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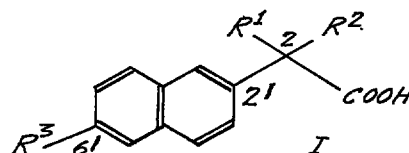


(54) IMPROVEMENTS IN OR RELATING TO 2-(6'-
 SUBSTITUTED-2'-NAPHTHYL) PROPIONIC ACID
 DERIVATIVES AND SALTS THEREOF

(71) We, SYNTEX CORPORATION,
 a Panamanian corporation, of Apartado, Postal 7386, Panama, Panama,
 do hereby declare the invention for
 5 which we pray that a patent may be
 granted to us, and the method by which it is
 to be performed, to be particularly described
 in and by the following statement:—

The present invention is directed to 2 - (6'-
 10 substituted - 2' - naphthyl)propionic acid deri-
 vatives and the corresponding pharmaceutically
 acceptable salts thereof, optionally substituted
 at position 3 of the propionic acid moiety which
 15 are used in the treatment and alleviation of
 inflammation, pain and pyrexia, as well as
 associative conditions thereof, by administering
 an effective therapeutic dose of the novel com-
 pounds.

One aspect of the present invention provides
 20 the resolved d- and l-forms of the compounds
 of the following formula and the sodium, potas-
 sium, calcium, magnesium, aluminum, am-
 monium, R_3N , ethanolamine, 2 - (diethyl-
 amine)ethanol, 2 - (dimethylamine)ethanol,
 25 arginine, lysine, caffeine, procaine, methylgluc-
 amine or ethylenediamine salts thereof:



wherein R is lower alkyl, monocyclic aralkyl
 or monocyclic aryl;

one of R^1 and R^2 is hydrogen and the other 30
 is methyl or difluoromethyl; and

R^3 is methyl, ethyl, isopropyl, cyclopropyl,
 trifluoromethyl, vinyl, ethynyl, fluoro, chloro,
 methoxy, methoxymethoxy, difluoromethoxy,
 methylthio, methoxymethylthio or difluoro- 35
 methylthio; with the proviso that when the
 other of R^1 and R^2 is methyl R^3 is cyclo-
 propyl, vinyl, ethynyl, methoxymethoxy or
 methoxymethylthio.

Another aspect of the invention provides, 40
 as the resolved d- and l-forms or as a racemic
 mixture, the magnesium, ammonium, R_3N ,
 ethanolamine, methyl glucamine or ethylenedi-
 amine salts of the compounds of formula I,
 with the proviso that R is other than ethyl. 45

The numerals (2, 2' and 6') indicate the

positions used herein in the nomenclature of the 2 - (6' - substituted - 2' - naphthyl)-propionic acid derivatives.

5 In the preferred embodiment of the present invention one of R¹ and R² is hydrogen and the other is methyl; and R³ is methyl, trifluoromethyl, fluoro, chloro, methoxy, difluoromethoxy, methylthio or difluoromethylthio.

10 The term "lower alkyl" defines those aliphatic hydrocarbon groups of 1 to 6 carbon atoms. Typical lower alkyls include methyl, ethyl, isopropyl, butyl, 3 - pentyl, isohexyl and hexyl.

15 The term "monocyclic aryl" defines those phenyl groups optionally substituted with one to three methyl, ethyl, propyl or isopropyl groups. Typical monocyclic aryls include phenyl, o - tolyl, p - tolyl, 2,6 - dimethylphenyl, p - ethylphenyl, 3,5 - diethylphenyl, m - propylphenyl and 2,4 - diisopropylphenyl.

20 The term "monocyclic aralkyl" defines those lower alkyl groups substituted with a monocyclic aryl group. Typical monocyclic aralkyls include benzyl, 3 - phenylpropyl, and phenethyl, 3 - (p - tolyl)propyl, 2 - (3,5 - dimethylphenyl)butyl and 5 - phenylpentyl.

25 When one of R¹ and R² is hydrogen and the other is methyl or difluoromethyl, the compounds of formula I exist as pairs of an enantiomorph. Each enantiomorph or optical isomer of the compounds of formula I are included within the present invention. The present compounds of formula I that exist as pairs of enantiomorphs can be administered as racemic mixtures or they can be administered as individual enantiomorphs. In some instances, one enantiomorph exhibits greater anti-inflammatory, analgesic, and/or anti-pyretic activity than the corresponding other enantiomorph.

40 The compounds of formula I exhibit anti-inflammatory, analgesic, and anti-pyretic activity; accordingly, these compounds are employed in the treatment and alleviation of inflammation, pain and pyrexia in mammals.

45 The compounds of formula I are especially useful in the treatment of inflammation, such as inflammatory conditions of the muscular skeletal system, skeletal joints and other tissues. Accordingly, these compounds are useful in the treatment of conditions characterized by inflammation, such as rheumatism, contusion, lacerations, arthritis, bone fractures, post-traumatic conditions and gout. In those cases in which the above conditions include pain and pyrexia coupled with inflammation, the instant compounds are useful for the relief of these conditions as well as the inflammation.

60 A measure of anti-inflammatory activity according to the Carrageenin induced edema in Winter et al. *The Proceedings of a Society for Experimental Biology and Medicine*, Vol. III, 544 (1962) shows d 2 - (6' - methoxy - 2' - naphthyl)propionic acid to have over 11 times the activity of phenyl butazone, 2 - (6' - chloro - 2' - naphthyl)propionic acid, to have over 2

times the activity of phenylbutazone, 2 - (6' - methylthio - 2' - naphthyl)propionic acid to have over 4 times the activity of phenyl butazone; the sodium salt of d 2 - (6' - methoxy - 2' - naphthyl)propionic acid to have over 10 times the activity of phenyl butazone; the calcium salt of d 2 - (6' - methoxy - 2' - naphthyl)propionic acid to have over 10 times the activity of phenyl butazone; the 2 - (dimethylamino)ethanol salt of d 2 - (6' - methoxy - 2' - naphthyl)propionic acid to have over 4 times the activity of phenyl butazone. Similar standard assays to measure the anti-pyretic activity show d 2 - (6' - methoxy - 2' - naphthyl)propionic acid to have over 20 times the potency of aspirin; 2 - (6' - chloro - 2' - naphthyl)propionic acid to have over 5 times the potency of aspirin in this activity; and sodium 2 - (6' - methoxy - 2' - naphthyl)propionate to have over 20 times the activity of aspirin in this activity.

The preferred manner of administration is oral administration which provides the use of the convenient daily dosage regimen which can be adjusted according to the degree of affliction. Generally, a daily dose of from 1 mg. to 60 mg. of the active compound per kilogram of body weight of the mammal is employed. Most conditions respond to the treatment comprising a dosage level in the order of 2 mg. to 50 mg. For such oral administration a pharmaceutically acceptable nontoxic composition can be formed by the incorporation of any of the normally employed excipients. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, melt, rice, flour, chalk, silica gel, magnesium stearate, sodium stearate, glyceryl monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene glycol, water and ethanol. These compositions take the forms of solutions, suspensions, tablets, pills, capsules, powders and sustained release formulations. In addition, these compounds can be administered in conjunction with other medicinal agents depending upon the specific condition being treated.

The salt derivatives of the compounds of formula I are prepared by treating the corresponding free acids of the compounds of formula I with at least one molar equivalent of a pharmaceutically acceptable base. Representative pharmaceutically acceptable bases are sodium hydroxide, potassium hydroxide, ammonium hydroxide, calcium hydroxide, trimethylamine, triethylamine, tripropylamine, β - (dimethylamino)ethanol, β - (diethylamino)ethanol, arginine, lysine, caffeine and procaine. The reaction is conducted in an aqueous solution, alone or in combination with an inert, water miscible organic solvent, at a temperature of from about 0°C to about 100°C, preferably at room temperature. Typical inert, water miscible organic solvents include methanol, ethanol, isopropanol, butanol, dioxane or tetrahydrofuran. When divalent metal salts are

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prepared, such as the calcium salts or magnesium salts of the compounds of formula I, the free acid starting material is treated with at least one half molar equivalents of pharmaceutically acceptable base. When the aluminum salts of the compounds of formula I are prepared, at least one-third molar equivalents of the pharmaceutically acceptable base are employed.

In the preferred embodiment of the present invention, the calcium salts and magnesium salts of the compounds of formula I are prepared by treating the corresponding sodium or potassium salts of the compound of formula I with at least one-half molar equivalents of calcium chloride or magnesium chloride, respectively, in an aqueous solution, alone or in combination with an inert water miscible organic solvent, at a temperature of from about 20°C to about 100°C.

In the preferred embodiment of the present invention, the aluminum salts of the compounds of formula I are prepared by treating the corresponding free acids of the compounds of formula I with at least one-third molar equivalent of an aluminum alkoxide such as aluminum triethoxide or aluminum tripropoxide, in a hydrocarbon solvent, such as benzene, xylene or cyclohexane, at a temperature of from 20°C to about 115°C.

The salt products are isolated by conventional means. For example, the reaction mixtures are evaporated to dryness and the salts can be further purified by conventional methods.

The free acids of the compounds of formula I can be prepared by any of several methods. One such method by which they can be prepared is described in detail in our British Patent Specification No. 1,211,134. This method involves the reaction of a β -substituted naphthalene with acetyl chloride in nitrobenzene in the presence of at least 3 molar equivalents of aluminum chloride to afford the corresponding 6 - substituted - 2 - acetylnaphthalene derivative. The resulting derivative is heated with morpholine in the presence of sulfur at about 150°C; the resulting product is refluxed with concentrated hydrochloric acid to furnish the corresponding 2 - (6' - substituted - 2' - naphthyl)acetic acid derivative. The addition of the C-2 substituents is carried forth by several methods. The addition of an alkyl substituent at the C-2 position is carried out by esterifying the 2 - (6' - substituted - 2' - naphthyl)acetic acid derivative by conventional methods; such as by treatment with a diazoalkane, such as diazomethane, in either or with an alkanol such as methanol, in the presence of boron trifluoride to afford the corresponding alkyl ester. The ester product is then treated with sodium hydride in an ether solvent, such as 1,2 - dimethoxyethane; and then treated with a methyl halide, such as methyl iodide, to afford the corresponding 2 - (6' - substituted -

2' - naphthyl)propionic acid alkyl ester.

The 2 - difluoromethyl moiety is introduced by treating the 2 - (6' - substituted - 2' - naphthyl)acetic acid alkyl ester with an alkali metal, such as sodium metal, or an alkali metal hydride, such as sodium hydride, in a dialkyl carbonate, such as diethylcarbonate, to afford the corresponding 2 - alkoxy carbonyl compound. The latter is treated with chlorodifluoromethane and an alkali metal alkoxide, such as potassium *t* - butoxide in an organic ether solvent, preferably 1,2 - dimethoxyethane, to afford the corresponding 2 - alkoxy carbonyl - 2 - difluoromethyl derivative. This derivative is base hydrolyzed and neutralized to furnish the corresponding 2 - (6' - substituted - 2' - naphthyl) - 2 - carboxy - 2 - difluoromethylacetic acid derivative which is decarboxylated by heating to about 150°C, until the evolution of carbon dioxide ceases, to give the corresponding 2 - (6' - substituted - 2' - naphthyl) - 2 - difluoromethylacetic acid derivative.

The optical isomers can be resolved by conventional means, such as selective biological degradation. The optical isomers can also be resolved by the preparation of diastereo isomer salts of the 2 - (6' - substituted - 2' - naphthyl)propionic acid derivatives with resolved optically active amine bases and then separating the thus formed diastereo isomers by fractional crystallization. The separated diastereo isomer salts are then acid cleaved to yield the respective optical isomers of the 2 - (6' - substituted 2' - naphthyl)propionic acid derivatives.

Those compounds containing a trifluoromethyl group are preferably prepared from the corresponding 2 - (6' - methyl - 2' - naphthyl)propionic acid alkyl ester derivatives by treating the latter with chlorine and phosphorus trichloride in the presence of light to afford the corresponding 6' - trichloromethyl derivatives; which are refluxed with antimony trifluoride in a hydrocarbon solvent to furnish the corresponding 2 - (6' - trifluoromethyl - 2' - naphthyl)propionic acid alkyl ester derivative.

Those compounds containing a 6 - difluoromethoxy substituent are preferably prepared from the corresponding 2 - (6' - alkoxy - 2' - naphthyl)propionic acid alkyl ester derivative by refluxing the latter with 48% hydrobromic acid in acetic acid to furnish the corresponding 6' - hydroxy derivative. The hydroxy derivative is treated with chlorodifluoromethane and an alkali metal hydroxide in aqueous dioxane or tetrahydrofuran to furnish the corresponding 2 - (6' - difluoromethoxy - 2' - naphthyl)propionic acid alkyl ester derivative. By utilizing a 2 - (6' - methylthio - 2' - naphthyl)propionic acid alkyl ester derivative in the above process the corresponding 2 - (6' - difluoromethylthio - 2' - naphthyl)acetic acid alkyl ester derivative is obtained.

The following examples are inclined to further illustrate the invention herein described

and claimed. The examples are not intended as limitations of the present invention. Furthermore, many of the products and some of the processes given in the examples represent intermediate compounds or intermediate steps in the process of the present invention.

Example 1

- To a mixture of 1.6 g. of 2 - methoxynaphthalene, 1.6 g. of acetyl chloride, and 20 ml. of nitrobenzene, there are added 4.0 g. of aluminum chloride. The resulting mixture is stirred for 48 hours at 25°C; then it is washed with water until free of chloride ion. The mixture is dried over sodium sulfate and evaporated under reduced pressure. The residue, 2 - acetyl - 6 - methoxynaphthalene, is refluxed in 2 ml. of morpholine containing one-half gram of sulfur for two hours; the reaction mixture is then filtered and evaporated. The resulting reaction derivative is extracted with diethyl ether; the extracts are combined and evaporated. The residue is refluxed in 10 ml. of concentrated hydrochloric acid for two hours, cooled to 25°C, and neutralized with aqueous sodium hydroxide. The mixture is then extracted with ether and the extracts are combined, washed with water to neutrality, dried and evaporated to yield 2 - (6' methoxy - 2' - naphthyl)acetic acid.
- Similarly, 2 - (6' - chloro - 2' - naphthyl)acetic acid, 2 - (6' - fluoro - 2' - naphthyl)acetic acid, 2 - (6' - cyclopropyl - 2' - naphthyl)acetic acid, 2 - (6' - methylthio - 2' - naphthyl)acetic acid, 2 - (6' - methyl - 2' - naphthyl)acetic acid, 2 - (6' - ethyl - 2' - naphthyl)acetic acid, 2 - (6' - isopropyl - 2' - naphthyl)acetic acid, 2 - (6' - cyclopropyl - 2' - naphthyl)acetic acid, 2 - (6' - vinyl - 2' - naphthyl)acetic acid and 2 - (6' - ethynyl - 2' - naphthyl)acetic acid are prepared from the corresponding β - substituted naphthalenes by means of the above process.

Example 2

Part A

- To a mixture of 22 g. of methyl 2 - (6' - methoxy - 2' - naphthyl)acetate (prepared by treating 20.5 g. of 2 - (6' - methoxy - 2' - naphthyl)acetic acid with 4.5 g. of diazomethane in ether), and 2.5 g. of sodium hydride in 150 ml. of 1,2 - dimethoxyethane; 25 g. of methyl iodide are added. The reaction mixture is allowed to stand for several hours; then it is diluted with ethanol followed by water and extracted with methylene chloride. The extracts are combined, washed with water to neutrality, dried over sodium sulfate, filtered and evaporated to yield methyl 1 - (6' - methoxy - 2' - naphthyl)propionate.

Part B

- The resulting product is added to a mixture of 15 g. of sodium carbonate, 200 ml. of methanol and 25 ml. of water. The reaction mixture

is allowed to stand for 24 hours; then the mixture is acidified with 200 ml. of two normal hydrochloric acid. The acidified mixture is extracted with methylene chloride; the extracts are combined, washed with water, dried over sodium sulfate and evaporated to yield 2 - (6' - methoxy - 2' - naphthyl)propionic acid.

Similarly, the following 2 - (6' - substituted - 2' - naphthyl)propionic acid derivatives are prepared from the corresponding 2 - (6' - substituted - 2' - naphthyl)acetic acid derivatives: 2 - (6' - methyl - 2' - naphthyl)propionic acid, 2 - (6' - ethyl - 2' - naphthyl)propionic acid, 2 - (6' - isopropyl - 2' - naphthyl)propionic acid, 2 - (6' - cyclopropyl - 2' - naphthyl)propionic acid, 2 - (6' - fluoro - 2' - naphthyl)propionic acid, 2 - (6' - chloro - 2' - naphthyl)propionic acid, 2 - (6' - trifluoromethyl - 2' - naphthyl)propionic acid, 2 - (6' - methylthio - 2' - naphthyl)propionic acid, 2 - (6' - vinyl - 2' - naphthyl)propionic acid, 2 - (6' - difluoromethoxy - 2' - naphthyl)propionic acid, and 2 - (6' - difluoromethylthio - 2' - naphthyl)propionic acid.

Example 3

A mixture of 24.4 g. of ethyl 2 - (6' - methoxy - 2' - naphthyl)acetate [prepared by treating 2 - (6' - methoxy - 2' - naphthyl)acetic acid 23 g. of 2 - (6' - methoxy - 2' - naphthyl)acetic acid with 6 g. of diazoethane in ether], 2.4 g. of sodium hydride, and 100 ml. of diethyl carbonate is stirred for four hours at 20°C. The product, diethyl 6 - methoxy - 2 - naphthylmalonate (isolated by methylene chloride extraction), is added to 125 ml. of 1,2 - dimethoxyethane saturated with chlorodifluoromethane and containing 33 g. of potassium tert-butoxide. The resulting reaction mixture is heated to 60°C and continually saturated with chlorodifluoromethane for four hours. The mixture is carefully neutralized by the addition of aqueous oxalic acid; the product, diethyl 2 - (6' - methoxy - 2' - naphthyl) - 2 - difluoromethylmalonate, is isolated by methylene chloride extraction and hydrolyzed by refluxing in 250 ml. of methanol containing 5 g. of potassium hydroxide and 5 ml. of water. The cooled mixture is acidified with oxalic acid and the product, 2 - (6' - methoxy - 2' - naphthyl) - 2 - difluoromethylmalonic acid, is extracted with methylene chloride. The dried product is decarboxylated by heating to 180°C for six hours to give 2 - (6' - methoxy - 2' - naphthyl) - 2 - difluoromethylacetic acid [2 - (6' - methoxy - 2' - naphthyl) - 3,3 - difluoropropionic acid].

In a similar manner, the 2 - difluoromethyl moiety is introduced on the 2 - (6' - substituted - 2' - naphthyl)acetic acid ester derivatives of Example 1. For example, 2 - (6' - methyl - 2' - naphthyl) - 2 - difluoromethylacetic acid, 2 - (6' - ethyl - 2' - naphthyl) - 2 - difluoro - 2 - methyl acetic acid, 2 - (6' - cyclopropyl - 2' - naphthyl) - 2 - difluoromethyl-

acetic acid, 2 - (6' - trifluoromethyl - 2' - naphthyl) - 2 - difluoromethylacetic acid, 2 - (6' - fluoro - 2' - naphthyl) - 2 - difluoromethylacetic acid, 2 - (6' - chloro - 2' - naphthyl) - 2 - difluoromethylacetic acid, 2 - (6' - methylthio - 2' - naphthyl) - 2 - difluoromethylacetic acid, and 2 - (6' - vinyl - 2' - naphthyl) - 2 - difluoromethylacetic acid, are prepared from the corresponding methyl or ethyl 2 - (6' - substituted - 2' - naphthyl)-acetates.

Example 4

Part A

A mixture of 26 g. of methyl 2 - (6' - methylthio - 2' - naphthyl)propionate 200 ml. of glacial acetic acid, and 2 ml. of 48% hydrobromic acid are refluxed for 24 hours. The mixture is diluted with one liter of water and extracted with methylene chloride. The extracts are combined, washed with water, dried over sodium sulfate, filtered, and evaporated to yield 2 - (6' - thio - 2' - naphthyl)propionic acid.

Part B

The above product is added to a mixture of 150 ml. of dioxane and 150 ml. of aqueous 20% sodium hydroxide. The resulting mixture is heated to 65°C and saturated with chlorodifluoromethane. The resulting mixture is allowed to stand for two hours while continuously bubbling in chlorodifluoromethane. The cooled reaction mixture is then acidified by the addition of aqueous 1N hydrochloric acid and extracted with diethyl ether. The extracts are combined, washed with water to neutrality, dried over sodium sulfate, filtered, and evaporated to yield 2 - (6' - difluoromethylthio - 2' - naphthyl)propionic acid.

By employing methyl 2 - (6' - methoxy - 2' - naphthyl) - 3,3 - difluoropropionate in place of methyl 2 - (6' - methylthio - 2' - naphthyl)propionate in the above process, 2 - (6' - difluoromethoxy - 2' - naphthyl) - 3,3 - difluoropropionic acid is obtained.

In a similar manner, the methyl or ethyl 2 - (6' - methylthio - 2' - naphthyl)acetate derivatives and methyl or ethyl 2 - (6' - methoxy - 2' - naphthyl)acetate derivatives of Examples 1—3 can be cleaved and etherified to the corresponding 2 - (6' - difluoromethylthio - 2' - naphthyl)propionic acid derivatives and 2 - (6' - difluoromethoxy - 2' - naphthyl)propionic acid derivatives respectively. For example, 2 - (6' - difluoromethylthio - 2' - naphthyl) - 3,3 - difluoropropionic acid and 2 - (6' - difluoromethoxy - 2' - naphthyl)propionic acid are prepared from methyl 2 - (6' - methylthio - 2' - naphthyl) - 3,3 - difluoropropionate and methyl 2 - (6' - methoxy - 2' - naphthyl)propionate respectively.

Example 5

Chlorine gas is bubbled through a mixture of 23 g. of methyl 2 - (6' - methyl - 2' - naphthyl)propionate and 1 g. of phosphorus pentachloride in 200 ml. of carbon tetrachloride in the presence of light until 21.3 g. of chlorine have been taken up. The reaction mixture is diluted with 200 ml. of pyridine, filtered, further diluted with 500 ml. of ether, washed with water to neutrality, dried over sodium sulfate, and evaporated to yield methyl 2 - (6' - trichloromethyl - 2' - naphthyl)propionate. The above product is then refluxed in a mixture of 500 ml. of chlorobenzene and 17.9 g. of antimony trifluoride. The cooled reaction mixture is washed with water, dried over sodium sulfate, and evaporated to yield methyl 2 - (6' - trifluoromethyl - 2' - naphthyl)propionate. The product is hydrolyzed by means of the process described in Part B of Example 2.

Similarly, methyl 2 - (6' - trifluoromethyl - 2' - naphthyl) - 2 - difluoropropionate is prepared from methyl 2 - (6' - methyl - 2' - naphthyl) - 3,3 - difluoropropionate by means of the above process.

Example 6

Part A

A solution of 50:50 d and 1 2 - (6' - methoxy - 2' - naphthyl)propionic acid in methanol is prepared by dissolving 230 g. of the racemic mixture in 4.6 l. of warm methanol. The resulting solution is boiled until it becomes turbid; then sufficient methanol is added to make the solution clear again. This hot solution is added to a solution of 296 g. of cinchonidine in 7.4 l. of methanol heated to about 60°C. The solutions are combined while stirring and the combined mixture is then allowed to obtain room temperature over a two hour period. After the reaction mixture has obtained room temperature, it is stirred for an additional two hours and then filtered. The filtered salt is washed with several portions of ice cold methanol. The resulting washed salt is then dried under vacuum.

Part B

A saturated solution of the above salt in methanol is prepared by initially dissolving 100 g. of the above salt in 4 l. of methanol heated to about 60°C. The mixture is then refluxed and additional salt is added until the solution becomes turbid; at this point, methanol is added to make the solution clear again. The resulting mixture is allowed to cool to room temperature. After the cooled mixture is allowed to stand for two hours, it is filtered. The filtered salt is washed to yield the cinchonidine salt of d 2 - (6' - methoxy - 2' - naphthyl)propionic acid.

The above recrystallization is repeated 9 times using 2.5 l. of methanol in place of 4 l. to yield the cinchonidine salt of d 2 - (6' - methoxy - 2' - naphthyl)propionic acid.

Part C

The filtrates from Part A and Part B are combined and evaporated. The resulting salt

is added to 1500 ml. of hot ethanol; the hot mixture is slowly allowed to cool to 0°C over 12 hours, then the cooled mixture is filtered. The filtered salt crystals are washed 5 times with ice cold ethanol. The salt is then recrystallized an additional 4 times, first from 1350 ml. of ethanol:water (26:1), secondly from 1150 ml. of ethanol:water (55.2), thirdly from 900 ml. of ethanol:water (27:1) and lastly from 675 ml. of ethanol:water (26:1) to yield the salt of cinchonidine and 1 2 - (6'-methoxy - 2' - naphthyl)propionic acid.

Part D

One hundred grams of the cinchonidine salt of 1 2 - (6' - methoxy - 2' - naphthyl)propionic acid is added to a stirred mixture of 600 ml. of ethylacetate and 450 ml. of two normal aqueous hydrochloric acid. After the mixture has been stirred for two hours, the ethylacetate later is removed and washed with water to neutrality, dried over sodium sulfate and evaporated to yield 1 2 - (6' - methoxy - 2' - naphthyl)propionic acid.

Similarly, d 2 - (6' - methoxy - 2' - naphthyl)propionic acid is prepared from the cinchonidine salt of d 2 - (6' - methoxy - 2' - naphthyl)propionic acid.

In a similar manner, the racemate 2 - (6' - substituted - 2' - naphthyl)propionic acid derivatives of Examples 2, 4 and 5 and the 2 - (6' - substituted - 2' - naphthyl) - 3,3 - difluoropropionic acid derivatives of Examples 3—5 can be resolved by means of the above procedure. For example, d 2 - (6' - methyl - 2' - naphthyl)propionic acid and 1 2 - (6' - methyl - 2' - naphthyl)propionic acid can be resolved from a racemic mixture of 2 - (6' - methyl - 2' - naphthyl)propionic acid; and d 2 - (6' - methylthio - 2' - naphthyl) - 3,3 - difluoropropionic acid and 1 2 - (6' - methylthio - 2' - naphthyl) - 3 - difluoropropionic acid can be resolved from a racemic mixture of 2 - (6' - methylthio - 2' - naphthyl) - 3,3 - difluoropropionic acid by means of the above described process.

Example 7

A mixture of 23 g. of methyl 2 - (6' - hydroxy - 2' - naphthyl)propionate (prepared by refluxing methyl 2 - (6' - methoxy - 2' - naphthyl)propionate with boron tribromide in methylene chloride and then hydrolyzing the resulting 6' - orthoboric ester with aqueous alkali), 25 g. of chlorodimethyl ether and 500 ml. of dimethylformamide is allowed to stand at room temperature for 12 hours. The reaction mixture is then evaporated to yield methyl 2 - (6' - methoxymethoxy - 2' - naphthyl)propionate.

By employing methyl 2 - (6' - thio - 2' - naphthyl) - 3,3 - difluoropropionate in the above process, methyl 2 - (6' - methoxymethylthio - 2' - naphthyl) - 3,3 - difluoropropionate is obtained.

Example 8

To a solution of 22.6 g. of 2 - (6' - vinyl - 2' - naphthyl)propionic acid and 100 ml. of chloroform, there are added 320 g. of 5% solution of bromine and chloroform at -10°C. The resulting mixture is allowed to stand for 2 hours. The mixture is then evaporated to dryness. The residue is taken up in 250 ml. of diethyl ether and added to a mixture of liquid ammonia and 8 g. of sodium amide. The resulting ammonia mixture is allowed to stand for 10 hours; the mixture is then evaporated to dryness. The residue is taken up in diethyl ether, washed with 1/10 normal hydrochloric acid, and water to neutrality, dried over sodium sulfate and evaporated to yield 2 - (6'-ethynyl - 2' - naphthyl)propionic acid.

In a similar manner, 2 - (6' - ethynyl - 2' - naphthyl) - 2,2 - difluoromethylene acetic acid is prepared from 2 - (6' - vinyl - 2' - naphthyl) - 2,2 - difluoromethylene acetic acid by means of the above process.

Example 9

To a mixture of 4 g. of sodium hydroxide and 500 ml. of methanol are added 24.6 g. of 2 - (6' - methylthio - 2' - naphthyl)propionic acid. The mixture is stirred for 1 hour at 50°C. The cooled mixture is then evaporated to give the sodium salt of 2 - (6' - methylthio - 2' - naphthyl)propionic acid.

By employing potassium hydroxide, triethyl amine, lysine, caffeine, or procaine in place of sodium hydroxide in the above process, the potassium, triethylamine, lysine, caffeine, or procaine salt of 2 - (6' - methylthio - 2' - naphthyl)propionic acid is obtained.

By means of the above procedure, the addition salts of the 2 - (6' - substituted - 2' - naphthyl)propionic acid derivatives prepared in Examples 2—8 can be prepared.

Example 10

To a mixture of 4 g. of sodium hydroxide and 500 ml. of aqueous methanol, there is added 23 g. of d 2 - (6' - methoxy - 2' - naphthyl)propionic acid. The mixture is stirred for three hours at room temperature; the mixture is then evaporated to give sodium d 2 - (6' - methoxy - 2' - naphthyl)propionate.

By employing 5.6 g. of potassium hydroxide in place of sodium hydroxide in the above procedure, potassium d 2 - (6' - methoxy - 2' - naphthyl)propionate is obtained. By employing 3.71 g. of calcium hydroxide in place of sodium hydroxide in the above process, calcium di[d 2 - (6' - methoxy - 2' - naphthyl)propionate] is obtained.

Similarly, the sodium, potassium and calcium salts of the other 2 - (6' - substituted - 2' - naphthyl)propionic acid derivatives of Examples 2—8 are prepared by means of the above process. For example

sodium 1 2 - (6' - methoxy - 2' - naphthyl)propionate,

- sodium d and 1 2 - (6' - methoxy-2'-naphthyl)propionate,
 sodium d and 1 2 - (6' - trifluoromethyl-2' - naphthyl)propionate,
 5 sodium d and 1 2 - (6' - methoxy - 2'-naphthyl)propionate,
 sodium d and 1 2 - (6' - difluoromethoxy-2' - naphthyl)propionate,
 sodium d and 1 2 - (6' - chloro - 2'-naphthyl)propionate
 10 sodium d and 1 2 - (6' - methylthio - 2'-naphthyl)propionate,
 sodium d and 1 2 - (6' - difluoromethylthio - 2' - naphthyl)propionate,
 15 sodium d and 1 2 - (6' - vinyl - 2' - naphthyl)propionate,
 sodium d and 1 2 - (6' - ethyl - 2' - naphthyl) - 3,3 - difluoro propionate,
 sodium d and 1 2 (6' - cyclopropyl - 2'-naphthyl) - 3,3 - difluoropropionate,
 20 sodium d and 1 2 - (6' - fluoro - 2' - naphthyl) - 3,3 - difluoropropionate,
 sodium d and 1 2 - (6' - methoxy - 2'-naphthyl) - 3,3 - difluoropropionate,
 25 sodium d and 1 2 - (6' - difluoromethoxy-2' - naphthyl) - 3,3 - difluoropropionate,
 sodium d and 1 2 - (6' - methylthio - 2'-naphthyl) - 3,3 - difluoropropionate,
 sodium d and 1 2 - (6' - methyl - 2'-naphthyl) - 3,3 - difluoropropionate,
 30 sodium d and 1 2 - (6' - isopropyl - 2'-naphthyl) - 3,3 - difluoropropionate,
 sodium d and 1 2 - (6' - chloro - 2'-naphthyl) - 3,3 - difluoropropionate,
 35 sodium d and 1 2 - (6' - vinyl - 2' - naphthyl) - 3,3 - difluoropropionate,
 sodium d and 1 2 - (6' - trifluoromethyl-2' - naphthyl) - 3,3 - difluoropropionate, and
 sodium d and 1 2 - (6' - ethynyl - 2'-naphthyl) - 3,3 - difluoropropionate are prepared from the corresponding 2 - (6' - substituted - 2' - naphthyl)propionic acid derivatives by means of the above process.
- salts by means of the process described in Example 10. For example,
 the calcium salt of 2 - (6' - methyl - 2'-naphthyl)propionic acid,
 the calcium salt of 2 - (6' - ethyl - 2'-naphthyl)propionic acid,
 the calcium salt of 2 - (6' - trifluoromethyl-2' - naphthyl)propionic acid,
 the calcium salt of 2 - (6' - methoxy - 2'-naphthyl)propionic acid,
 the calcium salt of 2 - (6' - difluoromethoxy - 2' - naphthyl)propionic acid,
 the calcium salt of 2 - (6' - chloro - 2'-naphthyl)propionic acid,
 the calcium salt of 2 - (6' - fluoro - 2'-naphthyl)propionic acid,
 the calcium salt of 2 - (6' - methylthio-2' - naphthyl)propionic acid,
 the calcium salt of 2 - (6' - difluoromethylthio - 2' - naphthyl)propionic acid,
 the calcium salt of 2 - (6' - methyl - 2'-naphthyl) - 3,3 - difluoropropionic acid,
 the calcium salt of 2 - (6' - trifluoromethyl-2' - naphthyl) - 3,3 - difluoropropionic acid,
 the calcium salt of 2 - (6' - chloro - 2'-naphthyl) - 3,3 - difluoropropionic acid,
 the calcium salt of 1 2 - (6' - methoxy - 2'-naphthyl) - 3,3 - difluoropropionic acid,
 the calcium salt of 2 - (6' - methoxy - 2'-naphthyl) - 3,3 - difluoropropionic acid,
 the calcium salt of 2 - (6' - difluoromethylthio - 2' - naphthyl) - 3,3 - difluoropropionic acid,
 the calcium salt of 2 - (6' - ethynyl - 2'-naphthyl) - 3,3 - difluoropropionic acid,
 the calcium salt of 2 - (6' - methyl - 2'-naphthyl) - 3,3 - difluoropropionic acid, and
 the calcium salt of 2 - (6' - methylthio-2' - naphthyl) - 3,3 - difluoropropionic acid are prepared from the corresponding sodium or potassium 2 - (6' - substituted - 2' - naphthyl)propionate derivatives (prepared by the process described in Example 10) by means of the above process.

Example 11

- 45 To a mixture of 5.55 g. of calcium chloride and 300 ml. of water, there is added a solution of 25.2 g. of sodium d 2 - (6' - methoxy-2' - naphthyl)propionate and 300 ml. of water; the resulting mixture is allowed to stand for 12 hours at room temperature. The mixture is then filtered, and the filtered salt is washed with several portions of ice cold water. The washed salt is dried under vacuum to yield the calcium salt of d 2 - (6' - methoxy - 2'-naphthyl)propionate.

- 50 By employing 4.77 g. of magnesium chloride in the above process, the magnesium salt of d 2 - (6' - methoxy - 2' - naphthyl)propionate is obtained.

- 60 By means of the above process, the calcium and magnesium salts of the other 2 - (6' - substituted - 2' - naphthyl)propionic acid derivatives of Examples 2—8 are prepared after initially preparing the sodium or potassium

Example 12

- To a mixture of 16.2 of aluminum triethoxide and 1 l. of benzene, there are added 69 g. of d 2 - (6' - methoxy - 2' - naphthyl)propionic acid. The resulting mixture is refluxed for 24 hours; the mixture is then cooled and evaporated under reduced pressure to give the aluminum salt of d 2 - (6' - methoxy - 2'-naphthyl)propionic acid.

- By means of the above procedure, the aluminum salts of the other 2 - (6' - substituted - 2' - naphthyl)propionic acid derivatives of Examples 2—8 can be prepared. For example

- the aluminum salt of 2 - (6' - methyl - 2'-naphthyl)propionic acid,
 the aluminum salt of 2 - (6' - difluoromethoxy - 2' - naphthyl)propionic acid,
 the aluminum salt of 2 - (6' - fluoro - 2'-naphthyl)propionic acid,

- the aluminum salt of 2 - (6' - ethynyl - 2' - naphthyl)propionic acid,
the aluminum salt of 2 - (6' - isopropyl - 2' - naphthyl) - 3,3 - difluoropropionic acid,
5 the aluminum salt of 1 2 - (6' - methoxy - 2' - naphthyl)propionic acid,
the aluminum salt of 2 - (6' - methoxy - 2' - naphthyl) - 3,3 - difluoropropionic acid,
10 the aluminum salt of 2 - (6' - chloro - 2' - naphthyl) - 3,3 - difluoropropionic acid,
the aluminum salt of 2 - (6' - methylthio - 2' - naphthyl - 3,3 - difluoropropionic acid, and
the aluminum salt of 2 - (6' - acetyl - 2' - naphthyl) - 3,3 - difluoropropionic acid are
15 prepared from the corresponding 2 - (6' - substituted - 2' - naphthyl)propionic acid derivatives by means of the above described process.

Example 13

- 20 To a mixture of 50 ml. of concentrated aqueous ammonia in 500 ml. of methanol, there are added 23 g. of d 2 - (6' - methoxy - 2' - naphthyl)propionic acid. The resulting mixture is stirred for two hours and is then
25 evaporated to dryness to yield the ammonium salt of d 2 - (6' - methoxy - 2' - naphthyl)propionate.

- By employing trimethylamine, triethylamine or tri - *n* - propylamine in place of ammonia in the above process, trimethylammonium d 2 - (6' - methoxy - 2' - naphthyl)propionate, triethylammonium d 2 - (6' - methoxy - 2' - naphthyl)propionate, and tri - *n* - propylammonium d 2 - (6' - methoxy - 2' - naphthyl)propionate, respectively, are obtained. By
35 means of the above process the ammonium, trimethylamine, triethylamine and tripropylamine salts of the 2 - (6' - substituted - 2' - naphthyl)acetic acid derivatives of Examples
40 2—8 can be prepared. For example

- ammonium 1 2 - (6' - methoxy - 2' - naphthyl)propionate,
ammonium 2 - (6' - methyl - 2' - naphthyl)propionate,
45 ammonium 2 - (6' - acetyl - 2' - naphthyl)propionate,
ammonium 2 - (6' - isopropyl - 2' - naphthyl)propionate,
ammonium 2 - (6' - trifluoromethyl - 2' - naphthyl)propionate,
50 ammonium 2 - (6' - chloro - 2' - naphthyl)propionate,
ammonium 2 - (6' - methylthio - 2' - naphthyl)propionate,
55 ammonium 2 - (6' - methyl - 2' - naphthyl) - 3,3 - difluoropropionate,
ammonium 2 - (6' - fluoro - 2' - naphthyl) - 3,3 - difluoropropionate,
ammonium 2 - (6' - difluoromethoxy - 2' - naphthyl) - 3,3 - difluoropropionate,
60 ammonium 2 - (6' - methoxy - 2' - naphthyl) - 3,3 - difluoropropionate, and
ammonium 2 - (6' - vinyl - 2' - naphthyl) - 3,3 - difluoropropionate are prepared from the

corresponding 2 - (6' - substituted - 2' - naphthyl)propionic acid derivatives. 65

Example 14

To a mixture of 27.3 g. procaine and 500 ml. of aqueous methanol, there are added 23 g. of d 2 - (6' - methoxy - 2' - naphthyl)propionic acid; the resulting mixture is stirred for 16 hours at room temperature. The mixture is then evaporated under reduced pressure to give the procaine salt of d 2 - (6' - methoxy - 2' - naphthyl)propionic acid. 70 75

In a similar manner, by employing 14.6 g. of lysine, 17.4 g. of arginine or 19.4 g. of caffeine in place of procaine in the above process, the lysine, arginine or caffeine salt of d 2 - (6' - methoxy - 2' - naphthyl)propionic acid is, respectively, obtained. 80

Similarly, the lysine, caffeine, arginine and procaine salts of the 2 - (6' - substituted - 2' - naphthyl)acetic acid derivatives of Examples 2—8 can be prepared. For example 85

the procaine salt of 2 - (6' - cyclopropyl - 2' - naphthyl)propionic acid,
the procaine salt of 2 - (6' - fluoro - 2' - naphthyl)propionic acid,
the procaine salt of 2 - (6' - difluoro - methylthio - 2' - naphthyl)propionic acid,
the procaine salt of 2 - (6' - isopropyl - 2' - naphthyl) - 3,3 - difluoropropionic acid,
the procaine salt of 1 2 - (6' - methoxy - 2' - naphthyl)propionic acid, 95
the procaine salt of 2 - (6' - trifluoromethyl - 2' - naphthyl) - 3,3 - difluoropropionic acid,
the procaine salt of 2 - (6' - methyl - 2' - naphthyl)propionic acid,
the procaine salt of 2 - (6' - chloro - 2' - naphthyl) - 3,3 - difluoropropionic acid,
the procaine salt of 2 - (6' - methoxy - 2' - naphthyl) - 3,3 - difluoropropionic acid,
the procaine salt of 2 - (6' - difluoromethoxy - 2' - naphthyl) - 3,3 - difluoropropionic acid, 100
the procaine salt of 2 - (6' - methyl - 2' - naphthyl) - 3,3 - difluoropropionic acid, and
the procaine salt of 2 - (6' - difluoromethylthio - 2' - naphthyl) - 3,3 - difluoropropionic acid are prepared from the corresponding 2 - (6' - substituted - 2' - naphthyl)propionic acid derivatives. 105 110

Example 15

The anti-inflammatory activity of the following 2 - (6' - substituted - 2' - naphthyl)propionic acid derivatives was compared with that of phenylbutazone by means of a carageenin-induced rat paw inflammation test described by C. A. Winter et al., *The Proceedings of the Society for Experimental Biology and Medicine*, 111, 544—47, (1962). 115 120

The test was modified in that female rats weighing 80—90 grams were employed and the degree of inflammation was measured one hour after the injection of carageenin in units of rear paw weight rather than rear paw volume. The results are shown in the following table. 125

Compound Tested	No. of Rats	Dose Range Tested Mg./rat	Relative Potency to phenylbutazone (phenylbutazone=1)
2,2-dimethylamine salt of d 2-(6'-methoxy-2'-naphthyl)-propionic acid	89	0.033—2.7	5
d 2-(6'-methoxy-2'-naphthyl)propionic acid	209	0.033—2.7	11
2-(6'-methylthio-2'-naphthyl)propionic acid	17	0.1—0.9	4
2-(6'-difluoromethoxy-2'-naphthyl)-propionic acid	48	0.1—2.7	3
the calcium salt of 2-(6'-methoxy-2'-naphthyl)-propionic acid	110	0.036	10
d1 2-(6'-chloro-2'-naphthyl)propionic acid	53	0.1—2.7	2
sodium salt of d 2-(6'-methoxy-2'-naphthyl)-propionic acid	117	0.033—0.94	10
the 2-(dimethylamino)-ethanol salt of d 2-(6'-methoxy-2'-naphthyl)-propionic acid	89	0.033—2.7	5

Example 16

The anti-pyretic activity of the following 2 - (6' - substituted - 2' - naphthyl)propionic acid derivatives was compared to the anti-pyretic activity of aspirin.

Anti-pyretic activity — Female rats weighing 90—100 grams were used. The "normal" rectal temperature of the rats was recorded at hour 0, followed by the injection of 2 ml. of yeast suspension (the yeast suspension is prepared by suspending one cake of Fleischman's yeast in 22 ml. 0.9% NaCl) subcutaneously (1 ml. dorsally, 1 ml. ventrally). The injection sites are massaged to spread the suspension beneath the skin. The yeast injection induces elevated body temperature. At hour 17, the rats were massaged again to stimulate a further increase in body temperature. (It was found that handling the rats at the time the second

temperature was taken resulted in a rise in body temperature). At hour 18, the second rectal temperature was recorded, after which the test material was administered orally by gavage in 1 ml. aqueous vehicle. (The aqueous vehicle consists of 0.9% NaCl, 0.4% polysorbate 80, 0.5% carboxymethyl cellulose, 0.9% benzyl alcohol and water). The third rectal temperature was obtained two hours after administration of the test material.

The degree of anti-pyretic activity was measured as a reduction in temperature (F°) from the second to the third temperature readings (temperature at hour 18—temperature at hour 20) with respect to a control. The results are shown in the following table. For each compound tested, half the rats were given the higher dosage and half were given the lower dosage.

25

30

35

Compound Tested	No. of Rats	Dose Range Tested Mg/rat	Relative Potency to Aspirin (Aspirin=1)
d 2-(6'-methoxy-2'-naphthyl)propionic acid	40	0.2 and 0.6	22
d and 1 2-(6'-chloro-2'-naphthyl)propionic acid	10	0.2 and 0.6	5
the sodium salt of d 2-(6'-methoxy-2'-naphthyl)-propionic acid	20	0.2 and 0.6	20

Example 17

- 5 The analgesic activity of the following 2-(6' - substituted - 2' - naphthyl)propionic acid derivatives was compared with that of aspirin. The test used was a mouse writhing test, which consists of orally administering the compound to be tested by gavage in an aqueous vehicle at time 0 to 18—20 male Swiss-Webster mice.
- 10 Twenty minutes later 0.25 ml. of a 0.02% solution of phenylquinone (which is prepared by dissolving 4 mg. of phenylquinone in 0.5 ml. absolute ethanol, and adding the ethanol solution to 19.5 ml. warmed distilled water)

is injected intraperitoneally. This solution induces writhing. 15

End point: the total number of mice that writhe and the average number of writhes per mouse.

The degree of analgesic activity was measured as the difference in the average number of writhes between the control animals (animals receiving by gavage an aqueous vehicle with no compound) and the tested animals (animals receiving the compound to be tested). 20
25 The results are shown in the following table.

Compound	No. of mice	Total Dose	Activity compared to Aspirin (Aspirin=1)
d 2-(6'-methoxy-2'-naphthyl)propionic acid	154	0.006—.384	8
the sodium salt of d 2-(6'-methoxy-2'-naphthyl)-propionic acid	80	.048—.384	5
2-(6'-chloro-2'-naphthyl)-propionic acid	60	0.006—0.9	5

Example 18

Ingredients	Quantity per tablet, mgs.
calcium di[d 2 - (6'-methoxy 2' - naphth yl) propionate]	10
cornstarch	200
sucrose	40

The above ingredients are thoroughly mixed and pressed into single scored tablets.

Example 19

Ingredients	Quantity per tablet, mgs.
d 2 - (6' - methoxy - 2'- naphthyl)propionic acid	5
cornstarch	100
lactose	393
magnesium stearate	2

The above ingredients are mixed intimately and pressed into single scored tablets.

Example 20

Ingredients	Quantity per capsule, mgs.
the potassium salt of di 2 - (6' - methyl - 2' naphthyl)propionic acid	60
lactose	190

The above ingredients are mixed and introduced into a hard-shell gelatin capsule.

Example 21

Ingredients	Quantity per capsule, mgs.
the sodium salt of d 2- (6' - methoxy - 2'- naphthyl)propionic acid	60
lactose	182
magnesium stearate	8

The above ingredients are mixed and introduced into a hard-shell gelatin capsule.

Example 22

The ethanolamine salt of d 2 (6' - methoxy - 2' - naphthyl)propionic acid is prepared from d 2 - (6' - methoxy - 2' - naphthyl)propionic acid by means of the process described in Example 14, except 6.1 g. of ethanolamine is used in place of procaine.

In a similar manner, the ethanolamine salts of the 2 - (6' - substituted - 2' - naphthyl)propionic derivatives of Examples 2—8 can be prepared.

Example 23

The 2 - (diethylamino)ethanol salt of d 2 - (6' - methoxy - 2' - naphthyl)propionic acid is prepared from d 2 - (6' - methoxy - 2' - naphthyl)propionic acid by means of the process described in Example 14, except 11.8 g. of 2 - (diethylamino)ethanol is used in place of procaine.

In a similar manner, the 2 - (diethylamino)ethanol salts of the 2 - (6' - substituted - 2' - naphthyl)propionic acid derivatives of Examples 2—8 can be prepared.

Example 24

The 2 - (dimethylamino)ethanol salt of d 2 - (6' - methoxy - 2' - naphthyl)propionic acid is prepared from d 2 - (6' - methoxy - 2' - naphthyl)propionic acid by means of the process described in Example 14, except 9.0 g. of 2 - (dimethylamino)ethanol is used in place of procaine.

In a similar manner, the 2 - (dimethylamino)ethanol salts of the 2 - (6' - substituted - 2' - naphthyl)propionic acid derivatives of Examples 2—8 can be prepared.

Example 25

The methyl glucamine salt of d 2 - (6' - methoxy - 2' - naphthyl)propionic acid is prepared from d 2 - (6' - methoxy - 2' - naphthyl)propionic acid by means of the process described in Example 14, except 19.5 g. of methyl glucamine is used in place of procaine.

In a similar manner, the methyl glucamine salts of the 2 - (6' - substituted - 2' - naphthyl)propionic acid derivatives of Examples 2—8 can be prepared.

Example 26

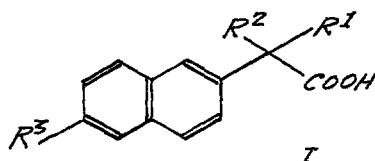
The ethylenediamine salt of d 2-(6'-methoxy-2'-naphthyl)propionic acid is prepared from d 2-(6'-methoxy-2'-naphthyl)propionic acid by means of the process described in Example 14, except 6.0 g. of ethylenediamine is used in place of procaine.

In a similar manner, the ethylenediamine salts of the 2-(6'-substituted-2'-naphthyl)propionic acid derivatives of Examples 2-8 can be prepared.

Preferred compounds of the present invention include the sodium, potassium, calcium and procaine salts of d 2-(6'-methyl-2'-naphthyl)propionic acid and 1 2-(6'-methyl-2'-naphthyl)propionic acid; d 2-(6'-trifluoromethyl-2'-naphthyl)propionic acid and 1 2-(6'-trifluoromethyl-2'-naphthyl)propionic acid; d 2-(6'-chloro-2'-naphthyl)propionic acid and 1 2-(6'-chloro-2'-naphthyl)propionic acid; d 2-(6'-difluoromethoxy-2'-naphthyl)propionic acid and 1 2-(6'-difluoromethoxy-2'-naphthyl)propionic acid; d 2-(6'-methylthio-2'-naphthyl)propionic acid and 1 2-(6'-methylthio-2'-naphthyl)propionic acid; d 2-(6'-difluoromethylthio-2'-naphthyl)propionic acid and 1 2-(6'-difluoromethylthio-2'-naphthyl)propionic acid; d 2-(6'-fluoro-2'-naphthyl)propionic acid and 1 2-(6'-fluoro-2'-naphthyl)propionic acid; d 2-(6'-difluoromethoxy-2'-naphthyl)-3,3-difluoropropionic acid and 1 2-(6'-difluoromethoxy-2'-naphthyl)-3,3-difluoropropionic acid; and d 2-(6'-methoxy-2'-naphthyl)-2-difluoromethylacetic acid and 1 2-(6'-methoxy-2'-naphthyl)-2-difluoromethylacetic acid.

WHAT WE CLAIM IS:—

1. The magnesium, ammonium, R_3N , ethanolamine, methyl glucamine, or ethylenediamine salt of a compound of the formula:



wherein,

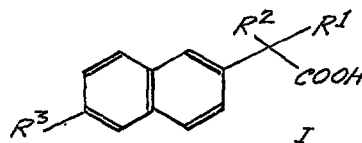
one of R^1 and R^2 is hydrogen and the other is methyl or difluoromethyl; and

R^3 is methyl, ethyl, isopropyl, cyclopropyl, trifluoromethyl, vinyl, ethynyl, fluoro, chloro, methoxy, methoxymethoxy, difluoromethoxy, methylthio, methoxymethylthio or difluoromethylthio;

R is lower alkyl (except ethyl), monocyclic aralkyl or monocyclic aryl; as a mixture of the d- and l-forms or as a resolved salt having dextrorotatory or laevorotary optical activity.

2. A resolved isomer, having dextrorotatory

or laevorotary optical activity, of a compound of the formula:



wherein,

one of R^1 and R^2 is hydrogen and the other is methyl or difluoromethyl; and

R^3 is methyl, ethyl, isopropyl, cyclopropyl, trifluoromethyl, vinyl, ethynyl, fluoro, chloro, methoxy, methoxymethoxy, difluoromethoxy, methylthio, methoxymethylthio or difluoromethylthio;

the corresponding sodium, potassium, calcium, magnesium, aluminum, ammonium, R_3N , ethanolamine, 2-(diethylamino)ethanol, 2-(dimethylamino)ethanol, arginine, lysine, caffeine, procaine, methyl glucamine, or ethylenediamine salts thereof; and

R is lower alkyl, monocyclic aralkyl or monocyclic aryl; with the proviso that when the other of R^1 and R^2 is methyl, R^3 is cyclopropyl, vinyl, ethynyl, methoxymethoxy, or methoxymethylthio.

3. The compounds according to Claim 1, wherein one of R^1 and R^2 is hydrogen and the other is methyl; and R^3 is methyl, trifluoromethyl, fluoro, chloro, methoxy, difluoromethoxy, methylthio or difluoromethylthio.

4. The sodium salt of d 2-(6'-methoxy-2'-naphthyl)propionic acid.

5. The potassium salt of d 2-(6'-methoxy-2'-naphthyl)propionic acid.

6. The calcium salt of d 2-(6'-methoxy-2'-naphthyl)propionic acid.

7. The sodium, potassium, calcium and procaine salts of d 2-(6'-methyl-2'-naphthyl)propionic acid and 1 2-(6'-methyl-2'-naphthyl)propionic acid.

8. The sodium, potassium, calcium and procaine salts of d 2-(6'-trifluoromethyl-2'-naphthyl)propionic acid and 1 2-(6'-trifluoromethyl-2'-naphthyl)propionic acid.

9. The sodium, potassium, calcium and procaine salts of d 2-(6'-chloro-2'-naphthyl)propionic acid and 1 2-(6'-chloro-2'-naphthyl)propionic acid.

10. The sodium, potassium, calcium and procaine salts of d 2-(6'-difluoromethoxy-2'-naphthyl)propionic acid and 1 2-(6'-difluoromethoxy-2'-naphthyl)propionic acid.

11. The sodium, potassium, calcium and procaine salts of d 2-(6'-methylthio-2'-naphthyl)propionic acid and 1 2-(6'-methylthio-2'-naphthyl)propionic acid.

12. The sodium, potassium, calcium and procaine salts of d 2-(6'-difluoromethylthio-2'-naphthyl)propionic acid and 1 2-

Example 26

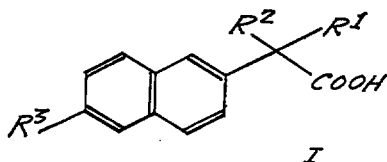
The ethylenediamine salt of d 2-(6'-methoxy-2'-naphthyl)propionic acid is prepared from d 2-(6'-methoxy-2'-naphthyl)propionic acid by means of the process described in Example 14, except 6.0 g. of ethylenediamine is used in place of procaine.

In a similar manner, the ethylenediamine salts of the 2-(6'-substituted-2'-naphthyl)propionic acid derivatives of Examples 2-8 can be prepared.

Preferred compounds of the present invention include the sodium, potassium, calcium and procaine salts of d 2-(6'-methyl-2'-naphthyl)propionic acid and 1 2-(6'-methyl-2'-naphthyl)propionic acid; d 2-(6'-trifluoromethyl-2'-naphthyl)propionic acid and 1 2-(6'-trifluoromethyl-2'-naphthyl)propionic acid; d 2-(6'-chloro-2'-naphthyl)propionic acid and 1 2-(6'-chloro-2'-naphthyl)propionic acid; d 2-(6'-difluoromethoxy-2'-naphthyl)propionic acid and 1 2-(6'-difluoromethoxy-2'-naphthyl)propionic acid; d 2-(6'-methylthio-2'-naphthyl)propionic acid and 1 2-(6'-methylthio-2'-naphthyl)propionic acid; d 2-(6'-difluoromethylthio-2'-naphthyl)propionic acid and 1 2-(6'-difluoromethylthio-2'-naphthyl)propionic acid; d 2-(6'-fluoro-2'-naphthyl)propionic acid and 1 2-(6'-fluoro-2'-naphthyl)propionic acid; d 2-(6'-difluoromethoxy-2'-naphthyl)-3,3-difluoropropionic acid and 1 2-(6'-difluoromethoxy-2'-naphthyl)-3,3-difluoropropionic acid; and d 2-(6'-methoxy-2'-naphthyl)-2-difluoromethylacetic acid and 1 2-(6'-methoxy-2'-naphthyl)-2-difluoromethylacetic acid.

WHAT WE CLAIM IS:—

1. The magnesium, ammonium, R_3N , ethanolamine, methyl glucamine, or ethylenediamine salt of a compound of the formula:



wherein,

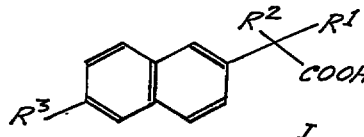
one of R^1 and R^2 is hydrogen and the other is methyl or difluoromethyl; and

R^3 is methyl, ethyl, isopropyl, cyclopropyl, trifluoromethyl, vinyl, ethynyl, fluoro, chloro, methoxy, methoxymethoxy, difluoromethoxy, methylthio, methoxymethylthio or difluoromethylthio;

R is lower alkyl (except ethyl), monocyclic aralkyl or monocyclic aryl; as a mixture of the d- and l-forms or as a resolved salt having dextrorotatory or laevorotatory optical activity.

2. A resolved isomer, having dextrorotatory

or laevorotatory optical activity, of a compound of the formula:



wherein,

one of R^1 and R^2 is hydrogen and the other is methyl or difluoromethyl; and

R^3 is methyl, ethyl, isopropyl, cyclopropyl, trifluoromethyl, vinyl, ethynyl, fluoro, chloro, methoxy, methoxymethoxy, difluoromethoxy, methylthio, methoxymethylthio or difluoromethylthio;

the corresponding sodium, potassium, calcium, magnesium, aluminum, ammonium, R_3N , ethanolamine, 2-(diethylamino)ethanol, 2-(dimethylamino)ethanol, arginine, lysine, caffeine, procaine, methyl glucamine, or ethylenediamine salts thereof; and

R is lower alkyl, monocyclic aralkyl or monocyclic aryl; with the proviso that when the other of R^1 and R^2 is methyl, R^3 is cyclopropyl, vinyl, ethynyl, methoxymethoxy, or methoxymethylthio.

3. The compounds according to Claim 1, wherein one of R^1 and R^2 is hydrogen and the other is methyl; and R^3 is methyl, trifluoromethyl, fluoro, chloro, methoxy, difluoromethoxy, methylthio or difluoromethylthio.

4. The sodium salt of d 2-(6'-methoxy-2'-naphthyl)propionic acid.

5. The potassium salt of d 2-(6'-methoxy-2'-naphthyl)propionic acid.

6. The calcium salt of d 2-(6'-methoxy-2'-naphthyl)propionic acid.

7. The sodium, potassium, calcium and procaine salts of d 2-(6'-methyl-2'-naphthyl)propionic acid and 1 2-(6'-methyl-2'-naphthyl)propionic acid.

8. The sodium, potassium, calcium and procaine salts of d 2-(6'-trifluoromethyl-2'-naphthyl)propionic acid and 1 2-(6'-trifluoromethyl-2'-naphthyl)propionic acid.

9. The sodium, potassium, calcium and procaine salts of d 2-(6'-chloro-2'-naphthyl)propionic acid and 1 2-(6'-chloro-2'-naphthyl)propionic acid.

10. The sodium, potassium, calcium and procaine salts of d 2-(6'-difluoromethoxy-2'-naphthyl)propionic acid and 1 2-(6'-difluoromethoxy-2'-naphthyl)propionic acid.

11. The sodium, potassium, calcium and procaine salts of d 2-(6'-methylthio-2'-naphthyl)propionic acid and 1 2-(6'-methylthio-2'-naphthyl)propionic acid.

12. The sodium, potassium, calcium and procaine salts of d 2-(6'-difluoromethylthio-2'-naphthyl)propionic acid and 1 2-



(6' - difluoromethylthio - 2' - naphthyl)propionic acid.

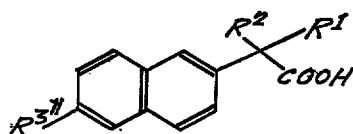
13. The sodium, potassium, calcium and procaine salts of d 2 - (6' - fluoro - 2' - naphthyl)propionic acid and 1 2 - (6' - fluoro - 2' - naphthyl)propionic acid.

14. The sodium, potassium, calcium and procaine salts of d 2 - (6' - Difluoromethoxy - 2' - naphthyl) - 3,3 - difluoropropionic acid and 1 2 - (6' - difluoromethoxy - 2' - naphthyl) - 3,3 - difluoropropionic acid.

15. The sodium, potassium, calcium and procaine salts of d 2 - (6' - Methoxy - 2' - naphthyl) - 2 - difluoromethylacetic acid, 1 2 - (6' - methoxy - 2' - naphthyl) - 2 - difluoromethylacetic acid.

16. A process for preparing a compound of claim 1 or claim 2, which includes either or both of the following steps:

- (1) resolving a compound of Formula I to obtain a d- or l-isomer; and
(2) reacting a compound of Formula I with a base to form the corresponding salt; and optionally one or more of the following steps:
(3) the hydrolysis of an ester of a compound of Formula I;
(4) decarboxylation of a 2 - (6' - substituted - 2' - naphthyl) - 2 - difluoromethylmalonic acid;
(5) etherification of a compound represented by the formula



- wherein R^{3''} is a hydroxy or thiol group; and
(6) dehydrobrominating a 2 - [6' - (1,2-dibromoethyl) - 2' - naphthyl]propionic acid to yield a 2 - (6' - ethynyl - 2' - naphthyl)propionic acid.

17. A method of effecting treatment of inflammation, pain and pyrexia in non-humans, which comprises administering an effective therapeutic dose of a compound of claim 1 or claim 2.

18. A method of effecting treatment according to claim 17 wherein the compound is present as the resolved isomer having dextro-rotatory optical activity.

19. A method of effecting treatment according to claim 18 wherein the compound is the sodium salt of d 2 - (6' - methoxy - 2' - naphthyl)propionic acid.

20. A method of effecting treatment according to claim 18 wherein the compound is the potassium salt of d 2 - (6' - methoxy - 2' - naphthyl)propionic acid.

21. A method of effecting treatment according to claim 18 wherein the compound is the calcium salt of d 2 - (6' - methoxy - 2' - naphthyl)propionic acid.

22. A method of effecting treatment according to claim 18, substantially as described and exemplified herein.

23. Compounds according to claim 1 or claim 2 substantially as herein described and exemplified.

24. Process according to claim 16 substantially as herein described and exemplified.

25. Compounds of the formula (I) or their corresponding salts whenever prepared by the process claimed in claim 16 or claim 24.

26. A therapeutic composition comprising a compound as claimed in any of claims 1 to 15, claim 23 or claim 25 and an acceptable carrier thereof.

27. A therapeutic composition according to claim 26 substantially as herein described and exemplified.

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