

Description

The present invention relates to the obtaining of a 2-phenyl propionic acid by a new process.

A more particular subject of the invention is the
5 obtaining of 2-phenyl propionic acid the phenyl nucleus of which is substituted by an amino acid.

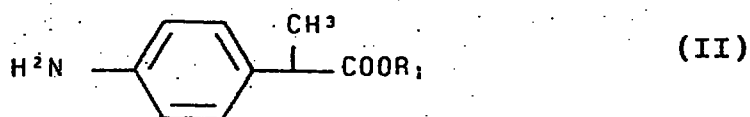
A specific subject of the invention is a new process for the synthesis of 2(R-aminophenyl) propionic acids and, in particular, of 2-(4-methallylaminophenyl) propionic acid. In
10 fact, the literature, such as for example the US Patent 3,957,850 has shown the difficulty of carrying out the alkylation of the amine function carried by such phenyl-propionic acids. Now, it has turned out that the selective mono-alkylation of these 2-(4-aminophenyl) propionic acids is
15 important insofar as it leads to a significant increase in the pharmacological activity and/or a reduction in the degree of toxicity...

On the other hand, the NN-disubstituted derivatives are, in general, significantly less active and may, therefore,
20 constitute an additional load the elimination of which is often difficult and leads to significant losses in the yield in the final stages of the synthesis.

This is why finding a new synthesis method which produces only a limited formation of dialkylated derivatives
25 with nitrogen or which permits their separation in much easier conditions has proved important.

This problem was able to be resolved according to the invention by a process which consists of subjecting a 2(4-aminophenyl) propionic derivative of formula II:

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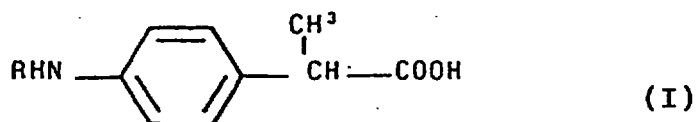


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in which R₁ is an alkyl radical having 1 to 6 carbon atoms or hydrogen

in solution in an inert organic water-immiscible and non-

polar solvent, to the action of an alkylation agent in heterogeneous phase, in the presence of a phase transfer catalyst and a basic agent in aqueous medium, in order to obtain a 2-(4-R aminophenyl) propionic acid of general formula I:



in which R is a lower alkyl radical, optionally substituted by a hydroxyl, a lower alkenyl radical having 2 to 6 carbon atoms, a lower alkynyl radical having 2 to 4 carbon atoms, a lower aralkyl radical.

In a preferred manner, the R radical is a methallyl. It can also be an alkenyl radical such as allyl, an aralkyl radical such as benzyl, a substituted alkyl radical such as beta-hydroxyethyl.

The phase transfer catalyst is a quaternary ammonium salt or a phosphonium salt, soluble in both types of solvents. Methyltrioctyl ammonium chloride is preferably used, marketed under the name ALIQUAT 336, as well as other ammonium or phosphonium salts, such as methyl triphenyl phosphonium bromide, trimethyl phenyl ammonium chloride, tetrabutyl ammonium bromide and benzyl tributyl ammonium chloride.

The quantity of catalyst used is about 10 g per mole of 2-(4-aminophenyl) propionic acid or its alkyl ester used. The concentration of 2-(4-aminophenyl) propionic acid or of the ester of this acid is about one mole per 400 ml of water-immiscible organic solvent.

The concentration of alkylation agent which is preferably a methallyl halide, such as methallyl chloride or methallyl bromide, is 1 to 1.4 mole per mole of 2-(4-aminophenyl) propionic acid or of the alkyl ester of this acid. 1.1 to 1.4 mole of methallylation agent is preferably used per mole of 2-(4-aminophenyl) propionic acid or of one of its alkyl esters.

The 2-(4-methallylaminophenyl) propionic acid formed in this reaction remains in the organic phase because the quantity of basic agent is almost that of the stoichiometry and this explains why the product recovered is directly 2-(4-methallylaminophenyl) propionic acid itself and not one of its salts. Under these conditions, there is no salification reaction and isolation of the acid is made easier.

The basic agent capable of fixing the hydrogen acid or the anion formed during the alkylation reaction is a strong base, preferably an alkali metal hydroxide such as sodium hydroxide. The concentration used is preferably 1 to 1.1 mole of base per 1 mole of acid or ester of 2-(4-aminophenyl) propionic acid, dissolved in water at a concentration of the order of 10%.

The reaction is carried out at a temperature below that of the boiling point of the organic solvent and, preferably, between 80 and 85°. It is preferable to operate under an inert atmosphere, such as for example by bubbling through nitrogen.

The duration of the reaction is at least two hours. No advantage is gained and a better yield is not obtained when the reaction is continued for longer than 4 hours.

After the reaction, the supernatant organic phase is separated off and washed with water. The organic phase is extracted with about 1N soda. It is then acidified to pH 1 with 1N hydrochloric acid. The by-products (in particular dialkylated derivatives) are insoluble in this solution and are eliminated by extraction with an organic solvent.

This acid solution is treated with activated charcoal, filtered and brought to pH 3 by the addition of soda or an alkali metal salt of a weak acid.

The 2-(4-alkylaminophenyl) propionic acid which crystallizes is separated out by filtration. It is washed with water and dried.

It was noted with interest that when an alkyl ester of 2-(4-aminophenyl) propionic acid is used at the start, the alkylation reaction carried out under these conditions is accompanied by the saponification of the ester function so

that the product obtained is directly 2-(4-alkylaminophenyl) propionic acid.

The 2-(4-methallylaminophenyl) propionic acid thus obtained is a known product (B. DUMAITRE cf Chimie
5 Thérapeutique 14 (1979) p. 207-214) whose analgesic and anti-inflammatory properties are the subject of numerous publications.

However, the production of 2-(4-methallylaminophenyl) propionic acid had up to now been held up because the
10 synthesis methods were all hindered by a stage which was difficult to achieve: alkylation of the amino derivative by a methallyl halide. This stage consists of subjecting, beforehand or not, the amino derivative to the action of a methallylation agent and it had proved up to now impossible
15 to avoid the simultaneous formation of a mono methallylamino derivative and of a dimethallyl amino derivative. It was noted, in particular, that a labile partial blocking of the amine function which could have avoided this secondary reaction was quickly inoperative because it was difficult to
20 eliminate subsequently. Therefore, the different synthesis methods lead inescapably to the formation of this by-product, with no therapeutic use, and the elimination of which required an additional stage and a significant reduction in the overall yield of the synthesis.

25 The following examples illustrate the invention.

Example 1

Place:

- 165 g (1 mole) of 2-(4-aminophenyl) propionic acid
- 30 - 400 cm³ of toluene
- 100 g of methallyl chloride (1.1 mole)
- 10 g of Aliquat 336
- 250 cm³ of water
- 92.5 cm³ of 32% soda lye (1 mole)

35 in a reaction vessel provided with good agitation, a condenser, a thermometer and a nitrogen supply.

Heat the mixture for 3 hours at 85°.

Decant, wash the toluene solution twice with water.

Extract this toluene phase with 1 litre of 1N soda. Pour the alkaline solution into 1.5 litres of 1N hydrochloric acid (pH = 0.8). Extract three times with toluene. Add charcoal (filter). Bring the pH to 3 by the slow addition of 1N soda under vigorous agitation. Separate off the precipitate formed, wash it with water and dry it.

In this way 140 g (yield = 64%) of creamy white crystals are isolated. M.p. = approx. 107°.

10 Example 2

In an identical manner to that of Example 1, 135 g of 2-(4-methallylamino-phenyl) propionic acid is obtained starting with 179 g of methyl 2-(4-aminophenyl) propionate, using Aliquat 336.

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Examples 3 to 7

In an identical manner to that of Example 1, 2-(4-methallylamino-phenyl) propionic acid is obtained starting with 2-(4-aminophenyl) propionic acid using the following phase transfer catalysts:

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Example	Catalyst used	Yield
3	T E B A	57%
4	Methyl triphenyl phosphonium bromide	58%
5	Phenyl trimethyl ammonium chloride	57.5%
6	Tetrabutyl ammonium bromide	58.5%
7	Benzyl tributyl ammonium chloride	62%

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Claims:

1) A process for obtaining 2-phenyl propionic acids substituted by an amino radical, characterized in that a 2-(4-aminophenyl) propionic derivative of formula II:



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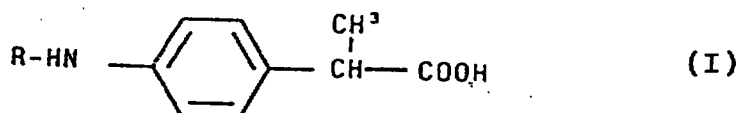
in which R_1 is an alkyl radical having 1 to 6 carbon atoms or hydrogen

in solution in an inert organic, water-immiscible and non-polar solvent, is subjected to the action of an alkylation

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agent in heterogeneous phase, in the presence of a phase transfer catalyst and a basic agent in aqueous medium in order to obtain a 2-(4-R aminophenyl) propionic acid of general formula I:

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in which R is a lower alkyl radical optionally substituted by a hydroxyl, a lower alkenyl radical, a lower alkynyl radical or a lower aralkyl radical.

2) A process according to claim 1 in which the R radical is the methallyl radical.

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3) A process according to claim 1 in which the water-immiscible organic solvent is a liquid aromatic hydrocarbon.

4) A process according to claim 1 in which the phase transfer catalyst is a quaternary ammonium salt soluble in both the hydrophobic solvents and in water.

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5) A process according to claim 1 in which the phase transfer catalyst is a triphenylalkyl phosphonium salt.

6) A process according to claim 4 in which the phase transfer catalyst is methyltrioctyl ammonium bromide.



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- 7) A process according to one of claims 1 to 6 in which the quantity of phase transfer catalyst introduced into the reaction medium is of the order of 10 g per mole of 2-(4-aminophenyl) propionic acid.
- 5 8) A process according to one of claims 1 to 7 in which the concentration of 2-(4-aminophenyl) propionic derivative is about 1 mole per 400 ml of water-immiscible organic solvent.
- 9) A process according to one of claims 1 to 8 in which the concentration of alkylation agent is comprised between 1 and
- 10 1.4 mole per mole of 2-(4-aminophenyl) propionic acid.
- 10) A process according to claim 9 in which the concentration of methallylation agent varies from 1.1 to 1.4 mole per mole of 2-(4-aminophenyl) propionic acid.