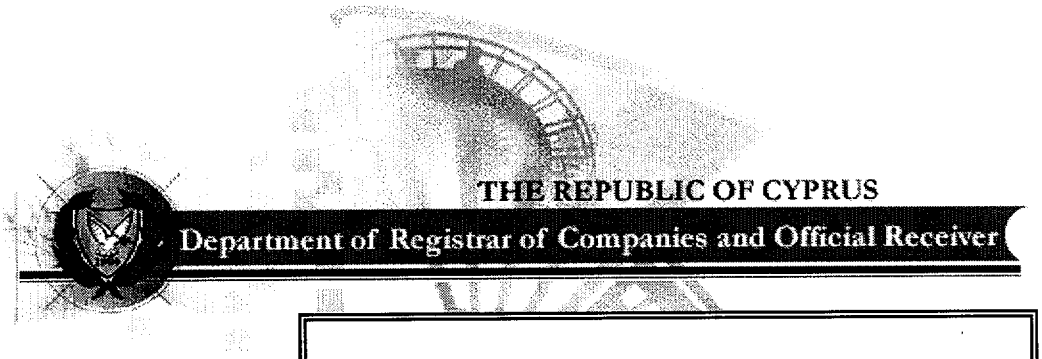

ΚΥΠΡΙΑΚΟ ΓΡΑΦΕΙΟ ΔΙΠΛΩΜΑΤΩΝ ΕΥΡΕΣΙΤΕΧΝΙΑΣ

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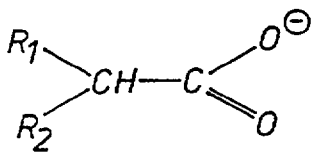
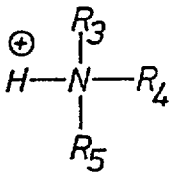
(54) Salts of 2-(2,6-dichloroanilino)-phenyl acetic acid

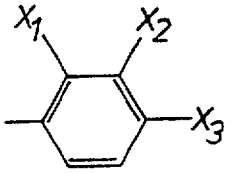
(57) Salts of the formula:





(I)

wherein R_1 is a group of the formula



(IIa)

wherein X_1 is a 2,6-dichloroanilino and X_2 and X_3 are hydrogen, R_2 is hydrogen and R_3, R_4 and R_5 each are 2-hydroxyethyl, or one of R_3, R_4 and R_5 is hydrogen and the others each are ethyl, 2-hydroxyethyl, 2-hydroxypropyl or together are 3-oxa-1,5-pentylene, or R_3 is hydrogen, R_4 is methyl and R_5 is 2,3,4,5,6-pentahydroxyhexyl derived from D-glucamine, or one of R_3, R_4 and R_5 is tris-(hydroxymethyl)-methyl and the others are hydrogen; have *anti-inflammatory* and *analgesic activity*.

GB 2 143 528 A

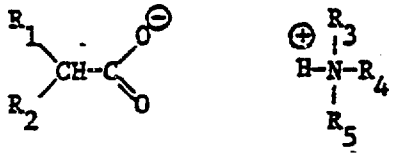
Formulae in the printed specification were reproduced from drawings submitted after the date of filing, in accordance with Rule 20(14) of the Patents Rules 1982.

SPECIFICATION

Novel carboxylic acid salts and the production thereof

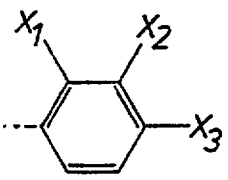
The present invention relates to novel carboxylic acid salts and the production thereof.

The present invention provides a compound of the formula



(I)

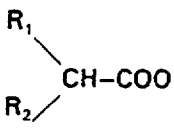
wherein R_1 is a group of the formula



(IIa)

wherein X_1 is a 2,6-dichloroanilino and X_2 and X_3 are hydrogen, R_2 is hydrogen and R_3, R_4 and R_5 each are 2-hydroxyethyl, or one of R_3, R_4 and R_5 is hydrogen and the others each are ethyl, 2-hydroxyethyl, 2-hydroxypropyl or together are 3-oxa-1,5-pentylene, or R_3 is hydrogen, R_4 is methyl and R_5 is 2,3,4,5,6-pentahydroxyhexyl derived from D-glucamine, or one of R_3, R_4 and R_5 is tris-(hydroxymethyl)-methyl and the others are hydrogen.

The compounds of the formula



(IIIa)

wherein R_1 and R_2 are as defined above or some salts thereof, are known. These compounds and their salts with bases are used, for example, as non-steroidal antiinflammatory agents for treating inflammatory conditions. The preparations containing these compounds are administered for the most part orally and also enterally or parenterally.

The object of treating different forms of inflammatory diseases, especially of rheumatism of soft tissues, consists in avoiding the side-effects which are primarily connected with systemic therapy. This object is preferably attained by topical therapy if penetration of the active ingredient into the site of the inflammation can be successfully ensured. Successful therapy by percutaneous administration, however, frequently fails when using compounds of the formula (IIIa), because penetration of a therapeutically effective amount of active ingredient through the skin into the affected tissue cannot be adequately ensured.

The present invention is based on the surprising observation that the compounds of the formula (I) possess excellent percutaneous penetration and absorbtion properties.

In addition, the compounds of the formula I have marked anti-inflammatory and analgestic properties. The anti-inflammatory activity can be demonstrated e.g. by the marked reduction in the swelling in rats' paws in the kaolin edema test in accordance with Helv. Physiol. Acta *25*, 156 (1967), by rubbing e.g. a gel containing about 0.5 to 5% of active ingredient into the backs of test animals from which the hair has been removed (see Arzneimittel-Forschung *27 (I)*, 1326, 1977). Further, the anti-inflammatory activity of the active ingredient, e.g. in the form of a gel having a concentration of about 0.5 to 5 %, when applied topically, can be deduced from the inhibition of abscess formulation induced by subcutaneous injection of carageen in rats (see Arzneimittel-Forschung *27 (I)*, 1326, 1977).

Assays using compounds of the formula I in the phenyl-p-benzoquinone writhing test (J. Pharmacol. Therap. *125*, 237, 1959) in the dosage range from about 1.0 to 120 mg p.o. indicate a marked analgesic activity.

Accordingly, the compounds of the formula I are most suitable anti-inflammatory agents for percutaneous application and can also be used as analgesics.

The invention relates in particular to novel compounds of the formula I, wherein R_1 is a group of the formula IIa, in which X_1 is 2,6-dichloroanilino, X_2 and X_3 are hydrogen, R_2 is hydrogen, and one of R_3, R_4 and R_5 is hydrogen and the others are ethyl, or each of R_3, R_4 and R_5 is 2-

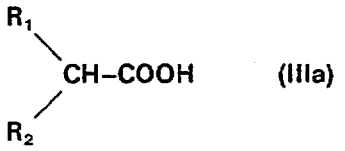
hydroxyethyl.

The invention relates specifically to the novel compounds obtained in the Examples and to the methods of preparing them described therein.

Depending on the choice of starting materials and procedures, the compounds of the formula I can be obtained in the form of a possible isomer or of a mixture of isomers, for example optical isomers such as enantiomers or diastereomers, or geometrical isomers such as cis-trans-isomers. The optical isomers are in the form of the pure antipodes and/or racemates. Resultant racemates or mixtures of geometrical isomers can be separated into the pure constituents on the basis of the chemico-physical differences between the components. Thus, for example, racemates of optical antipodes can be resolved into the corresponding antimers by methods which are known per se, e.g. by chromatographic methods, by fractional crystallisation, with microorganisms or enzymes. Further, it is possible to enrich e.g. optical antipodes by conversion of the other antimer in a racemic mixture. The isomers of novel compounds of the formula I also constitute an object of the invention.

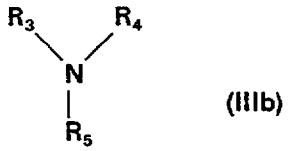
The invention also relates to the production of novel compounds of the formula I, which are obtained by methods which are known per se.

A preferred process variant comprises e.g. reacting an organic carboxylic acid of the formula



(IIIa)

wherein R_1 and R_2 are as defined above or a base salt thereof which is different from a salt of the formula I, with an at least equimolar amount of the amine of the formula



(IIIb)

wherein R_3, R_4 and R_5 are as defined above or an acid addition salt thereof, and, if desired, converting a resultant compound of the formula I into another compound of the formula I and/or resolving a resultant mixture of isomers into its individual components.

The molar ratio of acid of the formula (IIIa) and amine of the formula (IIIb) depends on the choice of desired salt or on the number of substituted amino groups in the corresponding compound of the formula (IIIb).

As acid addition salts of amines of the formula (IIIb) there are used e.g. corresponding hydrohalides, such as hydrochlorides.

The reaction of a compound of the formula (IIIa) with a compound of the formula (IIIb) is preferably conducted in an inert solvent or diluent, if necessary with cooling and heating, e.g. in a temperature range from about 0° to 100°C, preferably at room temperature, in a closed vessel and/or in an inert gas atmosphere, e.g. nitrogen.

Examples of suitable solvents and diluents are: water, alcohols such as lower alkanols, e.g. methanol or ethanol, ethers such as di-lower alkyl ethers, e.g. diethyl ether, cyclic ethers such as dioxane or tetrahydrofurane, ketones such as di-lower alkyl ketones, e.g. acetone, carboxylic acid esters such as lower alkanecarboxylic acid esters, e.g. ethyl acetate, amides such as N,N-di-lower alkylamides, e.g. N,N-dimethyl formamide, sulfoxides such as di-lower alkyl sulfoxides, e.g. dimethyl sulfoxide, or mixtures thereof.

The starting materials of the formulae (IIIa) and (IIIb) are known.

The invention also relates to those embodiments of the process in which the starting materials are prepared *in situ*, or in which a starting material is obtained from a derivative under the reaction conditions and/or is used in the form of a mixture of isomers or of a pure isomer.

The starting materials of the formula (IIIa) can be formed e.g. under the reaction conditions from corresponding esters, such as lower alkyl esters, by hydrolysis in the presence of a base, such as an amine, e.g. dimethylamine. An amine of the formula (IIIb) can be used e.g. in the form of an acid addition salt, such as a halide, e.g. a hydrochloride, and liberated in the presence of a base, such as an amine.

The pharmaceutical preparations for topical application contain the compounds of the formula I together with a pharmaceutically acceptable carrier or excipient. The daily dosage of the active ingredient depends on the age and individual condition of the patient and also on the mode of application.

Suitable pharmaceutical preparations for topical application are primarily creams, ointments

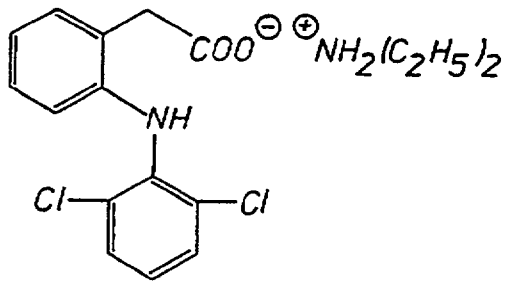
and gels, as well as pastes, foams, tinctures and solutions, which contain from about 0.5 to about 5 % of active ingredient.

The pharmaceutical preparations for topical application are obtained in known manner, for example by dissolving or suspending the active ingredient in the base or in a part thereof, if necessary. When processing the active ingredient in the form of a solution, it is usually dissolved in one of the two phases before the emulsification, and when processing the active ingredient in the form of a suspension, it is mixed with a part of the base before the emulsification and than added to the remainder of the formulation.

The invention also relates to the use of the novel compounds of the formula I as anti-inflammatory agents for percutaneous application and/or as analgesics, preferably in the form of suitable pharmaceutical preparations.

The following Examples illustrate the invention but in no way limit the scope thereof.

Example 1: To a solution of 2 g of 2-(2,6-dichloroanilino)phenylacetic acid in 40 ml of ether are added 2 ml of diethylamine. The solution is refluxed for 10 minutes, then cooled and concentrated under reduced pressure, whereupon diethylammonium-2-(2,6-dichloroanilino)phenylacetate crystallises out. The colourless crystals are isolated by filtration (m.p. 110°–115°C with decompos.) and dried at room temperature in a high vacuum.



Example 2: With efficient stirring, a solution of 4.53 g of tris-(hydroxymethyl)methylamine in 10 ml of water is added dropwise at room temperature and in the course of 10 minutes to a solution of 10 g of 2-(2,6-dichloroanilino)phenylacetic acid in 230 ml of ethyl acetate, whereupon a salt immediately precipitates. The batch is subsequently stirred for half an hour at room temperature and the solvent is removed by rotary evaporation. The white crystalline residue is dissolved in 1 litre of acetone/water (1:1) at about 50°C. The hot solution is concentrated in a rotary evaporator until the first crystals precipitate. The residue is left to crystallise at 0°C, and the precipitated white flocculent crystals are collected on a suction filter and dried in a high vacuum. The resultant tris-(hydroxymethyl)methylammonium-2-(2,6-dichloroanilino)phenylacetate has a melting point of 202°–204°C.

Example 3: With efficient stirring, a solution of 5.52 g of triethananolamine in 30 ml of ethyl acetate is added dropwise at room temperature and in the course of 10 minutes to a solution of 10 g of 2-(2,6-dichloroanilino)phenylacetic acid in 230 ml or ethyl acetate, whereupon a salt precipitates immediately. The batch is subsequently stirred for about half an hour at room temperature and the solvent is removed in a rotary evaporator. The white crystalline residue is dissolved in a small amount of hot ethanol and crystallised at 0°C. The white crystals are filtered with suction and dried in a high vacuum. The so obtained triethanolammonium-2-(2,6-dichloroanilino)-phenylacetate melts at 137°–138°C.

Example 4: With efficient stirring, a suspension of 3.89 g of diethanolamine in 30 ml of ethyl acetate is added dropwise at room temperature and in the course of 10 minutes to a solution of 10 g of 2-(2,6-dichloroanilino)phenylacetic acid in 230 ml of ethyl acetate, whereupon a salt precipitates immediately. The batch is subsequently stirred for half an hour at room temperature and the solvent is removed in a rotary evaporator. The yellowish crystalline residue is dissolved in a small amount of boiling ethanol. The solution is left to stand at 0°C and diathanolammonium-2-(2,-dichloroanilino)-phenylacetate with a melting point of 130°–132°C crystallises out.

Example 5: With efficient stirring, 3.22 g of morpholine in 30 ml of ethyl acetate are added dropwise at room temperature and in the course of 10 minutes to a solution of 10 g of 2-(2,6-dichloroanilino)-phenylacetic acid in 230 ml of ethyl acetate. A salt precipitates about 10 minutes after addition of the morpholine. The batch is then stirred for 1 hour at room temperature and the solvent is removed by rotary evaporation. The white crystalline precipitate is dissolved in boiling ethanol. Morpholinium-2-(2,6-dichloroanilino)-phenylacetate with a melting point of 162°–165°C crystallises out at 0°C.

Example 6: With efficient stirring, 4.93 g of diisopropanolamine in 30 ml of ethyl acetate

are added dropwise at room temperature and in the course of 5 minutes to a solution of 10 g of 2-(2,6-dichloroanilino)phenylacetic acid in 230 ml of ethyl acetate. A salt precipitates after a short time. The batch is stirred for 1 hour and the solvent is removed by rotary evaporation. The white crystalline precipitate is dissolved in a small amount of hot ethanol and the solution is left to stand at 0°C, whereupon diisopropanolammonium-2-(2,6-dichloroanilino)phenylacetate with a melting point of 165°–170°C crystallises out.

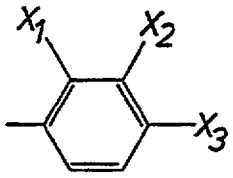
Example 7: A suspension of 6.64 g of N-methyl-D-glucamine in 100 ml of ethanol together with 10 g of 2-(2,6-dichloroanilino)phenylacetic acid in 230 ml of ethyl acetate are stirred at room temperature overnight under nitrogen. Fine, white crystals precipitate after 2 hours. The solvent is then removed by rotary evaporation and the white tacky residue is dissolved in a small amount of hot water. The clear solution is slowly cooled to 0°C and left to stand overnight at 0°C. The oily, semi-crystalline precipitate obtained is collected over 2-days on a celite and cloth filter. The filter cake is dried for a week at 60°C/100 mm Hg and then pulverised. The so obtained N-methyl-D-glucammonium-2-(2,6-dichloroanilino)-phenylacetate melts at 127°–130°C.

CLAIMS

1. A compound of the formula

(I)

wherein R_1 is a group of the formula



(IIa)

wherein X_1 is a 2,6-dichloroanilino and X_2 and X_3 are hydrogen R_2 is hydrogen and R_3, R_4 and R_5 each are 2-hydroxyethyl, or one of R_3, R_4 and R_5 is hydrogen and the others each are ethyl, 2-hydroxyethyl, 2-hydroxypropyl or together are 3-oxa-1,5-pentylene, or R_3 is hydrogen, R_4 is methyl and R_5 is 2,3,4,5,6-pentahydroxyhexyl derived from D-glucamine, or one of R_3, R_4 and R_5 is tris-(hydroxymethyl)-methyl and the others are hydrogen.

2. A compound of the formula I according to claim 1 of the formula I, wherein R_1 is a group of the formula IIa, in which X_1 is 2,6-dichloroanilino, X_2 and X_3 are hydrogen, R_2 is hydrogen, and one of R_3, R_4 and R_5 is hydrogen and the others are ethyl, or each of R_3, R_4 and R_5 is 2-hydroxyethyl.

3. Diethylammonium-2-(2,6-dichloroanilino)phenylacetate.

4. Tris-(hydroxymethyl)-methylammonium-2-(2,6-dichloroanilino)-phenylacetate.

5. Triethanolammonium-2-(2,6-dichloroanilino)phenylacetate.

6. Diethanolammonium-2-(2,6-dichloroanilino)phenylacetate.

7. Morpholinium-2-(2,6-dichloroanilino)phenylacetate.

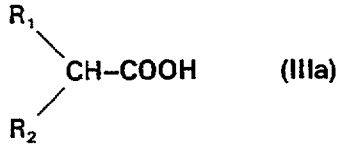
8. Diisopropanolammonium-2-(2,6-dichloroanilino)phenylacetate.

9. N-Methyl-D-glucammonium-2-(2,6-dichloroanilino)phenylacetate.

10. A compound according to claim 1, substantially as described with reference to any of Examples 1 to 7.

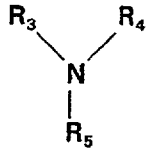
11. A compound according to any one of claims 1 to 10 for use as anti-inflammatory agent and/or analgesic in a therapeutic method of treating humans or animals.

12. A process for the production of a compound of the formula I according to any one of claims 1 to 10, which process comprises reacting an organic carboxylic acid of the formula



(IIIa)

wherein R_1 and R_2 are as defined in claim 1 or a base salt thereof which is different from a salt of the formula I, with an at least equimolar amount of the amine of the formula



(IIIb)

wherein R_3, R_4 and R_5 are as defined in claim 1 or an acid addition salt thereof and, if desired, converting a resultant compound of the formula I into another compound of the formula I and/or separating a resultant mixture of isomers into the individual components.

13. A process according to claim 12, wherein the starting materials are prepared *in situ* or a starting material is obtained under the reaction conditions from a derivative and/or is used in the form of a mixture of isomers or of a pure isomer and/or salt.

14. A process according to claim 12, substantially as described with reference to any of Examples 1 to 7.

15. A compound according to claim 1, when produced by a process claimed in any of claims 12 to 14.

16. Use of a compound of the formula I according to any one of claims 1 to 10 for the production of pharmaceutical preparations for topical application.

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