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# COMPOSITION AND METHODS FOR TREATING INFLAMMATION

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## ABSTRACT OF THE DISCLOSURE

New substituted salicylic acids and nontoxic pharmaceutically acceptable salts, esters, and amides derived therefrom. The substituted salicyclic acids described herein are useful as anti-inflammatory compounds. Also included herein are methods of preparing said salicylic acid compounds, pharmaceutical compositions having said salicylic acid compounds as an active ingredient and methods of treating inflammation by administering these particular compositions to patients.

## BACKGROUND OF THE INVENTION

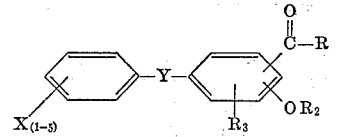
The development of anti-inflammatory compounds in the past two decades has seen the growth of a great many new drugs. Most of these have been steroids of the 11-oxygenated pregnane series. These, while highly effective, have the drawback of causing many side effects. There is a need in the market for equally effective compounds of much simpler structure and having less side effects.

## SUMMARY OF THE INVENTION

Generally, this invention relates to new substituted salicylic acid compounds and processes for producing the same. This invention also relates to pharmaceutical compositions containing said salicylic acid compounds as an active ingredient and to methods of treating inflammation by administering these particular compositions to patients.

## DESCRIPTION AND PREFERRED EMBODIMENTS

This invention relates to new substituted salicylic acids and processes for producing the same. More specifically, this invention relates to substituted salicylic acids, esters, amides, anhydrides and non-toxic pharmaceutically acceptable salts thereof. Still more specifically, this invention relates to compounds having the following general formula:

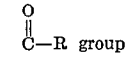



(I)

wherein: R may be hydroxy, amino, loweralkoxy (such as methoxy, ethoxy, butoxy, pentoxy, etc.), loweralkylamino (methylamino, propylamino, pentylamino, etc.), di(loweralkyl)amino (dimethylamino, dibutylamino, propylpentylamino, etc.), diloweralkylaminoloweralkylamino, diloweralkylaminoloweralkoxy, hydroxyloweralkoxy (3-hydroxypropoxy, 2-hydroxypropoxy, 4-hydroxybutoxy, etc.), polyhydroxyloweralkoxy (2,3-dihydroxypropoxy, 2,3,4,5,6-pentahydroxyhexyloxy, etc.), loweralkoxyloweralkoxy (ethoxyethoxy), phenylloweralkoxy (benzyloxy, phenethoxy, etc.), phenoxy, substituted phenoxy (such as loweralkoxyphenoxy, halophenoxy, diloweralkylaminophenoxy, loweralkanoylaminophenoxy, carboxyphenoxy and carboloweralkoxyphenoxy), phenylamino (anilino), hydrazino, morpholino, N-piperidino, pyrrolidino, or hydroxyloweralkylamino; $R_2$ may be hydrogen, acyl (preferably loweracyl such as formyl, acetyl, propionyl, butyryl,



etc.), alkyl (preferably loweralkyl such as methyl, ethyl, propyl, isopropyl, butyl, pentyl, etc.), or alkoxy carbonyl (preferably loweralkoxy carbonyl such as methoxy carbonyl, ethoxy carbonyl, etc.); $R_3$ may be hydrogen, halogen (such as chloro, bromo, fluoro, or iodo, preferably fluoro or chloro), haloalkyl (preferably halololoweralkyl such as trifluoromethyl, etc.), alkyl (preferably loweralkyl, such as methyl, ethyl, propyl, isopropyl, butyl, pentyl, etc.), cycloalkyl (cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl), or alkoxy (preferably loweralkoxy such as methoxy, ethoxy, isopropoxy or butoxy); X may be hydrogen, alkyl (preferably loweralkyl, such as methyl, ethyl, propyl, isopropyl, butyl, pentyl, etc.), hydroxy, alkoxy (preferably loweralkoxy such as methoxy, acetoxy, isopropoxy or butoxy), acyloxy (such as benzoyloxy, acetoxy or propionoxy), halogen (such as chloro, bromo, fluoro or iodo, preferably fluoro or chloro), haloalkyl (preferably halololoweralkyl such as trifluoromethyl, etc.), nitro, amino, alkylamino (preferably loweralkylamino such as methylamino, propylamino, pentylamino, etc.), diloweralkylamino (dimethylamino, dibutylamino, propylpentylamino, etc.), acylamino (preferably loweracylamino such as formylamino, acetylamino, propionylamino, butyrylamino, etc.), mercapto, alkylmercapto (preferably loweralkylmercapto such as methylmercapto, ethylmercapto, etc.), alkylsulfinyl (preferably loweralkylsulfinyl such as methylsulfinyl, ethylsulfinyl, butylsulfinyl, etc.), alkylsulfonyl (preferably loweralkylsulfonyl such as methyl sulfonyl, ethylsulfonyl, butylsulfonyl, etc.) sulfonamido, sulfonylamido, alkylaminoalkyl (preferably loweralkylaminoloweralkyl such as methylaminomethyl, ethylaminomethyl, etc.), hydroxyalkyl (preferably hydroxyloweralkyl such as hydroxymethyl, hydroxyethyl, hydroxypropyl, etc.), alkoxyalkyl (preferably loweralkoxyloweralkyl such as methoxymethyl, methoxyethyl, ethoxyethyl, ethoxy propyl, etc.), mercaptoalkyl (preferably mercaptoloweralkyl such as mercaptomethyl, mercaptoethyl, etc.). alkylmercaptoalkyl (preferably loweralkylmercaptoloweralkyl such as methylmercaptomethyl, ethylmercaptoethyl, ethylmercaptopropyl, etc.), cyano, carboxy, carboalkoxy (carbomethoxy, carboethoxy, etc.), carboamyl, aryl (such as phenyl, halophenyl, tolyl, salicyl), aralkyl such as benzyl, aryloxy, or arylalkoxy; Y is methylene, carbonyl, vinylene, ethynylene, ethylene, cyclopropyl, acetyl, imidocarbonyl or substituted imidocarbonyl; provided that the $OR_2$ group is always ortho to the




Representative compounds of this invention are as follows:

4-(p,o, or m-fluorobenzoyl)-salicylic acid;
5-(p,o, or m-fluorobenzoyl)-salicylic acid;
4-(p,o, or m-fluorophenacetyl)-salicylic acid;
5-(p,o, or m-fluorophenacetyl)-salicylic acid;
5-(p,o, or m-B-phenethyl)-salicylic acid;
4-(p,o, or m-fluorostyryl)-salicylic acid; and
5-(p,o, or m-fluorostyryl)-salicylic acid;

and the corresponding salts, esters, anhydrides, and amides.

This invention also relates to a method of treating inflammation in patients (animal or human) using a compound of Formula I, particularly an especially preferred compound as the active constituent.

The compounds of the instant invention can be used to treat inflammation by reducing inflammation and relieving pain in such diseases as rheumatoid arthritis, osteoarthritis, gout, infectious arthritis and rheumatic fever.

The compounds of Formula I also have anti-pyretic and analgesic activity and would be adminisered and used

in the same manner and in the same dosage ranges as if they were being used to treat inflammation as discussed further on.

The treatment of inflammation in accordance with the method of the present invention is accomplished by orally, rectally, topically, or parenterally administering to patients a composition of a compound of Formula I, particularly the especially preferred compounds in a nontoxic pharmaceutically acceptable carrier.

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

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

The active compounds of Formula I and of the compositions of this invention are present in an amount sufficient to treat inflammation, that is to reduce inflammation. Advantageously, the composition will contain the active ingredient, namely, the compounds of Formula I in an amount of from about 1 mg. to 100 mg. per kg. body weight per day (50 mg. to 7 g. per patient per day), preferably from about 2 mg. to 50 mg./kg. body weight per day (100 mg. to 3 g. per patient per day).

The method of treatment of this invention comprises administering to a patient (animal or human) a compound of Formula I, particularly an especially preferred compound admixed with a non-toxic pharmaceutical carrier such as exemplified above. The compounds of Formula I and particularly the especially preferred compounds will be administered in an amount of from 1 mg. to 100 mg./kg. body weight per day, preferably from about 2 mg. to about 50 mg. per kilogram body weight per day and especially from 4 mg. to 20 mg./kg. body weight per day. The most rapid and effective anti-inflammatory effect is obtained from oral administration of a daily dosage of from about 4 to 20 mg./kg./day. It should be understood, however, that although preferred dosage ranges are given, the dose level for any particular patient depends upon the activity of the specific compound employed. Also many other factors that modify the actions of drugs will be taken into account by those skilled in the art in the therapeutic use of medicinal agents, particularly those of Formula I, for example, age, body weight, sex, diet, time of administration, route of administration, rate of excretion, drug combination, reaction sensitivities and severity of the particular disease.

The benzoylsalicylic acids may be prepared by reacting a substituted benzoic acid or benzoyl chloride with a substituted phenol to produce a hydroxybenzophenone. The hydroxybenzophenone is then carboxylated to produce a benzoyl salicylic acid. The carboxylation reaction may be accomplished by heating the hydroxybenzophenone under pressure with carbon dioxide gas. The product can then be isolated from the reaction mixture by methods known in the art. The temperature at which the carboxylation reaction can take place is from 50 to 300° C. The reaction can also take place at from atmospheric pressure to high pressure, preferably however at 200° C., and at about 1600 p.s.i. pressure.

The benzoylsalicylic acids may also be prepared by reacting a substituted benzoic acid or benzoyl chloride with anisole to produce a benzoylanisole. The benzoylanisole may then be demethylated to form a hydroxybenzophenone and carboxylated as described above to form the benzoyl salicylic acids of this invention. Direct benzoylation of a salicylate also yields the benzoylsalicylic moiety.

The benzoylanisole may also be reduced to form benylanisole which is then demethylated and carboxylated as described above to form the benzylsalicylic acids of this invention.

The phenacetylsalicylic acids may be produced by reacting a substituted phenylacetic acid with a substituted anisole to produce phenacetyl anisole which is demethylated and carboxylated as described above to produce the phenacetylsalicyclic acids of this invention.

Fries rearrangement of an o-phenacetyl salicylic acid also yields the phenacetylsalicyclic acids.

The styrylsalicylic acids may be prepared by the hydrogenation of an aqueous solution of a phenacetylsalicylic acid to form a ($\alpha$-hydroxy-$\beta$-phenethyl)salicylic acid which is dehydrated to form the styrylsalicylic acid compounds of this invention.

The phenylcyclopropyl salicylic acids of this invention may be prepared by treating styrylsalicylic acid with methylene iodide and a zinc-copper couple.

The phenethynyl salicylic acids of this invention may be produced by dehydrohalogenating a dihalophenethylsalicylic acid compound.

The compounds of this invention, where R is a group such that an ester is the final compound, (i.e. R=alkoxy), are prepared by any esterification procedure, using an esterifying agent containing the appropriate R group. For example, the acid compounds of this invention may be reacted with the appropriate loweralkanol (preferably methanol) at elevated temperatures in the presence of a strong acid, such as hydrochloric acid, sulfuric acid, p-toluenesulfonic acid, and the like, to form the desired ester.

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

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

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

The following examples are presented to further illustrate the invention:

## EXAMPLE 1

The preparation of 4-fluoro-4'-hydroxybenzophenone

A mixture of p-fluorobenzoic acid (0.01 m.), phenol (0.015 m.) and polyphosphoric acid (20 g.) is heated at 100° C. for ½ hour, allowed to cool, added to stirred water (500 ml.) and the resultant mixture extracted with chloroform. The chloroform extracts are washed with water, dried, filtered and concentrated, and the residual material chromatographed on a silica gel column using an ether-petroleum ether (v./v. 5–80% ether) system as eluant to yield 4-fluoro-4'-hydroxybenzophenone.

When other substituted benzoic acids are used above, for example, o- and m-fluorobenzoic acids, o-, m- and p-methylmercaptobenzoic acids, o-, m- and p-methylsulfinylbenzoic acids, o-, m- and p-methylsulfonylbenzoic acids, o-, m- and p-methoxybenzoic (anisic) acids, the biphenylcarboxylic acids, the benzylbenzoic acids, the phenoxybenzoic acids, the benzyloxybenzoic acids, the acetylbenzoic acids and the phthalic acid monomethyl esters, the corresponding mono-substituted p-benzoylphenols are obtained.

When poly substituted benzoic acids are used in the above example, e.g. the dimethoxybenzoic acids, the dimethylbenzoic acids, the trimethoxybenzoic acids, etc., the corresponding polysubstituted p-benzoylphenols are obtained.

When anisole is used in place of phenol in the above examples, the corresponding p-(substituted benzoyl)anisoles are obtained.

Other methods of Friedel-Crafts benzoylation are also applicable, such as using $AlCl_3$, $ZnCl_2$, $TiCl_4$, etc., and may be used in place of the polyphosphoric acid method.

## EXAMPLE 2

The preparation of 4-(p-fluorobenzoyl)-m-cresol

A mixture of p-fluorobenzoyl chloride (0.1 m.), m-cresol (0.1 m.), anhydrous aluminum chloride (0.2 m.), and nitrobenzene (100 ml.) is heated at 60° C. for 18 hours. The mixture is cooled in ice, 2.5 N hydrochloric acid added to decompose the reaction mixture, the layers separated, the aqueous portion extracted well with either, the organic layers combined, dried, concentrated in vacuo, the residue chromatographed on a silica gel column using an ether-petroleum ether system (v./v. 0–80% ether) as eluant yielding 4-(p-fluorobenzoyl)-m-cresol.

When benzoyl chloride, or the stable benzoyl halides corresponding to the acids used in Example 1 are used in the above example, the correspondingly substituted benzoyl cresol is obtained.

When phenol, m-chlorophenol, m-fluorophenol and o-cyclohexylphenol are used in place of m-cresol in the above experiment, the corresponding p-(substituted-benzoyl) substituted phenol is obtained.

When the methyl ethers (anisoles) of the above phenols are reacted with the above benzoyl chlorides at room temperature for 24 hours, the corresponding p-(substituted benzoyl)-substituted anisoles are obtained.

When methyl 3-hydroxybenzoate is reacted with the benzoyl halides as above, the corresponding methyl 6-(substituted-benzoyl)-3-hydroxy-benzoate is obtained.

When resorcinol monomethyl ether is reacted with the benzoyl halides as above, the corresponding 3-methoxy-4-(substituted-benzoyl)-phenol is obtained.

## EXAMPLE 3

The preparation of p-methoxyphenyl)-(p-methylphenyl)-methane

To a portion of zinc amalgam (prepared from 10 g. of mossy zinc) is added water (8 ml.), concentrated hydrochloric acid (18 ml.), toluene (10 ml.) and 4-methoxy-4'-methylbenzophenone (5 g.). The mixture is refluxed for 24 hours, during which time three 5 ml. portions of concentrated hydrochloric acid are added at intervals of 6 hours. On cooling, ether is added, the layers separated, the organic layer washed with water, dried, concentrated in vacuo to crude p-(methoxyphenyl)-(p-methylphenyl)-methane. Purification may be effected here by column chromatography or distillation, but the crude material, contaminated with corresponding phenol, is generally used in the following (demethylation) step as is.

When the benzoylanisoles of Examples 1 and 2 (excluding the nitro, acetyl substituted ones) are used in the above examples, the corresponding diphenylmethane derivative is obtained. With the acetylbenzoylanisoles, the ethyl analogs are obtained, both carbonyls being reduced.

The above compounds, including the nitro and acetyl substituted ones, may also be made by direct benzylation of anisole under the conditions of Example 2.

Zinc chloride in chloroform may be used in the above procedure instead of aluminum chloride in nitrobenzene or carbon disulfide.

## EXAMPLE 4

The preparation of p-(4-fluorobenzoyl)-phenol

A mixture of p-(4-fluorobenzoyl)-anisole (5 g.) and pyridine hydrochloride (25 g.) under a dry nitrogen atmosphere is placed in an oil bath set at 230° C., kept 10 minutes, cooled, and the mixture extracted well with chloroform. The chloroform extracts are washed with water, dried, and chromatographed on a silica gel column using an ether-petroleum ether (v./v. 5–100% ether) system as eluant yielding p-(4-fluorobenzoyl)-phenol.

When the methoxy compounds of Examples 1, 2 and 3 are dimethylated as above, the corresponding substituted benzoyl and substituted-benzyl phenols are obtained.

## EXAMPLE 5

The preparation of 5-(p-fluorobenzoyl)-salicylic acid

An intimately ground mixture of p-(4-fluorobenzoyl)-phenol (5 g.) and anhydrous potassium carbonate (15 g.) is heated at 200° C. in a 1200–1400 p.s.i. carbon dioxide atmosphere for 8 hours. The mixture is cooled, added to water (30 ml.), stirred, filtered, and the filtrate acidified with dilute hydrochloric acid yielding 5-(p-fluorobenzoyl)-salicylic acid.

When the phenols of Examples 1, 2, and 4, and 4-hydroxy-3-methylbenzophenone, 2 - chloro-5-hydroxybenzophenone, 4-hydroxy - 3' - trifluoromethylbenzophenone, 2 (and 3) methyl-4-(phenylacetyl)-phenol and 4-phenylacetylphenol are carbonated as in the above example, the corresponding salicylic acids are obtained.

The 5-substituted salicylic acids may also be prepared via direct benzoyl and benzylation of the corresponding salicylic acid via the Friedel-Crafts procedure of Example 2.

## EXAMPLE 6

The preparation of o-(p-fluorophenylacetyloxy)-benzoic acid

A mixture of salicylic acid (0.145 m.), pyridine (30 ml.), and ether (100 ml.) is cooled in an ice-bath and p-fluorophenylacetyl chloride (0.15 m.) added dropwise. After the resulting mixture is stirred at room temperature for three hours, it is poured onto a mixture of ice (200 g.) and concentrated hydrochloric acid (30 ml.), extracted with ether (slight heating needed), the ether layer extracted with sodium bicarbonate solution, the aqueous layer filtered, acidified with acetic acid, and the product, o-(p-fluorophenylacetyloxy)-benzoic acid collected.

When other phenacetyl chlorides are used above, as the o- and m-isomers, phenacetyl chloride itself, and the methyl, methoxy, chloro, etc. phenacetyl chlorides, the corresponding phenacetoxybenzoic acids are obtained.

EXAMPLE 7

The prepartion of (5-[p-fluorophenacetyl]-salicylic acid)

To a suspension of o-(p-fluorophenacetoxy)-benzoic acid (0.04 m.) in cold nitrobenzene (50 ml.) is added anhydrous aluminum chloride (10.6 g., 0.08 m.) in portions. The resulting mixture is allowed to stir overnight at room temperatures, poured onto a mixture of ice (100 g.) and concentrated hydrochloric acid (50 ml.), and the system extracted with ether. The organic layer is extracted with dilute sodium hydroxide solution, the aqueous layer filtered and acidified, and the (5-[p-fluorophenacetyl]-salicylic acid) collected.

When the other phenacetoxybenzoic acids of Example 6 are used above, the corresponding 5-(substituted-phenacetyl)-salicylic acids are obtained.

These salicylic acids are also obtained via phenylacetylation of phenols (or anisoles) followed by carbonation (as in Example 1–5).

If anisoles are used in place of phenols, the demethylation step (Example 4) is included.

EXAMPLE 8

The preparation of 5-(substituted-β-phenethyl)-salicylic acids

When the substituted-phenacetylanisoles of Example 7 are reduced to the β-phenethyl compounds via the procedure of Example 3, and these demethylated and carbonated as per Examples 4 and 5, the corresponding 5-(substituted-β-phenethyl)-salicylic acids are obtained.

These compounds are also prepared via catalytic platinum oxide hydrogenation of the 5-(substituted styryl)-salicylic acids prepared in the following Example 9.

EXAMPLE 9

The preparation of 5-(α-hydroxy-β-phenethyl)-salicylic acid

To an ice cooled solution of 5-phenacetylsalicylic acid (2.5 g.) in a mixture of water (50 ml.) and 12 N sodium hydroxide solution (2 ml.) is added sodium borohydride (1.0 g. in four equal portions over 0.5 hour, the mixture allowed to stir at 2–7° C. for two hours, then at room temperature overnight. The mixture is acidified with dilute hydrochloric acid, extracted with ether, the ether layer dried over magnesium sulfate, filtered, concentrated in vacuo, and the residue triturated with hexane to yield 5-(α-hydroxy-β-phenethyl)-salicylic acid.

The 5-(α-hydroxy-β-phenethyl)-salicylic acid is then refluxed with 50 ml. of benzene, cooled, filtered, the collected solid dissolved in ether, benzene added, the ether boiled away until crystallization starts, the mixture cooled and filtered to yield 5-styrylsalicylic acid.

When the other phenacetylsalicylic acids of Example 7 are treated as above, the corresponding substituted α-hydroxy-β-phenethylsalicylic acids and styrylsalicylic acids are obtained.

EXAMPLE 10

The preparation of 2-acetoxy-5-(p-fluorobenzoyl)-benzoic acid

To a mixture of 5-(p-fluorobenzoyl)-salicylic acid (0.04 m.) in pyridine (15 ml.) is added acetic anhydride (28 ml.) and the resultant mixture heated on the steam cone for 1.5 hours, protected from moisture. On cooling, the mixture is added to water (500 ml.) with stirring, the aqueous system extracted well with chloroform, the chloroform extracts washed with 1 N hydrochloric acid, water, dried over magnesium sulfate filtered and concentrated to 2-acetoxy-5-(p-fluorobenzoyl)-benzoic acid.

When propionic or butyric anhydride is used in place of acetic anhydride in the above reaction, the corresponding propionoxy or butyroxy compound is obtained.

When the salicylic acids of Examples 5, 8, and 9 are reacted as above, the corresponding 2-acyloxy-benzoic acids are obtained. In the case of the phenacetylsalicylic acids, enol-acetate is formed also. Limiting the amount of anyhydride is necessary here, unless the enol-acetate is desired.

EXAMPLE 11

The preparation of methyl 2-acetoxy-5-(p-fluorobenzoyl)-benzoate

When 2-acetoxy-5-(p-fluorobenzoyl)-benzoic acid and diazomethane (ethereal) are reacted together at room temperature or below, methyl 2-acetoxy-5-(p-fluorobenzoyl)-benzoate is obtained.

When the other acetates of Example 10 are utilized in the above procedure, the corresponding methyl 2-acetoxy-benzoates are obtained.

Other diazo compounds may be used, as for example, diazoethane, the yield the corresponding esters.

EXAMPLE 12

The preparation of methyl 5-(p-fluorobenzoyl)-salicylate

A mixture of 5-(p-fluorobenzoyl)-salicylic acid (0.03 m.) and anhydrous methanol (100 ml.) containing anhydrous hydrogen chloride (or 1 ml. of concentrated sulfuric acid) is heated overnight the solvent removed in vacuo, the residue partitioned between chloroform-water, the chloroform layer washed with dilute bicarbonate solution, dried, filtered and concentrated in vacuo to yield methyl 5-(p-fluorobenzoyl)-salicylate.

When ethanol is used in place of methanol, the ethyl ester is obtained.

When the salicylic acids of Examples 5, 7, 8 and 9 are used above, the corresponding esters are obtained.

Diazomethane may also be used to prepare the esters, and in some cases is preferred over the alcohol-acid procedure.

EXAMPLE 13

The preparation of methyl 5-(p-aminobenzoyl)-4-methyl-salicylate

A mixture of methyl 4-methyl-5-(p-nitrobenzoyl)-salicylate (0.01 m.) in methanol-dioxane (1:1) (200 ml.) is reacted with hydrogen at room temperature, 40 p.s.i. pressure, in the presence of 10% palladium on charcoal (0.3 g.), and the reaction stopped when three equivalents of hydrogen have been absorbed. The mixture is filtered, the cake washed well with methanol, the filtrate concentrated in vacuo, the residue chromatographed on a silica gel column using a methanolmethylene chloride system (v./v. 0–50% methanol) as eluant yielding methyl 5-(p-aminobenzoyl)-4-methylsalicylate.

When the o- or m-nitro isomers are used in the above reaction, the corresponding amino compound is obtained.

EXAMPLE 14

The preparation of methyl 5-(m-hydroxybenzoyl)-salicylate

When methyl 5-(m-methoxybenzoyl)-salicylate is reacted with pyridine hydrochloride via the procedure ot Example 4, methyl 5-(m-hydroxybenzoyl)-salicylate is obtained.

When the corresponding o-, m- or p-methylthiobenzoyl salicylates are reacted similarly, methyl 5-(o-, m- or p-mercaptobenzoyl)-salicylates are obtained, and when the methoxybenzoyl- and methylthiobenzoyl- 3- and 4-substituted salicylates are used above, the corresponding phenols and thiophenols are obtained.

EXAMPLE 15

The preparation of 5-(p-acetamidobenzoyl)-2-acetoxy-4-methylbenzoic acid

When 5-(p-aminobenzoyl)-4-methylsalicylic acid is reacted with acetic anhydride as per Example 10, 5-(p-acetamidobenzoyl)-2-acetoxy-4-methylbenzoic acid is obtained.

When the mercapto- and hydroxy-benzoyl salicylic acids of Example 14 are used above, the corresponding acetthiol and acetoxybenzoyl compounds are obtained.

EXAMPLE 16

The preparation of methyl 5-(p-cyanobenzoyl)-salicylate

A mixture of methyl 5-(p-chlorobenzoyl)-salicylate (0.02 m.), cuprous cyanide (0.03 m.) and N-methylpyrrolidone (25 ml.) is de-aerated, covered with a nitrogen atmosphere, heated to 180° C., kept 3 hours, allowed to cool, partitioned between chloroform, 7% hydrochloric acid containing ferric chloride (0.03 m.), the organic layer separated, dried, concentrated, and the residue chromatographed on a silica gel column using an ether-petroleum ether system as eluant (v./v. 5–90% ether) yielding methyl 5-(p-cyanobenzoyl)-salicylate.

EXAMPLE 17

The preparation of 5-(p-carbamylbenzoyl)-salicylic acid

To concentrated sulfuric acid (5 ml.) at 3–5° C., stirring is added 5-(p-cyanobenzoyl)-salicylic acid (0.01 m.), and the mixture stirred for 5 hours, added to ice-water (100 cc.), and the 5-(p-carbamylbenzoyl)-salicylic acid collected.

EXAMPLE 18

The preparation of 5-(p-carboxybenzoyl)-salicylic acid

A mixture of 5-(p-carbomethoxybenzoyl)-salicylic acid (0.01 m.), water (100 ml.) and sodium hydroxide (0.1 m.) is stirred and heated gently for solution, kept one hour, filtered, and the filtrate added to 2.5 N hydrochloric acid (100 ml.) with stirring, and the 5-(p-carboxybenzoyl)-salicylic acid collected.

EXAMPLE 19

The preparation of 1-(4-acetoxy-3-carbomethoxyphenyl)-1-phenylethylene

To methyl 2-acetoxy-5-benzoylbenzoate (0.01 m.) in anhydrous ether, ice-cooled, is added a suspension of triphenylphosphine methylene (0.01 m.) in anhydrous ether (100 ml.) over 2 hours, and the resultant mixture allowed to stir for three days. The mixture is filtered, the cake washed well with ether, the combined ether solutions washed with water, dried, concentrated in vacuo, and the residual material chromatographed on a silica gel column using an ether-petroleum ether system (v./v. 0–60% ether) as eluant yielding 1-(4-acetoxy-3-carbomethoxyphenyl)-1-phenylethylene.

When the fluoro, chloro, methoxy, methyl, trifluoromethyl, etc. substituted benzoylbenzoates of Examples 1 and 2 are used above, the correspondingly substituted diphenylethylenes are obtained.

EXAMPLE 20

The preparation of 1-(4-acetoxy-3-carbomethoxyphenyl)-2-phenylcyclopropane

A mixture of zinc-copper couple (0.035 m.), iodine (0.002 m.), methylene iodide (0.03 m.), methyl 2-acetoxy-5-styrylbenzoate (0.005 m.) and anhydrous ether (20 ml.) is stirred under reflux for 48 hours. The cooled reaction mixture is filtered, the cake washed well with ether, the combined filtrate-washings washed with 5% hydrochloric acid, 5% sodium sulfite solution, water, then dried, filtered, the ether removed in vacuo, and the residual material chromatographed on a silica gel column using an ether-petroleum system (v./v. 0–70% ether) as eluant yielding 1-(4-acetoxy-3-carbomethoxyphenyl)-2-phenylcyclopropane.

When the unsymmetrical diphenylethylene of Example 19 is used above, 1-(4-acetoxy-3-carbomethoxyphenyl)-1-phenylcyclopropane is obtained.



EXAMPLE 21

The preparation of 5-benzoyl-4-trifluoromethylsalicylic acid

A stainless steel lined shaker is charged with 5-acetoxy-2-benzoylbenzoic acid (0.02 m.) under a dry nitrogen atmosphere, the system cooled to Dry-Ice temperatures, and sulfur tetrafluoride (0.1 m.) condensed into the shaker. The mixture is then heated at 100° C. for eight hours, cooled, vented, the residual material taken up in either, filtered and concentrated. Chromatography of the residue on a silica gel column using an ether-petroleum ether system (v./v. 0–70% ether) as eluant yields 4-acetoxy-2-trifluoromethylbenzophenone.

Mild hydrolysis of this ester (refluxing sodium bicarbonate in aqueous methanol) yields the corresponding phenol, which is carbonated via the procedure of Example 5 to yield 5-benzoyl-4-trifluoromethylsalicylic acid.

EXAMPLE 22

The preparation of 5-(p-fluorobenzoyl)-o-anisic acid

To a mixture of 5-(p-fluorobenzoyl)-salicyclic acid (0.01 m.), sodium hydroxide (0.1 m.) and water (50 ml.) at 85° C. is added dimethylsulfate (0.08 m.) over 10 minutes, and the resultant mixture heated for 10 hours. The mixture is acidified with dilute hydrochloric acid, the solid collected, the filtrate extracted with chloroform, the chloroform extracts added to the solid, and the chloroform removed in vacuo. The crude acid is then purified via recrystallization or chromatography of its methyl ester (prepared with diazomethane), followed by regeneration of the pure 5-(p-fluorobenzoyl)-o-anisic acid.

This acid may also be prepared via direct p-fluorobenzoylation of o-anisic acid using the procedures of Examples 2 and 3.

EXAMPLE 23

The preparation of methyl 2-carboxy-4-(p-fluorobenzoyl)-phenyl carbonate

To a mixture of 5-(p-fluorobenzoyl)-salicylic acid (0.01 m.), dimethylaniline (0.02 m.) and benzene (30 ml.) is added methyl chloroformate (0.011 m.) over one hour with constant shaking and cooling. When the odor of the chlorocarbonate is essentially absent, hydrochloric acid (1 N, 100 ml.) is added and the mixture filtered. The benzene layer is separated, dried, filtered, and the solvent removed in vacuo to yield methyl 2-carboxy-4-(p-fluorobenzoyl)-phenyl carbonate.

EXAMPLE 24

The preparation of methyl 2-acetoxy-5-(p-bromomethylbenzoyl)-benzoate

A mixture of methyl 2-acetoxy-5-(p-methylbenzoyl)-benzoate (0.05 m.), N-bromosuccinimide (0.05 m.) (purified just before use by pumping out at 0.5 mm. over $P_2O_5$), carbon tetrachloride (500 ml.) and dibenzoyl peorxide (0.002 m.) is refluxed gently for 3 hours, cooled, the succinimide removed by filtration, and the solvent removed in vacuo to yield crude methyl 2-acetoxy-5-(p-bromomethylbenzoyl)-benzoate used as in the following three examples.

EXAMPLE 25

The preparation of methyl 5-(p-hydroxymethylbenzoyl)-salicylate

A mixture of methyl 2-acetoxy-5-(p-bromomethylbenzoyl)-benzoate (0.01 m.), silver acetate (0.01 m.) and acetic acid (30 ml.) is heated gently for 3 hours, cooled, filtered, and the filtrate concentrated in vacuo to crude methyl 2 - acetoxy - 5 - (p - acetoxymethylbenzoyl)-benzoate. Anhydrous methanol (50 ml.) and p-toluenesulfonic acid (0.3 g.) is added, the mixture is refluxed for 3 hours, concentrated in vacuo, distributed between water-chloroform, the chloroform layer dried, con-

centrated in vacuo, and the residual material chromatographed on a silica gel column using an ether-petroleum ether system (v./v. 5–90% ether) as eluant yielding methyl 5-(p-hydroxymethylbenzoyl)-salicylate.

When potassium thiolacetate is used in place of silver acetate in the above reaction, methyl 5-(p-mercaptomethylbenzoyl)-salicylate is obtained.

## EXAMPLE 26

### The preparation of methyl 5-(p-methoxymethylbenzoyl)-salicylate

Methyl 2 - acetoxy - 5 - (p - bromomethylbenzoyl)-benzoate (0.01 m.) is added to a stirred solution of sodium methoxide (0.02 m.) in anhydrous methanol, the mixture heated gently for two hours, cooled, a trace of dilute hydrochloric acid added to neutralize the mixture, the solvents removed in vacuo, and the residue chromatographed on a silica gel column using an ether-petroleum ether system (v./v. 0–60% ether) as eluant yielding methyl 5-(p-methoxymethylbenzoyl)-salicylate.

When potassium methylmercaptide is used in place of sodium methoxide, methyl 5-(p-methylthiomethylbenzoyl)-salicylate is obtained.

## EXAMPLE 27

### The preparation of 5-(p-dimethylaminomethylbenzoyl)-salicylic acid

When 4-hydroxy-4'-methylbenzophenone is acetylated as per Example 10, and the resultant acetoxy compound treated with N-bromosuccinimide via Example 24, 4-acetoxy-4'-bromomethylbenzophenone is obtained.

A mixture of the above bromomethyl compound (0.02 m.) and methanolic dimethylamine is heated for several hours, the solvents removed in vacuo, the residue taken up in 2.5 N hydrochloric acid, filtered, basified, and the resultant 4 - dimethylaminomethyl - 4' - hydroxybenzophenone collected.

Carbonation of this phenol via the procedure of Example 5 yields 5-(p-dimethylaminomethylbenzoyl)-salicylic acid.

When aqueous ammonium hydroxide is used in place of methanolic dimethylamine in the above sequence, 5-(p-aminomethylbenzoyl)-salicylic acid is obtained.

## EXAMPLE 28

### The preparation of methyl 5-(p-dimethylaminobenzoyl)-salicylate

A mixture of methyl 5-(p-aminobenzoyl)-salicylate (0.01 m.) and dimethylsulfate (0.02 m.) is heated at 120° C. for 4 hours, nitrogen atmosphere, the mixture partitioned between chloroform-dilute sodium bicarbonate solution, the chloroform layer dried, filtered, and concentrated in vacuo, the residual material chromatographed on a silica gel column using a methanol-methylene chloride system (v./v. 0–50%) as eluant yielding methyl 5-(p-dimethylaminobenzoyl)-salicylate.

## EXAMPLE 29

### The preparation of 3-carboxy-4-hydroxydiphenylacetylene

To methyl 2-acetoxy - 5 - styrylbenzoate (0.02 m.) in anhydrous ether (100 ml.) (stirring, dry nitrogen atmosphere), is added dropwise bromine (0.02 m.) over ½ hour, the reaction allowed to stir another hour, and the solvent removed in vacuo, displacing traces of hydrogen bromide by repeated solvent removals.

The crude dibromide is then added to a cooled mixture of potassium hydroxide (0.1 m.) in absolute ethanol (50 ml.) (heated initially for solution) over ½ hour, refluxed 24 hours, the mixture added to water (200 ml.), filtered, and the aqueous mixture carefully acidified with hydrochloric acid and the 3-carboxy-4-hydroxydiphenylacetylene collected.

## EXAMPLE 30

### The preparation of 5-(p-fluoro-β-phenethyl)-salicylamide

A mixture of methyl 5-(p-fluoro-β-phenethyl)-salicylate and concentrated ammonium hydroxide (5-fold excess) is heated at 100° C. in a sealed tube for six hours. After cooling, water is added, and the 5-(p-fluoro-β-phenethyl)-salicylamide collected.

When monomethylamine, dimethylamine, ethylamine, diethylamine, morpholine, piperidine, etc. are used in place of ammonium hydroxide, the corresponding substituted amides are obtained.

## EXAMPLE 31

### The preparation of N,N-diethylaminoethyl 5-(p-fluorobenzoyl)-salicylate

To a mixture of 5-(p-fluorobenzoyl)-salicylic acid (0.01 m.) and N,N-diethylethanolamine (0.01 m.) in anhydrous tetrahydrofuran is added a solution of N,N-dicyclohexylcarbodiimide (0.01 m.) in a minimum of the same solvent. The mixture is stoppered, shaken well, and allowed to stand overnight. The precipitated dicyclohexylurea is removed by filtration, the filtrate concentrated in vacuo, the residue partitioned between ether and 1 N hydrochloric acid, the layers separated, the aqueous layer washed once with ether and made basic with saturated sodium bicarbonate solution. Extraction with chloroform, followed by removal of the chloroform in vacuo (high vacuum pump to remove traces of starting amine) yields N,N-diethylaminoethyl 5-(p-fluorobenzoyl)-salicylate.

## EXAMPLE 32

### The preparation of sodium 5-(p-fluorobenzoyl)-salicylate

Solutions of 5-(p-fluorobenzoyl)-salicylic acid (0.001 m.) in methanol and sodium hydroxide (0.001 m.) in water are mixed, heated for solution, filtered, and the filtrate concentrated in vacuo to leave sodium 5-(p-fluorobenzoyl)-salicylate.

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

When two equivalents of the above bases are used, the corresponding di sodio- and di potassio salts are obtained.

## EXAMPLE 33

### The preparation of the diethylaminoethanol salt of 5-(p-fluorobenzoyl)-salicylic acid

N,N-diethylethanolamine (0.001 m.) in ether (5 ml.) is added to a stirred solution of 5-(p-fluorobenzoyl)-salicylic acid (0.001 m.) in chloroform-methanol, the resultant mixture allowed to stir for one hour, the salt collected or the solvent removed in vacuo to yield the diethylaminoethanol salt of 5-(p-fluorobenzoyl)-salicylic acid.

When piperidine, morpholine, triethylamine, N-methylpiperidine, N-methylmorpholine, tributylamine or other organic amines are used in place of diethylethanolamine in the above example, the corresponding salt is obtained.

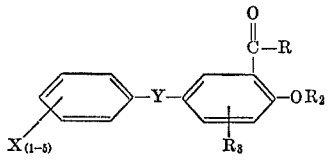
## EXAMPLE 34

### The preparation of N-(4-acetoxy-3-carbomethoxybenzhydrylidene)-p-fluoroaniline

Borom trifluoride etherate (1.5 ml.) is added to a solution of methyl 2-acetoxy-5-benzoylbenzoate (0.05 m.), and freshly distilled p-fluoroaniline (0.08 m.) in chloroform (20 ml.) at room temperature, and the resultant mixture allowed to stir at room temperature for an extended period of time. Additional chloroform and a small amount of methanol is added as needed. The mixture is filtered, the cake washed with fresh chloroform, the chloro filtered and concentrated dried, to yield N-(4-acetoxy-3-carbomethoxybenzhydrylidene)-p-fluoroaniline.

We claim:

1. A method of treating inflammation which comprises administering to a patient 2 mg. to 50 mg. per kg. body weight per day of a compound of the formula:



wherein:

X is hydrogen, loweralkoxy, halogen, halologweralkyl or diloweralkylamino; and

Y is methylene, carbonyl, vinylene, ethylene or ethynylene;

R is hydroxy;

$R_2$ is hydrogen or loweralkanoyl; and

$R_3$ is hydrogen, loweralkyl, halogen, and a pharmaceutically acceptable non-toxic acid addition salt thereof;

provided that X is not halogen when Y is methylene.

2. A method of treatment according to claim 1 wherein the compound to be administered is 5-(p-fluorobenzoyl)-salicylic acid.

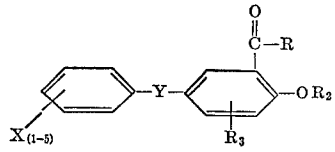
3. A method of treatment according to claim 1 wherein the compound to be administered is 2-acetoxy-5-(p-fluorobenzoyl-benzoic acid.

4. A method of treatment according to claim 1 wherein the compound to be administered is 5-(p-fluorophenylacetyl)-salicylic acid.

5. A method of treatment according to claim 1 wherein the compound to be administered is 5-(p-β-phenethyl)-salicylic acid.

6. A method of treatment according to claim 1 wherein the compound to be administered is 5-(p-fluorostyryl)-salicylic acid.

7. A method of treating inflammation which comprises administering to a patient 2 mg. to 50 mg. per kg. body weight per day of a compound of the formula:





wherein:

X is hydrogen, loweralkoxy, halogen, halologweralkyl or diloweralkylamino; and

Y is methylene;

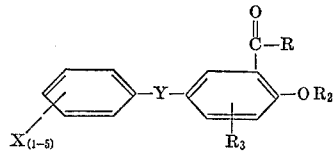
R is hydroxy;

$R_2$ is hydrogen or loweralkanoyl; and

$R_3$ is hydrogen, loweralkyl, halogen, and a pharmaceutically acceptable non-toxic acid addition salt thereof;

provided that X is not halogen when Y is methylene.

8. A pharmaceutical composition for the treatment of inflammation consisting of at least one member selected from a compound of the formula in an amount to provide 100 mg. to 3 gm. per patient per day:



wherein:

X is hydrogen, loweralkyl, loweralkoxy, halogen, halologweralkyl or diloweralkylamino;

Y is methylene, carbonyl, vinylene, ethylene or ethynylene;

R is hydroxy;

$R_2$ is hydrogen or loweralkanoyl;

$R_3$ is hydrogen, halogen, loweralkyl, and a pharmaceutically acceptable non-toxic acid addition salt thereof;

provided that X is not halogen when Y is methylene; as an active ingredient together with a pharmaceutically acceptable carrier.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