

1211134

NO DRAWINGS

- (21) Application No. 1197/68 (22) Filed 9 Jan. 1968
(31) Convention Application No. 608 997 (32) Filed 13 Jan. 1967 in
(33) United States of America (US)
(31) Convention Application No. 694 771 (32) Filed 7 Dec. 1967 in
(33) United States of America (US)
(45) Complete Specification published 4 Nov. 1970
(51) International Classification C 07 d 5/04, 7/04, 87/28, 27/04, 29/12,
51/70; C 07 c 63/52, 69/76, 103/10; A 61 k 27/00
(5)



ERRATA

SPECIFICATION No. 1,211,134

- Page 2, line 27, for "hydroxyl" read "hydroxy"
Page 2, line 33, for "R¹⁵" read "R¹⁶"
Page 3, line 25, for "thiether" read "thioether"
Page 5, line 53, for "R² and R¹⁰" read "R² or R¹⁰"
Page 7, line 34, for "Carboxynaphthalene" read "Carboxynaphthalene"
Page 11, line 53, for "dimethoxyoxyethane" read "dimethoxyethane"
Page 12, line 2, for "evaluation" read "evolution"
Page 18, line 19, for "naphylacetates" read "naphthylacetate"
Page 18, line 59, for "methoxycarbonylmethyl" read "methoxycarbonylmethyl"
Page 23, line 54, for "methyl" read "methylene"
Page 29, line 39, for "R⁵" read "R⁶"
Page 31, line 19, for "R¹³" read "R¹⁶"
Page 33, line 3, for "Claim 24" read "Claim 34"
Page 37, line 1, for "accoding" read "according"

THE PATENT OFFICE
5th January 1971

8B2A3 8B2Y 8B3AX 8B3B2A2 8B3BX 8B3C2 8B3Y
8B4

(54) IMPROVEMENTS IN OR RELATING TO NAPHTHALENE DERIVATIVES

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

SEE ERRATA SLIP ATTACHED

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 (52) Index at acceptance



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 565 566 56Y 595 59Y 606 60Y 640 64Y 664 66Y
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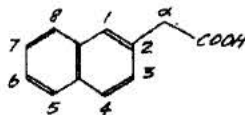
(54) IMPROVEMENTS IN OR RELATING TO NAPHTHALENE DERIVATIVES

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

SEE SEPARATE SHEET FOR CLAIMS

This invention relates to novel compositions useful as anti-inflammatory, analgesic, anti-pyretic and anti-pruritic agents. It also relates to novel methods for treating conditions marked by inflammation, pain, pyrexia, and pruritus. It further relates to novel compounds which are thus useful and to methods for their preparation, as well as to certain novel intermediates thereof.

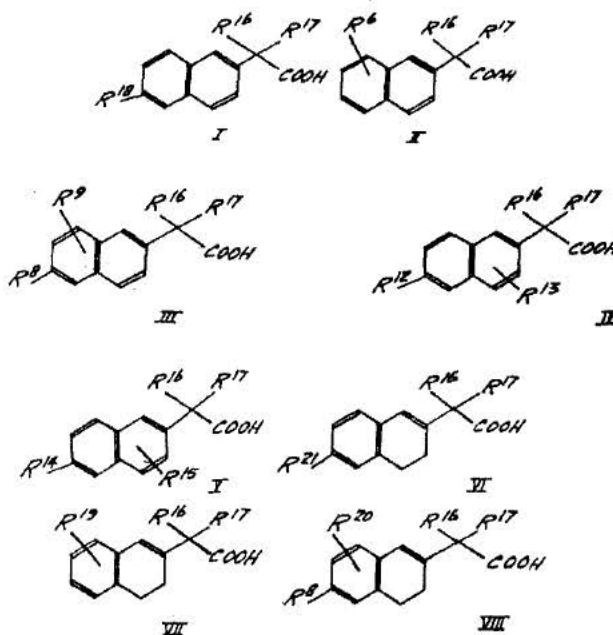
The present compounds are derivatives of 2-naphthylacetic acid, a compound which can be represented by the formula:



The arabic numerals and the alpha symbol indicate the positions used herein in the nomenclature of 2-naphthylacetic acid derivatives.

The present invention provides compounds applicable for effecting treatment of inflammation, pain, pyrexia, and pruritus, as well as associative conditions thereof, by administering an effective quantity of a 2-naphthylacetic acid derivative as hereinafter defined or the corresponding amide, ester, hydroxamic acid or addition salt thereof, which salt is derived from a pharmaceutically acceptable non-toxic base.

These thus useful 2-naphthylacetic acid derivatives can be represented by the following general formulae:



wherein each of R^8 (at position 1, 4, 7 or 8) and R^{19} (as position 1, 7 or 8) is alkyl, trifluoromethyl, fluoro, chloro, hydroxy, hydrolyzable ester, oxyether or thioether, provided that when R^{15} and R^{17} are hydrogen or one of R^{16} and R^{17} is methyl or ethyl, R^{19} (when at position 1) is other than hydroxy;

R^6 is alkyl, fluoro, chloro, hydroxy, hydrolyzable ester, oxyether or thioether;

each of R^9 (at position 1, 4, 7 or 8) and R^{20} (at position 1, 7 or 8) is alkyl, fluoro, chloro, hydroxy, hydrolyzable ester, oxyether or thioether, provided that when R^9 is hydroxy, oxyether or thioether, R^9 or R^{20} is the identical group or alkyl, fluoro, chloro or hydrolyzable ester; provided that when one of R^9 or R^{20} is hydroxyl, oxyether or thioether, R^9 is the identical group or alkyl, fluoro, chloro, or hydrolyzable ester;

each of R^{12} and R^{15} (at position 1 or 4) is hydroxy, oxyether or thioether;

each of R^{13} (at position 1 or 4) and R^{14} is alkoxy or alkylthio, provided when R^{12} or R^{15} is alkoxy or alkylthio, R^{13} or R^{14} respectively is a different alkoxy or alkylthio group;

one of R^{15} and R^{17} is hydrogen, the other being hydrogen, methyl, ethyl, difluoromethyl, fluoro or chloro; or

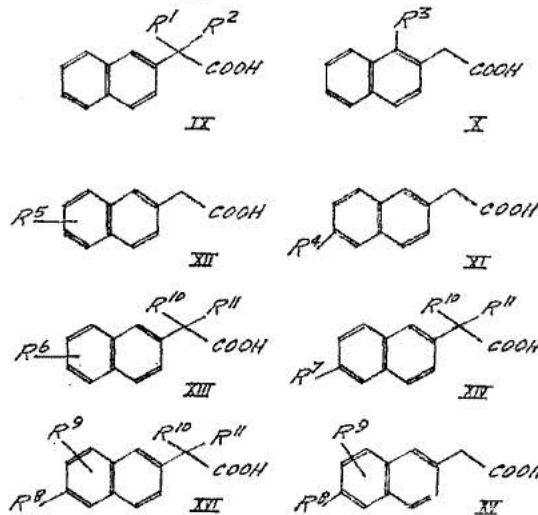
R¹⁶ and R¹⁷ taken together are alkylidene, halomethylene or ethylene;

R¹⁸ is hydrogen, alkyl, cycloalkyl, trifluoromethyl, hydroxymethyl, alkoxymethyl, vinyl, ethynyl, fluoro, chloro, hydroxy, hydrolyzable ester, oxyether, thioether, formyl, carboxy, alkoxycarbonyl, acetyl, cyano or aryl;

R²¹ is hydrogen, alkyl, cycloalkyl, trifluoromethyl, fluoro, chloro, hydroxy, hydrolyzable ester, oxyether, thioether or aryl; provided that at least one of R¹⁶, R¹⁷, and R²¹ is other than hydrogen; provided that when one of R¹⁶ and R¹⁷ is methyl or ethyl, R²¹ is other than hydrogen; or a

corresponding amide, ester, hydroxamic acid or pharmaceutically acceptable addition salt thereof.

Several classes of novel naphthylacetic acid derivatives of general formulae I—VIII include those of the following general formulae:



wherein one of R¹ and R³ is hydrogen and the other is difluoromethyl, fluoro or chloro; or

R¹ and R² taken together are alkylidene, halomethylene, or ethylene;

R³ is trifluoromethyl, hydrolyzable ester, difluoromethoxy, alkoxymethoxy, 4'-alkoxytetrahydropyran-4'-yloxy, tetrahydrofuran-2'-yloxy, tetrahydropyran-2'-yloxy, or thioether;

R⁴ is cycloalkyl, hydroxymethyl, alkoxymethyl, trifluoromethyl, vinyl, ethynyl, a hydrolyzable ester, alkoxymethoxy, alkylthiomethylthio, difluoromethoxy, alkoxy-methylthio, alkylthiomethoxy, difluoromethylthio, formyl, carboxy, alkoxycarbonyl, acetyl, cyano, or aryl;

each of R⁵ (at position 4, 7 or 8) and R⁶ (at position 1, 4, 7 or 8) is alkyl, trifluoromethyl, fluoro, chloro, hydroxy, hydrolyzable ester, oxyether or thiether; provided that R⁵ (when at position 7) is other than alkyl;

R⁷ is alkyl, cycloalkyl, hydroxymethyl, alkoxymethyl, trifluoromethyl, vinyl, ethynyl, fluoro, chloro, hydroxy, hydrolyzable ester, oxyether, thioether, formyl, carboxy, alkoxycarbonyl, acetyl, cyano or aryl;

each of R⁸ and R⁹ (at position 1, 4, 7 or 8) is alkyl, fluoro, chloro, hydroxy, hydrolyzable ester, oxyether or thioether; provided that when one of R⁸ or R⁹ is hydroxy, oxyether or thioether, the other is the identical group or alkyl, fluoro, chloro or hydrolyzable ester;

one of R¹⁰ and R¹¹ is hydrogen, the other being methyl, ethyl, difluoromethyl, fluoro or chloro; or

R¹⁰ and R¹¹ taken together are alkylidene, halomethylene, or ethylene; provided that when one of R¹⁰ or R¹¹ is methyl or ethyl, R⁶ (when at position 1 or 7) is other than alkyl; or

a corresponding amide, ester, hydroxamic acid or pharmaceutically acceptable addition salt thereof.

By the terms which define an "alkyl" grouping are meant lower molecular weight, branched, or straight chain hydrocarbon groups of six or less carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, tertbutyl, pentyl and hexyl. By the term "cycloalkyl" is meant cyclic hydrocarbon groups of three to seven carbon atoms, such as cyclopropyl, cyclopentyl and cyclohexyl.

By the term "alkoxy" is intended a straight or branched chain hydrocarbon ether group of six or less carbon atoms, including methoxy, ethoxy, 2-propoxy, butoxy and 3-pentoxy.

By the terms which define an "alkoxymethyloxy" grouping are meant methylether groups substituted with one alkoxy group; typical alkoxymethyloxy groups include methoxymethyloxy, ethoxymethyloxy and isopropoxymethyloxy.

By the term "alkylthio" is intended straight or branched chain hydrocarbon thioether groups of six or less carbon atoms, including methylthio, ethylthio, propylthio, 2-propylthio, 2-butylthio, pentylthio and 3-hexylthio.

The term "alkylthiomethyloxy" as used herein denotes methylether groups substituted with an alkylthio group; typical alkylthiomethyloxy groups include methylthiomethyloxy, 2-propylthiomethyloxy and pentylthiomethyloxy.

The term "alkylthiomethylthio" as used herein denotes methylthio ether groups substituted with an alkylthio group, including methylthiomethylthio and ethylthiomethylthio.

By the terms which define an "alkoxymethylthio" grouping are meant methylthio ether groups substituted with one alkoxy group, such as methoxymethylthio, ethoxymethylthio and 2-propoxymethylthio.

By the term "aryl" is intended unsubstituted and *p*-mono substituted phenyl derivatives, such as phenyl, *p*-tolyl, *p*-fluorophenyl, *p*-chlorophenyl, *p*-hydroxyphenyl, *p*-methoxyphenyl and *p*-ethylphenyl.

By the term "halomethylene" is meant mono- or dihalomethylene groups wherein halo is fluoro or chloro. The preferred halomethylenes includes fluoromethylene, difluoromethylene, fluorochloromethylene, and chloromethylene.

The term "hydrolyzable ester" as used herein denotes those hydrolyzable ester groups conventionally employed in the art, preferably those derived from hydrocarbon carboxylic acids or their salts. The term "hydrocarbon carboxylic acid" defines both substituted and unsubstituted hydrocarbon carboxylic acids. These acids can be completely saturated or possess varying degrees of unsaturation (including aromatic), can be of straight chain, branched chain, or cyclic structure and, preferably, contain from one to twelve carbon atoms inclusive. In addition, they can be substituted by functional groups, for example, hydroxy, alkoxy containing up to six carbon atoms inclusive, acyloxy containing up to twelve carbon atoms inclusive, nitro, amino and halogeno, attached to the hydrocarbon backbone chain. Typical hydrolyzable esters thus included within the scope of the term and the present invention are acetate, propionate, butyrate, valerate, caproate, enanthate, caprylate, pelargonate, acrylate, undecenoate, phenoxyacetate, benzoate, phenylacetate, diphenylacetate, diethylacetate, trimethylacetate, *t*-butylacetate, trimethylhexanoate, methylneopentylacetate, cyclohexylacetate, cyclopentylpropionate, adamantate, glycolate, methoxyacetate, hemisuccinate, hemiadipate, hemi- β,β -dimethylglutarate, acetoxyacetate, 2-chloro-4-nitrobenzoate, aminoacetate, diethylaminoacetate, piperidinoacetate, β -chloropropionate, trichloroacetate and β -chlorobutyrate.

The term "oxyether" as used herein denotes those ether groups conventionally employed in the art, preferably those derived from normal chain, branched chain, aromatic hydrocarbons and oxo heterocyclic hydrocarbons. The term "hydrocarbon" defines both saturated and unsaturated hydrocarbons. Those designated hydrocarbons are optionally substituted with groups such as hydroxy, alkoxy, halo and alkylthio. Preferably the hydrocarbons contain from one to twelve carbon atoms inclusive. Typical oxyethers thus include alkoxy, difluoromethoxy, alkoxymethyloxy, alkylthiomethyloxy, tetrahydrofuran-2'-yloxy, tetrahydropyran-2'-yloxy, and 4'-alkoxytetrahydropyran-4'-yloxy.

The term "thioether" as used herein denotes those ether groups conventionally employed in the art, preferably those derived from normal chain, branched chain, cyclic and aromatic hydrocarbons. The term "hydrocarbon" defines both substituted and unsubstituted hydrocarbons. These hydrocarbons are optionally substituted with groups such as hydroxy, alkoxy, alkylthio and halo. Preferably the hydrocarbons contain from 1 to 12 carbon atoms. Typical thioethers thus include alkylthio, difluoromethylthio, alkoxymethylthio and alkylthiomethylthio.

Also included within the scope of the present invention are the corresponding amides, esters, hydroxamic acids, and addition salts of the present 2-naphthylacetic acids.

In the preferred embodiment of this invention, the amides, esters, hydroxamic acids, or addition salts of the present 2-naphthylacetic acid derivatives are the preferred derivatives when the 2-naphthylacetic acid derivatives are substituted with tetrahydro-

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