United States Patent

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[54] SUBSTITUTED BIPHENYL ACETIC ACID DERIVATIVES

3 Claims, No Drawings

[52] **U.S. Cl.** ..... **260/515 A,** 260/141, 260/247, 260/247.1, 260/247.2 A, 260/247.5 R, 260/247.9 H, 260/268.30, 260/284, 260/285, 260/287 R, 260/293 R, 260/293.4 R, 260/294 A, 260/294.7 E, 260/310 R, 260/326.3, 260/326.5 C, 260/326.8, 260/326.82, 260/326.84, 260/326.85, 260/439 R, 260/448 R, 260/465 R, 260/470, 260/471 R, 260/472, 260/473 R, 260/475.5 C, 260/501.11, 260/501.12, 260/501.16, 260/501.17, 260/516, 260/518 R, 260/520, 260/544 M, 260/556 AR, 260/558 R, 260/562 R, 260/568, 260/571, 260/576, 260/578, 260/580, 260/592, 260/607 R, 260/609 D, 260/618 R, 260/611 R, 260/999

[51] **Int. Cl.** **C07c 63/52,** C07c 69/76

[50] **Field of Search** 260/515, 469

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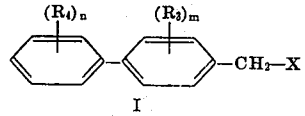
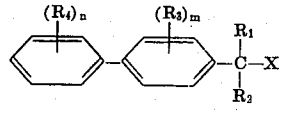
ABSTRACT: The invention relates to new substituted biphenyl acetic acids and derivatives thereof. These novel compounds are useful as antiinflammatory agents and for the control of arthritic conditions.

SUBSTITUTED BIPHENYL ACETIC ACID DERIVATIVES

This invention relates to new biphenyl aliphatic acids, aldehydes, alcohols, and derivatives thereof and to methods of preparation of the same. More specifically, this invention relates to substituted-biphenylacetic acids and the esters and amides thereof as well as to the corresponding aldehydes, alcohols, acetals, ethers, and the nontoxic salts thereof. More specifically, also, the compounds embraced within the scope of the present invention may be represented by the following structural formulas:



I



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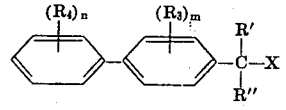

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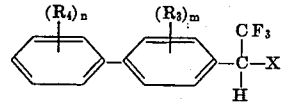


IV

wherein:

R′ is halogen, lower alkoxy (such as methoxy, ethoxy, propoxy, and the like), or lower alkyl (such as methyl, ethyl, butyl, and the like);

R″ is hydrogen, or lower alkyl when R′ is also lower alkyl;

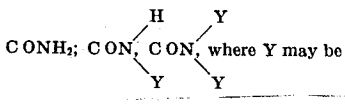
R_1 is hydrogen;

R_2 is lower alkyl, lower alkenyl, lower alkynyl, halo lower alkyl, and when R_1 and R_2 are taken together, are methylene, ethylidene, or form with the α-carbon a cyclopropyl group;

R_3 and R_4 may be hydrogen, lower alkyl (such as methyl, ethyl, propyl, butyl, and the like), halogen, trihalomethyl, lower alkylthio, mercapto, amino, di(lower alkyl)amino (such as dimethylamino, dipropylamino, ethylmethylamino, ethylbutylamino, and the like), cyano, nitro, carboxamido, di(lower alkyl) carbamyl, lower alkanoylamino, lower alkylsulfonyl, di(lower alkyl)sulfamyl (such as dimethylsulfamyl, dipropylsulfamyl, methylpropylsulfamyl, ethylbutylsulfamyl, and the like), phenyl, trifluoracetyl, acetyl, or trifluoromethylthio. In formulas I, II, and III, at least one of R_3 and R_4 must be other than hydrogen at any one time, whereas in formula IV, R_3 and R_4 may be hydrogen as well as any of the other groups.

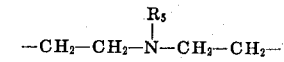
n and *m* are each a number from 0 to 2; no more than one of *n* and *m* is to be zero at any one time, and in addition, when one of *n* or *m* is 2, the other may be no more than 1.

X may be COOH: COOR, wherein R may be lower alkyl, lower alkenyl (such as prop-2-en, but-3-en, and the like), lower alkynyl (such as prop-2-yn, pent-3-yn), cyclo lower alkyl (such as cyclopropyl, cyclobutyl, cyclopentyl, and the like), phenyl, lower alkanoylaminophenyl, carboxyphenyl, carboxamidophenyl, lower alkoxy lower alkyl (such as methoxymethyl, ethoxymethyl, methoxyethyl, ethoxyethyl, and the like), poly lower alkoxy lower alkyl (such as dimethoxypropyl, diethoxypropyl, and the like), poly hydroxy lower alkyl (such as 1,4-dihydroxybutyl, 2,3-dihydroxypropyl, and the like), di(lower alkyl)amino lower alkyl (such as dimethylaminoethyl, diethylaminoethyl, diethylaminobutyl, and the like);

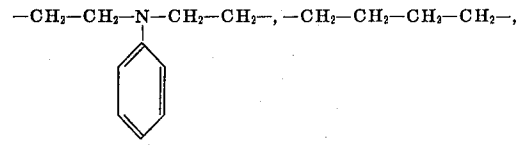


CONH₂; where Y may be

lower alkyl, hydroxy lower alkyl (such as hydroxyethyl, 3-hydroxypropyl, 3-hydroxybutyl, and the like), poly hydroxy lower alkyl (such as dihydroxypropyl, dihydroxypentyl, and the like), phenyl lower alkyl (such as phenylethyl, phenylpropyl, phenylbutyl, and the like), phenyl, lower alkoxyphenyl (such as methoxyphenyl, ethoxyphenyl, propoxyphenyl, and the like), halogenophenyl (such as chlorophenyl, fluorophenyl, and the like), trifluoromethylphenyl, cyclohexyl, carboxymethyl, 1-carboxyl-3-carbamylpropyl, N-dilower alkyl carboxamidomethyl (such as N,N-dimethylcarboxamidomethyl, dipropylcarboxamidomethyl, N,N,-diethylbutylcarboxamidomethyl, and the like), N,N-dilower alkylamino lower alkyl (such as dimethylaminoethyl, dipropylaminoethyl, ethylbutylaminoethyl, and the like), N-lower alkyl pyrrolidyl (such as N-methyl-3-pyrrolidyl, N-ethyl-3-pyrrolidyl, and the like), N-lower alkyl pyrrolidyl lower alkyl (such as N-ethyl-2-pyrrolidylmethyl, N-methyl-3-pyrrolidylmethyl, and the like), or Y may form a heterocyclic group with the nitrogen when Y is the group —CH_2—CH_2—O—CH_2—CH_2—,



in which R_5 is lower alkyl (such as methyl, ethyl, propyl, butyl, and the like), —CH_2—CH_2—NH—CH_2—CH_2—,



—CH_2—CH_2—N—CH_2—CH_2—, —CH_2—CH_2—CH_2—CH_2—,

—CH_2—CH_2—N—CH_2—CH_2—, and

—CH_2—CH_2—CH_2—CH_2—CH_2—; CH_2OH: CH_2OR_6 where R_6 is alkyl (such as ethyl, propyl, butyl, pentyl, and the like); CHO; $CH(OR_7)_2$ where R_7 is alkyl (such as ethyl, propyl, butyl, pentyl, and the like); and the pharmaceutically nontoxic salts of the acid. These salts may be the ammonium, alkali and alkali earth, amine, magnesium, aluminum, iron salts and the like.

In the preferred aspects of this invention, X is COOH or COOR (where R is methyl, diethylaminoethyl, and the like), but especially COOH; R_2 is hydrogen or lower alkyl (methyl, ethyl, pentyl, and the like); R_1 is hydrogen; R_3 and R_4 are hydrogen, halogen (chloro, fluoro, and bromo), lower alkyl (methyl, ethyl, butyl), or trifluoromethyl, but especially a halogen (chloro and fluoro); *n* and *m* are 0 to 1; R′ is fluoro or R′ and R″ together, lower alkyl, but especially fluoro.

Representative compounds encompassed within the scope of the present invention include 2-chloro-4-biphenylacetic acid, 2-methyl-4-biphenylacetic acid, 4′chloro-4-biphenylacetic acid, 4′-bromo-4-biphenylacetic acid, 4′-fluoro-4-biphenylacetic acid, α-methyl-2-chloro-4-biphenylacetic acid, α-methyl-4′4-biphenylacetic acid, α-methyl-2′-chloro-4-biphenylacetic acid, α-trifluoro-methyl-4-biphenylacetic acid, α-trifluoromethyl-4′-fluoro-4-biphenylacetic acid, and α-trifluoromethyl-2′-chloro-4-biphenylacetic acid.

We have found that the compounds described above have a high degree of anti-inflammatory activity and are effective in the prevention and inhibition of granuloma tissue formation. Certain of them possess this activity in high degree and are of value in the treatment of arthritic and dermatological disorders and in like conditions which are responsive to treatment with anti-inflammator agents. For these purposes, they are normally administered orally in tablets or capsules, the optimum dosage depending, of course, on the particular compound being used and the type and severity of the condition being treated. Although the optimum quantities of these compounds of this invention to be used in such manner will depend on the compound employed and the particular type of disease condition treated, oral dose levels of preferred com-

pounds in the range of 1–2000 mg. per day are useful in control of arthritic conditions, depending on the activity of the specific compound and the reaction sensitivity of the patient.

The α-substituted biphenylacetic acid compounds of the invention possessing an asymmetric carbon atom are ordinarily present in the form of a racemic mixture. The resolution of such racemates can be carried out by a vast number of known methods. Thus, some racemic mixtures can be precipitated as eutectics instead of mixed crystals and can thus be quickly separated and in such cases can sometimes be selectively precipitated. The more common method of chemical resolution is, however, greatly preferred. By this method diastereomers are formed from the racemic mixture by reaction with an optically active resolving agent. Thus, an optically active base can be reacted with the carboxyl group. The difference in solubility between the diastereomers formed permits the selective crystallization of one form and regeneration of the optically active acid from the mixture. There is, however, a third method of resolving which shows great promise. This is one or the other forms of biochemical procedures using selective enzymatic reaction. Thus, the racemic acid can be subjected to an asymmetric oxidase or decarboxylase which will, by oxidation or decarboxylation, destroy one form, leaving the other form unchanged. Even more attractive is the use of a hydroylsase on a derivative of the racemic mixture to form preferentially one form of the acid. Thus, esters or amides of the acids can be subjected to an esterase which will selectively saponify one enantiomorph and leave the other unchanged.

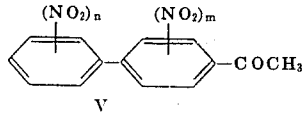
When the free acid is resolved into (*d*) and (*l*) enantimorphs, the anti-inflammatory activity is found to reside virtually completely in the (*d*)somer. The desired (*d*) isomer of the free acid may be prepared by any one of the preceding described resolving methods, preferably working from the free acid as the starting material. For example, amide or salt diastereomers of the free acid may be formed with optically active amines, such as quinine, brucine, cinchonidine, cinchonine, hydroxyhydrindamine, methylamine, morphine, α-phenylethylamine, phenyloxynaphthylmethylamine, quinidine, l-fenchylamine, strychnine, basic amino acids such as lysine, arginine, amino acid esters, and the like. Similarly, ester diastereomers of the free acid may be formed with optically active alcohols, such as borneol, menthol, 2-octanol and the like. Especially preferred is the use of cinchonidine to give the readily decomposable diastereomer salt which may then be resolved by dissolving in a solvent such as acetone, and distilling the solvent at atmospheric pressure until crystals begin to appear and further crystallization produced by allowing the mixture to cool to room temperature, thereby separating the two enantiomorphs. The (*d*) acid may then be recovered from its salt by partitioning the salt between an organic solvent, such as benzene or ether, and dilute hydrochloric acid.

Derivatives of the resolved (*d*) form the free acid then may be prepared in the usual way. These derivatives generally are more active than racemates of the same compounds. Consequently, the (*d*) form of these compounds, substantially free of the (*l*) form, is a still further aspect of this invention.

For purposes of further clarity, the preparation of the compounds of this invention will be discussed under four separate areas. Each area will refer to the structural formulas I, II, III, or IV previously described.

Structural Formula I

The compounds of structural formula I, wherein X is COOH, may be prepared by two separate syntheses (designated as processes A and B) from the known p-phenylacetophenone compounds of the structural formula:



V

The nitro substituent on the ketone compound may be converted to the desired R_3 and R_4 group by an appropriate series of known reactions. This conversion is carried out at various steps of the synthesis, depending upon the effect upon the substituent during the reactions to the final acetic acid compound. At whatever stage the conversion is carried out, the procedure is similar. For example, using the nitro ketone, the nitro group may be reduced such as, in the presence of palladium under an atmosphere of hydrogen to form the amino group. The amino group may be reacted with an organic halide, such as methyl iodide, to form the mono- or disubstituted amino group, or it may be acylated (using an alkanoic acid, halide or anhydride) to form an alkanoylamino group. The amino group may also be diazotized and the diazo replaced by a hydroxyl group, which, in turn, may be alkylated to form an alkoxy group. The diazonium salt derived from the amino group may also be treated with ethyl xanthate followed by saponification of the xanthate under alkaline conditions to give the mercapto group, which, if desired, may then be alkylated with a dialkyl sulfate or alkyl halide to the alkyl mercapto group. The alkyl mercapto group may be oxidized, for example, with potassium permanganate in alkaline solution, to the alkylsulfonyl group. In addition the mercapto group may be oxidized to a sulfonic acid group which may be treated with thionyl chloride and an amine to obtain the di(alkyl)sulfonamides. Also the diazonium compound may be reacted with a cuprous halide in the cold under acid conditions to form a halide group, or it may be reacted with cuprous cyanide to form a cyano group, which may then be subjected to acid hydrolysis to form a carboxamido group.

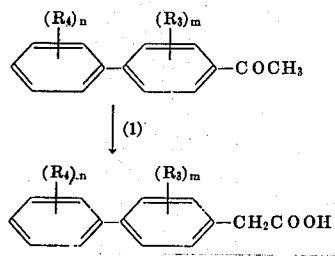
The trifluoromethyl group may be formed from a carboxyl group. After the formation of the biphenylacetic acid, the acid side chain is converted to the ester or tertiary amide. This compound is then reacted to obtain a cyano group on the phenyl ring. The cyano is converted to the carboxyl group via an imido ester which is treated with sulfur tetrafluoride and converted to the trifluoromethyl group. The protected side chain may then be converted to the acid by hydrolysis. In addition, the carboxyl group may be converted to the acid halide with thionyl halide, subsequently reduced to the aldehyde group, further reduced to the hydroxymethyl group, which is converted to the chloromethyl group, which group may then be converted to a methyl substituent. If other lower alkyl substituents are desired, the aldehydo group may be converted to a lower alkene by means of a Wittig reaction using the appropriately substituted triphenylphosphorane compound, and the lower alkene then reduced to the desired lower alkyl substituent. This preparation of the lower alkyl group is carried out on the acetic acid ester compound and the ester subsequently hydrolyzed or saponified to the final desired acid.

When more than one substituent is to be present and each is to be the same group, the conversion from the nitro compound is carried out with multiple nitro substituents. However, when different substituents are desired, the ketone containing less than three nitro groups may either be converted to the desired group or groups followed by nitration of the compound obtained and subsequent reaction of the nitro to obtain mixed substituents on the biphenyl ring, or, the desired ketone may be prepared from an appropriately substituted benzene and a substituted bromo aniline compound. In this method, the amino group on the aniline is used to form the biphenyl moiety and the bromo group on the aniline is used to form the ketone moiety. For example, 2-chloro-4-bromoaniline and fluorobenzene are refluxed with i-amyl nitrite to form a mixture of the 4-bromo-2-chloro-4′-fluorobiphenyl and the 2′-fluorobiphenyl compounds. Either biphenyl compound may be reacted with magnesium in an inert solvent to obtain the Grignard reagent. This compound is then treated with cadmium chloride to obtain the corresponding diphenyl cadmium compound. This compound is then treated with a lower alkyl acid chloride to give the corresponding ketone. This procedure can also be used to prepare the starting ketone containing a lower alkyl group, or a trihalomethyl group, by using

the appropriately substituted benzene and/or aniline compound as starting material.

When R_4 is to be a phenyl group, still another procedure is employed. For example, p-terphenyl or an appropriately substituted terphenyl with at least one of the end rings unsubstituted, is reacted with acetyl chloride under Friedel-Crafts conditions to form a p-biphenyl-acetophenone.

The appropriately substituted p-phenylacetophenones, obtained as described above, may then be converted to the desired acid of formula I, by one of two processes:

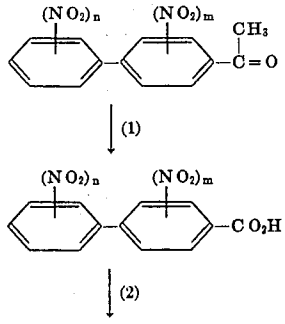


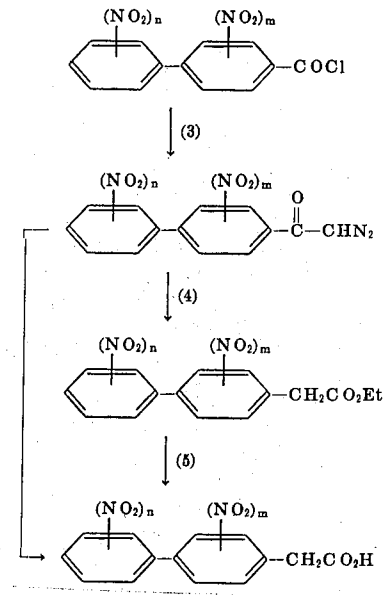
In this process, the p-phenylacetophenone may be reacted with ammonium polysulfide in an inert solvent, such as dioxane or pyridine, at elevated temperatures under pressure for at least several hours to obtain the desired acid. Alternatively, it is preferred to carry out this step in an organic amine with sulfur at elevated temperatures and subsequent hydrolysis at any suitable temperature of the thioamide formed with an alkali or alkali earth base. The preferred amines which are used as solvents in this reaction are generally dimethylamine, morpholine, methylamine, piperidine, and anhydrous ammonia especially morpholine. The reaction may be carried out at any suitable elevated temperature, preferably at or near the reflux temperature of the system. (With low boiling amines, a bomb is used). The subsequent hydrolysis may preferably be carried out with such bases as sodium hydroxide or potassium hydroxide at elevated temperatures.

When groups which are easily reduced or oxidized are desired—such as the nitro, amino, and cyano groups—the biphenylacetic acid is prepared first followed by appropriate reactions on the acid compound. For example, the nitro, amino, or cyano substituted-biphenylacetic acid compound may be prepared by nitration of the unsubstituted biphenylacetic acid and subsequent reaction to the desired amino or cyano group. The nitration may be carried out in sulfuric acid with fuming nitric acid at low temperatures, such as −5° to +10° C., preferably at or around 0° C.; or with fuming nitric acid alone or with concentrated nitric acid at low temperatures (−15° to 10° C.), preferably −5° to 0° C.; or with fuming nitric acid in acetic acid at low temperatures, or by any other known conditions which will afford the appropriate nitration. The nitro compound may then be catalytically reduced to the amino group. Such catalysts as platinum and palladium and the like are representative of this catalytic reduction. The amine may be diazotized by well-known methods and the diazo compound reacted with a cyanide salt, such as cuprous cyanide, to form the desired cyano group.

Process B

The alternative preparation of these α-unsubstituted acids of formula I may be illustrated as follows:





In this process, the acetophenone compound (Step 1) is reacted with an alkali hypohalite followed by treatment of the reaction mixture with sulfur dioxide and acidification of the solution to precipitate a p-phenylbenzoic acid compound. In Step 2, the acid is converted to its acid halide by well-known means, e.g., reaction with a thionyl halide in an inert solvent. The acid halide is subsequently treated with a solution of ethereal diazomethane to form the corresponding diazoketone (Step 3). This diazo compound is then reacted with silver oxide in alcohol (Step 4) to form the corresponding biphenylacetic ester. The ester is then converted by any known means to the desired biphenylacetic acid compound (Step 5). Alternatively, the diazoketone may be reacted with silver oxide in H_2O to form the free acid compound directly.

In this synthesis, only the acetophenone compounds containing the halogen, trifluoromethyl nitro, di(lower alkyl)sulfonyl, or di(lower alkyl)carboxamido may be used as the starting material and maintained throughout the subsequent reactions. When it is desired to obtain any other R_3 or R_4 group, the nitro acetophenone compounds may be used as the starting material and the nitro substituent converted to the desired group at the acetic acid stage of the synthesis (Step 4 or 5) employing the appropriate reactions, as previously described. However, such groups as cyano, benzylthio, or lower alkylthio may also be placed on the ring by appropriate conversion of the nitro group at any stage of the synthesis from the benzoic acid compound to the final acetic acid compound.

Reactions and Conditions of Process B

Step 1.

Reaction with an alkali or alkali earth hypohalite, such as sodium hypobromite, potassium hypochlorite, and the like, especially sodium hypobromite, with or without an inert solvent at any suitable temperature (R.T. to reflux), preferably at or near the reflux temperature of the solvent; consumption of the excess hypohalite with any suitable reducing agent, preferably sulfur dioxide, followed by acidification of the reaction mixture with any suitable acid, such as a mineral acid (hydrohalic acid, sulfuric acid, and the like), preferably dilute hydrochloric acid; the reaction is preferably carried out in an inert solvent; suitable solvents are dioxane, ethers (dimethoxyethane, tetrahydrofuran), alcohols, and the like, preferably dioxane.

Step 2.

Reaction by any known means, such as reaction with an acid halide of an inorganic acid, such as thionyl chloride, phosphorus pentachloride, phosphorus oxychloride, phosphorus trichloride, and the like, preferably thionyl chloride in an inert solvent [ethers, chloroform, aromatic solvents (benzene, toluene) and the like], preferably

chloroform or ethers at any suitable temperature (0°-reflux), preferably at elevated temperatures, but especially at or near the reflux temperature of the system.

Step 3.

Reaction with diazomethane in an inert solvent, such as ethers, chloroform, aromatic solvents (benzene, toluene) and the like, preferably ether, (THF) tetrahydrofuran or chloroform, but especially ether at any suitable temperature (R.T. or below), preferably 0° to −5° C.

Step 4.

Reaction with an alcohol and a catalyst, such as silver oxide, copper, or platinum, preferably silver oxide, either in the alcohol as solvent also or in an inert solvent, such as aromatic solvents, ethers, and the like, preferably using the alcohol as solvent, at any suitable temperature (R.T. to reflux), preferably at elevated temperatures, but especially at elevated temperatures, but especially at or near the reflux temperature of the system.

Step 5.

Saponification or hydrolysis by any known means, such as reaction with a base and subsequent neutralization of the mixture with a mineral acid.

Step 6.

Same as step (4) except an inert solvent, such as dioxane, is used and water is used in place of the alcohol.

In reaction step (1), the excess hypohalite is consumed prior to acidification of the reaction mixture; however, this is not necessary, and acidification may be carried out directly. The amount of hypohalite and/or acid used is not critical; only the yield of the desired acid will be affected by changing amount of either of them.

Reaction step (2) is a common reaction of converting an acid to an acid halide, and although a method has been indicated, many other methods well known in the art may also be employed.

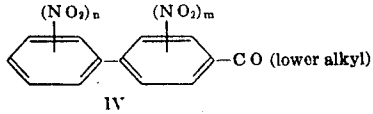
Step (3) in the above illustration is carried out by reacting the acid halide, preferably the acid chloride, in an inert solvent with a solution of an excess of diazomethane in an inert solvent. The inert solvent used is not critical; therefore, any solvent inert to the reactants, such as aromatic solvents (benzene, toluene) or various ethers, may be used. It is preferred, however, to use ether or THF. In order to avoid side reactions and loss of yield, the acid halide inert solvent mixture is generally added to an excess of diazomethane solution at reduced temperatures. However, any molar ratio of diazomethane and the acid halide, low temperatures to slightly elevated temperatures, are within the contemplation of this invention. This reaction step is preferably carried out at 0° to −5° C., adding the acid chloride-ether solution to at least 3 moles of a solution of diazomethane in ether.

In reaction step (4), it is highly preferred as a safety precaution to first remove the excess diazomethane from the previous step. Almost any alcohol may be used in this step, and generally the alcohol which will yield the desired ester, as described in this invention, is used. When the alcohol is also suitable as a solvent, it is preferred over the use of an inert solvent; however, when solubility or other factors dictate the use of an inert solvent, the results are the same. The amount of alcohol is not critical and will only determine the extent of ester formation.

In reaction step (5), any of the many well-known methods of converting an ester to an acid may be used; the method indicated is only one of such methods.

Preparation of Compounds of Structural Formula II

The compounds of structural formula II, wherein X is COOH and R_3 and R_4 are as previously defined, may be prepared by two separate syntheses (designated as process A and B) from a ketone compound of the formula:

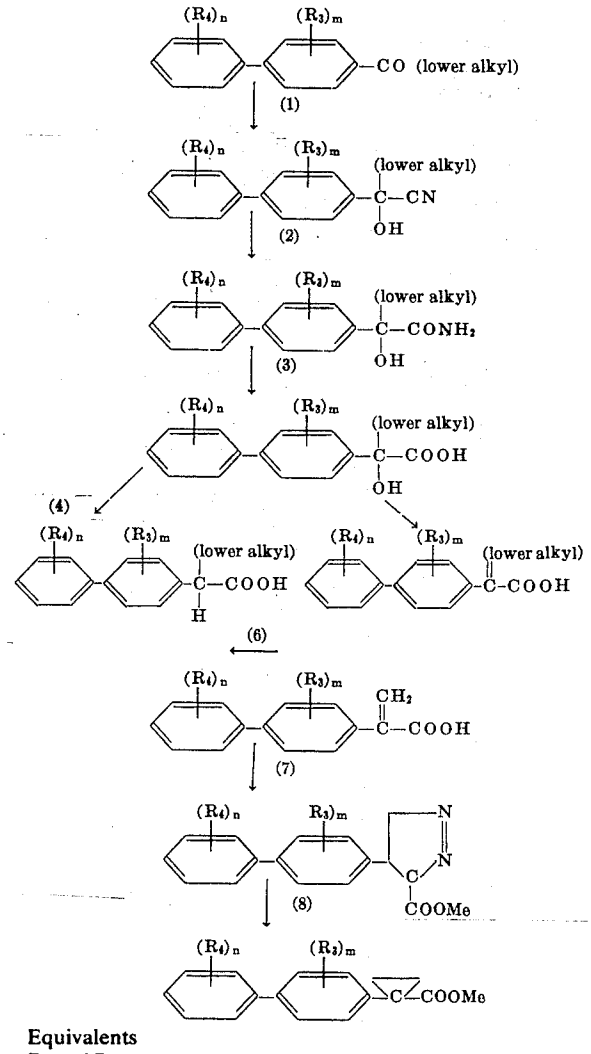


IV

The compounds of formula II require the starting ketone to be methyl, when the α-methyl compound is desired and higher alkyl groups when compounds other than α-methyl are desired, such as α-ethyl and α-butyl. Therefore, the procedures described in the literature for the preparation of the p-phenyl acetophenone nitro compounds are used, varying the reactants, to obtain the proper ketone compound. For example, when a nitro biphenyl compound is used, and a lower alkyl is desired other than α-methyl a lower alkanoic acid halide other than an acetyl halide as described in the literature, is reacted with the biphenyl under Friedel-Crafts conditions to obtain the desired ketone compound, or, as described in the literature, known biphenyl ketones may be nitrated in the appropriate positions to obtain other nitro substituted biphenyl lower ketones.

In the first process (Process A), the appropriately substituted ketone is converted to a cyanohydrin, which is treated with a mineral acid to form a hydroxy amide. The hydroxy amide is then converted to the hydroxy acid compound. The hydroxy acid may then either be converted directly to the desired α-lower alkyl acetic acid compound or first to the α-alkylidene acetic acids of this invention, which may then be converted to the α-cyclopropyl or α-pyrrolizino acetic acids (using the α-methylene compound when the latter two groups are desired) or to the α-lower alkyl acetic acid. This process is used to prepare the compounds of structural formula II excepting the α-halo lower alkyl, α-alkene and α-alkyne, process B is used for this purpose. This process may be illustrated as follows:

PROCESS A FOR PREPARATION OF FORMULA II



Equivalents

R_3 and R_4 are as previously indicated, excepting such groups as later indicated.

Reactions and Conditions

Step 1.

Reaction with a cyano compound, such as sodium cyanide, potassium cyanide, hydrogen cyanide, lower ketone cyanohydrin, and the like [preferably hydrogen cyanide with an amine such as a primary, secondary, or tertiary aliphatic amine (ethylamine, propylamine, diethylamine, and trimethylamine, piperidine)] in a solvent such as lower alkanols (methanol, ethanol, propanol, and the like), liquid hydrogen cyanide ethers, dioxane, tetrahydrofuran, water, mixtures of water and the above organic solvents, lower alkanoic acids (acetic, propionic, and the like), and mixtures of the acids and above solvents, preferably, however, using liquid hydrogen cyanide as the reactant as well as the solvent, at any suitable temperature, preferably −10°–25° C., but especially 0°–5° C., until the reaction is substantially complete.

Step 2

Reaction with a mineral acid (hydrogen chloride, hydrogen bromide, sulfuric acid, phosphoric acid, and the like, preferably fortified hydrochloric acid) in an inert solvent, such as lower alkanols (methanol, ethanol, propanol), ether, dioxane, tetrahydrofuran, and the like, preferably employing the acid as the solvent also, between temperatures of 0° and 50° C., preferably at or below room temperature until the reaction is substantially complete.

Step 3.

Reaction with aqueous alkali or alkali earth hydroxides, such as sodium, potassium, barium, lithium, and strontium hydroxides, or nonaqueous alkali and alkali earth hydroxides with lower alkanols (methanols, propanol, and the like), ethylene glycol, and the like, aqueous ammonium hydroxide organic amines, (such as lower aliphatic amines, and the like) preferably aqueous sodium or potassium hydroxide, but especially concentrated aqueous sodium hydroxide (6–12 or) using the above aqueous hydroxides as the solvents or lower alkanols as the solvents, preferably using the aqueous hydroxide reactants as solvents also, at any desirable temperature (0° C. to reflux,) preferably at or near reflux, until the reaction is substantially complete.

Step 4.

Reaction with an acid such as lower aliphatic acids (acetic acid, propionic acid ad the like), aromatic acids, inorganic acids, such as phosphoric acid, hydrochloric acid, and the like; and with phosphorus and iodine or hydrogen iodide preferably phosphorus and iodine, using the above acids as solvents also or in ether, dioxane, tetrahydrofuran, and the like, preferably the above acids as solvents at elevated temperature (75°–150° C., preferably 100°–120° C.) until the reaction is substantially complete.

Step 5.

Reaction in an acid medium using strong acids such as p-toluene sulfonic acid, p-nitrobenzenesulfonic acid, benzenesulfonic acid, trichloroacetic acid, a mixture of acetic acid and sulfuric acid, and the like (preferably toluenesulfonic acid) in an inert solvent such as aromatic compounds (benzene, toluene, xylene, and the like), dioxane, tetrahydrofuran, lower alkanoic acids (acetic acid, propionic acid, and the like) preferably acetic acid or tetrahydrofuran at elevated temperatures (75°–150° C., preferably at or near the reflux temperature of the system) until the reaction is substantially complete.

Step 6.

Reduction over a catalyst such a palladium, platinum, or Raney nickel, preferably 5–10 percent platinum oxide under moderate hydrogen pressure (5–60 pounds, preferably 40 pounds) in an inert solvent such as lower alkanols (methanol, ethanol, butanol, and the like), aromatic compounds (benzene, toluene, xylene, and the like), tetrahydrofuran, dioxane, acetic acid, and the like at any suitable temperature (0° C. to the reflux temperature of the system, preferably at room temperature) in ethanol until the reaction is substantially complete.

Step 7. Reaction with diazomethane in an inert solvent, such as aromatic hydrocarbons (benzene, toluene, and the like) or various ethers; at ambient temperatures until the reaction is complete.

Step 8.

Reaction at elevated temperatures until reaction is substantially complete. Preferably, reaction on a steam bath.

In Step (1) when it is desired to employ the cyanide salt, it is necessary to have the reaction mixture at a pH below 7. This is necessary in order to have the cyanide salt react as the acid. When the preferred procedure is used, namely, using hydrogen cyanide, the use of an amine, such as piperidine or a tertiary amine, is highly preferred, although not absolutely necessary.

In Step (2) an acid condition is necessary to obtain this reaction, and those acids as previously indicated may be used. The reaction may be run above a temperature of 50° C. However, when higher temperatures are used, a mixture of the desired compound as well as the alkylenyl acid is obtained, and it is possible that the reaction may be run at temperatures wherein only the alkylenyl acid compound is obtained.

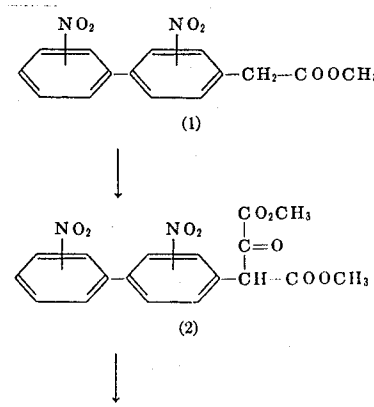
In Step (4), the reaction may be properly carried out only under acid conditions. A dilute to concentrated acid reaction mixture may be employed. However, it is preferred to use a concentrated reaction mixture, preferably an aliphatic acid such as acetic acid. The nitro ketones may be converted to the R_3 and/or R_4 substituents, as previously described prior to Step (1) above or the nitro ketone may be first converted to the nitro α-hydroxy acid compound (Step 3) and the nitro group converted to the desired substituent at this point. It is to be noted that when a nitro, trihalomethyl, cyano, carboxamido, or alkanoylamino group is desired, the 14-biphenyl acetic acid compound is prepared first after which the compound is nitrated to form the desired nitro compound, and the nitro compound subsequently converted to the other desired groups by the processes previously indicated.

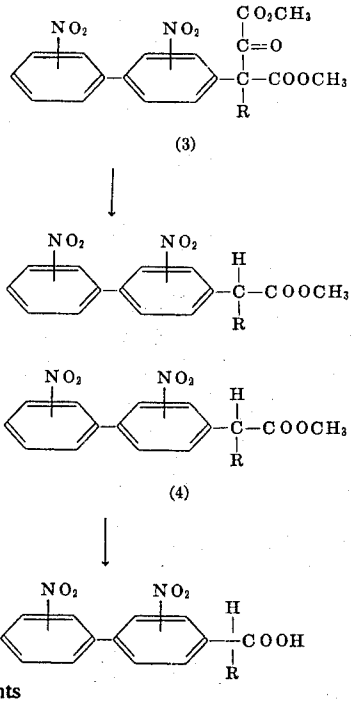
In Step (7), generally an excess of diazomethane in an inert solvent, such as ether, is added to the α-methylene compound at ambient temperatures. After addition, the excess diazomethane may be evaporated. When the α-methylene acid is used, the diazomethane also esterfies the free acid; therefore, the α-pyrazolino compound is obtained as the ester. This ester may be converted to the acid by hydrolysis or saponification and/or converted to other compounds of this invention.

In Step (8), the α-cyclopropyl compound is formed as the ester when obtained directly from Step (7). However, this step may be carried out on the free acid also. When the t-butyl ester is used, the free acid may be obtained from the ester by prolysis.

Process B for Preparation of Formula II

This process may be used when structural formula II is desired wherein X is COOH, R_1 is hydrogen, and R_2 is a lower alkyl, lower alkenyl, lower alkynyl, or halo lower alkyl. In this process, the α-unsubstituted-4-biphenylacetic acid compound of structural formula I, prepared as previously indicated, is converted to an ester, which through a series of reactions is alkylated to an α-substituted compound followed by conversion back to the desired acid. The process may be represented as follows:





Equivalents

R is a lower alkyl, lower alkenyl, lower alkynyl, or halo lower alkyl.

Reactions and Conditions of Process B

Step 1.

Reaction with a lower alkyl oxalate, such as dimethyl oxalate, diethyl oxalate, dibenzyl oxalate, and the like, preferably dimethyl oxalate and with a strong base, such as potassium t-butoxide, sodium t-butoxide, sodium ethoxide, sodium hydride methyl lithium, and the like, preferably and alkali t-butoxide and especially potassium t-butoxide in an inert solvent, such as aromatic solvents (benzene), ethers, and the like preferably aromatic solvents and especially benzene, at any suitable temperature (R.T.-reflux), preferably at elevated temperatures, but especially at or near the reflux temperature of the system until the reaction is substantially complete.

Step 2.

Reaction of the alkali enolate with a lower alkyl halide, (methyl iodide, isopropyl bromide, ethyl bromide, and the like), lower alkyl dihalide (β-chloropropyl iodine, γ-chlorobutyl iodide, β-bromopropyl iodide and the like) lower alkene halide (prop-2-en chloride, but-3-en bromide and the like) or with a lower alkyne halide (prop-2-yn bromide, but-3-yn chloride and the like) preferably a lower alkyl iodide and especially methyl iodide in an enolate salt-dissolving solvent, such as dimethylformamide, tetrahydrofuran, dimethoxyethane, and dimethylsulfoxide at any suitable temperature (R.T. to reflux), preferably at elevated temperatures until the reaction is substantially complete.

Step 3.

Reaction with an alkali alkoxide, such as sodium methoxide in an inert solvent, such as aromatic solvents, ethers, alcohols, and the like, preferably lower alcohols and especially methanol at any suitable temperature (R.T. to reflux), preferably elevated temperatures and especially at or near the reflux temperature of the system until the reaction is substantially complete, followed by addition to an aqueous dilute mineral acid, such as hydrohalic acids, sulfuric acid, and the like, preferably hydrochloric acid.

Step 4.

Conversion to the corresponding acid by any well-known means, such as saponification or hydrolysis, preferably saponification with an inorganic base and neutralization of the acid salt with a dilute mineral acid.

In reaction step (1), the type of ester used is not critical, since the ester is used primarily as a protecting group. The amount of alkoxide and/or oxalate used is only a factor in obtaining higher yields of enolate, therefore, less than equimolar ratios may be used. However, it is preferred to use an excess of both the alkoxide and oxalate.

In reaction steps (2) and (3), the molar ratios of reactants are not critical and, as in step (1), are only a factor in obtaining higher yields.

Reaction step (4) is simply the conversion of the ester back to its corresponding acid, which can be carried out by any known means, one such means being indicated and preferred. If it is desired, this step may be eliminated, and the esters of step (3) will represent still other compounds of structural formula II.

The R_3 and R_4 substituents of the starting α-unsubstituted-4-biphenylacetates in this process may be lower alkyl, nitro, halo, trifluoromethyl di(lower alkyl)sulfamyl, lower alkylthio, lower alkyl sulfonyl, and di(lower alkyl)-carbamyl. When the other R_3 and R_4 groups are desired, the α-substituted-nitro-substituted-4-biphenylacetic acid or ester final compound may be converted to the desired group by proper reaction of the nitro substituent according to the description described previously.

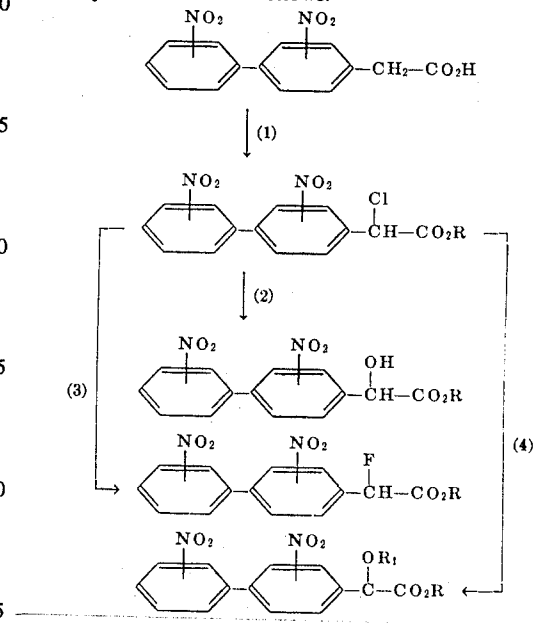
Preparation of Compounds of Structural Formula III

The procedure used to prepare these compounds depends upon the particular α-substituent desired.

A. To prepare the compounds of formula III, wherein X is COOH and R' and R'' are other than lower alkyl, an α-unsubstituted-4-biphenylacetic acid of structural formula I is reacted with sulfuryl chloride to form the α-chloro-4-biphenylacetic acid or reacted with sulfuryl chloride to form the α-chloro-4-biphenylacetic acid or reacted with thionyl chloride followed by sulfuryl chloride and an alcohol to form the α-chloro-4-biphenylacetate. The α-lower alkoxy acid compound may then be prepared from the α-chloro acid by reaction with sodium and a lower alkanol. The α-hydroxy acid or ester compound can be obtained by hydrolysis of the corresponding α-chloro compound. The α-fluoro acid or ester compound may be prepared by reacting the corresponding α-chloro or α-tosyl (from α-hydroxy) compound with potassium fluoride.

B. To prepare those compounds wherein X is COOH and R' and R'' are each lower alkyl, an α-unsubstituted-4-biphenylacetic acid of structural formula I is converted to the corresponding amide, which then is converted to the corresponding nitrile. The nitrile compound is then di-alkylated at the α-position and subsequently hydrolyzed to the desired free acid of formula III.

The process for the preparation of the compounds of Group (A) may be illustrated as follows:



Equivalents

R is H or lower alkyl;

R_1 is lower alkyl.

Reactions and Conditions of Process A

Step 1.

Reaction with a thionyl halide, sulfuryl chloride and a lower alkanol using the sulfuryl halide as solvent also or with an inert solvent, such as aromatic solvents (benzene, toluene, and the like) or alcohols and the like at any suitable temperature (R.T. to reflux), preferably at elevated temperatures and especially at or near the reflux temperature of the system, until the reaction is substantially complete to produce the compound wherein R is lower alkyl; or when the compound wherein R is hydrogen is desired, reaction with sulfuryl chloride without employing the thionyl halide and the lower alkanol.

Step 2.

Hydrolysis by any well-known means, such as reaction in water with a dilute inorganic base, such as dilute sodium hydroxide, potassium carbonate, and the like, or in water itself at any suitable temperature (R.T. to reflux), preferably at ambient temperatures, until the reaction is substantially complete.

Step 3.

Reaction with an alkali fluoride, such as sodium fluoride and potassium fluoride, in a high boiling alcohol, such as diethylene glycol, at elevated temperatures (75°–125° C.), preferably about 125° C., until the reaction is substantially complete.

Step 4.

Reaction with an alkali alkoxide and a lower alkanol in an inert solvent, such as aromatic solvents (benzene, toluene), or using the alcohol itself as the solvent at any suitable temperature (0° C., -reflux), preferably below room temperature until the reaction is substantially complete, and when R is hydrogen, followed by addition of a mineral acid, such as hydrohalic acid, sulfuric acid, and the like, preferably dilute hydrochloric acid, to make the reaction mixture acid.

In reaction step (1), it is not required that the ester be formed; therefore, the sulfuryl chloride may be used alone to chlorinate the α-position. It is preferred to use the sulfuryl compound both as the chlorinating agent and as solvent to produce the α-chloro acid. Although one may use the acid instead of the ester to place the desired α-substituent upon the molecule use of the ester is prepared.

Reaction step (2) can be easily carried out by placing the α-chloro compound, preferably the acid, in water and an inert solvent. The sole purpose of the solvent is to afford solubility of the reactant and it is not required when the reactant is soluble in water alone. The use of base increases the ability to hydrolyze the compound and although preferred, is not needed here.

In reaction step (3), it is preferred to use a small amount of potassium iodide to act as a catalyst. The reaction is generally carried out at temperatures of 125° C. and below.

In all of the above reactions, the R_3 and R_4 group may be halo, trihalomethyl, di(lower alkyl)sulfonamido, cyano, di(lower alkyl)carboxamido, nitro, or lower alkyl. When the other R_3 and R_4 groups are desired, the nitro substituent is used and converted to the desired group as described previously, after the final α-substituent is prepared.

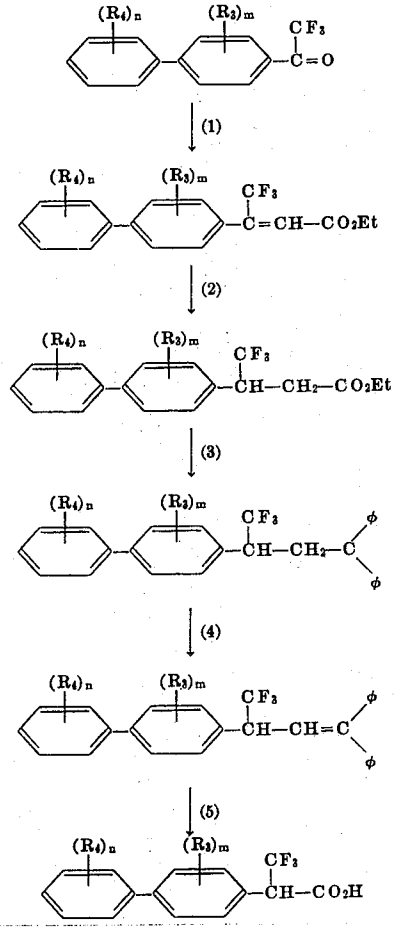
In the process for preparing the compounds of group (B), the α-unsubstituted acid is converted to the amide, as indicated previously. The amide is reacted with a dehydrating agent—such as PCl_5, P_2O_5, $POCl_3$. $SOCl_2$, and the like—preferably PCl_5, in an inert solvent which will dissolve both the dehydrating agent and the compound, preferably $POCL_3$ or pyridine as solvent, at any suitable temperature (R.T. to reflux), preferably at elevated temperatures, until the reaction is substantially complete. The nitrile thus produced is dialkylated by reaction with an alkali amide or hydride—such as potassium hydride or sodium amide—preferably the latter, and with a lower alkyl halide—such as methyl iodide, propyl bromide, and the like—preferably with methyl iodide, in an inert solvent (aromatic; benzene, toluene), preferably benzene, at temperatures above 0° C., preferably at elevated temperatures and especially at 75°–85° C., until the reaction is substantially complete. The α-dilower alkyl nitrile compound is then hydrolyzed by any one of many well-known means, such as dilute aqueous mineral acid hydrolysis (hydrohalic acids, sulfuric acid), preferably hydrochloric acid, in an inert solvent in which both the water and nitrile are soluble, such as acetic acid, at any suitable temperature (R.T. to reflux), preferably at elevated temperatures, until the hydrolysis is substantially complete to afford the α-dilower alkyl compounds of structural formula III.

In the reactions of group B, the substituents on the starting acid may not be, amino, mercapto, di(lower alkyl) amino, cyano or lower alkanoylamino. When these groups are desired the α-di(lower alkyl) group is first made from the nitro α-unsubstituted acid, followed by reaction of the nitro group to the desired substituent, as described previously.

Preparation of Compounds of Structural Formula IV

The preparation of compounds of formula IV, wherein X is COOH, may be carried out by the following process.

In this process the starting material is the known 4-biphenyl trifluoromethyl ketone or a substituted 4-biphenyl trifluoromethyl ketone, which is prepared by procedures similar to those previously described, e.g., the Friedel-Crafts reaction of an appropriately substituted biphenyl compound with trifluoroacetic anhydride. This starting trifluoromethyl ketone is treated with a lower carbalkoxymethylene triphenylphosphorane to form the β-trifluoromethyl-4-biphenyl-prop-2-enoate compound, which is subsequently reduced to form an α-trifluoromethyl-4-biphenylpropionate. This ester is then reacted with a Grignard reagent to form a propan-1-ol compound. This compound is then dehydrated to form a prop-1-ene compound, which is then oxidized to form the desired α-trifluoromethyl-4-biphenylacetic acid compound. The process may be illustrated as follows:



Equivalents

R_3 and R_4 are as previously described with the exceptions

hereinbelow indicated.

Reactions and Conditions

Step 1.

Reaction with a lower carbalkoxymethylene triphenylphosphorane in an inert solvent, such as ethers and aromatic solvents (benzene, toluene, xylene, and the like), preferably aromatic solvents and especially toluene, at any suitable temperature (room temperature to reflux), preferably at elevated temperatures and especially at or near reflux, until the reaction is substantially complete.

Step 2.

Catalytic reduction in an inert solvent, such as alcohols, dioxane, and lower alkanoic acids, preferably lower alkanols and especially ethanol, in the presence of a catalyst, such as platinum oxide, palladium oxide, and the like preferably platinum oxide, under an atmosphere of hydrogen, preferably greater than 5 pounds of hydrogen pressure, but especially 35–55 pounds of hydrogen pressure, at any suitable temperature (0° C. to reflux), preferably at ambient temperatures until the reaction is substantially complete.

Step 3.

Reaction with diphenylmagnesium bromide in an inert solvent, such as ether or tetrahydrofuran, preferably ether, at any suitable temperature (0° C. to reflux), preferably at or near the reflux temperature of the system, until the reaction is substantially complete, followed by addition of an aqueous mineral acid (sulfuric acid, hydrochloric acid, hydrobromic acid, and the like) or with an aqueous ammonium halide solution, preferably with a dilute mineral acid, especially aqueous sulfuric acid.

Step 4.

Dehydration by heating at any suitable temperature until all of the water is substantially split out of the molecule.

Step 5.

Oxidation, such as by reaction with chromium trioxide in an inert solvent (lower alkanoic acids, such as acetic acid, propionic acid, and the like), preferably glacial acetic acid at any suitable temperature (room temperature to reflux), preferably at or near the reflux temperature of the system, until the reaction is substantially complete followed by addition of a mineral acid (hydrochloric acid, sulfuric acid, hydrobromic acid, and he like), preferably aqueous sulfuric acid.

In reaction step (3), the mineral acid or ammonium halide employed is used to hydrolyze the Grignard addition product. Under these circumstances, any of the many well-known means to hydrolyze Grignard addition products may be used.

In reaction step (4), it is preferred to first remove the solvents of the product from reaction step (3) before dehydrating the product. However, the dehydration step may be carried out directly on the reaction mixture of step (3). In this case, the reaction mixture of step (3) is continuously heated, whereupon the solvent is removed followed by the splitting off of water from the product. The temperature required in this dehydration step will vary depending upon the product involved. Therefore, as a practical matter, the crude mixture is heated to the minimum temperature required to split out the water without substantially affecting the product thus obtained.

In reaction step (5), any of the many well-known oxidation procedures for unsaturated compounds may be employed. In addition to the one procedure previously indicated, oxidation may also be carried out with the use of potassium permanganate under alkaline or acidic conditions. Another appropriate method is the ozonation of the unsaturated compound. In this procedure the unsaturated compound is placed in a solvent, such as methylene chloride, at low temperatures (approximately −75° C.), an excess of ozone added, the solvent removed and replaced by another solvent, such as glacial acetic acid, whereupon aqueous hydrogen peroxide is added to complete the oxidation. In the procedure previously described, the mineral acid is used to hydrolyze the chromate ester which is formed after the oxidation. Under these circumstances, any variety of procedures well known in the art may be used to hydrolyze this chromate ester.

In carrying out this process the R_3 and/or R_4 group is restricted to hydrogen, halogen, trihalomethyl, lower alkylthio, lower alkyl, phenyl, and diloweralkyl-sulfamyl. When it is desired to obtain the α-trifluoromethyl-4-biphenylacetic acid compound containing other substituents, the final acid compound is nitrated and then treated according to the procedures previously described to obtain the desired R_3 and/or R_4 substituent.

The compounds of formulas I, II, III, and IV of this invention, wherein X is other than COOH, may be prepared from the corresponding acid compounds.

The process for the preparation of the esters may be carried out by reaction of the corresponding acid with a strong acid, such as hydrochloric acid, sulfuric acid, toluenesulfonic acid, p-nitrotoluenesulfonic acid, benzenesulfonic acid, and the like (preferably 1–3 percent concentrated sulfuric acid), and with the appropriate alcohol. The alcohol may be used as a solvent also or an inert solvent, such as tetrahydrofuran, ether, or dioxane, may be used. The reaction may be carried out at any suitable temperature; however, it is preferably carried out at or near the reflux temperature of the system. Esterifications are well-known reactions in the art, and although a particular esterification reaction is indicated here, the acid may be esterified by any known means. When the alcohol is not suitable for use as a solvent, inert solvents are used along with the alcohol. When using phenol as the alcohol for the esterification step, it is highly preferred to azeotrope the water formed so as to allow ester formation. Another highly suitable procedure for this esterification step is the reaction of the acid with at least 1 mole of a diimide (such as dicyclohexylcarbodiimide) and the appropriate alcohol in an inert solvent, such as tetrahydrofuran.

The process for the preparation of the amide compounds of this invention, may be carried out by reacting the corresponding acid with thionyl chloride, thionyl bromide, phosphorus oxychloride, phosphorus oxybromide, phosphorus pentachloride, or phosphorus pentabromide in an inert solvent—such as ether, benzene, toluene, xylene, tetrahydrofuran, dioxane, and the like—followed by reaction with an excess of the desired amine at any suitable temperature (0° C. to room temperature preferred) or reaction with dicyclohexylcarbodiimide and an excess of the amine at any suitable temperature until the reaction is substantially complete. When primary amides are desired, ammonia maybe employed; when secondary amides are required, primary aliphatic or aromatic amines are employed—such as propylamine, benzylamine, β-phenethylamine, aniline, and the like. To obtain cyclic amides, N-unsubstituted cyclic amines—such as pyrrolidine, piperidine, morpholine, and the like—are employed. It is generally preferred to run this reaction with the amine acting as the solvent also; however, when this cannot be conveniently done, an inert solvent such as indicated above may be used. In addition, it is preferred to remove the excess reagent and acidic byproduct formed in this reaction prior to the addition of the amine. However, the acid may be neutralized by using an excess of the amine. An alternative procedure is to react the biphenyl acid compound with dicyclohexylcarbodiimide and the desired amine. The three components may be mixed at any suitable temperature (−10° C. to 50° C.), but are

preferably mixed at ambient temperatures for several hours. The dicyclohexylcarbodiimide procedure is exclusively used when the R_3 and R_4 groups are affected by the acid halide procedure. Such groups are the amino, monoalkyl and dialkylamino, and carboxamide.

The process for the preparation of the aldehyde compounds of this invention may be carried out by reacting the corresponding biphenyl acid compounds with a compound such as thionyl chloride, thionyl bromide, phosphorus pentachloride, phosphorus pentabromide, phosphorus oxychloride, phosphorus oxybromide, and the like, but preferably thionyl chloride in an inert solvent to form the acid halide and subsequent reduction of the acid chloride to the aldehyde. The inert solvents used may be benzene, toluene, xylene, ethers (diethyl ether, dioxane), tetrahydrofuran, or the like, preferably benzene or toluene. Any suitable temperature may be employed (room temperature to reflux); however, it is preferred to use temperatures at or near the reflux temperature of the system until the formation of the acid halide is substantially complete. The acid halide is then reacted with a Rosenmund catalyst such as 5 percent Pd on $BaSO_4$ with quinoline, or with a tritertiarybutoxy alkali or alkali earth aluminum hydride, such as potassium, sodium, or lithium aluminum hydride and the like. The reduction is preferably carried out with a tritertiarybutoxy alkali or alkali earth aluminum hydride, particularly with tritertiarybutoxy lithium aluminum hydride in tetrahydrofuran or ether. However, the inert solvent may also be benzene, toluene, xylene, ethers (diethyl ether, dioxane), and the like. The reaction may be carried out at any suitable temperature (−80° C. to room temperature), but preferably −35° to −15° C. until the reaction is substantially complete.

It is preferred to remove the inorganic acid formed after the acid halide preparation; otherwise, the inorganic acid would preferentially consume the subsequent addition of the hydride, However, if it is desired, the inorganic acid may remain if an excess of the hydride is used to react with the inorganic acid as well as with the acid halide. When the butoxide reagent is used, it is preferred to use temperatures below 0° C. If temperatures above 0° C. are used, the reduction will lead to the corresponding alcohol instead of the aldehyde. As indicated, although higher temperatures may be used, it is not economically feasible, for a reaction temperature will be reached wherein the corresponding alcohol will be almost exclusively produced. However, if the alcohol is desired, this is still another way of going directly from the acid to he alcohol.

In the preparation of these aldehydes, the acid starting materials containing the primary amino, or secondary amino group and carboxamido group may not be used unless these groups are protected in some way. Protection may be accomplished by benzylating the amino group prior to this reaction. During the reaction, the acid group will be reduced to the aldehyde and the protected amino group will be debenzylated to yield the desired amino group.

The process for the preparation of the acetal compounds of this invention may be carried out by reacting the previously prepared aldehyde compound with a lower alkanol in the presence of a strong acid. Examples of strong acids contemplated for this reaction are toluenesulfonic acid, p-nitrobenzenesulfonic acid, and mineral acids (hydrochloric acid, sulfuric acid, and borontrifluoride). It is preferred to use a catalytic amount of toluenesulfonic acid or concentrated hydrochloric acid in a lower alkanol (methanol, ethanol, butanol, and the like) at any suitable temperature. However, the solvents used may be aromatic compounds or combinations of the alcohol and ethers as well as the alcohol itself. The reaction temperature is not critical, and, therefore, temperatures from 0° C. to reflux may easily be used, although ambient temperatures are preferred. The quantity of acid is not critical; all that is required is that the acid be of sufficient strength to catalyze the reaction. Alternatively, the reaction may be carried out by employing the aldehyde and the appropriate lower alkyl orthoformate. When it is desired to isolate the acetal and water is to be used in the isolation, the reaction mixture must be neutralized with a base such as sodium carbonate so as to prevent the hydrolysis of the acetal back to the aldehyde.

The alcohols of this invention may be obtained by reaction of the corresponding acid compound with an alkali or alkali earth aluminum hydride. Almost any solvent may be used as long as it is inert to the hydride and the reactants have some degree of solubility in it. Preferred inert solvents are tetrahydrofuran and diethyl ether. The temperature of this reaction is not critical; therefore, under these conditions, temperatures from −15° C. to reflux are well within the contemplation of this invention. The complex metal hydrides—such as lithium, aluminum hydride, and the like—used may be less than the theoretical amount, however, it is preferred to use 200–400 percent excess of the preferred lithium aluminum hydride. After the reaction, the excess hydride is decomposed by addition of ethyl acetate or an active hydrogen reactant such as alcohols, water, or dilute aqueous mineral acids. The alcohol compound obtained from this reaction is in the form of its salt, and therefore an aqueous acid is used to convert the alcohol salt to the free alcohol. Such acids may be hydrochloric, ammonium chloride, sulfuric, and the like.

This portion of the reaction is preferably carried out at 0° to ambient temperatures by first adding water followed by dilute sulfuric acid. The ester may also be reduced catalytically using such catalysts as reuthenium. When the former procedure is used, the R_3 and R_4 substituents may only be lower alkylthio, halogen, trihalomethyl, lower alky, and dilower alkylamino. When the latter procedure is used the R_3 AND R_4 may be any group other than cyano, nitro or sulfonyl.

The ether compounds of this invention are prepared from the corresponding alcohols. The alcohol is reacted with a strongly basic condensing agent such as sodium hydride, potassium hydroxide, potassium tertiary butoxide, or sodamide and a lower alkyl halide, (methyl iodide, alkyl chloride, β-phenethyl bromide or ethyl bromide and the like), preferably sodium hydride and 50 percent excess of methyl iodide. Although dimethylformamide is generally used as the solvent, any nonactive hydrogen solvent may be used, such as aromatic solvents (benzene, toluene), ethers (diethyl ether, dioxane, tetrahydrofuran), and the like. The reaction is generally carried out at ambient temperatures; however, temperatures from 0°–50° C. may be conveniently used also. The quantity of reagents used will affect the yield of the ether; therefore, it is generally preferred to use an excess of the hydride and halide. Additionally, the excess hydride is used to consume any active hydrogen materials which may be present in the starting alcohol compound. Additionally, since this reaction employs a strongly basic condensing agent, as in the first alcohol synthesis, the same limitations as to substituents apply to this reaction as did with that alcohol synthesis.

It is to be noted that whenever a nitro group is desired on the biphenyl ring and the synthesis of the side chain will affect the nitro group, the nitro group is placed on the biphenyl ring by proper nitration after the side chain has been obtained.

The nontoxic salts of the acid compounds of this invention may be conveniently prepared by procedures well known in the art. For example, the biphenyl acetic acid maybe reacted with an inorganic base in an inert solvent and the solution evaporated to yield the desired salt.

The following examples are given by way of illustration:

EXAMPLE 1

3-Chloro-4-phenylacetophenone

Ta mixture of 1.85 grams of magnesium turnings in 8 ml. of ether is added a solution consisting of 11.5 grams of 4-bromo-2-chlorobiphenyl and 5 grams of ethyl bromide in 50 ml. of ether. The solution is brought to reflux and the remaining biphenyl solution is added over a period of 25 minutes, maintaining gentle reflux. The solution is then cooled and 7.0 grams of cadmium chloride is added portionwise over approximately 7 minutes. The solution is refluxed for 1 hour, after

which it is recooled to room temperature. A solution of 6 ml. of acetyl chloride in 20 ml. of ether is added wit stirring over a period of 5 minutes. The solution is then refluxed for approximately 2 hours, recooled to room temperature, and poured onto a mixture of 1 liter of ice in 56 ml. of 2.5*N* hydrochloric acid. The ether layer is separated and washed with 25 ml. of water and dried over magnesium sulfate. The ether solution is then chromatographed on a 500-gram silica gel column. The column is eluted with ether-petroleum ether (v/v 20–80 percent ether) to yield 3-chloro-4-phenylacetophenone.

EXAMPLE 2

4-Biphenylacetophenone

To a mixture of 0.05 mole of terphenyl and 0.05 mole of acetyl chloride in 80 ml. of carbon disulfide is added 0.06 mole of aluminum chloride in small portions over 30 minutes. This reaction mixture is then placed in a water bath at 68° C. and the bath allowed to come to room temperature. The reaction mixture is then stirred for 48 hours. The reaction mixture is then poured into a mixture of 10 ml. of concentrated hydrochloric acid and 200 grams of ice and water added to bring the volume to 500 ml. The reaction mixture is then stirred over a period of 1 hour. The reaction mixture is then extracted with (3×50 ml.) chloroform. The combined chloroform extract is then washed with an excess of water and dried over sodium sulfate. The chloroform extract is then filtered and the filtrate concentrated in vacuo of yield 4-biphenylacetophenone, m.p. 235.5°–236° C.

EXAMPLE 3

2-Methyl-4-phenylacetophenone

To a mixture of 1.85 grams of magnesium turnings in 8 ml. of ether is added with stirring 3 ml. of a solution of 10.6 grams of 4-bromo-3-methylbiphenyl and 5 grams of ethyl bromide and 50 ml. of dry ether. The mixture is heated in a water bath and the remaining portion of the bromobiphenyl solution is added dropwise over a period of 25 minutes. After complete addition, the reaction mixture is refluxed for approximately 2 hours. At this point, the mixture is cooled and 7.0 grams of cadmium chloride is added portionwise over a period of 3 minutes. The reaction mixture is refluxed for an additional hour, cooled, and a solution of 6 ml. of acetyl chloride and 20 ml. of ether is added. The mixture is refluxed again for an additional hour and cooled to room temperature. The mixture is then poured onto a solution of 1 liter of ice in 52 ml. of 2.5*N* hydrochloric acid. The ether layer is then separated and dried over magnesium sulfate. The ether solution is then concentrated in vacuo to yield a crude residue. This residue is then dissolved in a minimum amount of ether and chromatographed on a 430-gram silica gel column to yield 2-methyl-4-phenylacetophenone, m.p. 53°–55° C.

When 4-bromo-2-methylbiphenyl and 4-bromo-2-chlorobiphenyl are used in place of 4-bromo-3-methylbiphenyl in the above example, there are obtained 3-methyl-4-phenylacetophenone and 3-chloro-4-phenylacetophenone.

EXAMPLE 4

2-Chloro-4-biphenylmethyl ketone

To a cooled mixture of 14.2 grams of aluminum chloride in 100 ml. of ethylene dichloride is added a solution of 20 grams of 2-chlorobiphenyl and 8.5 grams of acetyl chloride in 50 ml. of ethylene dichloride. After complete addition, the mixture is allowed to slowly come to room temperature. The reaction mixture is then poured into 300 ml. of ice water and the resultant mixture is separated and the aqueous layer extracted with 150 ml. of methylene chloride. The combined organic layer is then concentrated in vacuo. The residue thus obtained is dissolved in a minimum amount of benzene and chromatographed on a 705-gram silica gel column using petroleum ether and benzene as eluents to yield 2'-chloro-4-biphenylmethyl ketone, m.p. 52°–53° C.

EXAMPLE 5

4-(p-Nitrophenyl)-benzoic acid

0.01 mole of 4-(p-nitrophenyl)-acetophenone in 30 ml. of dioxane is added to an aqueous solution of 0.05 mole of sodium hypobromite and the resulting mixture stirred at room temperature for 1 hour. The mixture is then warmed to 60° C. and stirred for an additional 2 hours at that temperature. The reaction mixture is then concentrated in vacuo. The alkaline solution is treated with sulfur dioxide and then acidified with dilute hydrochloric acid. The mixture is then filtered and the cake washed with (2×10 ml.) dilute hydrochloric acid. The cake is then dried in vacuo to yield 4-(p-nitrophenyl)-benzoic acid.

When 4-phenylacetophenone, 3-chloro-4-phenylacetophenone, 4-(p-dimethylsulfonylphenyl)-acetophenone, 4-(p-dimethylcarboxyamidophenyl)-acetophenone, 3-nitro-4-(p-nitrophenyl)-acetophenone, 3-nitro-4-phenylacetophenone, 4-(o-nitrophenyl)-acetophenone, 4-biphenylacetophenone, and 4-(m-nitrophenyl)-acetophenone are used in place of the 4-(p-nitrophenyl)-acetophenone in the above example, there are obtained the corresponding benzoic acids.

EXAMPLE 6

4-(p-Nitrophenyl)-diazoacetophenone

A. 4-(p-Nitrophenyl)-benzoic acid chloride

0.01 mole of 4-(p-nitrophenyl)-benzoic acid and 0.02 mole of thionyl chloride are added to 50 ml. of chloroform. After the initial reaction, the mixture is refluxed on a steam bath for 2 hours. The reaction mixture is then concentrated in vacuo, 20 ml. of benzene added, and again concentrated in vacuo.

B. 4-(p-Nitrophenyl)-diazoacetophenone

The residue obtained from part A is added to 30 ml. of cold ether and the ethereal solution added to an excess of diazomethane. The reaction mixture is allowed to warm to room temperature and stirred for 6 hours. The solvent is then removed in vacuo to yield crude 4-(p-nitrophenyl)-diazoacetophenone.

When the benzoic acid compounds obtained from example 5 are used in place of 4-(p-nitrophenyl)-benzoic acid in the above example, there are obtained the corresponding diazoacetophenones.

Similarly, when 4-(p-methylthiophenyl)-benzoic acid, 4-(p-cyanophenyl)-benzoic acid, 4-(p-benzylthiophenyl)-benzoic acid, and 3-nitro-4-phenylbenzoic acid are used in place of 4-(p-nitrophenyl)-benzoic acid in the above example, there are obtained the corresponding diazoacetophenones.

EXAMPLE 7

Ethyl 4'-nitro-4-biphenylacetate

To a solution of 0.01 mole of 4-(p-nitrophenyl)-diazoacetophenone in 50 ml. of ethanol at 55° C. is added portionwise a slurry of 3 grams of freshly precipitated silver oxide in 30 ml. of ethanol and the reaction mixture stirred. After evolution of the nitrogen subsides, the reaction mixture is refluxed for approximately 1 hour, subsequently treated with charcoal, filtered, and the filtrate concentrated in vacuo. The crude ester residue is purified by chromatography on an acid-washed alumina column using ether-ethyl acetate as the eluent.

When the diazoacetophenones obtained from example 6 are used in place of 4-(p-nitrophenyl)-diazoacetophenone in the above example, there are obtained the corresponding ethyl esters.

EXAMPLE 8

4-Nitro-4-biphenylacetic acid

A solution OF 15 grams of 4-(p-nitrophenyl)-diazoacetophenone in 100 ml. of dioxane is added dropwise with stirring to a mixture of 2 grams of silver oxide, 5 grams of

anhydrous sodium carbonate, and 3 grams of sodium thiosulfate in 200 ml. of water at 50°–60° C. The reaction mixture is stirred for an additional hour at a temperature of 90°–100bL C. The reaction mixture is then cooled, diluted with 200 ml. of water, and acidified with dilute nitric acid. The reaction mixture is then filtered and the cake washed with (3×25 ml.) dilute nitric acid. The cake is then dried in vacuo to yield 4'-nitro-4-biphenylacetic acid.

When the diazoacetophenones obtained from example 6 are used in place of 4-(p-nitrophenyl)-diazoacetophenone in the above example, there are obtained the corresponding 4-biphenylacetic acids.

EXAMPLE 9

4'-Nitro-4-biphenylacetic acid

A solution of 0.01 mole of potassium hydroxide in 3 ml. of water is added to a cool solution of 0.01 mole of ethyl 4'-nitro-4-biphenylacetate in 30 ml. of methanol. Additional water or methanol is added until the faintest cloudiness persists, and the mixture is stirred overnight at room temperature. To this reaction mixture is added an excess of water and the methanol is removed in vacuo. The aqueous mixture is then washed well with ether, made acidic with 2.5N hydrochloric acid, and extracted with (3 ×25 ml.) ether. The combined ether extracts are dried over anhydrous magnesium sulfate, the mixture filtered, and the ether removed in vacuo to yield 4'-nitro-4-biphenylacetic acid.

When the ethyl esters obtained from example 7 are used in place of ethyl 4'-nitro-4-biphenylacetate in the above example, there are obtained the corresponding 4-biphenylacetic acids.

EXAMPLE 10

4'-Amino-4-biphenylacetic acid

To a solution of 23 grams of 4'-nitro-4-biphenylacetic acid and 250 ml. of absolute ethanol is added **1/2** gram of platinum oxide. The mixture is then hydrogenated at room temperature for 1 hour. The product is then dissolved as much as possible by heating on a steam bath and filtered. The moist cake is treated with 500 ml. of hot ethanol and the catalyst removed by filtration. After removal of the combined solvents in vacuo, the product thus obtained is dissolved in ether, extracted with 2N hydrochloric acid, and recovered by neutralization and extraction of the aqueous layer with ether. The ether extract is then dried over sodium sulfate, filtered, and the solvent removed to yield 4'-amino-4-biphenylacetic acid.

When the nitro biphenylacetic acids obtained from example 9, the nitro ethyl esters obtained from example 7, and the nitro benzoic acid compounds obtained from example 5 are used in place of 4'-nitro-4-biphenylacetic acid in the above example, there are obtained the corresponding amino biphenylacetic acids, amino ethyl esters, and amino benzoic acid compounds respectively.

Similarly, when 4-(p-nitrophenyl)-acetophenone, 3-nitro-4-(p-nitrophenyl)-acetophenone, 3-nitro-4-phenylacetophenone, 4-(o-nitrophenyl)-acetophenone, 4-(p-nitrophenyl)-propiophenone, 4-(p-nitrophenyl)-butyrophenone, 3-nitro-4-(p-nitrophenyl)-propiophenone, 3-nitro-4-(p-nitrophenyl)-butyrophenone, 3-nitro-4-phenylpropiophenone, 3-nitro-4-phenylbutyrophenone, 4-(o-nitrophenyl)-propiophenone, 4-(o-nitrophenyl)-butyrophenone, 4-(m-nitrophenyl)-propiophenone, 4-(m-nitrophenyl)-butyrophenone (the propiophenones and butyrophenones are obtained by carrying out the Friedel-Crafts reaction using the propionic or butanoic acid chloride in place of acetyl chloride), and 4-(m-nitro-phenyl)-acetophenone are using in place of 4-nitro-4-biphenylacetic acid in the above example, there are obtained the corresponding amino ketone compounds.

EXAMPLE 11

4'-Chloro-4-biphenylacetic acid

A suspension of 9 grams of 4'-amino-4-biphenylacetic acid and 18 ml. of concentrated hydrochloric acid in 16 ml. of water is heated until the solid dissolves. The solution is then cooled to 0° C. (whereupon the hydrochloride precipitates) and 3.24 grams of sodium nitrite and 6 ml. of water are added to the chilled, stirred mixture. After the suspension has remained in the ice bath for 15 minutes, 13.2 grams of cuprous chloride dissolved in 240 ml. of concentrated hydrochloric acid is added dropwise with vigorous stirring to the chilled mixture. The mixture is then stirred overnight at room temperature. At this point, the reaction mixture is poured into 500 grams of ice, the product extracted with (5× 200 ml.) ether, and the combined ether extracts washed successively with water until neutral, dried over magnesium sulfate, filtered, and concentrated in vacuo to yield a residue of 4'-chloro-4-biphenylacetic acid.

When the amino-4-biphenylacetic acids and esters of the amino benzoic acid compounds obtained from example 10 are used in place of the 4'-amino-4-biphenylacetic acid in the above example, there are obtained the corresponding chloro-4-biphenylacetic acids, esters, and chlorobenzoic acid compounds.

Similarly, when the amino ketone compounds obtained from example 10 are used in place of 4'-amino-4-biphenylacetic acid in the above example, there are obtained the corresponding chloro ketone compounds.

When cuprous bromide in concentrated hydrobromic acid is used in place of cuprous chloride in concentrated hydrochloric acid in the above example, there is obtained 4'-bromo-4-biphenylacetic acid, m.p. 175°–177° C.

When an equivalent amount of fluoroboric acid is used in place of the cuprous chloride in concentrated hydrochloric acid in the above example, the reaction mixture stirred, decanted, and the residue placed in toluene, heated carefully, poured into water, and the organic layer separated, washed with water, dried over sodium sulfate, and concentrated in vacuo, there is obtained 4'-fluoro-4-biphenylacetic acid.

EXAMPLE 12

4'-Mercapto-4-biphenylacetic acid

To 19 grams of 4'-amino-4-biphenylacetic acid in 17 ml. of concentrated hydrochloric acid in 30 grams of ice is added 6.5 grams of sodium nitrite in a small volume of water. The reaction mixture is then added portionwise with stirring over a ½-hour period to 16.4 grams of potassium ethyl xanthate in 21 ml. of water heated at 40°–45° C. After stirring an additional hour, the reaction mixture is cooled and extracted with (3×75 ml.) ether. The combined ether extracts are then washed successively with water, dilute sodium hydroxide, and water to neutrality. The extract is then dried and evaporated in vacuo. The residue is then dissolved in 54 ml. of ethanol, and while refluxing the reaction mixture, 20.5 grams of potassium hydroxide pellets are added portionwise. After complete addition, the reaction mixture is refluxed until a few drops of water give an almost clear solution. The reaction mixture is then concentrated to dryness in vacuo. The residue is then dissolved in water and extracted three times with ether to remove the alkali insoluble material. The alkaline layer is charcoaled, acidified with 6N sulfuric acid, and extracted with ether. The ether solution is then dried over sodium sulfate and concentrated in vacuo to yield 4'-mercapto-4-biphenylacetic acid.

When the amino-4-biphenylacetic acids, esters, and amino benzoic acid compounds obtained from example 10 are used in place of 4'-amino-4-biphenylacetic acid in the above example, there are obtained the corresponding mercapto-4-biphenylacetic acids, esters, and mercapto benzoic acid compounds.

Similarly, when the amino ketone compounds obtained from example 10 are used in place of 4'-amino-4-biphenylacetic acid in the above example, there are obtained the corresponding mercapto ketone compounds.

EXAMPLE 13

4'-Methylmercapto-4-biphenylacetic acid

6 grams of 4'-mercapto-4-biphenylacetic acid is mixed with 16 ml. of water containing 1 gram of sodium hydroxide. To this reaction mixture is added dropwise 3.1 ml. of dimethylsulfate while stirring. The reaction mixture is stirred for an additional 2 hours. The reaction mixture is then extracted with ether and the ether extract washed with water, dried over sodium sulfate, and concentrated in vacuo. The residue is then dissolved in benzene and chromatographed on 168 grams of silica gel. The column is eluted with benzene to yield 4'-methylmercapto-4-biphenylacetic acid.

When dipropylsulfate is used in place of dimethylsulfate in the above example, there is obtained 4'-propylmercapto-4-biphenylacetic acid.

Similarly, when the mercapto-4-biphenylacetic acids, esters, and mercapto benzoic acid compounds obtained from example 12 are used in place of 4'-mercapto-4 -biphenylacetic acid in the above example, there are obtained the corresponding methylmercapto-4-biphenylacetic acids, esters, and methylmercapto benzoic acid compounds.

Similarly, when the mercapto ketone compounds obtained from example 12 are used in place of 4'-mercapto-4-biphenylacetic acid in the above example, there are obtained the corresponding methylmercapto ketone compounds.

EXAMPLE 14

4'-Methylsulfonyl-4-biphenylacetic acid

A mixture OF 0.01 mole of 4'-methylmercapto-4-biphenylacetic acid, excess potassium permanganate, and 50 ml. of 2N sodium hydroxide is stirred at room temperature for 2 hours. To the mixture is then added sufficient ethanol to consume the excess potassium permanganate. The reaction mixture is then filtered and the filtrate treated with an excess of dilute aqueous hydrochloric acid. This reaction mixture is then filtered and the cake washed with (2×15 ml.) water to obtain 4'-methylsulfonyl-4-biphenylacetic acid.

When 4'-propylmercapto-4-biphenylacetic acid and the methylmercapto-4-biphenylacetic acids, esters, and methylmercapto benzoic acid compounds obtained from example 13 are used in place of 4'-methylmercapto-4-biphenylacetic acid in the above example, there are obtained the corresponding 4'-propylsulfonyl-4-biphenylacetic acid, methylsulfonyl-4-biphenylacetic acids, esters, and methylsulfonyl benzoic acid compounds respectively.

Similarly, when the methylmercapto ketone compounds obtained from example 13 are used in place of 4'-methylmercapto-4-biphenylacetic acid in the above example, there are obtained the corresponding methylsulfonyl ketone compounds.

EXAMPLE 15

4'-(N,N-dimethylsulfonamido)-4-biphenylacetic acid

A. Ethyl 4'-(N,N-dimethylsulfonamido)-4-biphenylacetate

A solution of 0.1 mole of ethyl 4'-mercapto-4-biphenylacetate in 100 ml. of 1N sodium hydroxide solution is treated with a slight excess of potassium permanganate. When the oxidation is complete, the manganese dioxide is removed by filtration, the filtrate concentrated to a small volume, and the 4'-carboethoxymethyl-4-biphenylsulfonic acid is isolated by acidification with hydrochloric acid. The sulfonic acid compound is then thoroughly dried and heated at reflux with an excess of thionyl chloride. The excess thionyl chloride is then removed by distillation, leaving a residue of 4'-carobethoxymethyl-4-biphenylsulfonyl chloride. To this residue is added a solution of 100 ml. of chloroform with an excess of dimethylamine and the mixture stirred for an hour. The mixture is then washed with water, dried over sodium sulfate and concentrated in vacuo, to yield ethyl 4'-(N,N-dimethylsulfonamido)-4-biphenylacetate.

B. 4'-(N,N-dimethylsulfonamido)-4-biphenylacetic acid

A solution of the ethyl ester thus obtained in 90 percent ethanol containing 2 equivalents of sodium hydroxide is allowed to stand at room temperature for 18 hours. The mixture is then concentrated in vacuo and acidified with dilute hydrochloric acid to yield 4'-(N,N-dimethylsulfonamido)-4-biphenylacetic acid.

When the mercapto-4-biphenylacetates obtained from example 12 are used in place of ethyl 4'-mercapto-4-biphenylacetate in the above example, there are obtained the corresponding (N,N-dimethylsulfonamido)-4-biphenylacetic acids.

Similarly, when the mercapto ketone compounds obtained from example 12 are used in place of ethyl 4'-mercapto-4-biphenylacetate in the above example, there are obtained the corresponding N,N-dimethylsulfonamido ketone compounds.

EXAMPLE 16

4'-Fluoro-4-biphenylacetic acid

A solution of 0.01 mole of 4'-amino-4-biphenylacetic acid in 50 ml. of 5N hydrochloric acid is cooled to 5° C. and diazotized with 0.02 mole of sodium nitrite in 4 ml. of water. After the addition of 10 ml. of 50 percent fluoboric acid, the supernatant is decanted from the remaining reaction mixture. This remaining portion of the reaction mixture is warmed with 30 ml. of toluene on a steam bath until evolution of nitrogen ceases. The cooled mixture is extracted with dilute sodium hydroxide. The alkaline solution is treated with charcoal, filtered, acidified, and extracted with (3×25 ml.) ether. The ethereal solution is then washed, dried, and concentrated to yield 4'-fluoro-4-biphenylacetic acid.

When the amino-4-biphenylacetic acids and esters obtained from example 10 are used in place of 4'-amino-4-biphenylacetic acid in the above example, there are obtained the corresponding fluoro-4-biphenylacetic acids and esters.

Similarly, when the amino ketone compounds obtained from example 10 are used in place of 4'-amino-4-biphenylacetic acid in the above example, there are obtained the corresponding fluoro ketone compounds.

EXAMPLE 17

4'-Dimethylamino-4-biphenylacetic acid

To a solution of 0.005 mole of a hydrochloride of 4'-amino-4-biphenylacetic acid in 50 ml. of methanol is added ½ gram of anhydrous sodium acetate, 4 ml. of 37 percent formaldehyde, and 1½ grams of 10 percent palladium on charcoal. The mixture is then hydrogenated at room temperature and 40 p.s.i. The reaction mixture is filtered and the solids washed with fresh methanol. The combined methanol filtrate is then evaporated in vacuo and the residue is extracted with boiling benzene. The benzene extract is the evaporated in vacuo to yield 4'-dimethyl-amino-4-biphenylacetic acid.

When the amino-4-biphenylacetic acids obtained from example 10 are used in place of the 4'-amino-4-biphenylacetic acid in the above example, there are obtained the corresponding dimethylamino-4-biphenylacetic acids.

Similarly, when the amino ketone compounds obtained from example 10 are used in place of 4'-amino-4-biphenylacetic acid in the above example, there are obtained the corresponding dimethylamino ketone compounds.

EXAMPLE 18

Ethyl 4'-cyano-4-biphenylacetate

A mixture of 10 millimoles of ethyl 4'-amino-4-biphenylacetate, 3 ml. of concentrated hydrochloric acid, and 15 grams of ice is diazotized with ice-cooling by adding a concentrated aqueous solution of sodium nitrite until a slight excess of nitrous acid is present. The solution is then carefully neutralized by adding solid sodium carbonate. This reaction mixture is then slowly added to a solution of 15 millimoles of cuprous cyanide and 30 millimoles of potassium cyanide in 10 ml. of water maintained at 5° C. The temperature of the solution is slowly increased to 50°–60° C. until the diazonium salt has decomposed. The reaction mixture is then cooled and rendered acidic and is extracted with (3×25 ml.) benzene. The benzene solution is then dried and chromatographed on a silica gel column to yield ethyl 4'-cyano-4-biphenylacetate.

When the ethyl amino-4-biphenylacetates obtained from example 10 are used in place of the ethyl 4'-amino-4-biphenylacetate in the above example, there are obtained the corresponding ethyl cyano-4-biphenylacetates.

Similarly, when the amino ketone compounds obtained from example 10 are used in place of ethyl 4'-amino-4-biphenylacetate in the above example, there are obtained the corresponding cyano ketone compounds.

When the amino-4-biphenylacetic acids obtained from example 10 are used in place of ethyl 4'-amino-4-biphenylacetate in the above example, there are obtained the corresponding cyano-4-biphenylacetic acids.

EXAMPLE 19

Ethyl 4'-carbobenzyloxy14-biphenylacetate

A mixture of 0.01 mole of ethyl 4'-cyano-4-biphenylacetate, 0.01 mole of anhydrous benzyl alcohol, and 25 ml. of anhydrous benzene is cooled to 0° C., saturated with anhydrous hydrogen chloride, and the resulting mixture allowed to stand at room temperature for several days. The solvent is then removed in vacuo, the residue triturated well with ether, and the ether decanted from the residue. 250 ml. of water and 10 ml. of 2.5N hydrochloric acid is then added to the residue and the mixture refluxed for 2½ hours. The cooled reaction mixture is then extracted with (3×50 ml.) ether, the ether extract dried over anhydrous magnesium sulfate, charcoaled, and filtered. The ether filtrate is then concentrated in vacuo to yield ethyl 4'-carbo-benzyloxy-4-biphenylacetate.

When the ethyl cyano-4-biphenylacetates obtained from example 18 are used in place of ethyl 4'-cyano-4-biphenylacetate in the above example, there are obtained the corresponding ethyl carbobenzyloxy-4-biphenylacetates.

Similarly, when the cyano ketone compounds obtained from example 18 are used in place of ethyl 4'-cyano-4-biphenylacetate in the above example, there are obtained the corresponding carbobenzyloxy ketone compounds.

EXAMPLE 20

Ethyl 4'-carboxy-4-biphenylacetate

A solution of 0.01 mole of ethyl 4'-carbo-benzyloxy-4-biphenylacetate in 200 ml. of methanol is treated with hydrogen at room temperature and an initial pressure of 40 p.s.i. in the presence of 2½ grams of 5 percent palladium on carbon. When the theoretical yield of hydrogen is absorbed, the reaction mixture is filtered and the filtrate concentrated in vacuo. This residue is then partitioned between ether and dilute potassium hydrogen carbonate solution, the layers separated, the ether solution extracted with fresh bicarbonate solution, and the bicarbonate layers combined. The bicarbonate reaction mixture is then washed with ether, acidified with hydrochloric acid with cooling, and extracted with ether. The ether extract is then dried over anhydrous magnesium sulfate, charcoaled, filtered, and concentrated to yield ethyl 4'-carboxy-4-biphenylacetate.

When the ethyl carbobenzyloxy-4-biphenylacetates obtained from example 19 are used in place of ethyl 4' -carbobenzyloxy-4-biphenylacetate in the above example, there are obtained the corresponding ethyl carboxy-4-biphenylacetates.

Similarly, when the carbobenzyloxy ketone compounds obtained from example 19 are used in place of ethyl 4'-carbobenzyloxy-4-biphenylacetate in the above example, there are obtained the corresponding carboxy ketone compounds.

EXAMPLE 21

Ethyl 4'-trifluoromethyl-4-biphenylacetate

A mixture of 0.1 mole of ethyl 4'-carboxy-4-biphenylacetate and 0.3 mole of sulfur tetrafluoride is heated at 150° C. for 12 hours in a sealed stainless steel bomb. After cooling, the bomb is vented to release all gaseous material, the residue taken up in ether, washed with dilute potassium bicarbonate solution, water, and dried over anhydrous magnesium sulfate. The ether solution is then charcoaled, filtered, and the filtrate concentrated to a residue. The residue is then chromatographed on a 1-kilogram silica gel column using an ether-petroleum ether system (v/v 0–60 percent ether) as eluent to yield ethyl 4'-trifluoromethyl-4-biphenylacetate.

When the ethyl carboxy-4-biphenylacetates obtained from example 20 are used in place of ethyl 4'-carboxy-4-biphenylacetate in the above example, there are obtained the corresponding ethyl trifluoromethyl-4-biphenylacetates.

EXAMPLE 22

Ethyl 4'-carboxamido-4-biphenylacetate

0.1 mole of ethyl 4'-carboxy-4-biphenylacetate is slowly added to a cooled portion of 60 ml. of thionyl chloride and the resulting mixture refluxed for 2 hours. The excess thionyl chloride is then removed in vacuo. The residual acid halide is then taken up in 70 ml. of dry ether and the resulting ether solution slowly added to a stirred solution of 28 percent ammonium hydroxide over a period of 30 minutes. The reaction mixture is then allowed to stir for an additional hour at room temperature. The reaction mixture is then filtered and the cake air-dried to yield ethyl 4'-carboxamido-4-biphenylacetate.

When the equivalent amount of dimethylamine, dipropylamine, or methylethylamine in water is used in place of the ammonium hydroxide in the above example, there is obtained the corresponding 4'-dimethylcarboxamido, 4'-dipropylcarboxamido, or 4'-methylethylcarboxamido esters respectively.

Similarly, when the ethyl carboxy-4-biphenylacetates obtained from example 20 are used in place of ethyl 4'-carboxy-4-biphenylacetate in the above example, there are obtained the corresponding ethyl carboxamido-4-biphenylacetates.

Similarly, when the carboxy ketone compounds obtained from example 20 are used in place of ethyl 4'-carboxy-4-biphenylacetate in the above example, there are obtained the corresponding carboxamido ketone compounds, and when the equivalent amount of dimethylamine, dipropylamine, or methylethylamine in water is used in place of the ammonium hydroxide in the above example and the carboxy ketone compounds are used in place of ethyl 4'-carboxy-4-biphenylacetate in the above example, there are obtained the corresponding substituted carboxamido ketone compounds.

EXAMPLE 23

4'-Trifluoromethyl-4-biphenylacetic acid

A solution of0.01 mole of potassium hydroxide in 3 ml. of water is added to a cooled solution of0.01 mole of ethyl 4'-trifluoromethyl-4-biphenylacetate in 30 ml. of methanol, additional water or methanol added until the faintest cloudiness persists, and the resulting mixture stirred overnight at room temperature. Excess water is the added to the reaction mixture, the methanol removed in vacuo, and the aqueous mixture washed well with either. The aqueous mixture is then made acidic with 2.5N hydrochloric acid, extracted with (3×25 ml.) ether, and the combined ether extracts dried over anhydrous magnesium sulfate. The ether extract is then filtered and the filtrate concentrated in vacuo to yield 4'-trifluoromethyl-4-biphenylacetic acid.

When the ethyl trifluoromethyl-4-biphenylacetates obtained from example 21 are used in place of ethyl 4'-trifluoromethyl-4-biphenylacetate in the above example, there are obtained the corresponding trifluoromethyl-4-biphenylacetic acids.

Similarly, when the ethyl carboxamido-4-biphenylacetates obtained from example 22 are used in place of ethyl 4'-trifluoromethyl-4-biphenylacetate in the above example and 1,2-dimethoxyethane is used in place of methanol in the above example, there are obtained the corresponding carboxamido-4-biphenylacetic acids.

EXAMPLE 24

Methyl 2-methyl-4-biphenylacetate

A. Methyl 2-carboxychloro-4-biphenylacetate

The procedure of example 6, Part A, is used, using methyl 2-carboxy-4-biphenylacetate in place of 4-(p-nitrophenyl)-benzoic acid to obtain methyl 2-carboxychloro-4-biphenylacetate.

B. Methyl 2-aldehydo-4-biphenylacetate of tetrahydrofuran

The residue obtained from A above is reacted with 0.01 mole of lithium aluminum tritertiarybutoxy hydride in 50 ml. of tetrahydrofuran over a period of 3 hours at −10° C. The reaction mixture is then concentrated in vacuo to a residue to obtain crude methyl 2-aldehydo-4-biphenylacetate.

C. Methyl 2-hydroxymethyl-4-biphenylacetate

The residue obtained from B above is reacted with 0.01 mole of sodium borohydride in 25 ml. of methanol at 0° C. for 2 hours. The reaction mixture is then concentrated in vacuo to obtain methyl 2-hydroxymethyl-4-biphenylacetate.

D. Methyl 2-chloromethyl-4-biphenylacetate

The residue obtained from C above is treated with 25 ml. of thionyl chloride at room temperature overnight. The reaction mixture is then concentrated in vacuo to obtain a crude residue of methyl 2-chloromethyl-4-biphenylacetate.

E. Methyl 2-methyl-4-biphenylacetate

The residue obtained from D above is reacted with 1.0 gram of 10 percent palladium on charcoal in 15 ml. of methyl acetate at 50° C. over a period of 4 hours.

When the ethyl carboxy-4-biphenylacetates obtained from example 20 are used in place of the methyl 2-carboxy-4-biphenylacetate in the above example, there are obtained the corresponding ethyl methyl-4-biphenylacetates.

EXAMPLE 25

Methyl 2-ethyl-4-biphenylacetate

A. Methyl 2-ethylidene-4-biphenylacetate

To a solution of 0.01 mole of methyl 2-aldehydo-4-biphenylacetate in 50 ml. of benzene is added 0.01 mole of methylene triphenylphosphorane and the reaction mixture stirred at room temperature for 2 hours followed by heating the reaction at 80° C. for an additional 6 hours. The reaction mixture is then concentrated in vacuo to yield a crude residue of methyl 2-ethylidene-4-biphenylacetate.

B. Methyl 2-ethyl-4-biphenylacetate

The residue obtained from A above in 25 ml. of methanol is reacted with 0.2 gram of palladium on carbon under 40 p.s.i. of hydrogen pressure at room temperature until the theoretical amount of hydrogen is taken up. The reaction mixture is then filtered and the filtrate concentrated in vacuo to yield a crude residue of methyl 2-ethyl-4-biphenylacetate.

When ethylidene triphenylphosphorane is used in place of methylene triphenylphosphorane in part A of the above example and the product thereof is reacted as in part B above, there is obtained methyl 2-propyl-4-biphenylacetate.

Similarly, when the ethyl aldehydro-4-biphenylacetates obtained from example 24, part B, are used in place of the methyl 2-aldehydo-4-biphenylacetate in the above example, there are obtained the corresponding ethyl ethyl 4-biphenylacetates.

EXAMPLE 26

When the lower alkyl 4-biphenylacetates obtained from examples 24 and 25 are used in place of ethyl 4′-trifluoromethyl-4-biphenylacetate in example 23, there are obtained the corresponding lower alkyl 4-biphenylacetic acids.

EXAMPLE 27

Ethyl 4′-acetamido-4-biphenylacetate

To a solution of 0.01 mole of ethyl 4′-amino-4-biphenylacetate in 100 ml. of benzene is added 0.01 mole of acetic anhydride and the reaction mixture is then refluxed for 3 hours. The reaction mixture is then cooled to room temperature, washed with (3×50 ml.) water, the benzene solution dried over sodium sulfate and concentrated in vacuo to yield ethyl 4′-acetamido-4-biphenylacetate.

When the amino ethyl esters obtained from example 10 are used in place of ethyl 4′-amino-4-biphenylacetate in the above example, there are obtained the corresponding acetamido esters.

EXAMPLE 28

3-Methyl-4-biphenylacetic acid

A mixture of 3.5 grams of 2′-methyl-4′-phenylacetophenone, 1.03 grams of sulfur, and 8 ml. of morpholine is refluxed overnight under nitrogen. To the solution is then added 105 ml. of 15 percent potassium hydroxide and the reaction mixture refluxed for an additional 16 hours. The reaction mixture is then filtered while hot and the filtrate acidified with concentrated hydrochloric acid. The mixture is then filtered and the cake washed with (2×10 ml.) water. The cake is then placed in approximately 500 ml. of ethanol, the mixture boiled for several minutes, and filtered. The filtrate is taken to a small volume in vacuo. The solution is then heated and water added until it becomes turbid. The mixture is then cooled and filtered. The cake thus obtained is dissolved in chloroform and the solution evaporated to a small volume. The solution is then diluted with an excess of petroleum ether, cooled overnight, filtered, and the solid washed with petroleum ether and air-dried to yield 3-methyl-4-biphenylacetic acid, m.p. 138°–140° C.

When 3′-methyl-4′-phenylacetophenone, 2′-chloro-4′-phenylacetophenone, 4′-(p-bromophenyl)-acetophenone, and 4′-(p-methylphenyl)-acetophenone are used in place of 2′-methyl-4′-phenylacetophenone in the above example, there are obtained 2-methyl-4-biphenylacetic acid (m.p., 110.5°–111.5° C.), 2-chloro-4-biphenylacetic acid (m.p., 102.5°–104° C.), 4′-bromo-4-biphenylacetic acid (m.p., 175°–177° C.), 4′-methyl-4-biphenylacetic acid (m.p., 178°–180° C.), and 4′-chloro-4-biphenylacetic acid (m.p., 158°–160° C.).

Similarly, when the chloro-4′-phenylacetophenones, mercapto-4′-phenylacetophenones, methylmercapto-4′-phenylacetophenones, methylsulfonyl-4-phenylacetophenones, (N,N-dimethylsulfonamido)-4′-phenylacetophenones, fluoro-4′-phenylacetophenones, and dimethylamino-4′-phenylacetophenones obtained from examples 11, 12, 13, 14, 15, 16, and 17 are used in place of 2′-methyl-4′-phenylacetophenone in the above example, there are obtained the corresponding substituted 4-biphenylacetic acids.

EXAMPLE 29

2′-Chloro-4-biphenylacetic acid

A mixture of 3.8 grams of 2′-chloro-4-biphenylmethyl ketone, 1.03 grams of sulfur, and 8 ml. of morpholine is refluxed under nitrogen for 16 hours. To the reaction mixture is added 105 ml. of 15 percent potassium hydroxide and the reaction mixture refluxed for an additional 16 hours. The reaction mixture is then filtered while hot and the filtrate acidified with concentrated hydrochloric acid and cooled. The reaction mixture is then filtered, the cake washed with water and dissolved in a minimum amount of chloroform. The chloroform solution is then taken to a small volume and an excess of petroleum ether added. After crystallization begins, the mixture is cooled in an ice bath, subsequently filtered, and the solid thus obtained washed with petroleum ether and air-dried to yield 2′-chloro-4-biphenylacetic acid, m.p., 121°–123 °C.

EXAMPLE 30

α-Hydroxy-α-methyl-2-chloro-4-biphenylacetic acid

A. α-Hydroxy-α-methyl-2-chloro-4-biphenylacetonitrile

To a solution of 4 ml. of hydrogen cyanide containing 0.02 ml. of piperidine in an ice water bath is added 3.5 grams of 3′-chloro-4′-phenylacetophenone over a period of 8 minutes. The solution is stirred in the cold over a period of 80 minutes, during which time 2×0.02 ml. portions of piperidine are added.

B. α-Hydroxy-α-methyl-2-chloro-4-biphenylacetamide

To the solution of part A is added 2 ml. of ether and the solution then poured into 15 ml. of concentrated hydrochloric acid with stirring in an ice-salt bath. At this point, sufficient

gaseous hydrochloric acid is bubbled into the solution so as to saturate the solution. The solution is then allowed to warm to room temperature and is stirred overnight. 50 ml. of water is then added and the solution extracted with (3×50 ml.) ether. The ether solution is then washed with (3×15 ml.) water and dried over magnesium sulfate. The ether solution is then concentrated in vacuo to a solid.

C. α-Hydroxy-α-methyl-2-chloro-4-biphenylacetic acid

To 500 mg. of the solid thus obtained in part B in 13 ml. of ethanol is added a solution of 250 mg. of potassium hydroxide in 3 ml. of water and the mixture refluxed gently under nitrogen for 15 hours. To the solution is then added 25 ml. of water and the solution extracted with (3×25 ml.) ether. The aqueous solution is then made acid with dilute aqueous hydrochloric acid and filtered. The cake is then washed with (2×25 ml.) water and subsequently dried to yield α-hydroxy-α-methyl-2-chloro-4-biphenylacetic acid, m.p., 142.5°–145° C.

When the amino ketones, halo ketones, mercapto ketones, methylmercapto ketones, methylsulfonyl ketones, (N,N-dimethylsulfonamido) ketones, fluoro ketones, dimethylamino ketones, 4-biphenylacetophenone, and 4-phenylacetophenone obtained from examples 10, 11, 12, 13, 14, 15, 16, 17, and 2 respectively are used in place of 3'-chloro-4'-phenylacetophenone in the above example, there are obtained the corresponding α-hydroxy-α-methyl-substituted-4-biphenylacetic acids, α-hydroxy-α-ethyl-substituted-4-biphenylacetic acids, α-hydroxy-α-propyl-substituted-4-biphenylacetic acids, and α-hydroxy-α-methyl-4-biphenylacetic acids.

EXAMPLE 31

Ethyl 2'-chloro-4-biphenylglyoxalate

To a solution of 100 ml. of carbon tetrachloride and 15.7 grams of ethyl oxalyl chloride at −5° C. is added with stirring 17 grams of aluminum chloride followed by a solution of 21.7 grams of 2-chlorobiphenyl in 50 ml. of chloroform. After complete addition of the chloroform solution (approximately 1½ hours), 150 ml. of ethylene dichloride is added and the reaction mixture allowed to come to room temperature. The reaction mixture is then poured into 300 grams of ice and 10 ml. hydrochloric acid. The organic layer is separated, dried, and concentrated in vacuo. The residue is then dissolved in a minimum amount of benzene-petroleum ether and chromatographed on 1059 grams of silica gel and eluted with benzene to yield ethyl 2'-chloro-4-biphenylglyoxalate.

When 4-fluorobiphenyl is used in place of 2-chlorobiphenyl and ethylene dichloride is used in place of carbon tetrachloride in the above example, there is obtained ethyl 4'-fluoro-4-biphenylglyoxalate, m.p. 52°–53° C.

EXAMPLE 32

α-Hhydroxy-α-methyl-2'-chloro-4-biphenylacetic acid

To a mixture of 1.54 grams of magnesium turnings in 40 ml. of ether is added with stirring 9.3 grams of methyl iodide. After complete addition, more methyl iodide is added to consume any unreacted magnesium. This Grignard solution is then added dropwise to a cold, stirred solution of 12.9 grams of ethyl 2'-chloro-4-biphenylglyoxalate in 75 ml. of ether. After complete addition, the reaction mixture is allowed to stir in the cold for an additional hour. The reaction mixture is then refluxed for 3 hours, cooled, and poured into 200 ml. of ice-dilute sulfuric acid solution. The ether layer is then separated, washed with water, dried, and concentrated in vacuo to a crude syrup. The syrup is then placed in 150 ml. of 10 percent potassium hydroxide-methanol and refluxed for approximately 2 hours. The reaction mixture is then poured into approximately 500 ml. of water, acidified with 2.5N hydrochloric acid, extracted with (2×50 ml.) ether, and the ether solution dried and concentrated in vacuo to a residue. The residue is then dissolved in a minimum amount of methanol, charcoaled, filtered, and the filtrate concentrated in vacuo. The residue is then dissolved in a small volume of boiling benzene. Sufficient petroleum ether is then added to make the solution turbid, and after crystallization starts, a large excess of petroleum ether is added and the mixture allowed to remain at room temperature overnight. The mixture is then filtered and the cake washed with petroleum ether and air-dried to yield α-hydroxy-α-methyl-2'-chloro-4-biphenylacetic acid, m.p. 135°–137° C.

When ethyl 4'-fluoro-4-biphenylglyoxalate is used in the above example in place of ethyl 2'-chloro-4-biphenylglyoxalate, there is obtained α-hydroxy-α-methyl-4'-fluoro-4-biphenylacetic acid, m.p. 163°–164° C.

EXAMPLE 33

α-Methylene-2-chloro-4-biphenylacetic acid

A mixture of 1.5 grams of α-hydroxy-α-methyl-2-chloro-4-biphenylacetic acid, 260 mg. of p-toluenesulfonic acid and 30 ml. of toluene is refluxed for 5 hours and the water produced removed by means of a Dean Stark trap. The solution is then cooled to room temperature and filtered. The cake is washed with (2×25 ml.) benzene. The cake is then mixed with 25 ml. of ether and the ether solution washed with (2×10 ml.) water and dried over magnesium sulfate. The ether solution is then concentrated in vacuo to yield crude α-methylene-2-chloro-4-biphenylacetic acid, m.p. 131°–144° C.

When α-hydroxy-α-methyl-2'-chloro-4-biphenylacetic acid and α-hydroxy-α-methyl-4'-fluoro-4-biphenylacetic acid are used in place of α-hydroxy-α-methyl-2-chloro-4-biphenylacetic acid in the above example, there are obtained α-methylene-2'-chloro-4-biphenylacetic acid and α-methylene-4'-fluoro-4-biphenylacetic acid (m.p. 172°–174° C.).

Similarly, when the α-hydroxy-α-methyl-substituted-4-biphenylacetic acids, α-hydroxy-α-ethyl-substituted-4 - biphenylacetic acids, α-hydroxy-α-propyl-substituted-4-biphenylacetic acids, and the α-hydroxy-α-methyl-4-biphenylacetic acids obtained from example 30 and the 2'-chloro and 4'-fluoro compounds obtained from example 32 are used in place of α-hydroxy-α-methyl-2-chloro-4-biphenylacetic acid in the above example, there are obtained the corresponding α-methylene-substituted-4-biphenylacetic acids, α-ehtylidene-substituted-4-biphenylacetic acids, α-propylidene-substituted 4-biphenylacetic acids, α-methylene-4-biphenylacetic acids, and α-methylene, 2'-chloro, and 4'-fluoro 4-biphenylacetic acids.

EXAMPLE 34

α-Methyl-2-chloro-4-biphenylacetic acid

A mixture of 0.8 gram of α-methylene-2-chloro-4-biphenylacetic acid and 0.03 mg. of platinum oxide in 10 ml. of ethanol is hydrogenated at room temperature under 40 p.s.i. The solution is then filtered and the filtrate concentrated in vacuo. The crude material is then taken up in 25 ml. of ether and the ether solution washed with (1×15 ml.) water and dried over magnesium sulfate. The ether solution is then extracted with (3×25 ml.) aqueous sodium carbonate. The sodium carbonate solution is then made acid by the addition of sufficient dilute hydrochloric acid, and then extracted with (3×25 ml.) ether and the ether extract dried over magnesium sulfate. The ether solution is then concentrated in vacuo to a crude solid of α-methyl-2-chloro-4-biphenylacetic acid, m.p. 122°–128° C.

When α-methylene-2'-chloro-4-biphenylacetic acid and α-methylene-4'fluoro-4-biphenylacetic acid are used in place of α-methylene-2-chloro-4-biphenylacetic acid in the above example, there are obtained α-methyl-2'-chloro-4-biphenylacetic acid and α-methyl-4'-fluoro-4-biphenylacetic acid, m.p. 150°–152° C.

Similarly, when the α-alkylidene biphenylacetic acids obtained from example 33 are used in place of α-methylene-2-chloro-4-biphenylacetic acid in the above example, there are obtained the corresponding α-lower alkyl biphenylacetic acids.

EXAMPLE 35

α-Methyl-2-chloro-4-biphenylacetic acid

To a solution of 1.8 grams of α-hydroxy-α-methyl-2-chloro-4-biphenylacetic acid in 40 ml. of glacial acetic acid is added 0.79 gram of phosphorus and 0.32 gram of iodine. The mixture is then refluxed for 16 hours, filtered while hot, and the filtrate poured into 150 ml. of ice water. The mixture is then filtered and the cake thus obtained dissolved in chloroform, washed with water, dried over magnesium sulfate, charcoaled, and the solvent removed in vacuo to yield α-methyl-2-chloro-4-biphenylacetic acid.

When the α-hydroxy-α-lower alkyl-4-biphenylacetic acids obtained from example 30 are used in place of α-hydroxy-α-methyl-2-chloro-4-biphenylacetic acid in the above example, there are obtained the corresponding α-lower alkyl-4-biphenylacetic acids.

EXAMPLE 36

4'-Nitro-4-biphenylacetic acid
2'-Nitro-4-biphenylacetic acid
2-Nitro-4-biphenylacetic acid

A mixture of 100 ml. of glacial acetic acid and 150 ml. of nitric acid (d=1.42) is gradually added to 0.18 mole of ethyl 4-biphenylacetate in 100 ml. of glacial acetic acid. The reaction mixture is stirred at room temperature for 24 hours, at which time the reaction mixture is concentrated in vacuo to a residue. The residue is then chromatographed on a silica gel column using ether-petroleum ether as the eluent (0–100 percent) to yield the various fractions of ethyl 4'-nitro-4-biphenylacetate, ethyl 2'-nitro-4-biphenylacetate, and ethyl 2-nitro-4-biphenylacetate. The ether-petroleum ether fractions are then concentrated in dryness, and each residue is separately saponified using the method described in example 23 to yield the corresponding nitro 4-biphenylacetic acids.

When ethyl α-methyl-4-biphenylacetate, ethyl α-propyl-4-biphenylacetate, ethyl α-diethyl-4-biphenylacetate, ethyl α-fluoro-4-biphenylacetate, ethyl α-methoxy-4-biphenylacetate, and ethyl α-trifluoromethyl-4-biphenylacetate obtained from example 57 are used in place of ethyl 4-biphenylacetate in the above example, there are obtained the corresponding 4'-nitro, 2'-nitro, and 2-nitro 4-biphenylacetic acids.

EXAMPLE 37

When the nitro compounds obtained from example ⅜⅛ are used in place of the 4'-nitro-4-biphenylacetic acid in example 10, there are obtained the corresponding amino 4-biphenylacetic acids. When these amino 4-biphenylacetic acids are successively treated according to examples 11 through 14 and 16 through 27, there are obtained the corresponding appropriately substituted 4-biphenylacetic acids and esters.

When the mercapto compounds obtained from the above example are used in place of the 4'-fluoro-4-biphenylacetic acid of example 57 and the esters thus obtained treated in accordance with example 15, there are obtained the corresponding N,N-dimethylsulfonamido-4-biphenylacetic acids.

EXAMPLE 38

Methyl α-pyrazolino-2-chloro-4-biphenylacetate

To a solution of 0.0241 mole of α-methylene-2-chloro-4-biphenylacetic acid in 200 ml. of ether-ethyl acetate (1:1) is added an excess of a solution of diazomethane in ether. The reaction mixture is stirred at room temperature for 16 hours. At this point, the excess diazomethane is removed by the dropwise addition of acetic acid. The reaction mixture is concentrated in vacuo to a residue and the residue chromatographed on 500 grams of silica gel using 10 percent ether-petroleum ether as eluent to yield methyl α-pyrazolino-2-chloro-4-biphenylacetate.

When the α-methylene-substituted-4-biphenylacetic acids, α-methylene-2'-chloro-4-biphenylacetic acid, and α-methylene-4'-fluoro-4-biphenylacetic acid obtained from example 33 are used in place of α-methylene-2-chloro-4-biphenylacetic acid in the above example, there are obtained the corresponding methyl α-pyrazolino-4-biphenylacetates.

EXAMPLE 39

Methyl α-cyclopropyl-2-chloro-4-biphenylacetate

300 mg. of methyl α-pyrazolino-2-chloro-4-biphenylacetate is heated on a steam bath for 15 minutes. To the reaction mixture is then added 20 ml. of benzene and 300 mg. of osmium oxide and the reaction mixture stirred for 16 hours. The reaction mixture is then poured into 25 ml. of 2.5N hydrochloric acid. The organic layer is then separated, washed with water, dried and chromatographed on a silica gel column using benzene as eluent to yield methyl α-cyclopropyl-2-chloro-4-biphenylacetate.

When the methyl α-pyrazolino-substituted-4-biphenylacetates, methyl α-pyrazolino-2'-chloro-4-biphenylacetate, and methyl α-pyrazolino-4'-fluoro-4-biphenylacetate obtained from example 37 are used in place of methyl α-pyrazolino-2-chloro-4-biphenylacetate in the above example, there are obtained the corresponding methyl α-cyclopropyl-substituted-4-biphenylacetates, methyl α-cyclopropyl-2'-chloro-4-biphenylacetate, and methyl α-cyclopropyl-4'-fluoro-4-biphenylacetate respectively.

EXAMPLE 40

When the α-pyrazolino-4-biphenylacetates obtained from example 38 and the α-cyclopropyl-4-biphenylacetates obtained from example 39 are used in place of ethyl 4'-trifluoromethyl-4-biphenylacetate in example 23, there are obtained the corresponding α-pyrazolino-4-biphenylacetic acids and α-cyclopropyl-4-biphenylacetic acids.

EXAMPLE 41

When the α-pyrazolino-4-biphenylacetic acids obtained from example 40 are used in place of methyl α-pyrazolino-2-chloro-4-biphenylacetate in example 39 and the compound heated above its melting point, there is obtained the corresponding α-cyclopropyl-4-biphenylacetic acids.

EXAMPLE 42

4'-fluoro-4-biphenylacetamide

To 0.141 mole of 4'-fluoro-4-biphenylacetic acid is added dropwise over a period of 5 minutes 100 grams of thionyl chloride. The reaction mixture is heated on a steam bath for 3½ hours. The reaction mixture is then concentrated in vacuo and to the residue is added 100 ml. of ether. This ether reaction mixture is then added dropwise to 500 ml. of concentrated ammonium hydroxide. The reaction mixture is then stirred for an additional hour, filtered, and the cake washed with water until the washing is neutral. The cake is then dried in vacuo to yield 4'-fluoro-4-biphenylacetamide.

When the 4-biphenylacetic acids, halo-4-biphenylacetic acids, methylmercapto-4-biphenylacetic acids, methylsulfonyl-4-biphenylacetic acids, (N, N-dimethylsulfonamido)-4-biphenylacetic acids, fluoro-4-biphenylacetic acids, and trifluoromethyl-4-biphenylacetic acids obtained from examples 9, 11, 13, 14, 15, 16, and 23 respectively are used in place of 4'-fluoro-4-biphenylacetic acid in the above example, there are obtained the corresponding 4-biphenylacetamides.

EXAMPLE 43

4'-Flouro-4-biphenylacetonitrile

To 0.03 mole of 4'-fluoro-4-biphenylacetamide is added 0.031 mole of phosphorous pentachloride. After mixing for approximately 5 minutes, 30 ml. of phosphorous oxychloride is added to the reaction mixture, which is then heated on a steam bath for 1 hour. The phosphorous oxychloride is then removed in vacuo and the resulting reaction mixture is poured into 200 ml. of an ice water mixture. The reaction mixture is

stirred for 40 minutes and then extracted with (3×50 ml.) ether. The combined ether extract is then concentrated in vacuo to yield a crude residue of 4'-fluoro-4-biphenylacetonitrile.

When the 4-biphenylacetamides obtained from example 42 are used in place of 4'-fluoro-4-biphenylacetamide in the above example, there are obtained the corresponding 4-biphenylacetonitriles.

EXAMPLE 44

α, α-Dimethyl-4'-fluoro-4-biphenylacetonitrile

To a cooled, stirred mixture of 0.05 mole of 4'-fluoro-4-biphenylacetonitrile, 0.16 mole of sodium amide, and 70 ml. of anhydrous benzene is added 0.19 mole of methyl iodide. The reaction mixture is then allowed to warm to room temperature and then heated slowly to 58° C. for 1 hour. The reaction mixture is then refluxed for an additional 8 hours. To the cooled reaction mixture is then added dropwise 25 ml. of water, 50 ml. of 2.5N hydrochloric acid, and, finally, 50 ml. each of benzene and water. After stirring for several minutes, the layers are allowed to separate. The aqueous layer is extracted with (4×25 ml.) benzene and the combined benzene solution is dried over sodium sulfate. The benzene solution is then filtered and the filtrate concentrated to a residue to yield α, α-dimethyl-4'-fluoro-4-biphenylacetonitrile.

When ethyl iodide or propyl iodide are used in place of methyl iodide in the above example, there is obtained α, α-diethyl-4'-fluoro-4-biphenylacetronitrile or α, α-dipropyl-4'-fluoro-4-biphenylacetonitrile.

Similarly, when the 4-biphenylacetonitriles obtained from example 43 are used in place of 4'-fluoro-4-biphenylacetonitrile in the above example, there are obtained the corresponding α, α-dimethyl-4-biphenylacetonitrile compounds.

EXAMPLE 45

α, α-Dimethyl-4'-fluoro-4-biphenylacetic acid

To a mixture of 0.0052 mole of α, α-dimethyl-4'-fluoro-4-biphenylacetonitrile in 100 ml. of acetic acid is added 15 ml. of 20 percent hydrochloric acid and the reaction mixture refluxed for 19 hours. The cooled reaction mixture is then poured into a mixture of 500 ml. of ice water, extracted with ether, and the ether extract dried and concentrated to yield α, α-dimethyl-4'-fluoro-4-biphenylacetic acid.

When the 4-biphenylacetonitriles obtained from example 44 are used in place of α, α-dimethyl-4'-fluoro-4-biphenylacetonitrile in the above example, there are obtained the corresponding 4-biphenylacetic acid compounds.

EXAMPLE 46

Methyl α-methyl-4'-fluoro-4-biphenylacetate

A mixture of 0.2 mole of methyl 4'-fluoro-4-biphenylacetate, 40 grams of dimethyloxalate, and 40 grams of potassium tertiarybutoxide in 500 ml. of benzene is refluxed under nitrogen for 4 hours with stirring. The cooled reaction mixture is then filtered and the cake washed with (4×50 ml.) benzene followed by (4×50 ml.) ether and the cake dried in vacuo. A mixture of 0.05 mole of this cake and 0.06 mole of methyl iodide in 300 ml. of dimethylformamide is stirred at room temperature for 4 hours, then heated on a steam bath until the reaction mixture is neutral. To the cooled reaction mixture is then added 0.05 mole of sodium methoxide in 30 ml. of methanol and the reaction mixture heated for an additional 2 hours on a steam bath. The cooled reaction mixture is then added to 1 liter of iced-water containing 0.06 mole of hydrochloric acid. The reaction mixture is then extracted with (3×200 ml.) either and the combined ether extract washed with water, sodium carbonate, and water. The ether solution is then dried over sodium sulfate and concentrated in vacuo to yield methyl α-methyl-4'-fluoro-4-biphenylacetate.

When ethyl iodide or propyl iodide is used in place of methyl iodide in the above example, there is obtained methyl α-ethyl-4'-fluoro-4-biphenylacetate or methyl α-propyl-4'-fluoro-4-biphenylacetate.

Similarly, when the ethyl 4-biphenylacetates obtained from example 7, the ethyl halo-4-biphenylacetates, ethyl dilower alkylsulfonamido-4-biphenylacetates, ethyl lower alkylmercapto-4-biphenylacetates, ethyl dilower alkylsulfonyl-4-biphenylacetates, ethyl dilower alkylcarboxamido-4-biphenylacetates, and ethyl dilower alkylamino-4-biphenylacetates are used in place of methyl 4'-fluoro-4-biphenylacetate in the above example, there are obtained the corresponding α-ethyl-substituted-4-biphenylacetate compounds.

Similarly, when prop-2-en iodide, but-3-yn iodide, and 2-chloropropyl iodide are used in place of methyl iodide in the above example, there are obtained the corresponding α-prop-2-enyl, α-but-3-ynyl, and α-2-chloropropyl biphenyl compounds.

EXAMPLE 47

Methyl 2, α-dichloro-4-biphenylacetate

A mixture of 1.0 mole of 2-chloro-4-biphenylacetic acid and 300 ml. of thionyl chloride is refluxed for 2 hours. 450 ml. of sulfuryl chloride is then added over a period of 2–3 hours, maintaining a gentle reflux during the addition. The mixture is then allowed to stand overnight at room temperature, after which the excess thionyl and sulfuryl chlorides are removed in vacuo. The residue is then carefully poured into 200 ml. of stirred, cooled methanol and allowed to stand at room temperature for 2–3 hours. The excess methanol is then removed in vacuo to yield crude methyl 2,α-dichloro-4-biphenylacetate.

When the 4-biphenylacetic acids obtained from examples 9, 11, 12, 13, 14, 15, 16, 17, 23, and 27 and the 4-biphenylacetates obtained from examples 18, 21, 24, and 25 are used in place of 2-chloro-4-biphenylacetic acid in the above example, there are obtained the corresponding α-chloro-4-biphenylacetates.

EXAMPLE 48

2,α-Dichloro-4-biphenylacetic acid

A mixture of 1.0 mole of 2-chloro-4-biphenylacetic acid in 450 ml. of sulfuryl chloride is refluxed over a period of 2–3 hours. The mixture is then allowed to stand for 1 hour at room temperature and the excess sulfuryl chloride removed in vacuo to yield crude, 2,α-dichloro-4-biphenylacetic acid.

When the 4-biphenylacetic acids obtained from examples 9, 11, 12, 13, 14, 15, 16, 17, 23, and 27 are used in place of 2-chloro-4-biphenylacetic acid in the above example, there are obtained the corresponding α-chloro-4-biphenylacetic acids.

EXAMPLE 49

Methyl α-fluoro-2-chloro-4-biphenylacetate

To a mixture of 20 ml. of diethylene glycol, 0.02 mole of fused potassium fluoride, and 0.03 gram of potassium iodide maintained at 125° C. is added 0.0073 mole of methyl 2,α-dichloro-4-biphenylacetate. The reaction mixture is then stirred at 119°–121° C. for 19 hours. The reaction mixture is then allowed to cool to room temperature and poured into a stirred mixture of ice and water. The ice-water mixture is then extracted with 60 ml. of chloroform and the chloroform extract is washed with water and dried over sodium sulfate. The chloroform solution is then concentrated in vacuo and the residue taken up in benzene. The benzene reaction mixture is then concentrated in vacuo to yield crude methyl α-fluoro-2-chloro-4-biphenylacetate.

When the 4-biphenylacetates obtained from example 47 are used in place of 2,α-dichloro-4-biphenylacetate in the above example, there are obtained the corresponding α-fluoro-4-biphenylacetates.

EXAMPLE 50

When the α-chloro compounds obtained from examples 47 and 48 are placed in a mixture of water, methanol, and dilute sodium hydroxide and the reaction mixture is stirred for approximately 1 hour, there are obtained the corresponding hydroxy compounds.

EXAMPLE 51

α-Methoxy-2-chloro-4-biphenylacetic acid

A mixture of 0.004 mole of 2,α-dichloro-4-biphenylacetic acid in 35 ml. of anhydrous methanol is added to an ice-cooled solution of 0.21 grams of sodium in 40 ml. of anhydrous methanol. The reaction mixture is stirred in the ice bath until the reaction mixture is at room temperature. The reaction mixture is then stirred at room temperature for an additional 16 hours, whereupon the mixture is refluxed for 1 hour and allowed to come to room temperature again. Dilute hydrochloric acid is then added to the reaction mixture until the reaction mixture becomes acidic. The reaction mixture is then concentrated in vacuo and the residue partitioned between ether and water. The ether layer is removed washed with water, and extracted with aqueous potassium bicarbonate solution. The bicarbonate solution is then made acid with dilute hydrochloric acid and the reaction mixture extracted with chloroform. The chloroform extract is then dried over sodium sulfate and concentrated in vacuo. The residue is then recrystallized from benzene to yield α-methoxy-2-chloro-4-biphenylacetic acid, m.p. 129°–131.5° C.

When the α-chloro-4-biphenylacetates obtained from example 47 and the α-chloro-4-biphenylacetic acids obtained from example 48 are used in place of 2,α-dichloro-4-biphenylacetic acid in the above example, there are obtained the corresponding α-methoxy-4-biphenylacetates and α-methoxy-4-biphenylacetic acids.

EXAMPLE 52

α-Fluoro-2-chloro-4-biphenylacetic acid

To a mixture of 0.0057 mole of methyl α-fluoro-2-chloro-4-biphenylacetate in 20 ml. of ethanol is added a mixture of 0.0057 mole of potassium hydroxide in 2 ml. of water. The reaction mixture is then allowed to stir for 2 hours at room temperature. At this point, an excess of hydrochloric acid is added to the reaction mixture and it is thereafter concentrated in vacuo to yield crude α-fluoro-2-chloro-4-biphenylacetic acid.

When the fluoro-4-biphenylacetates obtained from example 49 are used in place of methyl α-fluoro-2-chloro-4-biphenylacetate in the above example, there are obtained the corresponding α-fluoro-4-biphenylacetic acids.

Similarly, when the α-hydroxy -4-biphenylacetates obtained from example 50 are used in place of methyl α-fluoro-2-chloro-4-biphenylacetate in the above example, there are obtained the corresponding α-hydroxy-4-biphenylacetic acids.

EXAMPLE 53

Ethyl β-trifluoromethyl-4-biphenyl-prop-2-enoate

0.01 mole of 4-biphenyl trifluoromethyl ketone and 0.01 mole of carbethoxymethylene triphenylphosphorane are refluxed overnight in 75 ml. of dry toluene. The reaction mixture is then filtered and concentrated in vacuo, the residue is chromatographed on 300 grams of silical gel and eluted with 25 percent benzene-petroleum ether to give the desired product. Ethyl β-trifluromethyl-4-biphenyl-prop-2-enoate is recrystallized from petroleum ether, m.p. 55°–57° C.

When 4-(4'-fluorobiphenyl)-trifluoromethyl ketone, 4-(2'-chlorobiphenyl)-trifluoromethyl ketone, 4-(4'-trifluoromethylbiphenyl)-trifluoromethyl ketone, 4-(2-ethylthiobiphenyl)-trifluoromethyl ketone, 4-(2'-carboxamidobiphenyl)-trifluoromethyl ketone, 4-(3'-ethylbiphenyl)-trifluoromethyl ketone, 4-(2'-acetylaminobiphenyl)-trifluoromethyl ketone, 4-(2-dimethylsulfonylbiphenyl)-trifluoromethyl ketone, and 4-(2'-dimethylsulfamylbiphenyl)-trifluoromethyl ketone are used in place of 4-biphenyl trifluoromethyl ketone in the above example, there are obtained the corresponding ethyl β-trifluoromethyl-4-biphenyl-prop-2-enoate compounds.

EXAMPLE 54

Ethyl β-trifluoromethyl-4-biphenylpropanoate β-trifluoromethyl-

0.0078 mole (2.50 grams) of ethyl β-trifluoromethyl-4-biphenyl-prop-2-enoate in 25 ml. of ethanol containing 0.1 gram of PtO_2 is reduced with hydrogen at 40 pounds of pressure and at room temperature. When an equivalent amount (0.0078 mole) of hydrogen is taken up, the reaction mixture is filtered and concentrated to yield crude ethyl β-trifluoromethyl-4-biphenylpropanoate.

When the prop-2-enoate compounds obtained from example 53 are used in place of ethyl β-trifluoromethyl-4-biphenyl-prop-2-enoate in the above example, there are obtained the corresponding propanoates.

EXAMPLE 55 3-(p-Biphenyl)-1,1-dipheyl-3-trifluoromethyl-prop-1-ene

A. 3-(p-Biphenyl)-1,1-diphenyl-3-trifluoromethyl-propan-1-ol

To 0.108 gram (0.023 mole) of magnesium, activated with iodine, in 25 cc. of dry ether containing 1 drop of methyl iodide is added dropwise 0.022 mole of bromobenzene in 15 cc. of Et_2O. The mixture is heated at reflux 2 hours after the addition is complete. To the cooled mixture is added 0.01 mole of ethyl β-trifluoromethyl-4-biphenyl-propanoate in 50 ml. of dry Et_2O and the reaction mixture allowed to reflux for 3 hours, then allowed to stir at room temperature overnight. The mixture is then poured onto a saturated ammonium chloride solution and extracted well with ether. The ether is washed with water, dried, and the ether solution concentrated in vacuo. The residue is chromatographed on 200 grams of silica gel (eluted with 40 percent ether in petroleum ether) to yield 3-(p-biphenyl)-1,1-diphenyl-3-trifluoromethyl-propan-1-ol.

B. 3-(p-Biphenyl)-1,1-diphenyl-3-trifluoromethyl-prop-1-ene

The crude alcohol obtained from part A is dehydrated by refluxing with p-toluenesulfonic acid in toluene for 3 hours. The reaction mixture is then cooled, washed with water, and concentrated. The residue is chromatographed on 200 grams silica gel and eluted with 10 percent benzene-petroleum ether to give 3-(p-bipheynl)-1,1-diphenyl-3-trifluoromethyl-prop-1-ene.

When the β-trifluoromethyl-4-substituted-biphenyl-propanoate compounds obtained from example 54. excluding the compounds containing the 2'-carboxamido, 2'-acetylamino, 2-dimethylsulfonyl, and 2'-dimethylsulfamyl groups, are used in place of β-trifluoromethyl-4-biphenyl-propanoate in part A of the above example and the product therefrom carried through part B of the above example, there are obtained the corresponding prop-1-ene compounds.

EXAMPLE 56

α-Trifluoromethyl-4-biphenylacetic acid

To a well-stirred solution of 0.01 mole of 3-(p-biphenyl)-1,1-diphenyl-3-trifluoromethyl-prop-1-ene in 10 ml. of chloroform and 50 ml. of glacial HOAc is added 0.01 mole of chromium trioxide in 5 ml. of water. After 1 hour, the acetic acid is removed in vacuum; 100 ml. of 10 percent sulfuric acid is added. The mixture is then extracted well with ether, the ether extracts washed with bisulfite solution, water, then dried and concentrated. The residue is recrystallized from hexane to yield β-trifluoromethyl-4-biphenylacetic acid.

When the prop-1-ene compounds obtained from example 55 are used in place of 3-(p-biphenyl)-1,1-diphenyl-3-trifluoromethyl-prop-1-ene in the above example, there are obtained the corresponding substituted-biphenylacetic acids.

EXAMPLE 57

Ethyl 4'-fluoro-4-biphenylacetate

A mixture of 0.05 mole of 4'-fluoro-4-biphenylacetic acid, 6 ml. of concentrated sulfuric acid, and 200 ml. of anhydrous ethanol (approximately 3 percent sulfuric acid) is stirred at room temperature overnight. The solution is then concentrated in vacuo to approximately ⅓ the volume. 200 ml. of water are added and the mixture extracted with (3×75 ml.) ether. The combined ether extracts are teen washed with saturated potassium bicarbonate solution and water. The ether solution is then dried over magnesium sulfate, filtered, and concentrated to a residue. The residue is then chromatographed on a silica gel column (wt./wt. 50:1 gram crude) using an ether-petroleum ether system (v/v 20–60 percent) as eluent to yield ethyl 4'-fluoro-4-biphenylacetate.

When a solution of gaseous hydrochloric acid in ethanol is used in place of the sulfuric acid-ethanol solution in the above example, there is obtained ethyl 4'-fluoro-4-biphenylacetate.

When methanol, n-propanol, i-butanol, prop-2-enol, but-3-ynol, cyclopropanol, phenol, p-acetylaminophenol, p-carboxyphenol, m-carboxamidophenol (in an inert solvent and azeotrope the water), methoxymethanol, methoxycyclopropanol, dimethoxycyclobutanol, glycerol, dimethylaminoethyl chloride, and aminocyclopropylmethyl chloride (when reacting the chloride compounds, reflux the acid and chloride compound in dry isopropanol for 12 hours) are used in place of ethanol in the above example, there are obtained the corresponding methyl 4'-fluoro-4-biphenylacetic acid esters.

Similarly, when the 4-biphenylacetic acids obtained from examples 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 23, 26, 27, 33, 34, 36, 37, 40, 45, 51, 52 (α-fluoro compounds), and 56 are used in place of 4'-fluoro-4-biphenylacetic acid in the above example, there are obtained the corresponding ethyl esters.

EXAMPLE 58

t-Butyl 4'-fluoro-4-biphenylacetate

0.05 mole of 4'-fluoro-4-biphenylacetic acid is treated with 0.2 mole of thionyl chloride and the resultant mixture gently heated on a steam bath for 2 hours. The excess thionyl chloride is then removed in vacuo. 50 ml. of benzene is added and the solvent again removed in vacuo. 50 ml. of fresh, dry 1,2-dimethoxyethane is then added and the resultant solution slowly added to a mixture of 0.06 mole of potassium tertiarybutoxide in 100 ml. of dimethoxyethane with ice-cooling. The resultant mixture is then stirred at room temperature for 4 hours and then concentrated to a residue in vacuo. The residue is then dissolved in ether, washed with sodium bicarbonate, dried, evaporated, and chromatographed on a silica gel column (wt./wt. 50:1 gram crude) using an ether-petroleum ether (v/v 20–60 percent) system as eluent to yield t-butyl 4'-fluoro-4-biphenylacetate.

When sodium ethoxide, sodium propoxide, sodium butoxide, sodium benzylate, sodium phenoxide, and sodium phenylethoxide are used in place of potassium t-butoxide in the above example, there are obtained the corresponding ethyl, n-propyl, i-butyl, benzyl, phenyl, and phenylethyl esters of 4'-fluoro-4-biphenylacetic acid respectively.

Similarly, when the 4-biphenylacetic acids obtained from examples 9, 11, 12, 13, 14, 15, 16, 17, 18, 23, 26, 33, 34, 36, 37, 40, 45, 51, 52 (α-fluoro compounds), and 56 (excluding those compounds containing an active hydrogen group) are used in place of 4'-fluoro-4-biphenylacetic acid in the above example, there are obtained the corresponding ethyl esters.

EXAMPLE 59

Methyl 4'-fluoro-4-biphenylacetate

To a solution of 0.01 mole of 4'-fluoro-4-biphenylacetic acid in 30 ml. of anhydrous tetrahydrofuran is added 0.011 mole of methanol followed by 0.011 mole of N,N'-dicyclohexylcarbodiimide (which has been dissolved in a minimum amount of tetrahydrofuran). The mixture is then shaken thoroughly for a minute and allowed to sit overnight stoppered. The mixture is then filtered, the precipitated N,N'-dicyclohexylurea obtained is washed with a small portion of fresh tetrahydrofuran, and the wash combined with the filtrate. The combined filtrates are concentrated to dryness. The residue is then taken up in 100 ml. of ether, washed with bicarbonate solution, water, dried over magnesium sulfate, filtered, and concentrated to a residue. This residue is then chromatographed on a silica gel column (wt./wt. 50:1 gram crude) using an ether-petroleum ether (v/v 20–60 percent) system as eluent to yield methyl 4'-fluoro-4-biphenylacetate.

When ethanol, n-propanol, i-butanol, benzyl alcohol, phenylethanol, N,N-diethylethanolamine, and N,N-dimethylethanolamine are used in place of methanol in the above example, there are obtained the ethyl, n-propyl, i-butyl, benzyl, phenylethyl, N,N-diethylaminoethyl, and N,N-dimethylaminoethyl esters of 4'-fluoro-4-biphenylacetic acid respectively. The esters from the N-substituted ethanolamines are extracted from the ether solution indicated in the above example using dilute hydrochloric acid, the acid solution washed well with ether, made slightly alkaline with ammonium hydroxide, extracted with ether, the combined ether extracts washed with water, dried over potassium carbonate and charcoal, filtered, and the resulting ether solution concentrated to a residue. The volatile ethanolamines are then removed in vacuo.

Similarly, when the 4-biphenylacetic acids obtained from examples, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 23, 26, 33, 34, 36, 37 ,40, 45, 51, 52 (α-fluoro compounds), and 56 are used in place of 4'-fluoro-4-biphenylacetic acid in the above example, there are obtained the corresponding ethyl esters.

EXAMPIE 60

Sodium 4'-fluoro-4-biphenylacetate

A solution of 0.01 mole of sodium hydroxide in 15 ml. of water is added with stirring to a solution of 0.01 mole of 4'-fluoro-4-biphenylacetic acid in 25 ml. of methanol. At this point, additional methanol is added as needed to obtain complete solution and the solution stirred for 1 hour. The solution is then evaporated in vacuo to obtain a residue of sodium 4'-fluoro-4-biphenyl-acetate.

When potassium hydroxide is used in place of sodium hydroxide in the above example, there is obtained the corresponding potassium salt.

When ethylamine, N,N-dimethylaminoethanol, N,N-diethylethanolamine, triethylamine, piperazine, morpholine, and choline are used in place of sodium hydroxide in the above example and are dissolved in methanol in place of water, there are obtained the corresponding ethylamine, N,N-dimethylaminoethanol, N,N-diethylethanolamine, triethylamine, piperazine, morpholine, and choline 4'-fluoro-4-biphenylacetic acid salts respectively.

Similarly, when the 4-biphenylacetic acids obtained from examples 9, 11, 12 13, 14, 15, 16, 17, 18, 23, 26, 33, 34, 36, 37, 40, 45, 51, 52 (α-fluoro compounds), and 56 (excluding those compounds containing an active hydrogen) are used in place of 4'-fluoro-4-biphenylacetic acid in the above example, there are obtained the corresponding sodium salts.

EXAMPLE 61

2(4'-Fluoro-4-biphenyl)-ethanol

To a well-stirred suspension of 0.005 mole of lithium aluminum hydride in 250 ml. of anhydrous ether is added dropwise a solution of 0.01 mole of 4'-fluoro-4-biphenylacetic acid with ice-cooling. The reaction mixture is stirred at room temperature for 1 hour, after which time 10 ml. of water is added dropwise with ice-cooling. The reaction mixture is then poured into dilute sulfuric acid and the aqueous layer is extracted with (2×25 ml.) ether. The combined ether extracts are washed with water, dilute bicarbonate, and water, then dried over sodium sulfate and concentrated in vacuo. The residue is then chromatographed on a silica gel column and

eluted with ether-petroleum ether (10–100 percent) to yield 2-(4'-fluoro-4-biphenyl)-ethanol.

When the 4-biphenylacetic acids obtained from examples 11, 13, 16, 17, 26, 40, 45, 51, 52 (α-fluoro compounds), and 56 (excepting those containing an active hydrogen, the trifluoromethyl-4-biphenylacetic acids of example 23, the halo, lower alkylthio, phenyl, dilower alkylamino, and fluoro 4-biphenylacetic acids of examples 33 and 34, and the lower alkyl trifluoromethyl 4-biphenylacetic acids of example 37 are used in place of 4'-fluoro-4-biphenylacetic acid in the above example, there are obtained the corresponding alcohols. The compounds of examples 10, 20, 22, 27, and 56 are used in place of 4'-fluoro-4-biphenylacetic acid in the above example, after benzylating the active hydrogen group, to obtain the corresponding alcohols.

EXAMPLE 62

Methyl 2-(4'-fluoro-4-biphenyl)-ethyl ether

To a well-stirred suspension of 0.01 mole of sodium hydride in 25 ml. of dry dimethylformamide, which has been cooled to 0° C., is added dropwise a solution of 0.01 mole of 2-(4'-fluoro-4-biphenyl)-ethanol in 10 ml. of dimethylformamide. The reaction mixture is stirred for 15 minutes and 0.015 mole of methyl iodide is then added dropwise. The mixture is allowed to stir overnight at room temperature. 200 ml. of water is added and the resultant mixture extracted well with ether. The combined ether extracts are washed with water, dried over sodium sulfate, and concentrated. The residue is chromatographed on 250 grams of silica gel and eluted with ether-petroleum ether (10–80 percent) to yield methyl 2-(4'-fluoro-4-biphenyl)-ethyl ether.

When ethyl iodide, allyl bromide, benzyl chloride, and ethoxyethyl chloride are used in place of methyl iodide in the above example, there are obtained the corresponding ethyl allyl, benzyl, and ethoxyethyl ethyl ethers respectively.

Similarly, when the alcohols obtained from example 61 are used in place of 2(4'-fluoro-4-biphenyl)-ethanol in the above example, there are obtained the corresponding methyl ethers.

EXAMPLE 63

4'-Fluoro-4-biphenylacetaldehyde

A. 4'-Fluoro-4-biphenylacetyl chloride

To a solution of 0.01 mole of 4'-fluoro-4-biphenylacetic acid in 50 ml. of benzene is added 0.011 mole of thionyl chloride. The solution is then heated on a steam bath for 1 hour, subsequently concentrated in vacuo to remove the solvent and any excess thionyl chloride. 25 ml. of benzene is then added and removed in vacuo to yield a residue of 4'-fluoro-4-biphenylacetyl chloride.

B. 4'-Fluoro-4-biphenylacetaldehyde

To a suspension of 0.01 mole of tritertiarybutoxy lithium aluminum hydride in 50 ml. of dry tetrahdyrofuran is added dropwise with stirring a solution of 0.01 mole of 4'-fluoro-4-biphenylacetyl chloride in 25 ml. of dry tetrahydrofuran. The reaction mixture is stirred at −10° C. for 3 hours followed by the addition of 200 ml. of 5 percent sulfuric acid added cautiously and the resultant mixture extracted with (3×75 ml.) ether. The combined ether extracts are washed with water, dried over sodium sulfate, and concentrated. The residue is chromatographed on 250 grams of silica gel and eluted with (10–90 percent) ether-petroleum ether to yield 4'-fluoro-4-biphenyacetaldehyde.

When the 4-biphenylacetic acids obtained from examples 9, 11, 13, 14, 15, 16, 17, 18, 23, 26, 36, 40, 45, 51, 52 (α-fluoro compounds), and 56 (excepting those containing an acitve hydrogen), and the 4-biphenylacetic acids of examples 33 and 34 (excepting those with an active hydrogen), and the lower alkyl, trifluoromethyl, cyano, and lower alkanoylamino 4-biphenylacetic acids obtained from example 37 are used in place of 4'-fluoro-4-biphenylacetic acid in the above example, there are obtained the corresponding aldehydes. when the compounds of examples 10, 20, 22, 27, 33, 34, and 56 containing active hydrogens are benzylated and subsequently treated according to the above procedure, there are obtained the corresponding aldehydes.

EXAMPLE 64

4'-Fluoro-4-biphenylacetaldehyde dimethyl acetal

To a solution of 0.01 mole of 4'-fluoro-4-biphenylacetaldehyde in 100 ml. of anhydrous methanol is added 0.001 mole of p-toluenesulfonic acid. The reaction mixture is stirred at room temperature for 5 days. A solution of sodium methoxide in methanol is then added until the solution is just alkaline to moistened litmus paper. The methanol is removed in vacuo and the residue taken up in ether and washed well with water. The ether solution is dried over sodium sulfate and concentrated. The residue is then chromatographed on neutral alumina. Elution with ether-petroleum ether (10–90 percent) gives the dimethyl acetal of 4'-fluoro-4-biphenylacetaldehyde.

When ethanol, n-propanol, and n-butanol are used in place of methanol in the above example, there are obtained the corresponding diethyl, dipropyl, and dibutyl acetals.

Similarly, when the aldehydes obtained from example 63 (excluding those containing an active hydrogen) are used in place of 4'-fluoro-4-biphenylacetaldehyde in the above example, there are obtained the corresponding dimethyl acetals.

Similarly, when the aldehydes of example 56 containing an active hydrogen are benzylated, then treated according to the above procedure, and then reduced according to example 11, there are obtained the corresponding acetals.

EXAMPLE 65

4'-Fluoro-4-biphenylacetamide

0.05 mole of 4'-fluoro-4-biphenylacetic acid is slowly treated with 0.2 mole of thionyl chloride. The resultant mixture is heated gently on a steam bath for 2 hours and the excess thionyl chloride removed in vacuo. To this concentrated material is added 40 ml. of 1,2-dimethoxyethane and the solution then added dropwise to 100 ml. of stirred ammonium hydroxide (approximately 30 percent) with ice-cooling. The 4'-fluoro-4-biphenylacetamide is collected washed with water, and dried in vacuo.

When methylamine, ethanolamine, propylamine, 2,3-dihydroxybutylamine, benzylamine, aniline, o-methoxy aniline, p-ethoxy aniline, p-chloro aniline, m-trifluoro-methyl aniline, cyclohexylamine, carbobenzyloxymethylamine, carboxymethylamine, glutamine, aminomethyl pyrrolidine, N-methyl pyrrolidine, 2-ethyl-N-methyl pyrrolidine, 3-aminomethyl-1-ethyl pyrrolidine, dimethylcarboxamidomethylamine 1-diethylaminopropylamine, morpholine, piperazine, N-ethyl piperazine, N-phenyl piperazine, N-hydroxyethyl piperazine, piperidine, and pyrrolidine are used in the above example in place of ammonium hydroxide, there are obtained the corresponding 4'-fluoro-4-biphenyl-substituted amides.

Similarly, when the 4-biphenylacetic acids obtained from examples 9, 11, 12, 13, 14, 15, 16, 17, 18, 23, 26, 36, 40, 45, 51, 52 (α-fluoro compounds), and 56 (excluding those compounds containing an active hydrogen), the 4-biphenylacetic acids of examples 33 and 34 (excepting those with an active hydrogen), and the lower alkyl, trifluoromethyl, cyano, lower alkyanoylamino, and carboxamide 4-biphenylacetic acids obtained from example 37 are used in place of 4'-fluoro-4-biphenylacetic acid in the above example, there are obtained the corresponding amides.

Similarly, when the compounds obtained from examples 10, 20, 22, 27, 33, 34, and 56 containing an active hydrogen are benzylated, subsequently treated in accordance with the above example, and then reacted according to example 11, there are obtained the corresponding amides.

EXAMPLE 66

4'-Fluoro-4-biphenylacetamide

To a solution of 0.01 mole of 4'-fluoro-4-biphenylacetic acid in 40 ml. of 1,2-dimethoxyethane is added 0.01 mole of triethylamine. The resulting mixture is ice-cooled, stirred, and 0.01 mole of i-butyl chloroformate is added. Stirring is then continued in the cold for an additional 30 minutes. The triethylamine hydrochloride is them removed by filtration and the filtrate cooled again. Dry dimethoxyethane saturated with dry ammonia gas is then added and the ammonia gas bubbled through the resultant mixture for approximately 1 minute. The mixture is then stirred at 5° C. for 16 hours. The solvent is removed in vacuo to yield 4'-fluoro-4-biphenylacetamide.

When methylamine, ethanolamine, propylamine, 2,3-dihydroxybutylamine, benzylamine, aniline, o-methoxy aniline, p-ethoxy aniline, m-trifluoromethyl aniline, cyclohexylamine, carbobenzyloxyamine, carboxymethylamine, glutamine, aminomethyl pyrrolidine, 3-aminomethyl-1-ethyl pyrrolidine, morpholine, piperazine, piperidine, and pyrrolidine are used in the above example in place of ammonia gas, there are obtained the corresponding 4'-fluoro-4-biphenyl-substituted amides.

Similarly, when the 4-biphenylacetic acids obtained from examples 9, 11, 12, 13, 14, 15, 16, 17, 18, 23, 26, 36, 40, 45, 51, 52 (α-fluoro compounds), and 56 (excluding those compounds containing an active hydrogen), the 4-biphenylacetic acids of examples 33 and 34 (excepting those with an active hydrogen), and the lower alkyl, trifluoromethyl, cyano, lower alkanoylamino, and carboxamido 4-biphenylacetic acids obtained from example 37 are used in place of 4'-fluoro-4-biphenylacetic acid in the above example, there are obtained the corresponding amides.

Similarly, when the compounds obtained from examples 10, 20, 22, 27, 33, 34, and 56 containing an active hydrogen group are benzylated, then treated in accordance with the above example, and subsequently reduced in accordance with the procedure of example 11, there are obtained the corresponding amides.

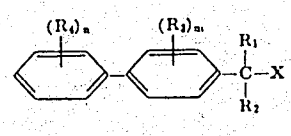
EXAMPLE 67

α-Methyl d-4'-fluoro-4-biphenylacetic acid

0.05 mole of cinchonidine is dissolved in boiling chloroform. To this boiling solution is added 0.05 mole of dl-4'-fluoro-4-biphenylacetic acid and the reaction mixture stirred for ½ hour. The reaction mixture is then concentrated in vacuo and the residue recrystallized from acetone. The recrystallization is repeated until the acid obtained from the hydrolysis of a small aliquot of the salt has a constant optical rotation.

We claim:

1. A compound of the formula



where

X is COOH or COOR (where R is methyl or diethylaminoethyl);

R_1 is hydrogen;

R_2 is lower alkyl;

R_3 and R_4 are fluoro; and

n and m are 0 to 1; no more than one of n and m is to be zero at any one time.

2. A compound according to claim 1 where

X is COOH;

R_1 is hydrogen;

R_2 is lower alkyl;

R_4 is fluoro;

m is 0; and

n is 1.

3. α-Methyl-4'-fluoro-4-biphenylacetic acid.

* * * * *