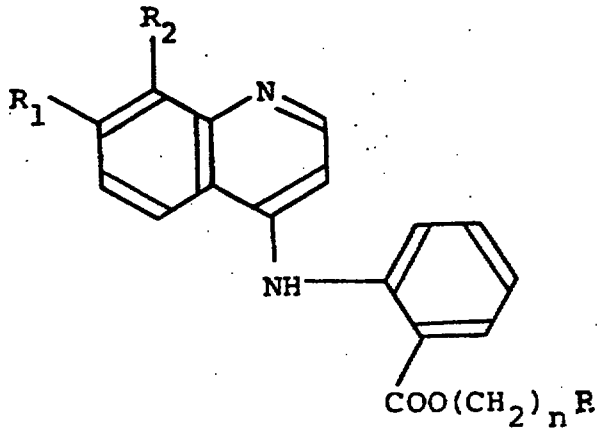
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N-(4-Quinolyl)-Anthranilic Acid Esters

DESCRIPTION:

The invention relates to anthranilic acid esters, to a process for the preparation thereof, and to pharmaceutical compositions containing them.

The invention provides anthranilic acid esters having the general formula I



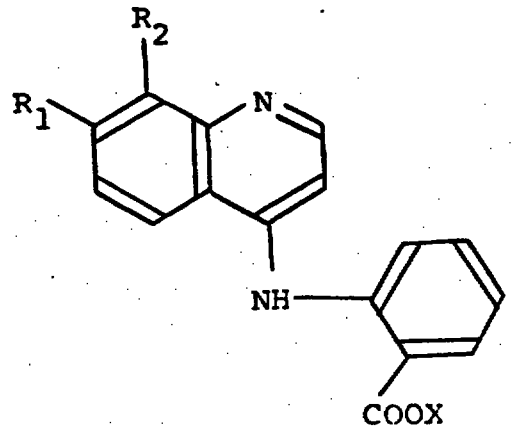
I

wherein n is 0, 1 or 2, one of R_1 and R_2 represents a chlorine atom or a trifluoromethyl group and the other represents a hydrogen atom, and R represents a 2-oxo-3--oxolanyl or 2-oxo-3-oxazolidinyl group.

The compounds according to the invention have been found to exhibit good analgesic and anti-inflammatory properties.

The invention further provides a process for the preparation of the compounds having the general formula I as above defined, the process comprising condensing a salt

of an N-(7- or 8-substituted-4-quinolyl)-anthranilic acid having the general formula II



II

wherein R_1 and R_2 are as hereinbefore defined and X represents an alkali metal with a halo derivative of the general formula

$$\text{Halo} - (CH_2)_n - R \qquad \text{III}$$

in which n and R are as hereinbefore defined.

The N-(7- or 8-substituted-4-quinolyl)-anthranilic acid salt is preferably the sodium salt (II, X = Na), whereas halo in formula (III) is generally chlorine or bromine.

The condensation is preferably carried out in the presence of an inert organic solvent, such as dimethylformamide. The reactants are generally used in equimolar proportions, the temperature ranging from 30° to 150°C.

The invention additionally provides a pharmaceutical composition comprising a compound having the general formula I as above defined in admixture with a

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pharmaceutically acceptable diluent or carrier.

The active compounds according to the invention exhibit a good analgesic and antiinflammatory action, whereas they show a low toxicity. The LD_{50} values, determined in the mouse both i.p. and per os, are respectively greater than 1000 and 3000 mg/Kg. This is valid for all the tested compounds.

The analgesic activities (ED_{50}), determined in the mouse with the writhing test (Sigmund et al., Proc. Soc. Exp. Biol. Med., 95, 729, 1957) were found to be between 6 and 18 mg/KG. The ED_{50} values for the antiinflammatory activity were found to be between 20 and 30 mg/Kg.

The following Examples illustrate the invention.

EXAMPLE 1

A mixture comprising 6.4 g of N-(7-chloro-4-quinolyl) anthranilic acid sodium salt and 3.28 g of 3-bromo-oxolan-2-one in 40 ml of dimethylformamide was heated under stirring at 40-45°C for five hours. At the end of the reaction, the solution thus obtained was filtered and poured into 250 ml of water. The

solid which precipitated was collected on a filter and treated with about 100 ml of chloroform. The whole was filtered again and, adding petroleum ether, N-(7-chloro-4-quinolyl)-anthranilic acid γ-butyrolactone ester was obtained. The product was collected and crystallized from isopropanol. Yield 4 g. mp 155-157°C.

EXAMPLE 2

A mixture comprising 12.8 g of N-(7-chloro-4-quinolyl)--anthranilic acid sodium salt, 6.64 g of 90% 3-(β-chloroethyl)-oxazolidin-2-one and 80 ml of dimethylformamide was heated under stirring at 120°C for five hours. At the end of the reaction, the mixture was cooled, filtered, and the solvent eliminated in vacuo. To the residue 80 ml of ether were added and the solid thus obtained was collected on filter and purified by chromatography on a silica gel column using ethyl acetate as eluent.

The desired product was crystallized from isopropanol to give 11.2 g of N-(7-chloro-4-quinolyl)-anthranilic acid β-(2-oxo-3-oxazolidinyl(-ethyl ester, melting at 122-124°C.

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EXAMPLE 3

A mixture comprising 10.62 g of N-(8-trifluoromethyl--4-quinolyl)-anthranilic acid sodium salt, 4.98 g of 90% 3-(β-chloroethyl)-oxazolidin-2-one and 60 ml of dimethylformamide was heated under stirring at 120°C for five hours. At the end of the reaction, the mixture was cooled, filtered, and poured into 300 ml of water. The crude product was extracted with ethyl acetate, the solvent evaporated off and the residue crystallized from ethanol to give 6 g of N-(8-trifluoromethyl-4-quinolyl)-anthranilic acid β-(2-oxo-3-oxazolidinyl)-ethyl ester, melting at 158-160°C.

EXAMPLE 4

A mixture comprising 10.62 g of N-(8-trifluoromethyl--4-quinolyl)-anthranilic acid sodium salt and 4.92 g of 3-bromo-oxolan-2-one in 60 ml of dimethylformamide was heated under stirring at 80°C for five hours. At the end of the reaction, the solution thus obtained was cooled, filtered and poured into 300 ml of water. The crude solid was extracted with ethyl acetate. The solvent was evaporated off and the residue crystallized from ethanol to give 7 g of N-(8-trifluoromethyl-4--quinolyl)-anthranilic acid γ-butyrolactone ester,

mp, 168-169°C.

EXAMPLE 5

A mixture comprising 10.62 g of N-(7-trifluoromethyl--4-quinolyl)-anthranilic acid sodium salt, 4.98 g of 90% 3-(β-chloroethyl)-oxazolidin-2-one and 60 ml of dimethylformamide was heated under stirring at 120°C for five hours. At the end of the reaction, the mixture was cooled, insoluble sodium chloride was filtered off, and the solvent was evaporated off in vacuo. The residue was treated with 200 ml of water and the solid, collected by filtration, crystallized from methylene dichloride : petroleum ether. 8.7 g of N-(7-trifluromethyl-4-quinolyl)--anthranilic acid β-(2-oxo-3-oxazolidinyl)-ethyl ester, melting at 124-125°C, were obtained.

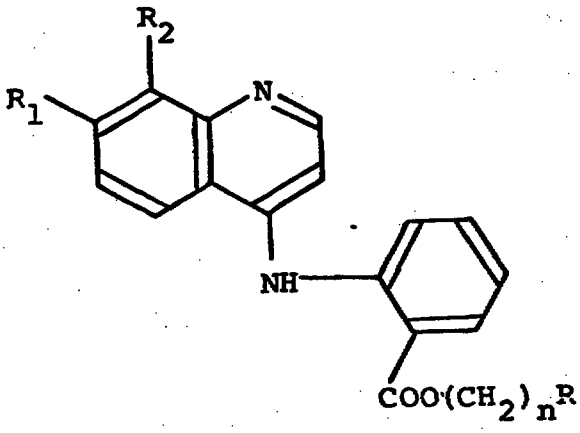
EXAMPLE 6

A mixture comprising 10.62 g of N-(7-trifluormethyl-4--quinolyl)- anthranilic acid sodium salt, 3.24 ml of 3-bromo-oxolan-2-one and 60 ml of dimethylformamide was heated under stirring at 80°C for five hours. At the end of the reaction, the mixture was cooled, the insoluble sodium bromide was filtered off, and the solvent was evaporated off in vacuo.

The residue was treated with 200 ml of water, the solid collected and crystallized from ethanol to give 7.7 g of N-(7-trifluoromethyl-4-quinolyl)--anthranilic acid γ-butyrolactone ester, melting 183-184°C.

CLAIMS

1. An anthranilic acid ester having the general formula I



I

wherein n is 0,1 or 2, one of R_1 and R_2 represents a chlorine atom or a trifluormethyl group and the other represents a hydrogen atom, and R represents a 2-oxo-3-oxolanyl or 2-oxo-3-oxazolidinyl group.

2. N-(7-chloro-4-quinolyl)-anthranilic acid γ-butyrolactone ester.

3. N-(7-chloro-4-quinolyl)-anthranilic acid β-(2-oxo-3-oxazolidinyl)-ethyl ester.

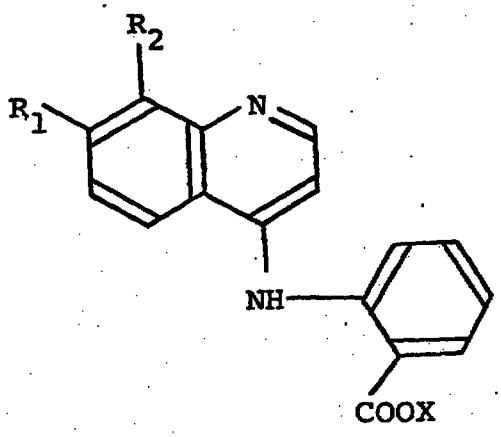
4. N-(8-trifluormethyl-4-quinolyl)-anthranilic acid β-(2-oxo-3-oxazolidinyl)-ethyl ester.

5. N-(8-trifluoromethyl-4-quinolyl)-anthranilic acid γ-butyrolactone ester.

6. N-(7-trifluoromethyl-4-quinolyl)-anthranilic acid β-(2-oxo-3-oxazolidinyl)-ethyl ester.

7. N-(7-trifluoromethyl-4-quinolyl)-anthranilic acid γ-butyrolactone ester.

8. A process for the preparation of an anthranilic acid ester according to claim 1, the process comprising condensing a salt of an N-(7- or 8-substituted-4-quinolyl)-anthranilic acid having the general formula II



II

wherein R_1 and R_2 are as defined in claim 1 and X represents an alkali metal with a halo derivative of the general formula III

$$\text{Halo} - (CH_2)_n - R \qquad \text{III}$$

wherein n and R are as defined in claim 1.

9. A process according to claim 8 carried out using equimolar proportions of the reactants in dimethylformamide as solvent at from 30°C to 150°C.

10. A process for the preparation of an anthranilic acid ester according to claim 1, the process being substantially as described herein with reference to any of the Examples.

11. A pharmaceutical composition comprising a compound according to any of claims 1 to 7 in admixture with a pharmaceutically acceptable diluent or carrier.