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PATENT SPECIFICATION

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Inventors: WILLIAM VANCE RUYLE, LEWIS HASTINGS SARETT and
ALEXANDER MATZUK

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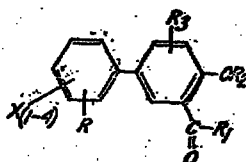
COMPLETE SPECIFICATION

Halo-Substituted 5-Phenylbenzoic Acids and their Derivatives

We, MERCK & Co. INC., a corporation duly organised and existing under the laws of the State of New Jersey, United States of America, of Rahway, New Jersey, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement: —

This invention is concerned with new biphenyl compounds, processes for producing them and pharmaceutical compositions containing them.

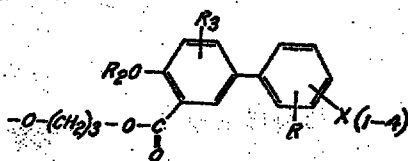
The compounds of the present invention have the following general formula:



where X is halogen (i.e. chloro, bromo, fluoro or iodo), X being on one or more of the phenyl carbon atoms; R is hydrogen, halogen (e.g. chloro, bromo or fluoro), C₁₋₆ alkyl (such as methyl, ethyl, butyl or pentyl) or C₁₋₆ alkoxy (such as methoxy, ethoxy or butoxy); R₁ is hydroxy, amino, C₁₋₆ alkoxy (such as methoxy, ethoxy, butoxy or pentoxy), C₁₋₆ alkylamino (e.g. methylamino, propylamino or pentylamino), di(C₁₋₆ alkyl)amino (e.g. dimethylamino, dibutylamino or propylpentylamino), di(C₁₋₆ alkyl)amino-(C₁₋₆ alkyl)amino, di(C₁₋₆ alkyl)-amino(C₁₋₆ alkoxy), C₁₋₆ hydroxyalkoxy (e.g. 3-hydroxypropoxy, 2-hydroxypropoxy or 4-hydroxybutoxy), C₁₋₆ polyhydroxyalkoxy (e.g. 2,3-dihydroxypropoxy or 2,3,4,5,6-pentahydroxyhexyloxy), (C₁₋₆ alkoxy)-(C₁₋₆ alkoxy) (e.g. ethoxyethoxy), phenyl-(C₁₋₆ alkoxy) (e.g. benzyloxy or phenethoxy), phenoxy, substituted phenoxy [e.g. where the substituent is C₁₋₆ alkoxy, di(C₁₋₆ alkyl)amino, C₁₋₆ alkanoylamino, benzyloxy - 2 - carboxy - 4 - (4' - fluorophenyl), carboxy or (C₁₋₆ alkoxy)carbonyl], (C₁₋₆ alkanoylamino)-(C₁₋₆ alkoxy), hydrazino, hydroxylamino, N-morpholino, N-(4-C₁₋₆ alkyl-piperidino)-N-[4-(C₁₋₆ hydroxyalkyl)-piperidino], (C₁₋₆ hydroxyalkyl)amino, a radical derived from a naturally occurring amino acid, such as glycine, phenylalanine, proline, methionine or taurine, and attached at the N atom, or a radical of formula:

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in which R, R₂, R₃ and X are such that the compound is symmetrical; R₂ is hydrogen, C₁₋₆ alkyl (such as methyl, ethyl, butyl or pentyl), C₁₋₆ alkanoyl (such as acetyl, propionyl or butyryl) or C₂₋₆ alkenyl (such as allyl or butenyl); and R₃ is hydrogen, 3-(C₂₋₆ alkenyl), (3 or 4)-(C₁₋₆ alkyl), C₁₋₆ alkoxy, benzyl or halo.

The invention also provides the pharmaceutically acceptable non-toxic salts of the acid [such as the ammonium, alkali metal (e.g. Na and K), alkaline-earth metal (e.g. Ca and Ba), magnesium, amine, aluminium, iron, choline, glucosamine, S-methyl methionine, piperazine, di(C₁₋₆ alkyl)amino-(C₁₋₆ alkanol), chloroquine and hydroxychloroquine salts]; the anhydrides of the acids and the mixed anhydrides of the acids and 2-acetoxy-benzoic acid.

In one preferred group of compounds R is hydrogen, R₁ is hydroxy, R₂ is hydrogen or C₁₋₆ alkanoyl (especially acetyl) and R₃ is hydrogen or C₁₋₆ alkyl (especially methyl).

In particularly preferred compounds in this group, X is a chlorine or fluorine (especially fluorine) atom attached to the 4-position of the phenyl residue and R₃, when alkyl, is attached to the 3-position.

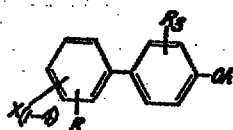
The invention is particularly described with reference to compounds having at least one fluorine atom attached to the phenyl residue, but it is not so limited since other compounds can be obtained by analogous procedures.

Representative compounds of this invention are as follows:

2-hydroxy-5-(4'-fluorophenyl)-benzoic acid
 2-hydroxy-5-(4'-fluorophenyl)-benzamide
 2-hydroxy-5-(4'-fluorophenyl)-3-methyl-benzoic acid
 2-hydroxy-5-(4'-fluorophenyl)-3-methyl-benzamide
 2-hydroxy-5-(4'-fluorophenyl)-benzmorpholide
 2-acetoxy-5-(4'-fluorophenyl)-3-methyl-benzoic acid
 2-acetoxy-5-(4'-fluorophenyl)-3-methyl-benzamide
 2-acetoxy-5-(4'-fluorophenyl)-benzoic acid
 2-acetoxy-5-(4'-fluorophenyl)-benzamide
 2-acetoxy-5-(4'-fluorophenyl)-benzmorpholide
 aluminium 2-acetoxy-5-(4'-fluorophenyl)-benzoate
 aluminium 2-hydroxy-5-(4'-fluorophenyl)-benzoate
 choline 2-acetoxy-5-(4'-fluorophenyl)-benzoate
 choline 2-hydroxy-5-(4'-fluorophenyl)-benzoate
 sodium 2-acetoxy-5-(4'-fluorophenyl)-benzoate
 sodium 2-hydroxy-5-(4'-fluorophenyl)-benzoate
 calcium 2-acetoxy-5-(4'-fluorophenyl)-benzoate
 2-hydroxy-5-(pentafluorophenyl)-benzoic acid
 2-acetoxy-5-(pentafluorophenyl)-benzoic acid
 β-diethylaminoethyl-2-hydroxy-5-(4'-fluorophenyl)-benzoate and
 β-diethylaminoethyl-2-acetoxy-5-(4'-fluorophenyl)-benzoate

It has been found that compounds described above have anti-inflammatory activity and are effective in the prevention and inhibition of edema and granuloma tissue formation. In addition, some of them have a useful degree of antipyretic and analgesic activity. The invention provides pharmaceutical compositions containing a compound in accordance with the invention together with an inert diluent, carrier or coating. Compounds of the present invention are normally administered orally in tablets or capsules, the optimum dosage depending on the particular compound being used and the type and severity of the condition being treated. Although the optimum quantities to be used will depend on the compound and the particular disease, oral dose levels of preferred compounds in the range of 50 mg. to 10 g. per day are useful in the control of said conditions, depending on the activity of the specific compound and the reaction sensitivity of the patient.

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



where A is an alkali metal ion and X, R₁ and R are as previously defined.

Some of these compounds are prepared from the individual phenyl portions of the above starting material by the well known Gomberg reaction. Others, where the biphenyl portion 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 or atom, followed by a Gomberg reaction with nitrobenzene or anisole or an R₁ substituted nitrobenzene or anisole, and 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; this in turn may be alkylated to form the corresponding 3-alkoxy-4-fluoronitrobenzene, and finally the nitro group may be reduced 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, 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 R₁ is methyl, it is preferred to carry out the following reaction sequence when R₁ is C₁₋₆ alkyl, for example, methyl. In this case the methyl 2-hydroxy-5-(4'-fluorophenyl)-benzoate compound of this invention is reduced to the corresponding alcohol. This alcohol compound is then acylated, and subsequently hydrogenated to the corresponding 4-(4'-fluorophenyl)-2-methylphenyl acetate. This compound is then saponified or hydrolysed to the corresponding phenol compound, which in turn is carbonated to form the 5-(4'-fluorophenyl)-2-hydroxy-3-methyl-benzoic acid. Further, when R₁ is to be an allyl group the following procedure is preferred: an ester of 5-(substituted phenyl)-2-hydroxy benzoic acid, e.g. methyl 5-(4'-fluorophenyl)-2-hydroxybenzoate, 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. By choosing a different carbonyl compound from acetone, other 3-(C₂₋₆ alkenyl) compounds can be prepared. Further, an additional method for preparing a compound in which R₁ is alkyl is by reduction of the above-noted 3-alkenyl 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.

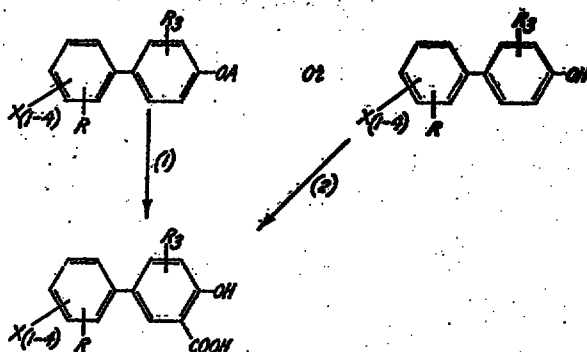
Another preferred process in accordance with the present invention comprises reacting 2-methyl-4-(4'-fluorophenyl)-phenol with carbon dioxide in the presence of an alkali metal carbonate under pressure at elevated temperatures and subsequent acidification to form 2-hydroxy-5-(4'-fluorophenyl)-2-methyl benzoic acid, followed optionally by reacting the 2-hydroxy-5-(4'-fluorophenyl)-2-methyl benzoic acid produced with acetic anhydride in the presence of a catalyst to form 2-acetoxy-5-(4'-fluorophenyl)-2-methyl benzoic acid.

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

The 4-(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 acid compounds of this invention may be prepared from the previously prepared alkali phenolate or phenol compound. The preparation of these acid com-

pounds is carried out by 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. The process may be shown as follows:



Definitions: As previously indicated.

Reactions and Conditions

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

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

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 esters of this invention (i.e. the compounds where R_1 is hydrocarboxy or substituted hydrocarboxy) are prepared by any esterification procedure, using an esterifying agent containing the appropriate R_1 group. For example, the benzoic acid compound of this invention may be reacted with the appropriate C_{1-6} alkanol (preferably methanol) at elevated temperatures in the presence of a strong acid, such as hydrochloric acid, sulfuric acid or *p*-toluenesulfonic acid, to form the desired ester.

The amides of this invention (i.e. the compounds where R_1 is amino or substituted amino), may be prepared by any suitable amidation reaction. For example, the benzoic acid compound (preferably the methyl or ethyl ester) may be reacted with ammonia, ammonium hydroxide, or an amino compound, at any suitable temperature (room temperature to reflux). When the $-NH_2$ 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 compound. When an amide derived from an amino acid is desired, it is preferred to react the benzoic acid final compound with isobutyl chloro-carbonate to form the mixed anhydride, react this compound with the desired amino acid ester and hydrolyse the product to form the desired amide.

The final compound in which R_2 is C_{1-6} alkanoyl (preferably acetyl), may be prepared by any suitable alkanoylation reaction. For example, the corresponding hydroxy benzoic acid, ester, or amide (preferably the ester), may be reacted with an anhydride of a C_{2-6} alkanoyl acid (preferably acetic anhydride) in the presence of a catalyst, such as sulfuric acid, pyridine or *p*-toluenesulfonic acid (preferably pyridine), at any suitable temperature, preferably an elevated temperature.

The final compound in which R_2 is C_{1-6} alkyl (preferably methyl), may be prepared by any appropriate alkylation reaction. For example the corresponding hydroxy

benzoic acid, ester, or amide (preferably the ester) may be reacted with a di(C₁₋₆ alkyl) sulfate (preferably dimethyl sulfate) or a C₁₋₆ alkyl *p*-toluenesulfonate in the presence of a base, such as an alkali metal carbonate, at any suitable temperature, preferably at or near reflux, with subsequent acidification of the reaction mixture, e.g. with hydrochloric acid or sulfuric acid.

The final compound in which R₂ is C₂₋₆ alkenyl (preferably allyl) may also be prepared by any appropriate alkenylation reaction. For example, the hydroxy benzoic 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 or sodium carbonate, in an inert solvent that affords at least some solubilization [such as dioxane, tetrahydrofuran, a C₁₋₆ alkanol, dimethoxy ethane or acetone (preferably a C₁₋₆ alkanol, such as methanol)] at any suitable temperature, preferably at an elevated temperature.

The salts of the final acid compounds of this invention may be prepared by any of the well known metathesis procedures. For example, the benzoic acid compound may be neutralized, e.g. with an inorganic base, such as sodium hydroxide, potassium hydroxide, ammonium hydroxide or barium hydroxide. The anhydrides of this invention may be prepared by any of the well known procedures, e.g. by converting the acid to its halide and reacting the halide with an acid having the above formula or with 2-acetoxy benzoic acid.

The introduction of R₁ and R₂ groups other than hydrogen may be carried out in any order.

The following examples are used by way of illustration. Examples 1—6 are concerned with the preparation of starting materials. Examples 7—19 (including 9A, 9B and 10A) are concerned with the preparation of compounds in accordance with the present invention.

EXAMPLE 1

4-Fluoro-3-methoxyaniline

A. 2-Fluoro-5-nitrophenol

A solution of 3.2 grams of 2-fluoro-5-nitroaniline, 3 ml of sulfuric acid (*d* 1.84) and 8 ml. of water is stirred into a solution of 1.5 grams of sodium nitrite in water, maintained below 5°C. After ten minutes, the excess of nitrous acid is destroyed by urea, the reaction mixture is filtered, and the filtrate is added to 40 ml. of boiling 50% sulfuric acid. After complete addition, the mixture is boiled for an additional 15 minutes and cooled, and the separated phenol is filtered and washed with water. It is then purified by recrystallization from hexane.

B. 2-Fluoro-5-nitroanisole

An intimate mixture of 2.0 grams of 2-fluoro-5-nitrophenol, 2.0 grams of potassium carbonate and 1.0 ml. of methyl sulphate is heated on the steam bath for 5 minutes and then steam-distilled, the volume of liquid in the flask being kept as small as possible. The 2-fluoro-5-nitroanisole passes over, and a further quantity is obtained by adding more potassium carbonate (1 gram) and methyl sulphate (0.5 ml.) to the residual liquor, which is then warmed and steam-distilled. The 2-fluoro-5-nitroanisole is then recrystallized from hexane.

C. 4-Fluoro-3-methoxyaniline

A suspension of 10 grams of 2-fluoro-5-nitroanisole and 100 ml. of dioxane is reduced catalytically under 40 p.s.i.a. of hydrogen and 1.0 gram of 5% Pd/C. After the uptake of hydrogen ceases, the catalyst is filtered, and the filtrate is concentrated *in vacuo* to yield 4-fluoro-3-methoxyaniline.

Alternatively, the compound may be prepared as follows:

A. 2-Fluoro-5-nitroanisole

To a stirred solution of 35 ml. of concentrated hydrochloric acid and 40 ml. of water is added 48 grams of 2-amino-5-nitroanisole. The mixture is warmed and then cooled to 0—5°C. To the stirred mixture is added dropwise 20 grams sodium nitrite in 120 ml. water, maintaining the temperature at 0—5°C. After addition is complete, the reaction mixture is filtered and cooled with stirring while 70 ml. fluoboric acid (48%) is added. The homogeneous solution is stirred in the cold for an additional hour, during which time a yellow precipitate forms. The precipitate is filtered, washed with cold water, ethanol and ether, and air-dried to yield 31.4 grams of the diazonium fluoborate.

A mixture of 21.4 grams diazonium fluoborate and 60 grams sand is stirred

while heating in an oil bath. When the evolution of gases commences the bath is lowered. After the reaction slows down, the bath is applied again. This procedure is repeated until evolution of gases has ceased. The reaction mixture is then heated at 200°C. for an additional half an hour. After cooling to room temperature the residue is extracted with chloroform. The extract is evaporated *in vacuo* and the residue subjected to a steam distillation. A white solid is formed in the distillate. The solid is extracted with ether, which is removed to yield 2.6 grams of the 2-fluoro-5-nitroanisole. A sample is recrystallized from ethanol to give a pure product with a melting point of 69—71°C.

Calculated for $C_7H_6FNO_2$:

Found: C, 49.13; H, 3.53; N, 8.19; F, 11.10.
C, 49.33; H, 3.60; N, 8.17; F, 10.96.

B. 4-Fluoro-3-methoxyaniline

A solution of 5.4 grams of 2-fluoro-5-nitroanisole in 125 ml of methanol is reduced by hydrogen at room temperature and 40 p.s.i. a pressure using 100 mg. of platinum oxide as catalyst. After the required uptake of hydrogen, the mixture is filtered, 50 ml. of 2.5 N hydrochloric acid is 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 of ether. The precipitate is filtered, washed with ether and dried *in vacuo* at room temperature. The 4-fluoro-3-methoxyaniline hydrochloride darkens at 250°C. and melts 260—265°C.

Calculated for $C_7H_8FNO \cdot HCl$:

Found: C, 47.33; H, 5.11; N, 7.89; F, 10.70; Cl, 19.96.
C, 47.35; H, 5.14; N, 7.66; F, 10.9; Cl, 20.05.

When 4'-fluoro-4-nitrobiphenyl is used in place of 2-fluoro-nitroanisole in part C of the above example, there is obtained 4-(4'-fluorophenyl)-aniline.

EXAMPLE 2

4'-Fluoro-2'-methoxy-4-nitrobiphenyl

A mixture of 7.7 grams of 4-fluoro-2-methoxyaniline, 200 ml. of nitrobenzene and 9.0 grams 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 petroleumbenzin to yield 4'-fluoro-2'-methoxy-4-nitrobiphenyl.

When pentafluoroaniline, 2-fluoroaniline or 4-fluoro-3-methoxyaniline (obtained from Example 1) is used in place of 4-fluoro-2-methoxyaniline in the above example, there is obtained 2', 3', 4', 5', 6'-pentafluoro-4-nitrobiphenyl, 2'-fluoro-4-nitrobiphenyl or 4'-fluoro-3'-methoxy-4-nitrobiphenyl respectively.

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

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.

EXAMPLE 3

4-(4'-Fluoro-2'-methoxyphenyl)-aniline

A mixture of 10 grams of 4'-fluoro-2'-methoxy-4-nitrobiphenyl in 250 ml. of ethanol is reduced by hydrogen at atmospheric pressure and at room temperature using 5% palladium-on-charcoal (0.5 gram) catalyst. After the required uptake of hydrogen, the mixture is filtered and the catalyst washed with fresh ethanol. The ethanolic solution is then concentrated *in vacuo*, and the residue recrystallized from ethanol to yield 4-(4'-fluoro-2'-methoxyphenyl)-aniline.

When 2', 3', 4', 5', 6'-pentafluoro-4-nitrobiphenyl, 2'-fluoro-4-nitrobiphenyl or 4'-fluoro-3'-methoxy-4-nitrobiphenyl obtained from Example 2 is used in place of 4'-fluoro-2'-methoxy-4-nitrobiphenyl in the above example, there is obtained 4-(pentafluorophenyl)-aniline, 4-(2'-fluorophenyl)aniline or 4-(4'-fluoro-3'-methoxyphenyl)-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.

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

EXAMPLE 4

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

A mixture of 8.0 grams of 3-chloro-4-fluoroaniline, 200 ml. of anisole and 9.0 grams of iso-amyl nitrite 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 on the steam bath for an additional 3 hours. The excess of anisole is removed *in vacuo*, and the residue is chromatographed on a silica gel column using petroleumbenzin as eluent to yield 4-(3'-chloro-4'-fluorophenyl)-anisole.

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

EXAMPLE 5

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

To a solution of 2.1 grams of 4-(3'-chloro-4'-fluorophenyl)anisole in 50 ml. of boiling acetic acid is added 5 ml. of hydriodic acid and the boiling is continued for 3 hours. Water is added, the reaction mixture is 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, 4-(4'-fluoro-3'-methylphenyl)-anisole, 4-(2',4'-difluorophenyl)-anisole, 4-(3'-fluorophenyl)anisole and 4-(4'-fluoro-2'-methylphenyl)-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, 4-(4'-fluoro-3'-methylphenyl)-phenol, 4-(2',4'-difluorophenyl)-phenol, 4-(3'-fluorophenyl)-phenol and 4-(4'-fluoro-2'-methylphenyl)-phenol.

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

EXAMPLE 6

4-(4'-Fluorophenyl)-phenol

A solution of 32.66 grams 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 grams).

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

When an alkyl, halo or alkoxy aniline compound obtained from Example 3 is 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-(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 grams of 4-(4'-fluorophenyl)-phenol and 27.2 grams of potassium carbonate is exposed to carbon dioxide at 1300 p.s.i. and 175°C. The dark mass obtained from this carbonation is then dissolved in 300 ml. of water and 200 ml. of methylene chloride, and the two layers are separated. The water layer is then extracted with 100 ml. of methylene chloride and then acidified with 2.5 normal hydrochloric acid. This mixture is then filtered and the cake dried *in vacuo* to yield 5.32 grams of the crude product. The crude product is then 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-(4'-fluoro-3'-methylphenyl)-phenol, 4-(2',4'-difluorophenyl)-phenol, 4-(3'-fluorophenyl)-phenol and 4-(4'-fluoro-2'-methylphenyl)-phenol, obtained from Example 5 and 4-(2'-fluorophenyl)-phenol, 4-(pentafluorophenyl)-phenol, 4-(4'-fluoro-2'-methoxyphenyl)-phenol, and 4-(4'-fluoro-3'-methoxyphenyl)-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-(4'-fluoro-3'-methylphenyl)-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-(4'-fluoro-2'-methylphenyl)-benzoic acid, 2-hydroxy-5-(2'-fluorophenyl)-benzoic acid, 5-(pentafluorophenyl)-benzoic acid (m.p. 201—203°C.), 2-hydroxy-5-(4'-fluoro-2'-methoxyphenyl)-benzoic acid, and 2-hydroxy-5-(4'-fluoro-3'-methoxyphenyl)-benzoic acid.

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

EXAMPLE 8

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

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

When the benzoic acid compounds obtained from Example 7 are used in place

of the 2-hydroxy-5-(4'-fluorophenyl)-benzoic acid in the above example, there are obtained the corresponding sodium salts.

Similarly, when choline, glucosamine, S-methylmethionine, 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, glucosamine, S-methyl-methionine, potassium, ammonium, barium, calcium, piperazine, chloroquine, hydroxychloroquine, dimethylaminoethanol and magnesium salts, respectively.

EXAMPLE 9

Methyl-2-hydroxy-5-(4'-fluorophenyl)-benzoate

A solution of 5.0 grams of 2-hydroxy-5-(4'-fluorophenyl)-benzoic 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 5.3 grams (as an oil) of methyl-2-hydroxy-5-(4'-fluorophenyl)-benzoate.

When the 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 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.

EXAMPLE 9A

1,3-bis-[5'-(4''-Fluorophenyl)-2'-acetoxy-benzoyloxy]-propane

A mixture of 0.1 mole of 2-acetoxy-5-(4'-fluorophenyl)-benzoic acid and 0.15 mole of thionyl chloride is heated at reflux until evolution of hydrogen chloride has practically ceased. Excess of thionyl chloride is removed *in vacuo*. To a solution of the resulting crude acid chloride in 100 ml. of pyridine is added 0.05 mole of propane-1,3-diol. After standing at 25°C. for 24 hours, the pyridine is removed *in vacuo* at a temperature lower than 40°C., and the residual product is taken up in benzene and washed with dilute hydrochloric acid and dilute sodium bicarbonate, and the washed product is chromatographed on a column of silica gel. Elution with benzene containing increasing proportions of acetone furnishes 1,3-bis-[5'-(4''-fluorophenyl)-2'-acetoxy-benzoyloxy]-propane.

Alternatively, the reaction may be carried out by reacting at room temperature for 5 hours a mixture of 0.1 mole of 2-acetoxy-5-(4'-fluorophenyl)-benzoic acid, 0.1 mole of dicyclohexylcarbodiimide and 0.1 mole of propane-1,3-diol in 20 parts of tetrahydrofuran. After the reaction, the mixture is filtered and the filtrate concentrated, dissolved in ether and washed with aqueous sodium bicarbonate. The ethereal solution is then dried over sodium sulfate and concentrated to yield the desired product.

When β -ethoxyethanol, benzyl alcohol, phenol, *p*-acetylaminophenol, 4-methoxyphenol, 4-dimethylaminophenol, methyl 2-hydroxybenzoate, benzyl-2-hydroxy-5-(4'-fluorophenyl)-benzoate β -dimethylaminoethanol, or β -diethylaminopropanol benzyl-2-hydroxybenzoate is used in place of 1,3-propanediol in the above example, there is obtained the corresponding 2-ethoxyethane, toluene, benzene, *p*-acetylaminobenzene, 4-methoxybenzene, 4-dimethylaminobenzene, 2-carbomethoxybenzene, 2-carbobenzyl-oxy-5-(4'-fluorophenyl)-benzene, β -dimethylaminoethyl-benzene, β -diethylamino-propyl-benzene, or 2-carbobenzoyloxy-benzene compound, respectively.

EXAMPLE 9B

Phenyl-2-acetoxy-5-(4'-fluorophenyl)-benzoate

A mixture of 2-acetoxy-5-(4'-fluorophenyl)-benzoic acid (0.1 mole), phosphorus oxychloride (0.1 mole) and phenol (0.12 mole) is heated at 75°C. until no more hydrogen chloride is evolved. The product, phenyl-2-acetoxy-5-(4'-fluorophenyl)-benzoate, is isolated by partitioning the reaction mixture between benzene and dilute sodium bicarbonate solution, and subjecting the benzene solution to chromatography on silica gel.

By substituting other phenolic compounds in the foregoing example, e.g. *p*-methoxyphenol, *p*-dimethylaminophenol, and *p*-acetaminophenol, the corresponding substituted phenyl esters, e.g. *p*-methoxyphenyl, *p*-dimethylaminophenyl and *p*-acetaminophenyl-2-acetoxy-5-(4'-fluorophenyl)-benzoic acid are obtained.

EXAMPLE 10

2-Hydroxy-5-(4'-fluorophenyl)-benzamide

A mixture of 5.3 grams of methyl-2-hydroxy-5-(4'-fluorophenyl)benzoate and 20 ml. of liquid ammonia is reacted in a bomb at 100°C. for 4 hours. After cooling, the bomb is opened and the ammonia allowed to evaporate. The residue is then recrystallized from benzene to yield 2-hydroxy-5-(4'-fluorophenyl)-benzamide (m.p. 206—207°C.).

When the benzoic acid methyl esters obtained from Example 9 are used in place of methyl-2-hydroxy-5-(4'-fluorophenyl)-benzoate in the above example, there are obtained the corresponding benzamide compounds.

Similarly, when methylamine, diethylamine, β -dimethylaminoethylamine, hydrazine, hydroxylamine, morpholine, N-ethylpiperidine, N-(β -hydroxyethyl)-piperidine, or β -hydroxyethylamine is used in place of ammonia in the above example, there is obtained the corresponding N-methylamine, N-diethylamide, N-(β -dimethylaminoethyl)-amide, hydrazide, N-hydroxyamide, morpholide, 4-ethylpiperidide, 4-(β -hydroxyethyl)-piperidide, or β -hydroxyethylamide, respectively.

EXAMPLE 10A

N-[2-Hydroxy-5-(4'-fluorophenyl)-benzoyl]-glycine

To a solution of 10 millimoles of 2-acetoxy-5-(4'-fluorophenyl)-benzoic acid and 10 millimoles of triethylamine in 25 ml. of dioxane and 5 ml. of acetone at 0—5°C. is added 10 millimoles of isobutylchlorocarbonate. After the mixture has been stirred at 0—5°C. for one hour, a solution of 10 millimoles of methyl glycinate in 6 ml. of water and 10 millimoles of triethylamine is added, and the stirring continued for another hour. After the addition of 75 ml. of water, the mixture is extracted with ether. The ethereal solution is washed successively with cold 1 N hydrochloric acid and cold saturated sodium bicarbonate solution, dried over sodium sulfate and evaporated. The residual material is saponified by treatment with 10 ml. of 2.5 N sodium hydroxide solution in 25 ml. of methanol for 0.5 hour. The methanol is removed by distillation *in vacuo* and the remaining aqueous solution is extracted with ether and then acidified with dilute hydrochloric acid. The product is filtered, washed, and dried. Recrystallization from benzene-hexane results in purification of the material.

By applying a similar process to the esters of other amino acids, suitably protected as needed, such as those of alanine, phenylalanine, tyrosine and taurine, the corresponding substituted amino acids are obtained.

EXAMPLE 11

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

A solution of 3.0 grams 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 12

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

To a solution of 0.1 mole of methyl-2-hydroxy-5-(4'-fluorophenyl)-benzoate in 400 ml. of methanol is added 0.1 mole of sodium methoxide, followed by addition of 0.1 mole of allyl chloride. This mixture is then heated at 100°C. for 4½ hours. The reaction mixture is then cooled, filtered, and concentrated *in vacuo* to an oil, filtered again, and distilled *in vacuo* to obtain methyl-2-allyloxy-5-(4'-fluorophenyl)-benzoate. This ester is then saponified by heating with ethanolic aqueous potassium hydroxide to obtain the corresponding potassium salt. This solution is then acidified with 2.5 N aqueous hydrochloric acid and the reaction mixture concentrated *in vacuo* to yield 2-allyloxy-5-(4'-fluorophenyl)-benzoic acid.

When the 2-hydroxy-benzoate compounds obtained from Example 9 are used in place of methyl-2-hydroxy-5-(4'-fluorophenyl)-benzoate in the above example, there are obtained the corresponding allyloxy-benzoic acid compounds.

Similarly, when 2-butenyl chloride is used in place of allyl chloride in the above example, there is obtained the corresponding 2-(2''-butenyloxy) compound.

EXAMPLE 13

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

A solution of 0.1 mole of methyl-2-hydroxy-5-(4'-fluorophenyl)-benzoate in 100 ml. of acetone is treated with 20 grams of potassium carbonate and 0.1 mole of dimethyl sulfate. The mixture is then heated at reflux for 3 hours. After cooling, the solvent is removed by distillation and the mixture is made barely acid with dilute aqueous hydrochloric acid. The reaction mixture is then extracted with methylene chloride and chromatographed on a silica gel column using a mixture of petroleum benzin and ether as eluent. The 2-methoxy-benzoate thus obtained is saponified by heating with dilute aqueous potassium hydroxide. The saponified reaction mixture is then made slightly acid with dilute aqueous hydrochloric acid and then concentrated *in vacuo* to yield 2-methoxy-5-(4'-fluorophenyl)-benzoic acid.

When the 2-hydroxy-benzoate compounds obtained from Example 9 are used in place of methyl-2-hydroxy-5-(4'-fluorophenyl)-benzoate in the above example, there are obtained the corresponding 2-methoxy-benzoate compounds.

Similarly, when diethyl sulfate or butyl tosylate is used in place of dimethyl sulfate in the above example, there is obtained the corresponding ethoxy or butoxy benzoic acid compound.

EXAMPLE 14

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

A solution of 0.01 mole of 2-acetoxy-4-(4'-fluorophenyl)-benzoic 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)-benzoic acid and 0.01 mole of pyridine in 30 ml. of benzene. The mixture is stirred at room temperature overnight and filtered, and the filtrate is washed with cold dilute sodium bicarbonate solution. After drying and removing 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)-benzoic 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 benzoic acid in pyridine is used in place of the 2-acetoxy-4-(4'-fluorophenyl)-benzoic acid pyridine solution in the above example, there is obtained the mixed anhydride of 2-acetoxy-4-(4'-fluorophenyl)-benzoic acid and 2-acetoxy benzoic acid.

EXAMPLE 15

{2''-Carboxy-4'''-(4'''-fluorophenyl)]-phenyl-2-acetoxy-5-(4'-fluorophenyl)-benzoate

0.01 mole of {2'' - carbobenzyloxy - 4'' - (4''' - fluorophenyl)] - phenyl - 2-acetoxy - 5 - (4' - fluorophenyl) - benzoate in 50 ml. of ethanol is hydrogenated in the presence of 10% palladium-on-charcoal until an equivalent amount of hydrogen is absorbed. The reaction mixture is then filtered and the filtrate concentrated *in vacuo*. The concentrate is then recrystallized from aqueous ethanol.

When the 2-carbobenzyloxy-benzene compound obtained from Example 9A is used in place of the benzoate in the above example, there is obtained the corresponding 2-carboxy compound.

EXAMPLE 16

5-(4'-Fluorophenyl)-2-hydroxy-3-methyl-benzoic acid

A. 4-(4'-Fluorophenyl)-2-hydroxymethyl-phenol

A solution of 5 g. of methyl-2-hydroxy-5-(4'-fluorophenyl)-benzoate in 25 ml. of ether is added to a stirred suspension of 1.28 g. of lithium aluminium hydride in 100 ml. of ether at a rate sufficient to maintain gentle reflux. Heating at reflux temperature is continued for 0.5 hour after the addition. The excess of hydride is decomposed with ethyl acetate, and sufficient dilute hydrochloric acid is added to make separation of the ethereal layer possible. The ethereal phase is washed with water, dried over magnesium sulfate, and concentrated to dryness. Trituration with hexane yields 3.93 g. of 4-(4'-fluorophenyl)-2-hydroxymethylphenol, m.p. 150—157°C. Recrystallization from aqueous ethanol furnishes pure material, m.p. 155—157°C.

B. 4-(4'-Fluorophenyl)-2-acetoxymethylphenyl acetate

A mixture of 3.0 g. of 4-(4'-fluorophenyl)-2-hydroxymethyl-phenol, 10 ml. of acetic anhydride, and 6 ml. of pyridine is heated on the steam bath for one hour. The reaction mixture is poured into ice water, stirred for 0.5 hour, and the product extracted into ether. After drying with magnesium sulfate and treating with activated charcoal, 4-(4'-fluorophenyl)-2-acetoxymethylphenyl acetate is obtained as an oil. The yield is 3.95 g.

C. 4-(4'-Fluorophenyl)-2-methylphenyl acetate

A solution of 3.9 g. of 4-(4'-fluorophenyl)-2-acetoxymethylphenyl acetate in 30 ml. of glacial acetic acid is hydrogenated at 40 p.s.i. and 70°C. until the uptake of hydrogen is one equivalent. The catalyst and solvent are removed, the product is taken up in ether, washed with dilute sodium bicarbonate solution and dried, and the solution is concentrated to dryness. The crude yield is 2.95 g. Chromatography of 2.6 g. of the crude product on 110 g. of silica gel and elution with benzene furnishes 2.1 g. of pure 4-(4'-fluorophenyl)-2-methylphenyl acetate, m.p. 71—73°C.

D. 4-(4'-Fluorophenyl)-2-methyl-phenol.

A mixture of 2.01 g. of 4-(4'-fluorophenyl)-2-methylphenyl acetate, 10 ml. of ethanol, and 10 ml. of 1.25 N sodium hydroxide is heated at reflux for 20 minutes. The reaction mixture is concentrated to dryness *in vacuo* and the residue redissolved in water. After acidification and extraction of the product with ether, 1.6 g. of 4-(4'-fluorophenyl)-2-methyl-phenol is obtained, m.p. 130—131°C.

E. 5-(4'-Fluorophenyl)-2-hydroxy-3-methyl-benzoic acid.

A mixture of 1.5 g. of 4-(4'-fluorophenyl)-2-methyl-phenol and 6 g. of anhydrous potassium carbonate is heated in a bomb at 175°C. and 850 p.s.i. carbon dioxide pressure for 16 hours. The reaction mixture is suspended in hot water and acidified, and the cooled mixture is extracted with ethyl acetate. The ethyl acetate is extracted repeatedly with portions of 1% solution of sodium bicarbonate. The pooled bicarbonate extracts are acidified and the product extracted into ether. After treatment with magnesium sulfate and activated charcoal, the ethereal solution is concentrated to a small volume. The addition of hexane causes the crystallization of 0.71 g. of 5-(4'-fluorophenyl)-2-hydroxy-3-methyl-benzoic acid, m.p. 211—213°C. (sublimes).

When the 3-unsubstituted ester compounds of Example 9, 9A or 9B are used in place of methyl-2-hydroxy-5-(4'-fluorophenyl)-benzoate in the above example, there are obtained the corresponding 3-methyl-benzoic acid compounds.

EXAMPLE 17

3-Allyl-5-(4'-fluorophenyl)-2-hydroxy-benzoic acid

A. Methyl-2-allyloxy-5-(4'-fluorophenyl)-benzoate

A mixture of 6.6 g. of methyl-5-(4'-fluorophenyl)-2-hydroxy-benzoate, 5.5 g. of potassium carbonate, 25 ml. of acetone, and 4.5 g. of allyl bromide is heated at reflux for 2 hours, and then stirred at 25°C. overnight. The reaction mixture is partitioned between 100 ml. of water and 100 ml. of ether and the ethereal solution is dried over magnesium sulfate and concentrated to a thick oil, 6.0 g. This material shows a strong absorption band in the infrared at 5.75 μ (non-bonded ester) and is homogeneous by thin layer chromatography.

B. Methyl-3-allyl-5-(4'-fluorophenyl)-2-hydroxy-benzoate

A sample of methyl-2-allyloxy-5-(4'-fluorophenyl)-benzoate is heated under a nitrogen atmosphere at 235°C. for 35 minutes. The crude product, which solidifies on cooling, is recrystallized from ethanol to obtain methyl-3-allyl-5-(4'-fluorophenyl)-2-hydroxy-benzoate, m.p. 76—77°C.

C. 3-Allyl-5-(4'-fluorophenyl)-2-hydroxy-benzoic acid

A mixture of 3.9 g. methyl-3-allyl-5-(4'-fluorophenyl)salicylate, 40 ml. of methanol, and 10 ml. of 2.5 N sodium hydroxide solution is heated at reflux for 15 minutes. The mixture is concentrated *in vacuo* to remove methanol, diluted to 60 ml. with water, and acidified with dilute hydrochloric acid. The product is collected by filtration, dried, and recrystallized from benzene. The yield of 3-allyl-5-(4'-fluorophenyl)-2-hydroxy-benzoic acid is 3.4 g. m.p. 170—172°C.

When the 3-unsubstituted ester compounds of Example 9, 9A and 9B are used in place of methyl-5-(4'-fluorophenyl)-2-hydroxy-benzoate in the above example, there are obtained the corresponding 3-allyl-benzoic acid compounds.

EXAMPLE 18

3-Propyl-5-(4'-fluorophenyl)-2-hydroxy-benzoic acid

A solution of 0.8 g. of 3-allyl-5-(4'-fluorophenyl)-2-hydroxy-benzoic acid in 25 ml. of ethanol is subjected to hydrogenation at 40 p.s.i. and 25°C. in the presence of 0.1 g. of platinum oxide. After the uptake of the required amount of hydrogen, the catalyst and solvent are removed, and the crude product is recrystallized from benzene. The yield of 3-propyl-5-(4'-fluorophenyl)-2-hydroxy-benzoic acid is 0.72 g., m.p. 188—190°C.

When the 3-allyl-benzoic acid compounds obtained from Example 11 are used in place of 3-allyl-5-(4'-fluorophenyl)-2-hydroxy-benzoic acid in the above example, there are obtained the corresponding 3-propyl-benzoic acid compounds.

EXAMPLE 19

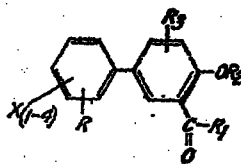
3-Propenyl-5-(4'-fluorophenyl)-2-hydroxy-benzoic acid

A mixture of 2 g. of 3-allyl-5-(4'-fluorophenyl)-2-hydroxy-benzoic acid, 5 g. of potassium hydroxide pellets and 2 ml. of water was heated under nitrogen in an oil bath at 170°C. for one hour with occasional stirring. The reaction mixture was cooled, dissolved in water, and the solution acidified. The product was extracted into ether. After drying the ether solution, and removing the ether, the product was recrystallized from benzene to yield 1.37 g., m.p. 196—200°C. One more recrystallization from benzene raised the m.p. to 198—201°C.

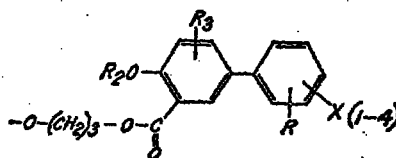
When the 3-allyl-benzoic acid compounds obtained from Example 17 are used in place of 3-allyl-5-(4'-fluorophenyl)-2-hydroxy-benzoic acid in the above example, there are obtained the corresponding 3-propenyl-benzoic acid compounds.

WHAT WE CLAIM IS:—

1. A compound of the formula:



in which X is halogen; R is hydrogen, halogen, C_{1-6} alkyl or C_{1-6} alkoxy; R_1 is hydroxy, amino, C_{1-6} alkoxy, di(C_{1-6} alkyl)amino-(C_{1-6} alkoxy), C_{1-6} hydroxyalkoxy, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, C_{1-6} polyhydroxyalkoxy, (C_{1-6} alkoxy)-(C_{1-6} alkoxy), phenyl-(C_{1-6} alkoxy), phenoxy, substituted phenoxy, (C_{1-6} alkanoylamino)-(C_{1-6} alkoxy), di(C_{1-6} alkyl)amino-(C_{1-6} alkyl)amino, hydrazino, hydroxylamino, N-morpholino, N-[4-(C_{1-6} alkyl)piperidino], N-[4-(C_{1-6} hydroxyalkyl)piperidino], C_{1-6} hydroxyalkylamino, a naturally occurring amino acid radical with attachment at the nitrogen, or a radical of formula:



in which R, R_2 , R_3 and X are such that the compound is symmetrical; R_2 is hydrogen, C_{1-6} alkyl, C_{1-6} alkanoyl or C_{2-6} alkenyl; and R_3 is hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, benzyl, C_{2-6} alkenyl or halo; the anhydrides of the acids and the mixed anhydrides of the acids and 2-acetoxy-benzoic acid.

2. A non-toxic pharmaceutically acceptable salt of a compound as claimed in claim 1.

3. A compound as claimed in claim 1 or 2, in which R, R_2 and R_3 are all hydrogen and R_1 is hydroxy.

4. A compound as claimed in claim 1 or 2, in which R_1 is hydroxy; R_2 is C_{1-6} alkanoyl and R and R_3 are both hydrogen.

EXAMPLE 18

3-Propyl-5-(4'-fluorophenyl)-2-hydroxy-benzoic acid

A solution of 0.8 g. of 3-allyl-5-(4'-fluorophenyl)-2-hydroxy-benzoic acid in 25 ml. of ethanol is subjected to hydrogenation at 40 p.s.i. and 25°C. in the presence of 0.1 g. of platinum oxide. After the uptake of the required amount of hydrogen, the catalyst and solvent are removed, and the crude product is recrystallized from benzene. The yield of 3-propyl-5-(4'-fluorophenyl)-2-hydroxy-benzoic acid is 0.72 g., m.p. 188—190°C.

When the 3-allyl-benzoic acid compounds obtained from Example 11 are used in place of 3-allyl-5-(4'-fluorophenyl)-2-hydroxy-benzoic acid in the above example, there are obtained the corresponding 3-propyl-benzoic acid compounds.

EXAMPLE 19

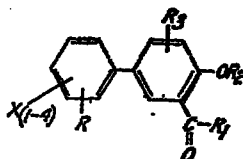
3-Propenyl-5-(4'-fluorophenyl)-2-hydroxy-benzoic acid

A mixture of 2 g. of 3-allyl-5-(4'-fluorophenyl)-2-hydroxy-benzoic acid, 5 g. of potassium hydroxide pellets and 2 ml. of water was heated under nitrogen in an oil bath at 170°C. for one hour with occasional stirring. The reaction mixture was cooled, dissolved in water, and the solution acidified. The product was extracted into ether. After drying the ether solution, and removing the ether, the product was recrystallized from benzene to yield 1.37 g., m.p. 196—200°C. One more recrystallization from benzene raised the m.p. to 198—201°C.

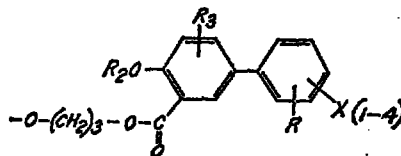
When the 3-allyl-benzoic acid compounds obtained from Example 17 are used in place of 3-allyl-5-(4'-fluorophenyl)-2-hydroxy-benzoic acid in the above example, there are obtained the corresponding 3-propenyl-benzoic acid compounds.

WHAT WE CLAIM IS:—

1. A compound of the formula:



in which X is halogen; R is hydrogen, halogen, C_{1-6} alkyl or C_{1-6} alkoxy; R_1 is hydroxy, amino, C_{1-6} alkoxy, di(C_{1-6} alkyl)amino-(C_{1-6} alkoxy), C_{1-6} hydroxyalkoxy, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, C_{1-6} polyhydroxyalkoxy, (C_{1-6} alkoxy)-(C_{1-6} alkoxy), phenyl-(C_{1-6} alkoxy), phenoxy, substituted phenoxy, (C_{1-6} alkanoylamino)-(C_{1-6} alkoxy), di(C_{1-6} alkyl)amino-(C_{1-6} alkyl)amino, hydrazino, hydroxylamino, N-morpholino, N-[4-(C_{1-6} alkyl)piperidino], N-[4-(C_{1-6} hydroxyalkyl)piperidino], C_{1-6} hydroxyalkylamino, a naturally occurring amino acid radical with attachment at the nitrogen, or a radical of formula:



in which R, R_2 , R_3 and X are such that the compound is symmetrical; R_2 is hydrogen, C_{1-6} alkyl, C_{1-6} alkanoyl or C_{2-6} alkenyl; and R_3 is hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, benzyl, C_{2-6} alkenyl or halo; the anhydrides of the acids and the mixed anhydrides of the acids and 2-acetoxy-benzoic acid.

2. A non-toxic pharmaceutically acceptable salt of a compound as claimed in claim 1.

3. A compound as claimed in claim 1 or 2, in which R, R_2 and R_3 are all hydrogen and R_1 is hydroxy.

4. A compound as claimed in claim 1 or 2, in which R_1 is hydroxy; R_2 is C_{1-6} alkanoyl and R and R_3 are both hydrogen.



5. A compound as claimed in claim 1 or 2, in which R_1 is hydroxy; R_2 is C_{1-6} alkyl and R and R_3 are both hydrogen.

6. A compound as claimed in claim 1 or 2, in which R is hydrogen; R_1 is hydroxy; R_2 is C_{1-6} alkanoyl and R_3 is C_{1-6} alkyl.

7. 2-Hydroxy-5-(4'-fluorophenyl)-benzoic acid.

8. 2-Acetoxy-5-(4'-fluorophenyl)-benzoic acid.

9. 2-Hydroxy-5-(4'-fluorophenyl)-benzamide.

10. 2-Hydroxy-5-(4'-fluorophenyl)-3-methyl-benzoic acid.

11. 2-Hydroxy-5-(4'-fluorophenyl)-3-methyl-benzamide.

12. 2-Acetoxy-5-(4'-fluorophenyl)-3-methyl-benzoic acid.

13. 2-Acetoxy-5-(4'-fluorophenyl)-3-methyl-benzamide.

14. 2-Acetoxy-5-(4'-fluorophenyl)-benzamide.

15. 2-Acetoxy-5-(4'-fluorophenyl)-benzmorpholide.

16. Aluminium 2-acetoxy-5-(4'-fluorophenyl)-benzoate salt.

17. Choline 2-acetoxy-5-(4'-fluorophenyl)-benzoate.

18. Sodium 2-acetoxy-5-(4'-fluorophenyl)benzoate.

19. 2-Hydroxy-5-(pentafluorophenyl)-benzoic acid.

20. 2-Acetoxy-5-(pentafluorophenyl)-benzoic acid.

21. β -Diethylaminoethyl-2-hydroxy-5-(4'-fluorophenyl)-benzoate.

22. β -Diethylamino-2-acetoxy-5-(4'-fluorophenyl)-benzoate.

23. 2-Hydroxy-5-(4'-fluorophenyl)-benzmorpholide.

24. Aluminium 2-hydroxy-5-(4'-fluorophenyl)-benzoate.

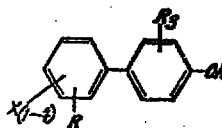
25. Choline 2-hydroxy-5-(4'-fluorophenyl)-benzoate.

26. Sodium 2-hydroxy-5-(4'-fluorophenyl)-benzoate.

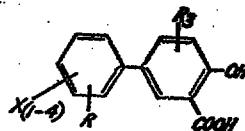
27. Calcium 2-hydroxy-5-(4'-fluorophenyl)-benzoate.

28. Calcium 2-acetoxy-5-(4'-fluorophenyl)-benzoate.

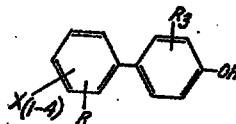
29. The process that comprises reacting a phenyl-phenolate of the formula:



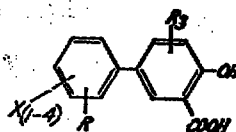
where A is an alkali metal and X, R and R_3 are as defined in claim 1, with carbon dioxide at elevated temperatures, followed by acidification, to form a biphenyl compound of the formula:



30. The process that comprises reacting a phenyl phenol compound of the formula:



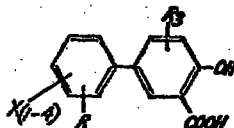
with carbon dioxide in the presence of an alkali metal carbonate under pressure at elevated temperatures and subsequently acidifying to form a biphenyl compound of the formula:



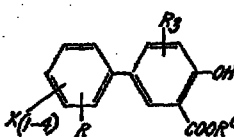
X, R and R_3 being as defined in claim 1.



31. The process that comprises esterifying a compound of the formula:

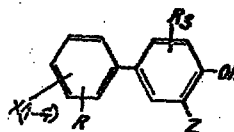


in which R, R₃ and X are as defined in claim 1 with an organic hydroxy compound of formula R^oOH where R^o is C₁₋₆ alkyl, di(C₁₋₆ alkyl)amino-(C₁₋₆ alkyl), C₁₋₆ hydroxyalkyl, C₁₋₆ polyhydroxyalkyl, (C₁₋₆ alkoxy)-(C₁₋₆ alkyl), phenyl-(C₁₋₆ alkyl), phenyl, substituted phenyl or (C₁₋₆ alkanoylamino)-(C₁₋₆ alkyl), to produce a compound of general formula:

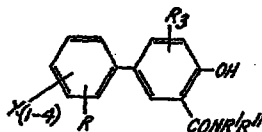


32. A process as claimed in claim 31, including the step of preparing the starting material by a process as claimed in claim 29 or 30.

33. The process that comprises amidating a compound of the formula:

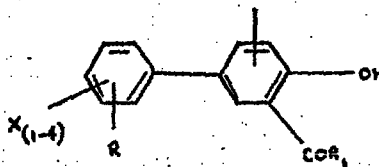


in which X, R and R₃ are as defined in claim 1 and Z represents —COOH, —COOR^o where R^o is as defined in claim 31, or —COY, where Y is a halogen, with an amide of formula HNR'R'', where —NR'R'' represents amino, C₁₋₆ alkylamino, di(C₁₋₆ alkylamino), di(C₁₋₆ alkyl)amino-(C₁₋₆ alkyl)amino, hydrazino, hydroxylamino, N-morpholino, N-[4-(C₁₋₆ alkyl)-piperidino], N-[4-(C₁₋₆ hydroxyalkyl)-piperidino], C₁₋₆ hydroxyalkylamino, or a naturally occurring amino acid radical with attachment at the nitrogen to produce a compound of the formula:

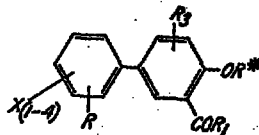


34. A process as claimed in claim 33, including the step, when Z is —COOH, of preparing the starting material by a process as claimed in claim 29 or 30, or, when Z is —COOR₁, of preparing the starting material by a process as claimed in claim 31 or 32, or, when Z is —COY, of preparing the starting material by converting a compound prepared by a process as claimed in any one of claims 29—32 to its corresponding halide.

35. The process that comprises reacting a compound having the general formula:



where X, R, R₁ and R₂ are as defined in claim 1, with an anhydride of a C₁₋₆ alkanolic acid in the presence of a catalyst, with a di(C₁₋₆ alkyl) sulfate or C₁₋₆ alkyl *p*-toluenesulfonate in the presence of a base, or with a C₂₋₆ alkenyl halide in the presence of a base containing an alkali metal or alkaline-earth metal cation, followed, when R₁ is hydroxy and a base is used, by neutralization, to produce a compound of general formula



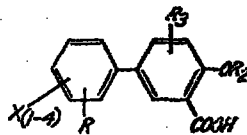
where R* is a C₁₋₆ alkanoyl, C₁₋₆ alkyl or C₂₋₆ alkenyl radical and X, R, R₁ and R₂ are as defined in claim 1.

36. A process as claimed in claim 35, including the step of preparing the starting material by a process as claimed in any one of claims 31-34.

37. A process as claimed in claim 35, in which R₁ represents hydroxy.

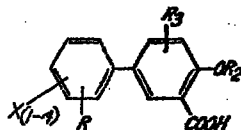
38. A process as claimed in claim 37, including the step of preparing the starting material by a process as claimed in claim 29 or 30.

39. A process as claimed in claim 29, 30, 37 or 38, including the further step of neutralizing the resulting product of formula:



where X, R, R₂ and R₃ are as defined in claim 1, with a base having a non-toxic cation to produce a non-toxic salt.

40. A process as claimed in claim 29, 30, 37 or 38, including the further step of converting the resulting product of formula:



where X, R, R₂ and R₃ are as defined in claim 1 to an acid halide and reacting the said halide with 2-acetoxy-benzoic acid or with a compound as claimed in claim 1 where R₁ represents hydroxy to produce an acid anhydride.

41. The process that comprises reacting 4-(4'-fluorophenyl)-phenol with carbon dioxide in the presence of an alkali metal carbonate under pressure at elevated temperatures and subsequently acidifying to form 2-hydroxy-5-(4'-fluorophenyl)-benzoic acid.

42. A process as claimed in claim 41, including the further step of reacting the 2-hydroxy-5-(4'-fluorophenyl)-benzoic acid produced with acetic anhydride in the presence of a catalyst to form 2-acetoxy-5-(4'-fluorophenyl)-benzoic acid.

43. The process that comprises reacting 2-methyl-4-(4'-fluorophenyl)-phenol with carbon dioxide in the presence of an alkali metal carbonate under pressure at elevated temperatures and subsequent acidification to form 2-hydroxy-5-(4'-fluorophenyl)-2-methyl-benzoic acid.

44. A process as claimed in claim 43, including the further step of reacting the 2-hydroxy-5-(4'-fluorophenyl)-2-methyl benzoic acid produced with acetic anhydride in the presence of a catalyst to form 2-acetoxy-5-(4'-fluorophenyl)-2-methyl benzoic acid.

45. A process substantially as hereinbefore described in any one of Examples 7-19, that produces a compound as claimed in claim 1 or 2.



46. A compound as claimed in claim 1 or 2, when prepared by a process as claimed in any one of claims 29—45 or its obvious chemical equivalent.

47. A pharmaceutical composition containing, as active ingredient, a compound as claimed in any one of claims 2—28 and 46, together with an inert diluent, carrier or coating.

48. A composition as claimed in claim 47, in the form of a tablet or capsule.

For the Applicants,
D. YOUNG & CO.,
Chartered Patent Agents,
9, Staple Inn,
London, W.C.1.

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