

$X_{(1-5)}$ is halogen (chloro, bromo, fluoro and iodo);

R is selected from the group consisting of hydrogen, halogen (chloro, bromo, and fluoro), lower alkyl (such as methyl, ethyl, butyl, pentyl, and the like), and lower alkoxy (such as methoxy, ethoxy, butoxy, and the like);

R_1 is selected from the group consisting of hydroxy, amino, lower alkoxy (such as methoxy, ethoxy, butoxy, pentoxy, and the like), lower alkylamino (methylamino, propylamino, pentylamino, and the like), di(lower alkyl)amino (dimethylamino, dibutylamino, propylpentylamino, and the like), diloweralkylaminoloweralkylamino, dloweralkylaminoloweralkoxy, hydroxyloweralkoxy, (3-hydroxypropoxy, 2-hydroxypropoxy, 4-hydroxybutoxy and the like), polyhydroxyloweralkoxy (2,3-dihydroxypropoxy, 2,3,4,5,6-pentahydroxyhexyloxy and the like), loweralkoxyloweralkoxy (ethoxyethoxy), phenyl-loweralkoxy (benzyloxy, phenethoxy and the like), phenoxy, substituted phenoxy (such as loweralkoxy, diloweralkylamino, loweralkanoylamino, benzyloxy-2-carboxy-4-(4'-fluorophenyl), loweralkanolyaminoloweralkoxy, hydrazino, (hydroxylamino), N-morpholino, N-(4-loweralkyl-piperidino)-N-[4-(hydroxyloweralkyl)-piperidino], (hydroxyloweralkyl)amino and a naturally occurring amino acid radical with attachment at the N, such as glycine, phenylalanine, proline, methionine and taurine;

R_2 is selected from the group consisting of hydrogen, lower alkyl (such as methyl, ethyl, butyl, pentyl, and the like), lower alkanoyl (such as acetyl, propionyl, butyryl, and the like), and lower alkenyl (such as allyl, butenyl, and the like); and

R_3 is selected from the group consisting of hydrogen, 3-lower alkenyl, 3- and 4-lower alkyl, lower alkoxy, benzyl and halo; the pharmaceutically non-toxic salts of the acid [such as the ammonium, alkali (Na,K) and alkali earth (Ca,Ba,Mg), amine, aluminum, iron, choline, glucosamine, and S-methyl methionine salts, piperazine, diloweralkylaminoloweralkanol, chloroquine, hydroxychloroquine and the like]; the anhydride of said acids and the mixed anhydrides of said acids and 2-acetoxy phenyl acetic acid.

In the more preferred aspects of this invention, is hydrogen or lower alkyl, particularly, methyl or lower alkoxy, particularly methoxy;

R_1 is hydroxy or amino, particularly hydroxy;

R_2 is hydrogen or lower alkanoyl, particularly acetyl;

R_3 is hydrogen or lower alkyl;

X is chloro or fluoro, particularly fluoro and is on the 4-position of the phenyl moiety.

Representative compounds of this invention are:

2-hydroxy-4(or 5)-(4'-fluorophenyl)-phenylacetamide;

2-hydroxy-4(or 5)-(4'-fluorophenyl)-3-methylphenylacetamide;

2-acetoxy-4(or 5)-(4'-fluorophenyl)-phenylacetamide;

2-acetoxy-4(or 5)-(4'-fluorophenyl)-phenylacetmorpholide;

2-hydroxy-4(or 5)-(4'-fluoro-2'-methoxyphenyl)-phenylacetic acid;

2-acetoxy-4(or 5)-(4'-fluoro-2'-methoxyphenyl)-phenylacetic acid;

2-hydroxy-4(or 5)-(4'-fluoro-2'-methylphenyl)-phenylacetic acid;

2-acetoxy-4(or 5)-(4'-fluoro-3'-methylphenyl)-phenylacetic acid;

2-hydroxy-3-allyl-4(or 5)-(4'-fluorophenyl)-phenylacetic acid; and

2-hydroxy-3-propyl-4(or 5)-(4'-fluorophenyl)-phenylacetic acid.

This invention also relates to a method of treating inflammation in patients using a compound of formula I, particularly an especially preferred compound as the active constituent.

The compounds of the instant invention can be used to reduce inflammation and relieve pain in such diseases as rheumatoid arthritis, osteoarthritis, gout, infectious arthritis and rheumatic fever. Furthermore, the compounds of the instant invention have better potency at the same dosage levels than similar type compounds known in the prior art and exhibit a lower incidence of side effects.

The compounds of formula I also have antipyretic and analgesic activity and would be administered and used in the same manner and in the same dosage ranges as if they were being used to treat inflammation as discussed further on.

The treatment of inflammation in accordance with the method of the present invention is accomplished by orally, parenterally, topically or rectally administering to patients (animal or human) a composition of a compound of formula I, particularly the especially preferred compounds in a non-toxic pharmaceutically acceptable carrier, preferably in tablet or capsule form.

The non-toxic pharmaceutical carrier may be, for example, either a solid or a liquid. Exemplary of solid carriers are lactose, corn starch, gelatin, talc, sterotix, stearic acid, magnesium stearate, terra alba, sucrose, agar, pectin, cab-o-sil, and acacia. Exemplary of liquid carriers are peanut oil, olive oil, sesame oil and water. Similarly, the carrier or diluent may include a time delay material such as glyceryl monostearate or glyceryl distearate alone or with a wax.

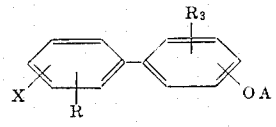
Several pharmaceutical forms of the therapeutically useful compositions can be used. For example, if a solid carrier is used, the compositions may take the form of tablets, capsules, powders, troches or lozenges, prepared by standard pharmaceutical techniques. If a liquid carrier is used, the preparation may be in the form of a soft gelatin capsule, a syrup or a liquid suspension. Creams, gels, and salves may be prepared in conventional manners for topical administration and suppositories may be prepared for rectal administration.

The active compounds of formula I and of the compositions of this invention are present in an amount sufficient to treat inflammation, that is to reduce inflammation. Advantageously, the composition will contain the active ingredient, namely, the compounds of formula I in an amount of from about 1 to 140 mg. per day), preferably from about 2 mg. to 70 mg./kg. body weight per day (100 mg. to 5 g. per patient per day).

The method of treatment of this invention comprises internally administering to a patient (animal or human), a compound of formula I, particularly an especially preferred compound admixed with a non-toxic pharmaceutical carrier such as exemplified above. The compounds of formula I and particularly the especially preferred compounds will be present in an amount of from 1 mg. to 140 mg./kg. body weight per day, preferably from about 2 mg. to about 70 mg. per kilogram body weight per day and especially from 4 mg. to 10 mg./kg. body weight per day. The most rapid and effective anti-inflammatory effect is obtained from oral administration of a daily dosage of from about 4 to 10 mg./kg./day. It should be understood, however, that although preferred dosage ranges are given, the dose level for any particular patient depends upon the activity of the specific compound employed. Also many other factors that modify the actions of drugs will be taken into account by those skilled in the art in the therapeutic

use of medicinal agents, particularly those of formula I, for example, age, body weight, sex, time of administration, route of administration, rate of excretion, drug combination, reaction sensitivities and severity of the particular disease.

The compounds of this invention may be prepared either from a biphenyl phenol or from the following type starting material:



(1-5)

wherein:

A is an alkali metal ion; and

X, R_3 and R are as previously defined.

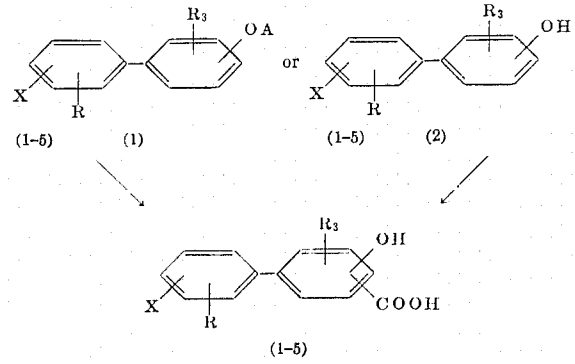
Some of these compounds are prepared from the individual phenyl moieties of the above starting material by the well-known Gomberg reaction. Others, where the biphenyl moiety is known, require the appropriate reactions to obtain the functional group, if needed, as well as the metal salts. However, all of the compounds may be obtained by first preparing an aniline compound containing an X and, if desired, an R group, followed by a Gomberg reaction with nitrobenzene or anisole or an R_3 substituted nitrobenzene or anisole, subsequently reacting either the nitro group or the methoxy group (from nitrobenzene or anisole) of the biphenyl compound thus prepared so as to obtain the alkali salt starting material. For example, 2-fluoro-5-nitroaniline may be diazotized to the corresponding 2-fluoro-5-nitrophenol which in turn may be alkylated to form the corresponding 3-alkoxy-4-fluoronitrobenzene, and finally reducing the nitro group to obtain the appropriate aniline compound needed for the Gomberg reaction. (When as in this cited example, the benzene compound contains an alkoxy group, the Gomberg reaction is carried out with nitrobenzene). The methoxy substituted aniline compound is then reacted with nitrobenzene in the presence of isoamyl nitrite. The nitrobiphenyl compound thus obtained may be readily reduced to the amino compound and subsequently diazotized to the corresponding hydroxy compound. Alternatively, when the aniline compound used in the Gomberg reaction does not have an alkoxy substituent on it, it may be reacted with an alkoxy benzene rather than nitrobenzene. Using this procedure, the alkoxy biphenyl compound obtained after the Gomberg reaction may, by one step, be converted to the corresponding hydroxy-biphenyl compound, for example, by reaction with hydriodic acid.

Although the above reaction sequence can be used when R_3 is methyl, it is preferred to carry out the following reaction sequence when R_3 is lower alkyl: For example, the methyl-2-hydroxy-5-(4'-fluorophenyl)-benzoate compound of this invention is reduced to the corresponding alcohol. This alcohol compound is then acylated, whereupon it is subsequently hydrogenated to the corresponding 4-(4'-fluorophenyl)-2-methylphenyl acetate. This compound is then saponified or hydrolyzed to the corresponding phenol compound, which in turn is carbonated to form the 5-(4'-fluorophenyl)-2-hydroxy-3-methyl-benzoic acid. Further, when R_3 is to be a lower alkenyl group, the following procedure is preferred: For example, methyl 5-(4'-fluorophenyl)-2-hydroxy benzoate is heated with potassium carbonate in acetone to form the corresponding 2-allyloxy compound. This product is then heated at high temperatures to cause a rearrangement to the corresponding 3-allyl-2-hydroxy compound. Further, an additional method for preparing an R_3 alkyl is by reduction, for example, of the above-noted 3-allyl compound to the corresponding 3-propyl compound. In addition, the 3-allyl compound above may be heated with potassium hydroxide to obtain a double bond shift to form the 3-propenyl compound.

In the Gomberg reaction mentioned above, a mixture of isomers of the biphenyl compound is obtained; therefore, in order to obtain the desired 4(and 5)-(substituted phenyl)-benzene compounds in a pure form a chromatographic separation is required.

The (substituted phenyl)-phenol compounds obtained as described above may then be converted to the corresponding alkali salt by any well-known means, for example, reaction with an appropriate alkali metal in an inert solvent.

The benzoic acid compounds may be prepared from the previously prepared alkali phenolate or phenol compound. The preparation of these acid compounds are carried out by using the well-known Kolbe-Schmidt carbonation procedure. In this carbonation step, the phenolate is reacted with carbon dioxide or the phenol is reacted with carbon dioxide in the presence of an alkali carbonate. Many of the acids which are not claimed in this invention can be used as starting materials for the novel esters and amides of this invention. The process may be shown as follows:



Equivalents: As previously indicated.

Reactions and Conditions:

Step 1. Reaction with carbon dioxide at elevated temperatures (above 75° C. preferably above 100° C.) with or without a solvent preferably without a solvent (or if the solvent is used, any high-boiling inert solvent may be used) until the reaction is substantially complete; and subsequent acidification of the mixture.

Step 2. Reaction with carbon dioxide in the presence of an alkali carbonate, such as potassium, sodium and the like, especially potassium, at elevated temperatures (above 75° C. preferably above 100° C.) with or without a solvent preferably without a solvent (or if the solvent is used, any high-boiling inert solvent may be used) until the reaction is substantially complete; and subsequent acidification of the reaction mixture.

Reaction steps 1 and 2 are the well-known Kolbe-Schmidt reaction. Since the reaction conditions are not critical, this invention contemplates not only the particular procedure shown but all other variations of this carbonation step which are well known in the art.

The phenylacetic acid compounds of this invention may be prepared by reacting the corresponding hydroxy benzoic acid with a lower alkanoic acid anhydride (preferably acetic anhydride) in the presence of a catalyst, such as sulfuric acid, pyridine, p-toluenesulfonic acid and the like (preferably pyridine), at any suitable temperature from room temperature to elevated temperatures (preferably at elevated temperatures) to form the desired R_2 compound which then undergoes the Arndt-Erstert synthesis to form the desired acetic acid compound. This synthesis involves three steps:

1. formation of the acid chloride by reacting the benzoic acid with any suitable chloride of the formula $SOCl_2$, $POCl_3$or R-COCl wherein R = alkyl, aryl or heteroaryl;

2. reaction of the acid chloride with diazomethane to form a diazoketone; and

3. rearrangement of the diazoketone, with loss of nitrogen, in the presence of a catalyst (silver, platinum, copper). An acid is formed in the presence of water, an ester is produced in an alcohol, and an amide results when ammonia is used.

The compounds of this invention, wherein R_1 is a group such that an ester is the final compound, (i.e. R_1 = alkoxy), are prepared by any esterification procedure, using an esterifying agent containing the appropriate R_1 group. For example, the

phenylacetic acid compounds of this invention may be reacted with the appropriate lower alkanol (preferably methanol) at elevated temperatures in the presence of a strong acid, such as hydrochloric acid, sulfuric acid, p-toluenesulfonic acid, and the like, to form the desired R_1 compound.

The compounds of this invention, wherein R_1 is a group such that an amide is the final compound (i.e., R_1 is amino), may also be present by any suitable amidation reaction. For example, the phenylacetic acid compound (preferably the methyl or ethyl ester) may be reacted with ammonia, ammonium hydroxide, or an amine compound, at any suitable temperature (room temperature to reflux). When the amino group is desired, it is preferred to carry out the reaction with ammonia in a bomb at temperatures above 100° C. to form the desired R_1 (amino) compound. Preferably, when an amide is desired which is derived from an amino acid, the following reaction sequence is followed: The phenylacetic acid final compound is reacted with isobutyl chlorocarbonate to form the mixed anhydride. This compound is in turn reacted when the desired amino acid ester and subsequently hydrolyzed to form the desired amide.

The final compound, wherein R_2 is lower alkanoyl (preferably acetyl), may be prepared by any suitable alkanoylation reaction. For example, the corresponding hydroxy phenylacetic acid, ester or amide (preferably the ester), may be reacted with a lower alkanoic acid anhydride (preferably acetic anhydride) in the presence of a catalyst, such as sulfuric acid, pyridine, p-toluenesulfonic acid, and the like (preferably pyridine), at any suitable temperature (room temperature to elevated temperatures) preferably at elevated temperatures to form the desired R_2 compound.

The final compound, wherein R_2 is lower alkyl (preferably methyl), may be prepared by any appropriate alkylation reaction. For example, the corresponding hydroxy phenylacetic acid, ester, or amide (preferably the ester), may be reacted with a di(lower alkyl)sulfate (preferably dimethyl sulfate) in the presence of a base (such as an alkali carbonate) at any suitable temperature (room temperature to reflux but preferably at or near reflux) with subsequent acidification of the reaction mixture, such as with hydrochloric acid, sulfuric acid, and the like, to form the desired R_2 compound.

The final compound, wherein R_2 is a lower alkenyl (preferably allyl), may also be prepared by any appropriate alkylation reaction. For example, the hydroxy phenylacetic acid, ester, or amide (preferably the ester), may be reacted with an alkenyl halide in the presence of a base containing an inorganic cation, such as sodium methoxide, potassium ethoxide, sodium carbonate, and the like, in an inert solvent which affords at least some solubilization [such as dioxane, tetrafuran, lower alkanol, dimethoxy ethane, acetone, and the like (preferably a lower alkanol, such as methanol)] at any suitable temperature (room temperature to elevated temperatures, preferably at elevated temperatures) to form the desired R_2 compound.

The salts of the final acid compounds of this invention may be prepared by any of the well-known metathesis procedures. For example, the phenylacetic acid compound may be reacted with an inorganic base, such as sodium hydroxide, potassium hydroxide, ammonium hydroxide, barium hydroxide, and the like. The anhydrides of this invention may be prepared by any of the well-known procedures in the art.

The preparation of these compounds containing the R_1 and R_2 groups other than hydrogen may be prepared in any order. The R_1 group could be placed on the molecule followed by addition of the R_2 substituent or by first obtaining the R_2 compound followed by addition of the R_1 group. The order of these reactions is not critical; they can be run in any desired fashion.

The following examples are used by way of illustration:

EXAMPLE 1

4-(4′-Fluorophenyl)aniline

A solution of 3 g. 4′-fluoro-4-nitrobiphenyl in 125 ml. methanol is reduced by hydrogen at room temperature and 40 p.s.i. pressure using 100 mg. platinum oxide catalyst. After the required uptake of hydrogen, the mixture is filtered, 50 ml. 2.5 N hydrochloric acid added and the resulting solution is evaporated in vacuo. After washing the residue with ether, it is dissolved in methanol, filtered and diluted with excess ether. The precipitate which is 4-(4′-fluorophenyl)aniline hydrochloride is filtered, washed with ether and dried in vacuo at room temperature.

EXAMPLE 2

2′,3′,4′,5′,6′-Pentafluoro-4-nitrobiphenyl and 2′,3′,4′,5′,6′-Pentafluoro-3-nitrobiphenyl

A mixture of 7.5 g. **of pentafluoroaniline**, 200 ml. of nitrobenzene, and 9.0 g. of iso-amyl nitrite, is warmed on the steam bath until a vigorous reaction with evolution of gas sets in. This evolution is allowed to proceed without heating until it has subsided, and the mixture is then heated on the steam bath for an additional 3 hours. The excess of nitrobenzene is removed in vacuo. The residue is purified for the desired isomer by elution from a silica gel column using petroleum-benzene to yield 2′,3′,4′,5′,6′4-nitrobiphenyl and 2′,3′,4′,5′,6′-pentafluoro-3-nitrobiphenyl.

When 2-fluoroaniline is used in place of pentafluoroaniline in the above example, there is obtained 2′-fluoro-4-nitrobiphenyl and 2′-fluoro-3-nitrobiphenyl.

When 2-nitrotoluene, 2-ethyl-nitrobenzene, 2-methoxy-nitrobenzene, 2-ethoxy-nitrobenzene, 2-chloro-nitrobenzene, 2-bromo-nitrobenzene, 3-nitrotoluene, 3-ethylnitrobenzene, 3-methoxy-nitrobenzene, 3-ethoxy-nitrobenzene, 3-chloro-nitrobenzene, or 3-bromo-nitrobenzene are used in place of nitrobenzene in the above example, there is obtained the corresponding 2- and 3-alkyl, halo or alkoxy biphenyls.

When 4-fluoroaniline and 2-methyl-nitrobenzene are used in the above example in place of 4-fluoro-2-methoxyaniline and nitrobenzene there is obtained 4′-fluoro-3-methyl-4-nitrobiphenyl and 4′-fluoro-4-methyl-3-nitrobiphenyl.

EXAMPLE 3

4-(Pentafluorophenyl)-aniline

A mixture of 5 g. of 2′,3′,4′,5′,6′4-nitrobiphenyl in 250 ml. of ethanol is reduced by hydrogen at atmospheric pressure and at room temperature using 5 percent palladium-on-charcoal (0.5 g.) catalyst. After the required uptake of hydrogen, the mixture is filtered and the catalyst washed with fresh ethanol. The ethanol solution is then concentrated in vacuo, and the residue recrystallized from aqueous ethanol to yield 4-(pentafluorophenyl)aniline.

When 2′-fluoro-4-nitrobiphenyl is used in place of 2′,3′,4′,5′,6′-pentafluoro-4-nitrobiphenyl in the above examples, there is obtained 4-(2′-fluorophenyl)-aniline.

When 2′-fluoro-3-nitrobiphenyl is used in place of 2′-fluoro-4-nitrobiphenyl according to the above procedure, there is obtained 3′-(2′-fluorophenyl)-aniline.

Similarly, when 4′-fluoro-2-methyl-3-nitrobiphenyl obtained from Example 2 is used in place of 2′,3′,4′,5′,6′-pentafluoro-4-nitrobiphenyl in the above example, there is obtained 2-methyl-3-(4′-fluorophenyl)-aniline.

When the 2- and 3-alkyl, halo or alkoxy biphenyls obtained from Example 2 are used in place of 4′-fluoro-2-methoxy-4-nitrobiphenyl in the above example, there are obtained the corresponding 2- or 3-alkyl, halo or alkoxy aniline compounds.

EXAMPLE 4

3-(3′-Chloro-4′-fluorophenyl)-anisole and 4-(3′-chloro-4′-fluorophenyl)-anisole

A mixture of 8.0 g. of 3-chloro-4-fluoroaniline, 200 ml. of anisole, and 9.0 grams of iso-amylnitrite, is warmed on a steam bath until a vigorous reaction with evolution of gas sets in. This evolution is allowed to proceed without heating until it

has subsided, and the mixture is then heated until it has subsided, and the mixture is then heated on the steam bath for an additional 3 hours. The excess anisole is removed in vacuo, and the residue is chromatographed on a silica gel column using petroleum-benzene as eluent to yield 3-(3'-chloro-4'-fluorophenyl)-anisole and 4-(3'-chloro-4-fluorophenyl)-anisole.

When 2-chloro-4-fluoroaniline, 2,4-difluoroaniline and 3-fluoroaniline are used in place of 3-chloro-4-fluoroaniline in the above example, there are obtained the corresponding 3(and 4)-(2'-chloro-4'-fluorophenyl)-anisole, 3(and 4)-(2',4'-difluorophenyl)-anisole and 3(and 4)-(3'-fluorophenyl)-anisole.

When 2-methylanisole, 2-ethylanisole, 2-benzylanisole, 3-methylanisole, 3-ethylanisole, 3-benzylanisole, 2-chloroanisole, 2-bromoanisole, 3-chloroanisole or 3-bromoanisole is used in place of anisole in the above example, there is obtained the corresponding 2- or 3- alkyl, benzyl or halo substituted biphenyl compound.

EXAMPLE 5

4'-(3'-Chloro-4'-fluorophenyl)-phenol

To a solution of 2.1 g. of 4-(3'-chloro-4'-fluorophenyl)-anisole in 50 ml. of boiling acetic acid is added 5 ml. of hydriodic acid and the boiling continued for 3 hours. Water is added and the reaction mixture cooled and the 4-(3'-chloro-4'-fluorophenyl)-phenol crystallizes. Further purification is then achieved by recrystallization of the solid from aqueous ethanol to yield 4-(3'-chloro-4'-fluorophenyl)-phenol.

When 4-(2'-chloro-4'-fluorophenyl)-anisole, 3-(2',4'-difluorophenyl)-anisole and 4-(3'-fluorophenyl)-anisole obtained from Example 4 are used in place of 4-(3'-chloro-4'-fluorophenyl)-anisole in the above example, there are obtained the corresponding 4-(2'-chloro-4'-fluorophenyl)-phenol, 3-(2',4'-difluorophenyl)-phenol and 4-(3'-fluorophenyl)-phenol.

When the 2- or 3-alkyl, benzyl or halo substituted biphenyl compounds obtained from Example 4 above are used in place of 4-(3'-chloro-4'-fluorophenyl)-anisole in the above example, there is obtained the corresponding 4-(substituted phenyl)-2- or 3-alkyl, benzyl or halo phenol compound.

EXAMPLE 6

4-(4'-Fluorophenyl)-phenol

A solution of 32.66 g. of 4-(4'-fluorophenyl)-aniline in 120 ml. of glacial acetic acid is cooled to 10°–12° C. To this solution is added slowly a solution of 12.25 grams of sodium nitrite in 120 ml. of water with stirring and continued cooling. Five minutes after this addition, the suspension of the diazonium acetate is added slowly to a boiling solution of 100 ml. of concentrated sulfuric acid and 200 ml. of water. After the final addition of the diazonium salt, the suspension is boiled for an additional 5 minutes and then allowed to cool to room temperature. The reaction mixture is then filtered and the cake dried in vacuo to yield 4-(4'-fluorophenyl)-phenol, (m.p. 152°–161° C., 24.07 g.).

When 4-(2'-fluorophenyl)-aniline, 3'-(pentafluorophenyl)-aniline, and 3-(4'-fluoro-3'-methoxyphenyl)-aniline, obtained from Example 3 are used in place of 4-(4'-fluoro-2'-methoxyphenyl)-aniline in the above example, there are obtained the corresponding 4-(2'-fluorophenyl)-phenol, 3-(pentfluorophenyl)-phenol, and 3-(4'-fluoro-3'-methoxyphenyl)-phenol.

When the alkyl, halo or alkoxy aniline compounds obtained from Example 3 are used in place of 4-(4'-fluorophenyl)-aniline in the above example, there is obtained the corresponding 2- or 3-alkyl, halo or alkoxy phenol compound.

Similarly, when 2-methyl-4-(4'-fluorophenyl)-aniline obtained from Example 3 is used in place of -(4'-fluorophenyl)-aniline in the above example, there is obtained 2-methyl-4-(4'-fluorophenyl)-phenol.

EXAMPLE 7

2-Hydroxy-5-(4'-fluorophenyl)-benzoic acid

A mixture of 10 g. of 4-(4'-fluorophenyl)-phenol and 27.2 g. of potassium carbonate is exposed to carbon dioxide at 1,300 p.s.i. and 175° C. The dark mass obtained from this carbonation is dissolved in 300 ml. of water and 200 ml. of methylene chloride and the two layers separated. The water layer is extracted with 100 ml. of methylene chloride and then acidified with 2.5 normal hydrochloric acid. This mixture is filtered and the cake dried in vacuo to yield 5.32 g. of the crude product. The crude product is recrystallized from benzene-methanol to yield 2.7 grams of material (m.p. 200°–204° C.). An additional crystallization of this semi-pure material from benzene-methanol yields analytically pure 2-hydroxy-5-(4'-fluorophenyl)-benzoic acid (m.p. 199°–203° C.).

When 4-(3'-chloro-4'-fluorophenyl)-phenol, 4-(2'-chloro-4'-fluorophenyl)-phenol, 4-(2',4'-difluorophenyl)-phenol and 4-(3'5 and 4'-(2'-fluorophenyl)-phenol and 4-(pentafluorophenyl)-phenol obtained from Example 6 are used in place of 4(4'-fluorophenyl)-phenol in the above example, there are obtained the corresponding 2-hydroxy-5-(3'-chloro-4'-fluorophenyl)-benzoic acid, 2-hydroxy-5-(2'-chloro-4'-fluorophenyl)-benzoic acid, 2-hydroxy-5-(2',4'-difluorophenyl)-benzoic acid (m.p. 210°–211° C.), 2-hydroxy-5-(3'-fluorophenyl)-benzoic acid (m.p. 196°–197° C.), 2-hydroxy-5-(2'-fluorophenyl)-benzoic acid (m.p. 201°–203° C.) and 2-hydroxy-5-(pentafluorophenyl)-benzoic acid (m.p. 241°–243° C.).

When the 3(or 4)-(substituted-phenyl) 2- or 3-alkyl, benzyl or halo phenol compounds of Example 5 or the 2- or 3-alkyl, halo or alkoxy phenol compounds of Example 6 are used in place of 4-(4'-fluoro-2'-methoxy-phenyl)-phenol in the above, there are obtained 2-hydroxy-3-methyl-4(and 5)-(4'-fluoro-2'-methoxyphenyl)-benzoic acid, 2-hydroxy-3-ethyl-4(and 5)-(4'-fluoro-2'methoxyphenyl)-benzoic acid, 2-hydroxy-3-methoxy-4(and 5)-(4'-fluoro-2'-methoxyphenyl)-benzoic acid, 2-hydroxy-3-3-ethoxy-4(and 5)-(4'-fluoro-2'-methoxyphenyl)-benzoic acid, 2-hydroxy-3-chloro-4(and 5)-(4'-fluoro-2'-methoxyphenyl)-benzoic acid, 2-hydroxy-3-bromo-4(and 5)-(4'-fluoro-2'-methoxyphenyl)-benzoic acid, 2-hydroxy-4-methyl-5-(4'-fluoro-2'-methoxyphenyl)-benzoic acid, 2-hydroxy-4-ethyl-5-(4'-fluoro-2'-methoxyphenyl)-benzoic acid, 2-hydroxy-4-methoxy-5-(4'-fluoro-2'-methoxyphenyl)-benzoic acid, 2-hydroxy-4-ethoxy-5-(4'-fluoro- 2'-methoxyphenyl)-benzoic acid, 2-hydroxy-4-chloro-5-(4'-fluoro-2'-methoxyphenyl)-benzoic acid, 2-hydroxy-4- bromo-5-(4'-fluoro-2'-methoxyphenyl)-benzoic acid, 2-hydroxy-3-methyl-4(and 5)-(3'-chloro-4'-fluorophenyl)-benzoic acid, 2-hydroxy-3-ethyl-4(and 5)-(3'-chloro-4'-fluorophenyl)-benzoic acid, 2-hydroxy-3-benzyl-4(and 5)-(3'-chloro-4'-fluorophenyl)-benzoic acid, 2-hydroxy-3-chloro-4(and 5)-(3'-chloro-4'-fluorophenyl)-benzoic acid, 2-hydroxy-3-bromo-4 (and 5)-(3'-chloro-4'-fluorophenyl)-benzoic acid, 2-hydroxy-3-chloro-4(and 5)-(3'-chloro-4'-fluorophenyl)-benzoic acid, 2-hydroxy-3-bromo-4(and 5)-(3'-chloro-4'-fluoro-phenyl-benzoic acid, 2-hydroxy-4-methyl-5-(2'-chloro-4'-fluorophenyl)-benzoic acid, 2-hydroxy-4-ethyl-5-(2'-chloro-4'-fluorophenyl)-benzoic acid, 2-hydroxy-4-benzyl-5-(2'-chloro-4'-fluorophenyl)-benzoic acid, 2-hydroxy-4-chloro-5-(2'-chloro-4'-fluorophenyl)-benzoic acid, and 2-hydroxy-4-bromo-5-(2'-chloro4'-fluorophenyl)-benzoic acid, respectively.

Similarly, when 2-methyl-4-(4'-fluorophenyl)-phenol obtained from Example 6 is used in place of 4-(4'-fluorophenyl)-phenol in the above example, there is obtained 2-hydroxy-5-(4'-fluorophenyl)-3-methyl-benzoic acid.

EXAMPLE 8

2-Acetoxy-5-(4'-fluorophenyl)-benzoic acid

A solution of 3.0 g. of 2-hydroxy-5-(4'-fluorophenyl)-benzoic acid in 12 ml. of pyridine and 8 ml. of acetic anhydride is heated on a steam bath for 20 minutes. The mixture is then poured onto ice and the product extracted with methylene chloride. The methylene chloride solution is dried and then evaporated. The residue is recrystallized from benzene to yield 2-acetoxy-5-(4'-fluorophenyl)-benzoic acid (m.p. 134°–137° C.).

When the 2-hydroxy-benzoic acid compounds obtained from Example 7 are used in place of 2-hydroxy-5-(4'-fluorophenyl)-benzoic acid in the above example, there are obtained the corresponding 2-acetoxy-benzoic acid compounds.

Similarly, when propionic acid anhydride is used in place of acetic anhydride, the corresponding 2-propionoxy compound is obtained.

EXAMPLE 9

2-Acetoxy-5-(p-fluorophenyl)-benzoyl chloride

A mixture of 4.3 g. of 2-acetoxy-5-(p-fluorophenyl)-benzoic acid and 40 ml. of thionyl chloride is refluxed for 30 minutes on the steam bath. The reaction mixture is concentrated in vacuo, 50 ml. benzene added and this solution reconcentrated in vacuo. The resulting oil is dried under vacuum to give 4.4 gm. of 2-acetoxy-5-(p-fluorophenyl-benzoyl chloride.

When the 2-acetoxy-4(or 5)-(phenyl)-benzoic acids of Example 8 are used in the above procedure the corresponding benzoyl chloride is obtained.

EXAMPLE 10

4-Acetoxy-3-diazomethylcarbonyl-4'-fluorobiphenyl

A solution of 4.4 g. of 2-acetoxy-5-(p-fluorophenyl)-benzoyl chloride in 40 ml. of dry ether is added slowly to the diazomethane prepared from 7.0 g. of N-nitrosomethylurea and contained in 350 ml. ether. The reaction mixture gradually becomes cloudy and is allowed to stir overnight at room temperature. The mixture is then concentrated to half volume, cooled and the precipitate collected to give 2.4 g. of 4-acetoxy-3-diazomethylcarbonyl-4'-fluorobiphenyl in two crops.

When any of the benzoyl chlorides of Example 9 are utilized in the above procedure the corresponding diazoketone is obtained.

EXAMPLE 11

5-(p-Fluorophenyl)-2-hydroxyphenylacetic acid

A solution of 2.4 g. of 4-acetoxy-3-diazomethylcarbonyl-4'-fluorobiphenyl in 25 ml. of warm dioxane is added slowly to a mixture of 100 ml. water, 0.8 g. of silver oxide, 1.6. g. potassium carbonate and 0.8 g. of sodium thiosulfate which has been heated to 65°–70°. The mixture is kept at 65°–70° for 30 minutes after the addition is complete and then refluxed for 1–2 minutes. The reaction mixture is filtered while hot, cooled and acidified with concentrated nitric acid. The precipitate is filtered and air dried to give 829 mg. of crude product. Recrystallization from toluene gives 0.54 g. of pure 5-(p-fluorophenyl)-2-hydroxyphenyl acetic acid.

When any of the diazoketones produced by the procedure of example 10 are utilized by the above procedure, there is obtained the corresponding 4(or 5)-phenyl-2-hydroxyphenyl acetic acid.

EXAMPLE 12

Sodium-2-hydroxy-5-(4'-fluorophenyl)-phenylacetate

A mixture of 0.1 mole of 2-hydroxy-5-(4'-fluorophenyl)-phenylacetic acid and 0.1 mole of sodium hydroxide in 100 ml. of water is stirred at room temperature for one-half hour. The reaction mixture is then concentrated in vacuo to yield sodium-2-hydroxy-5-(4'-fluorophenyl)-phenylacetate.

When the phenylacetic acid compounds obtained from Example 11 are used in place of the 2-hydroxy-5-(4'-fluorophenyl)-phenylacetic acid in the above example, there are obtained the corresponding sodium salts.

Similarly, when choline, glucosamine, S-methyl-methionine, potassium hydroxide, ammonium hydroxide, barium hydroxide, calcium hydroxide, piperazine, chloroquine, hydroxychloroquine, dimethylaminoethanol, and magnesium hydroxide, are used in place of sodium hydroxide in the above example, there are obtained the corresponding choline, glucoasmine, S-methyl-methionine, potassium, ammonium, barium, calcium, piperazine, chloroquine, hydroxychloroquine, dimethylaminoethanol and magnesium salts, respectively.

EXAMPLE 13

A. Methyl-2-hydroxy-5-(4'-fluorophenyl)-phenylacetate

A solution of 0.01 mole of 2-hydroxy-5-(4'-fluorophenyl)-phenylacetic acid in 20 ml. of methanol and 2 ml. of concentrated sulfuric acid is heated at reflux for 5 hours. The mixture is then cooled and partitioned between (75:150 ml.) water and ethyl acetate and the organic layer washed with dilute sodium bicarbonate solution. The organic layer is then dried over magnesium sulfate and concentrated in vacuo to yield methyl-2-hydroxy-5-(4'-fluorophenyl)-phenylacetate.

When the phenylacetic acid compounds obtained from Example 11 are used in place of 2-hydroxy-5-(4'-fluorophenyl)-phenylacetic acid in the above example, there are obtained the corresponding methyl esters.

Similarly, when ethanol and n-butanol are used in place of methanol in the above example, there are obtained the corresponding ethyl and n-butyl esters.

B. Phenyl 2-hydroxy-5-(4'-fluorophenyl)-phenylacetate

A mixture of 0.01 mole of 2-hydroxy-5-(4'-fluorophenyl)-phenylacetic acid, 2.8 g. of phenol and 1.7 g. of phosphorus oxychloride is heated at 114° C. until no more hydrogen chloride is evolved. The reaction mixture is cooled to room temperature and filtered. The resulting solid material is digested in dilute sodium carbonate solution, filtered, washed with water, dried and recrystallized from isopropyl alcohol to yield phenyl 2-hydroxy-5-(4'-fluorophenyl)-phenylacetate.

Following the above procedure but using an equivalent amount of 2-acetoxy-5-(4'-fluorophenyl)-phenylacetic acid in place of 2-hydroxy-5(4'-fluorophenyl)-phenylacetic acid, there is obtained phenyl 2-acetoxy-5-(4'-fluorophenyl)-phenylacetate.

C. β-Diethylaminoethyl 2-hydroxy-5-(4'-fluorophenyl)-phenylacetate hydrochloride

A mixture of (0.0175 mole) of 2-hydroxy-5-(4'-fluorophenyl)-phenylacetic acid, 2.4 g. of potassium carbonate in 50 ml. of isopropanol is refluxed for one-half hour 3.0 g. (0.0175 m.) of β-diethylaminoethylchloride. HCl is added and the mixture refluxed with stirring for 15 hours. The reaction mixture is then distributed between water and ethyl ether. The ether layer is then washed with water, dried and evaporated to a small volume. Dry hydrogen chloride gas is then passed into the ether solution and the resulting precipitate is filtered and recrystallized from acetone/ethyl ether to yield β-diethylaminoethyl 2-hydroxy-5-(4'-fluorophenyl)-phenylacetate hydrochloride.

EXAMPLE 14

N,N-Dimethyl-2-hydroxy-5-(4'-fluorophenyl)-phenylacetamide

A mixture of 0.01 mole of methyl-2-hydroxy-5-(4'-fluorophenyl)-phenylacetate and 20 ml. of dimethylamine is reacted in a bomb at 100° C. for 4 hours. After cooling, the bomb is opened and the excess dimethylamine removed. The residue is then recrystallized from benzene to yield N,N-dimethyl-2-hydroxy-5-(4'-fluorophenyl)-phenylacetamide.

When the phenylacetic acid methyl esters obtained from Example 13 are used in place of methyl-2-hydroxy-5-(4'-fluorophenyl)-benzoate in the above example, there are obtained the corresponding N,N-dimethyl-benzamide compounds.

EXAMPLE 15

Anhydride of 2-acetoxy-4-(4'-fluorophenyl)-phenylacetic acid

A solution of 0.01 mole of 2-acetoxy-4-(4'-fluorophenyl)-phenylacetic acid and 0.01 mole of thionyl chloride in 30 ml. of dry benzene is warmed until the formation of the substituted benzoyl chloride is complete. The resulting solution is concentrated to one-half volume in vacuo and is added to a solution of 0.01 mole of 2-acetoxy-4-(4'-fluorophenyl)-phenylacetic acid and 0.01 mole of pyridine in 30 ml. of benzene. The mixture is stirred at room temperature overnight, filtered, and the filtrate washed with cold dilute sodium bicarbonate solution. After drying and removal of benzene, the product is recrystallized from benzene-hexane.

Alternatively, the anhydride may be formed by reacting for 5 hours at room temperature 0.02 mole of 2-acetoxy-4-(4'-fluorophenyl)-phenylacetic acid and 0.01 mole of dicyclohexylcarbodiimide in 20 parts of tetrahydrofuran, followed by filtration and concentration of the filtrate to yield the anhydride.

When a solution of 2-acetoxy phenylacetic acid in pyridine is used in place of the 2-acetoxy-4-(4'-fluorophenyl)-phenylacetic acid pyridine solution in the above example, there is obtained the mixture anhydride of 2-acetoxy-4-(4'-fluorophenyl)-phenylacetic acid and 2-acetoxy phenylacetic acid.

EXAMPLE 16

A dry filled capsule is prepared from the following components:

2-acetoxy- 5-(4'-fluorophenyl)phenylacetic acid	300 mg.
corn starch	150 mg.
Cab-o-sil	5 mg.
Sterotix	15 mg.

A dry filled capsule can be prepared by using the following compounds as active ingredients instead of 2-acetoxy-5-(4'-fluorophenyl)-phenylacetic acid:

2-hydroxy-4(or 5)-(4'-fluorophenyl)-phenylacetic acid;
2-acetoxy-4(or 5)-(2',4'-difluorophenyl)-phenylacetic acid;
2-hydroxy-3-methyl-4(or 5)-(4'-fluorophenyl)-phenylacetic acid;
phenyl 4(or 5)-(4'-fluorophenyl)-2-hydroxy phenylacetate;
2-hydroxy-4(or 5)-(3'-fluorophenyl)-phenylacetic acid;
or any other preferred compounds as shown in the specification.

If capsules of lower potency are to be made, the capsule size could be reduced or the quantity of corn starch could be increased.

EXAMPLE 17

Compressed tablets are prepared with the following components:

2-acetoxy- 5-(4'-fluorophenyl)-phenylacetic acid	300 mg.
cornstarch	30 mg.
polyvinylpyrrolidone	10 mg.
magnesium stearate	3 mg.

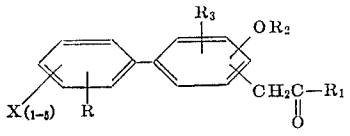
Tablets as above can be prepared by using the following compounds as active ingredients instead of 2-acetoxy-5-(4'-fluorophenyl)-phenylacetic acid:

2-hydroxy-4(or 5)-(4'-fluorophenyl)-phenylacetic acid;
2-acetoxy-4(or 5)-(2',4'-difluorophenyl)-phenylacetic acid;
2-hydroxy-3-methyl-4(or 5)-(4'-fluorophenyl)-phenylacetic acid;
phenyl 4(or 5)-(4'-fluorophenyl)-2-hydroxy phenylacetate;
-hydroxy
2-hydroxy-4(or 5)-(3'-fluorophenyl)-phenylacetic acid; or any other especially preferred compound as shown in the specification.

Tablets of other potentials would be made by altering the tablet size as necessary.

We claim:

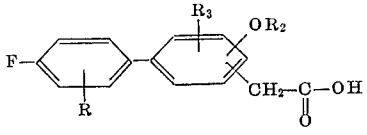
1. A compound of the formula:



or a pharmaceutically non-toxic acid addition salt thereof, wherein

X is chloro or fluoro;
R is hydrogen, loweralkyl or lower alkoxy;
R_1 is hydroxy or lower alkoxy;
R_2 is hydrogen or lower alkanoyl;
R_3 is loweralkyl or hydrogen.

2. A compound of the formula:



or a pharmaceutically non-toxic acid addition salt thereof, wherein:

R is methyl or methoxy;
R_2 is hydrogen or acetyl;
R_3 is hydrogen or methyl.

3. 2-Hydroxy-5-(4'-fluorophenyl)-phenylacetic acid.
4. 2-Hydroxy-4-(4'-fluorophenyl)-phenylacetic acid.

* * * * *