The title of the invention is:

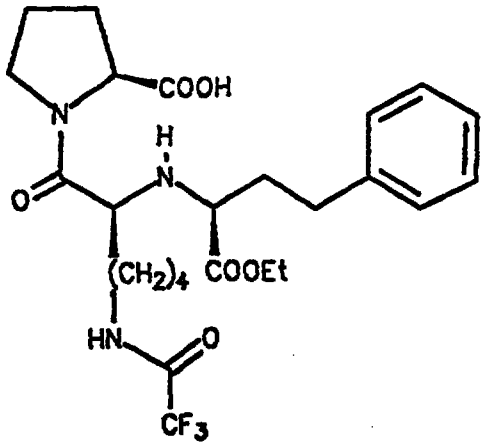
A process for purifying 1-[N^2-((S)-ethoxycarbonyl)-3-phenylpropyl)-N^6-trifluoroacetyl]-L-lysyl-L-proline (ethyl ester of lisinopril(Tfa))



A process for purifying 1-[N²-((S)-ethoxycarbonyl)-3-phenylpropyl)-N⁶-trifluoroacetyl]-L-lysyl-L-proline (ethyl ester of lisinopril(Tfa))

Description

The invention relates to a process for purifying 1-[N²-((S)-ethoxycarbonyl)-3-phenylpropyl)-N⁶-trifluoroacetyl]-L-lysyl-L-proline (compound I) by extraction and crystallisation.

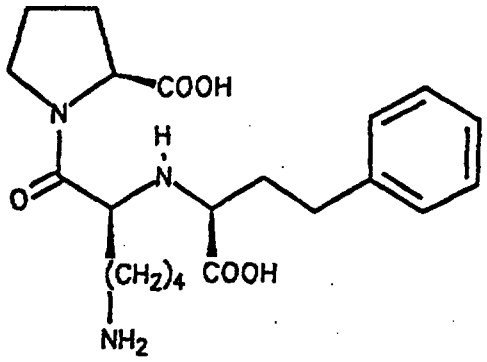


(I)

N-substituted aminoacids of this type are valuable intermediates for preparing inhibitors of angiotensin converting enzymes (ACE), which act as blood pressure regulators. I is the direct precursor of 1[N²-((S)-carboxy)-3-phenylpropyl)]-L-lysyl-L-proline (lisinopril) compound II, which exhibits surprising therapeutic results when used to control high blood pressure (Zerstril®, Coric®, Prinivil®).

According to the prior art, compound I is obtained by reductive amination of ethyl 2-oxo-4-phenylbutyrate using the dipeptide Lys(Tfa)-Pro.

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(II)

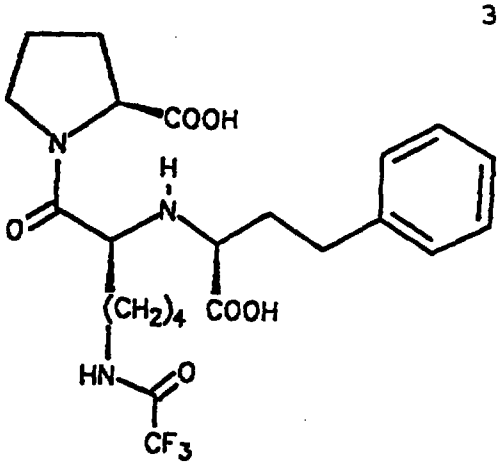
Such a process is described in J. Org. Chem. 1988, 53, 836 - 844. According to this, I is obtained in a yield of 42% by basic extraction of the crude reaction solution followed by extraction of the product in an organic solvent at pH 4.6 and finally crystallisation from methyl-tert.butyl ether/cyclohexane.

DE-OS 41 23 248 relates to the synthesis of I, which is obtained in a yield of 60% according to example 3. Working up the crude reaction solution obtained by this process includes crystallisation from methyl-tert.butyl ether in addition to a basic and an acidic extraction step. In principle, other processes which are not based on a reductive amination, but are less advantageous, are also known for preparing compound I (EP 0 336 368 A2).

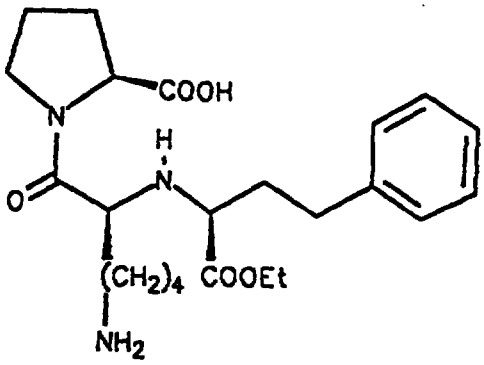
Basic extraction, extraction of the aqueous product phase being required in order to remove impurities from the amination reaction, however, is always associated with product losses due to amide and/or ester cleavage of I to give II, or of I to give compounds III and IV.

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(III)



(IV)

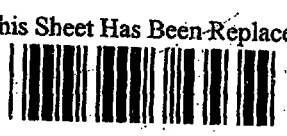
In order to minimise this loss of product, low temperatures, precisely set pHs and reaction times which are as short as possible have to be used. This is costly and is associated with difficulties, especially on an industrial scale.

Crystallisation from methyl-tert.butyl ether is connected with high losses of yield because, in order to directly obtain the diastereomerically pure compound (I), crystallisation is performed at high dilution, which reduces the yield. If (I) is allowed to crystallise from solutions at a higher concentration, an additional recrystallisation stage is required. The addition of cyclohexane (J. Org. Chem. 1988, 53, 836 - 844) during crystallisation in order to increase the yield is also described. In this case, however, there is a risk of separation as an oil, which makes isolation of the product difficult, not only on an industrial scale.

The object of the invention is an improved process for purifying (I).

This object is achieved by extracting, optionally several times, the crude product of (I) obtained after reductive amination by evaporating the reaction solution with a water/solvent two-phase system, the pH of the aqueous phase being adjusted to a value between 0 and 3.5, in particular

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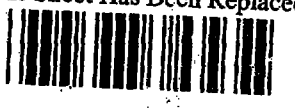
0.5 and 2, the remaining aqueous phase being adjusted to a pH between 3.5 and 6.3, in particular 3.9 and 4.8 after separation of the organic phase, using an alkaline compound, in particular NaOH or KOH, then extracting, optionally several times, with an organic solvent or solvent mixture which is not miscible with water, isolating (I) from the organic phase by evaporation and, after dissolving in a mixture of methyl-tert.butyl ether and methylcyclohexane, allowing the product (I) to crystallise out by cooling to temperatures of -40°C to +50°C, in particular -10°C to 30°C.

The crystalline product is then separated using known methods.

Acid extraction of the aqueous product solution, surprisingly, leads to only barely noticeable product losses with simultaneous higher purification of the aqueous product phase and this occurs even though the trifluoroacetylamide group can also be eliminated in acid medium. Unexpectedly, the solution also proved to be stable over a longer period of time (ca. 48 h) in the acid range, which represents a large technical simplification. An advantageous pH range for acid extraction is between 0 and 3.5, the range between 0.5 and 2 being particularly advantageous. Extraction can be performed at temperatures between 0°C and 60°C, preferably between 10°C and 40°C, in particular at room temperature. Extraction solvents which may be used are solvents which are not miscible with water such as e.g. toluene, methyl-tert.butyl ether, ethyl acetate, isopropyl acetate, methylene chloride, trichloroethane, chloroform or mixtures thereof.

The temperature ranges and solvent / solvent mixtures described above also apply to the second extraction step.

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Recrystallisation of product (I) is performed by the process according to the invention from a mixture of methyl-tert.butyl ether and methylcyclohexane at reduced temperatures. It is particularly advantageous to perform a pre-crystallisation from methyl-tert.butyl ether at the temperatures cited below with subsequent addition of methylcyclohexane to complete crystallisation. By adding methylcyclohexane, much purer products with a clearly reduced tendency for the product to separate as an oil than was possible according to the prior art are obtained. The ratio by volume of methyl-tert.butyl ether to methylcyclohexane in this case varies from 1:1 to 20:1, the ratio preferably being 2:1 to 10:1. Crystallisation takes place at temperatures between -40°C and 50°C, preferably between -10°C and 30°C.

The concentration range, expressed as the ratio of g of product (I) to ml of solvent, singly (methyl-tert.butyl ether) or together (with methylcyclohexane), varies from 1:0.5 to 1:30, preferably 1:1 to 1:10, naturally depending on the solubilities, which are predetermined by the temperature.

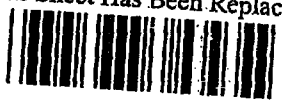
The process according to the invention is intended to be described in more detail by means of the following examples.

Example 1

1-[N^2-((S)-ethoxycarbonyl)-3-phenylpropyl)-N^6-trifluoroacety l]-L-lysyl-L-proline (compound I)

A reductive amination in accordance with patent application P 41 23 248.8 was performed, in the same way as described in example 3, page 10.

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Working up:
A 150 mmol batch of the reaction solution was largely evaporated under vacuum at a bath temperature of 45°C. The residue was taken up in 750 ml of water and stripped under vacuum for a short time. After the addition of 150 ml of 1,1,1-trichloroethane, the pH was adjusted to 1 using conc. HCl. The mixture was stirred for 10 minutes and the phases then separated. At 5°C, the pH in the aqueous phase was then adjusted to 4.6 and this was extracted with 2x 300 ml of 1,1,1-trichloroethane. The organic phase was evaporated under vacuum and taken up in 250 ml of methyl-tert.butyl ether. A thick slurry of crystals was produced by cooling to 5°C and seeding the mixture, and 65 ml of methylcyclohexane were added after 5 hours of vigorous stirring. After a further 2 hours at 5°C, the mixture was filtered under suction and dried under vacuum.
Yield: 54 g: (67.5% of theoretical), SSS-diastereomer content: >99%, $[\alpha]^{20}_D$: -25.6° [(c = 1 in MeOH/HCl (1:1)].

Example 2

1-[N^2-((S)-ethoxycarbonyl)-3-phenylpropyl)-N^6-trifluoroacetyl]-L-lysyl-L-proline (compound I)

A reductive amination in accordance with patent application P 41 23 248.8 was performed, in the same way as described in example 3, page 10.

Working up:
A 150 mmol batch of the reaction solution was largely evaporated at a bath temperature of 45°C. The residue was taken up in 750 ml of water and stripped under vacuum for a short time. After adding 120 ml of toluene and 30 ml of ethyl acetate, the pH was adjusted to 1 using conc. HCl. The mixture was stirred for 10 minutes and the phases then separated. At 5°C, the pH of the aqueous phase was then adjusted to 4.6 and this was extracted 1x with 400 ml of ethyl acetate. The organic phase was evaporated under

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vacuum and taken up in 250 ml of methyl-tert.butyl ether. A thick slurry of crystals was produced by cooling to 5°C and seeding the mixture, and 65 ml of cyclohexane were added after 5 hours of vigorous stirring. After a further 2 hours at 5°C, the mixture was separated under suction and dried under vacuum.

Yield: 54.4 g (68% of theoretical), SSS-diastereomer content: >99%, $[\alpha]^{20}_{D}$: 25.5° [(c=1 in MeOH/HCl (1:1)].

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Patent Claims

1. A process for purifying the crude product of 1-[N^2-((S)-ethoxycarbonyl)-3-phenylpropyl)-N^6-trifluoroacetyl]-L-lysyl-L-proline (I), especially when obtained by reductive amination, by two extraction steps using an organic solvent and crystallisation from methyl-tert.butyl ether, characterised in that
the crude product is treated in a first extraction step with a two-phase system comprising water and a solvent, the aqueous phase having a pH adjusted to between 0 and 3.5, and the crystallisation being performed with the addition of methylcyclohexane.

2. A process according to Claim 1, characterised in that the first extraction step is performed in a pH range of 0.5 to 2.

3. A process according to Claims 1 and 2, characterised in that
the organic solvent used is a mixture of toluene and ethyl acetate.

4. A process according to one or more of Claims 1 to 3, characterised in that
(I) is initially allowed to pre-crystallise from methyl-tert.butyl ether and the crystallisation procedure is subsequently completed by adding methylcyclohexane.

5. A process according to one or more of Claims 1 to 4, characterised in that
the ratio by volume of methyl-tert.butyl ether to methylcyclohexane is between 1:1 and 20:1.

* C L M S *

6. A process according to Claim 5, characterised in that the ratio by volume of methyl-tert.butyl ether to methylcyclohexane is between 2:1 and 10:1.

7. A process according to one or more of Claims 1 to 6, characterised in that crystallisation takes place at a temperature between -40°C and 50°C.

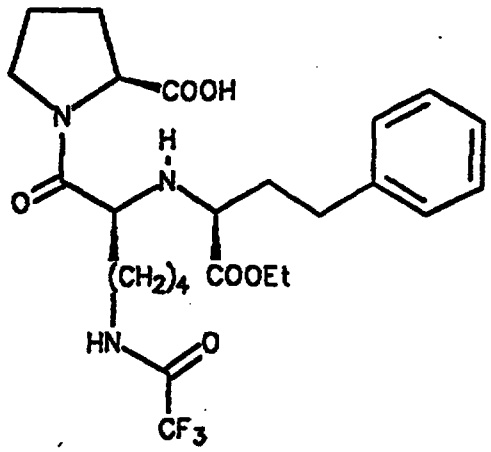
8. A process according to Claim 7, characterised in that crystallisation takes place at a temperature between -10°C and 30°C.

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* C L M S *

Abstract

The invention relates to a process for purifying 1-[N^2-((S)-ethoxycarbonyl)-3-phenylpropyl)-N^6-trifluoroacetyl]-L-lysyl-L-proline (compound I) by extraction and crystallisation.



(I)

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REPLACEMENT SHEET

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The title of the invention is:

A process for purifying 1-[N^2-((S)-ethoxycarbonyl)-3-phenylpropyl)-N^6-trifluoroacetyl]-L-lysyl-L-proline (ethyl ester of lisinopril(Tfa))

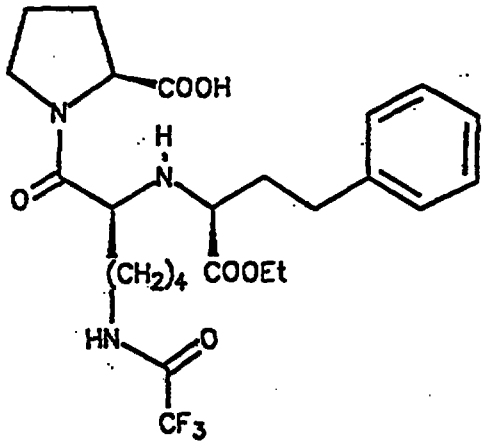
REPLACEMENT SHEET
26 NOV 1996

A PROCESS FOR PURIFYING 1-[N^2-((S) -ETHOXYCARBONYL) -3-PHENYLPROPYL) -N^6-TRIFLUOROACETYL] -L-LYSYL-L-PROLINE (ETHYL ESTER OF LISINOPRIL (TFA)

A process for purifying 1-[N^2-((S)-ethoxycarbonyl)-3-phenylpropyl)-N^6-trifluoroacetyl]-L-lysyl-L-proline (ethyl ester of lisinopril(Tfa))

Description

The invention relates to a process for purifying 1-[N^2-((S)-ethoxycarbonyl)-3-phenylpropyl)-N^6-trifluoroacetyl]-L-lysyl-L-proline (compound I) by extraction and crystallisation.

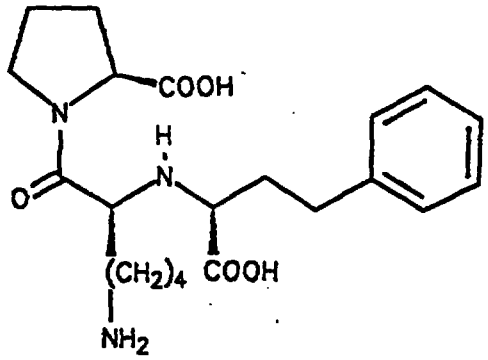


(I)

N-substituted aminoacids of this type are valuable intermediates for preparing inhibitors of angiotensin converting enzymes (ACE), which act as blood pressure regulators. I is the direct precursor of 1[N^2-((S)-carboxy)-3-phenylpropyl)]-L-lysyl-L-proline (lisinopril) compound II, which exhibits surprising therapeutic results when used to control high blood pressure (Zerstril®, Coric®, Prinivil®).

According to the prior art, compound I is obtained by reductive amination of ethyl 2-oxo-4-phenylbutyrate using the dipeptide Lys(Tfa)-Pro.

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26 NOV 1996



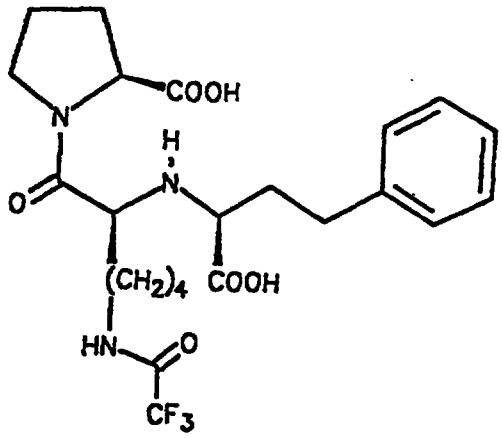
(II)

Such a process is described in J. Org. Chem. 1988, 53, 836 - 844. According to this, I is obtained in a yield of 42% by basic extraction of the crude reaction solution followed by extraction of the product in an organic solvent at pH 4.6 and finally crystallisation from methyl-tert.butyl ether/cyclohexane.

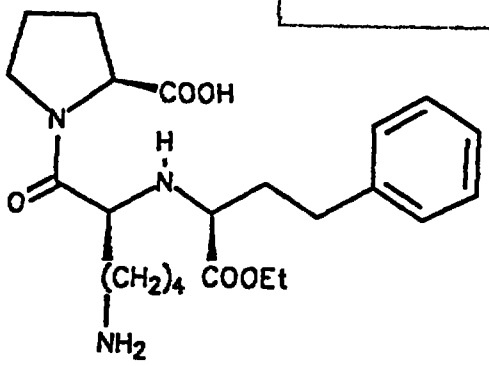
DE-OS 41 23 248 relates to the synthesis of I, which is obtained in a yield of 60% according to example 3. Working up the crude reaction solution obtained by this process includes crystallisation from methyl-tert.butyl ether in addition to a basic and an acidic extraction step. In principle, other processes which are not based on a reductive amination, but are less advantageous, are also known for preparing compound I (EP 0 336 368 A2).

Basic extraction, extraction of the aqueous product phase being required in order to remove impurities from the amination reaction, however, is always associated with product losses due to amide and/or ester cleavage of I to give II, or of I to give compounds III and IV.

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(III)



(IV)

In order to minimise this loss of product, low temperatures, precisely set pHs and reaction times which are as short as possible have to be used. This is costly and is associated with difficulties, especially on an industrial scale.

Crystallisation from methyl-tert.butyl ether is connected with high losses of yield because, in order to directly obtain the diastereomerically pure compound (I), crystallisation is performed at high dilution, which reduces the yield. If (I) is allowed to crystallise from solutions at a higher concentration, an additional recrystallisation stage is required. The addition of cyclohexane (J. Org. Chem. 1988, 53, 836 - 844) during crystallisation in order to increase the yield is also described. In this case, however, there is a risk of separation as an oil, which makes isolation of the product difficult, not only on an industrial scale.

The object of the invention is an improved process for purifying (I).

This object is achieved by extracting, optionally several times, the crude product of (I) obtained after reductive amination by evaporating the reaction solution with a water/solvent two-phase system, the pH of the aqueous phase being adjusted to a value between 0 and 3.5, in particular

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0.5 and 2, the remaining aqueous phase being adjusted to a pH between 3.5 and 6.3, in particular 3.9 and 4.8 after separation of the organic phase, using an alkaline compound, in particular NaOH or KOH, then extracting, optionally several times, with an organic solvent or solvent mixture which is not miscible with water, isolating (I) from the organic phase by evaporation and, after dissolving in a mixture of methyl-tert.butyl ether and methylcyclohexane, allowing the product (I) to crystallise out by cooling to temperatures of -40°C to +50°C, in particular -10°C to 30°C.

The crystalline product is then separated using known methods.

Acid extraction of the aqueous product solution, surprisingly, leads to only barely noticeable product losses with simultaneous higher purification of the aqueous product phase and this occurs even though the trifluoroacetylamide group can also be eliminated in acid medium. Unexpectedly, the solution also proved to be stable over a longer period of time (ca. 48 h) in the acid range, which represents a large technical simplification. An advantageous pH range for acid extraction is between 0 and 3.5, the range between 0.5 and 2 being particularly advantageous. Extraction can be performed at temperatures between 0°C and 60°C, preferably between 10°C and 40°C, in particular at room temperature. Extraction solvents which may be used are solvents which are not miscible with water such as e.g. toluene, methyl-tert.butyl ether, ethyl acetate, isopropyl acetate, methylene chloride, trichloroethane, chloroform or mixtures thereof.

The temperature ranges and solvent / solvent mixtures described above also apply to the second extraction step.

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Recrystallisation of product (I) is performed by the process according to the invention from a mixture of methyl-tert.butyl ether and methylcyclohexane at reduced temperatures. It is particularly advantageous to perform a pre-crystallisation from methyl-tert.butyl ether at the temperatures cited below with subsequent addition of methylcyclohexane to complete crystallisation. By adding methylcyclohexane, much purer products with a clearly reduced tendency for the product to separate as an oil than was possible according to the prior art are obtained. The ratio by volume of methyl-tert.butyl ether to methylcyclohexane in this case varies from 1:1 to 20:1, the ratio preferably being 2:1 to 10:1. Crystallisation takes place at temperatures between -40°C and 50°C, preferably between -10°C and 30°C.

The concentration range, expressed as the ratio of g of product (I) to ml of solvent, singly (methyl-tert.butyl ether) or together (with methylcyclohexane), varies from 1:0.5 to 1:30, preferably 1:1 to 1:10, naturally depending on the solubilities, which are predetermined by the temperature.

The process according to the invention is intended to be described in more detail by means of the following examples.

Example 1

1-[N^2-((S)-ethoxycarbonyl)-3-phenylpropyl)-N^6-trifluoroacety l]-L-lysyl-L-proline (compound I)

A reductive amination in accordance with patent application P 41 23 248.8 was performed, in the same way as described in example 3, page 10.

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Working up:
A 150 mmol batch of the reaction solution was largely evaporated under vacuum at a bath temperature of 45°C. The residue was taken up in 750 ml of water and stripped under vacuum for a short time. After the addition of 150 ml of 1,1,1-trichloroethane, the pH was adjusted to 1 using conc. HCl. The mixture was stirred for 10 minutes and the phases then separated. At 5°C, the pH in the aqueous phase was then adjusted to 4.6 and this was extracted with 2x 300 ml of 1,1,1-trichloroethane. The organic phase was evaporated under vacuum and taken up in 250 ml of methyl-tert.butyl ether. A thick slurry of crystals was produced by cooling to 5°C and seeding the mixture, and 65 ml of methylcyclohexane were added after 5 hours of vigorous stirring. After a further 2 hours at 5°C, the mixture was filtered under suction and dried under vacuum.
Yield: 54 g: (67.5% of theoretical), SSS-diastereomer content: >99%, $[\alpha]^{20}_{D}$: -25.6° [(c = 1 in MeOH/HCl (1:1)].

Example 2

1-[N^2-((S)-ethoxycarbonyl)-3-phenylpropyl)-N^6-trifluoroacetyl]-L-lysyl-L-proline (compound I)

A reductive amination in accordance with patent application P 41 23 248.8 was performed, in the same way as described in example 3, page 10.

Working up:
A 150 mmol batch of the reaction solution was largely evaporated at a bath temperature of 45°C. The residue was taken up in 750 ml of water and stripped under vacuum for a short time. After adding 120 ml of toluene and 30 ml of ethyl acetate, the pH was adjusted to 1 using conc. HCl. The mixture was stirred for 10 minutes and the phases then separated. At 5°C, the pH of the aqueous phase was then adjusted to 4.6 and this was extracted 1x with 400 ml of ethyl acetate. The organic phase was evaporated under

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vacuum and taken up in 250 ml of methyl-tert.butyl ether. A thick slurry of crystals was produced by cooling to 5°C and seeding the mixture, and 65 ml of cyclohexane were added after 5 hours of vigorous stirring. After a further 2 hours at 5°C, the mixture was separated under suction and dried under vacuum.

Yield: 54.4 g (68% of theoretical), SSS-diastereomer content: >99%, $[\alpha]^{20}_D$: 25.5° [(c=1 in MeOH/HCl (1:1)].

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REPLACEMENT SHEET
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Patent Claims

1. A process for purifying the crude product of 1-[N^2-((S)-ethoxycarbonyl)-3-phenylpropyl)-N^6-trifluoroacetyl]-L-lysyl-L-proline (I), especially when obtained by reductive amination, by two extraction steps using an organic solvent and crystallisation from methyl-tert.butyl ether, characterised in that
the crude product is treated in a first extraction step with a two-phase system comprising water and a solvent, the aqueous phase having a pH adjusted to between 0 and 3.5, and the crystallisation being performed with the addition of methylcyclohexane.

2. A process according to Claim 1,
characterised in that the first extraction step is performed in a pH range of 0.5 to 2.

3. A process according to Claims 1 and 2,
characterised in that
the organic solvent used is a mixture of toluene and ethyl acetate.

4. A process according to one or more of Claims 1 to 3,
characterised in that
(I) is initially allowed to pre-crystallise from methyl-tert.butyl ether and the crystallisation procedure is subsequently completed by adding methylcyclohexane.

5. A process according to one or more of Claims 1 to 4,
characterised in that
the ratio by volume of methyl-tert.butyl ether to methylcyclohexane is between 1:1 and 20:1.

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6. A process according to Claim 5, characterised in that the ratio by volume of methyl-tert.butyl ether to methylcyclohexane is between 2:1 and 10:1.

7. A process according to one or more of Claims 1 to 6, characterised in that crystallisation takes place at a temperature between -40°C and 50°C.

8. A process according to Claim 7, characterised in that crystallisation takes place at a temperature between -10°C and 30°C.

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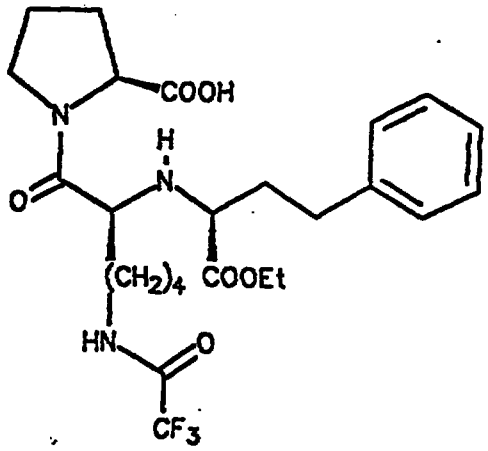


REPLACEMENT SHEET
26 NOV 1996

A PROCESS FOR PURIFYING 1-[N^2-((S) -ETHOXYCARBONYL) -3-PHENYLPROPYL) -N^6-TRIFLUOROACETYL] -L-LYSYL-L-PROLINE (ETHYL ESTER OF LISINOPRIL (TFA)

Abstract

The invention relates to a process for purifying 1-[N^2-((S)-ethoxycarbonyl)-3-phenylpropyl)-N^6-trifluoroacetyl]-L-lysyl-L-proline (compound I) by extraction and crystallisation.



(I)

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REPLACEMENT SHEET

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Claims

1. A process for purifying the crude product of 1-[N^2-((S)-ethoxycarbonyl)-3-phenylpropyl)-N^6-trifluoroacetyl]-L-lysyl-L-proline (I), in particular when obtained by reductive amination, by two extraction steps using an organic solvent and crystallisation from methyl-tert.butyl ether, characterised in that
in the first extraction step the crude product is treated with a two-phase system comprising water and a solvent, the aqueous phase having a pH adjusted to between 0 and 3.5, and that in the second extraction step the retained aqueous phase is adjusted to a pH between 3.5 and 6.3 using an alkaline compound and is treated with an organic solvent or solvent mixture which is not miscible with water, and crystallisation is performed with the addition of methylcyclohexane.

2. A process according to Claim 1,
characterised in that the first extraction step is performed at a pH between 0.5 and 2.

3. A process according to Claims 1 and 2,
characterised in that
the organic solvent used is a mixture of toluene and ethyl acetate.

4. A process according to one or more of Claims 1 to 3,
characterised in that
(I) is initially allowed to pre-crystallise from methyl-tert.butyl ether and the crystallisation procedure is subsequently completed by adding methylcyclohexane.

5. A process according to one or more of Claims 1 to 4,
characterised in that
the ratio by volume of methyl-tert.butyl ether to methylcyclohexane is between 1:1 and 20:1.

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REPLACEMENT SHEET
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6. A process according to Claim 5, characterised in that the ratio by volume of methyl-tert.butyl ether to methylcyclohexane is between 2:1 and 10:1.

7. A process according to one or more of Claims 1 to 6, characterised in that crystallisation takes place at a temperature between -40°C and 50°C.

8. A process according to Claim 7, characterised in that crystallisation takes place at a temperature between -10°C and 30°C.

