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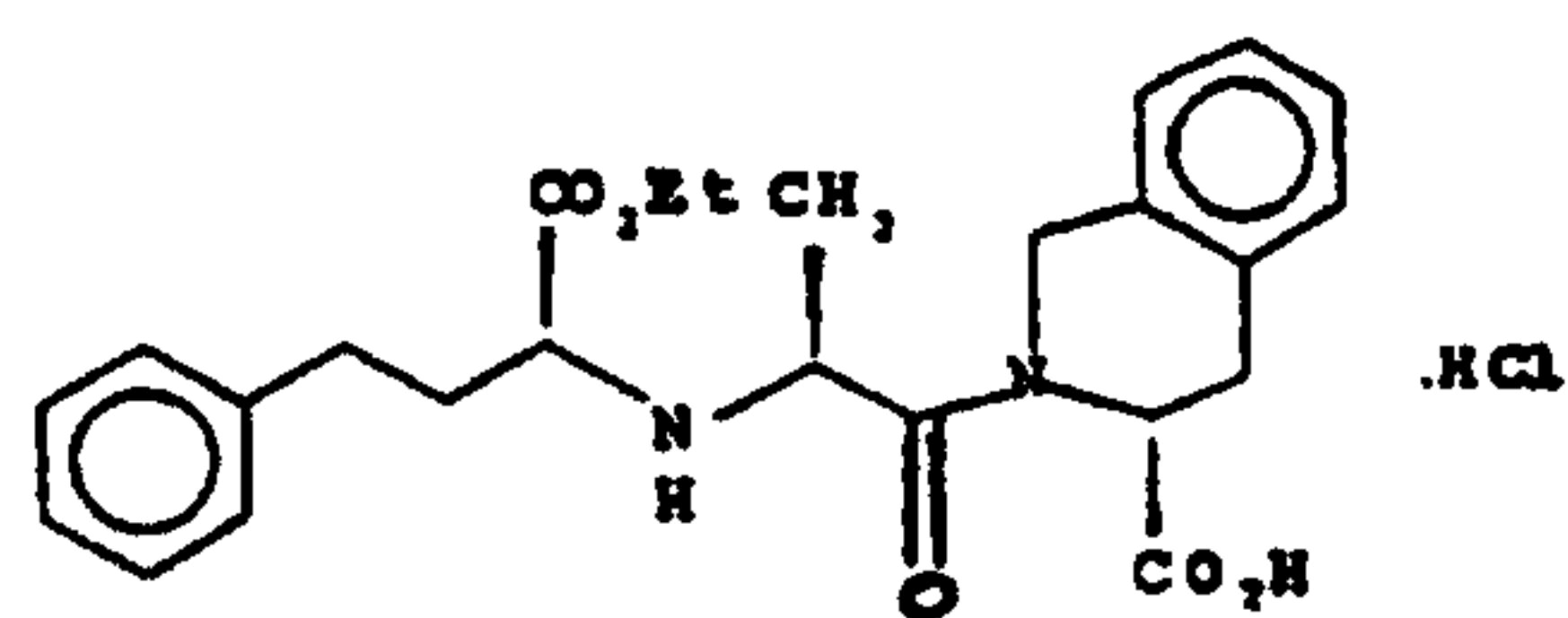
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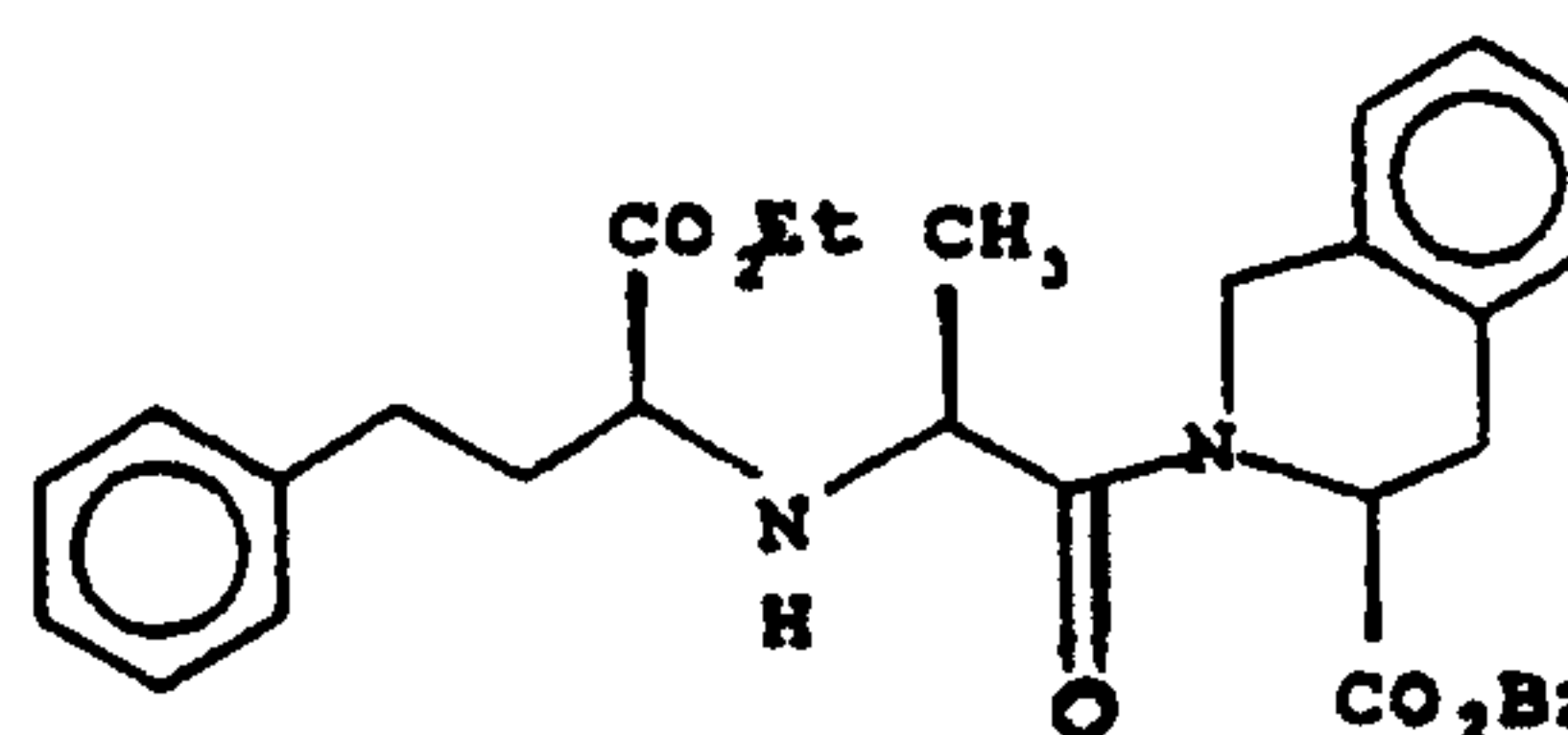
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(54) **PROCEDE POUR L'OBTENTION DE CHLORHYDRATE DE  
QUINAPRYL ET SOLVATES UTILES POUR L'ISOLEMENT  
ET LA PURIFICATION DE CHLORHYDRATE DE  
QUINAPRYL**

(54) **PROCESS FOR OBTAINING QUINAPRYL HYDROCHLORIDE  
AND SOLVATES USEFUL FOR ISOLATING AND PURIFYING  
QUINAPRYL HYDROCHLORIDE**



(I)



(II)

(57) L'invention concerne un procédé permettant d'obtenir du chlorhydrate de quinapryl (I) consistant à a) effectuer une hydrogénolyse de l'ester benzylique du quinapryl (II) par traitement dans un solvant alcoolique, avec acide chlorhydrique ou avec un chlorure d'hydrogène dissous dans l'isopropanol, et par hydrogénation; à b) retirer le solvant; à c) ajouter du toluène pour précipiter le quinapryl chlorhydrate comme solvate de toluène; à d) traiter ledit solvate avec un solvant de la classe 3 qui forme un solvate de chlorhydrate de quinapryl à partir duquel on peut l'éliminer par séchage sans le dégrader; et à e) sécher le solvate de l'étape d) pour obtenir (I). Ces solvates sont utiles pour isoler et purifier (I) un agent antihypertenseur.

(57) The process for obtaining quinapryl hydrochloride (I) comprises the following steps: a) hydrogenolysis of quinapryl benzyl ester (II) by treatment in an alcoholic solvent, with hydrochloric acid or with a solution of hydrogen chloride in isopropanol and hydrogenation; b) removing the solvent; c) addition of toluen to precipitate the quinapryl hydrochloride as toluen solvate; d) treating said solvate with a solvent of class 3 to form a solvate of quinapryl hydrochloride from which it can be dry-removed without degradation; and e) drying the solvate of step b) to yield (I). These solvates are useful to isolate and purify (I), an antihypertensive agent.

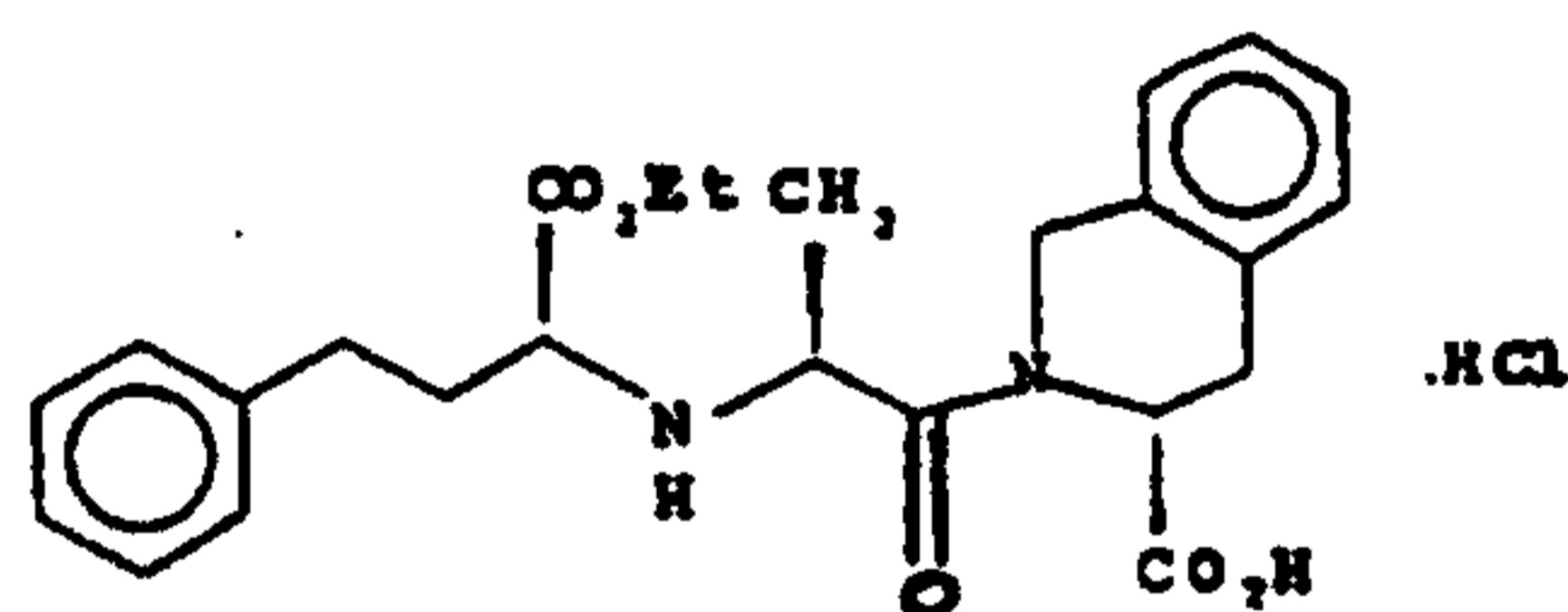


**PCT** ORGANIZACION MUNDIAL DE LA PROPIEDAD INTELECTUAL  
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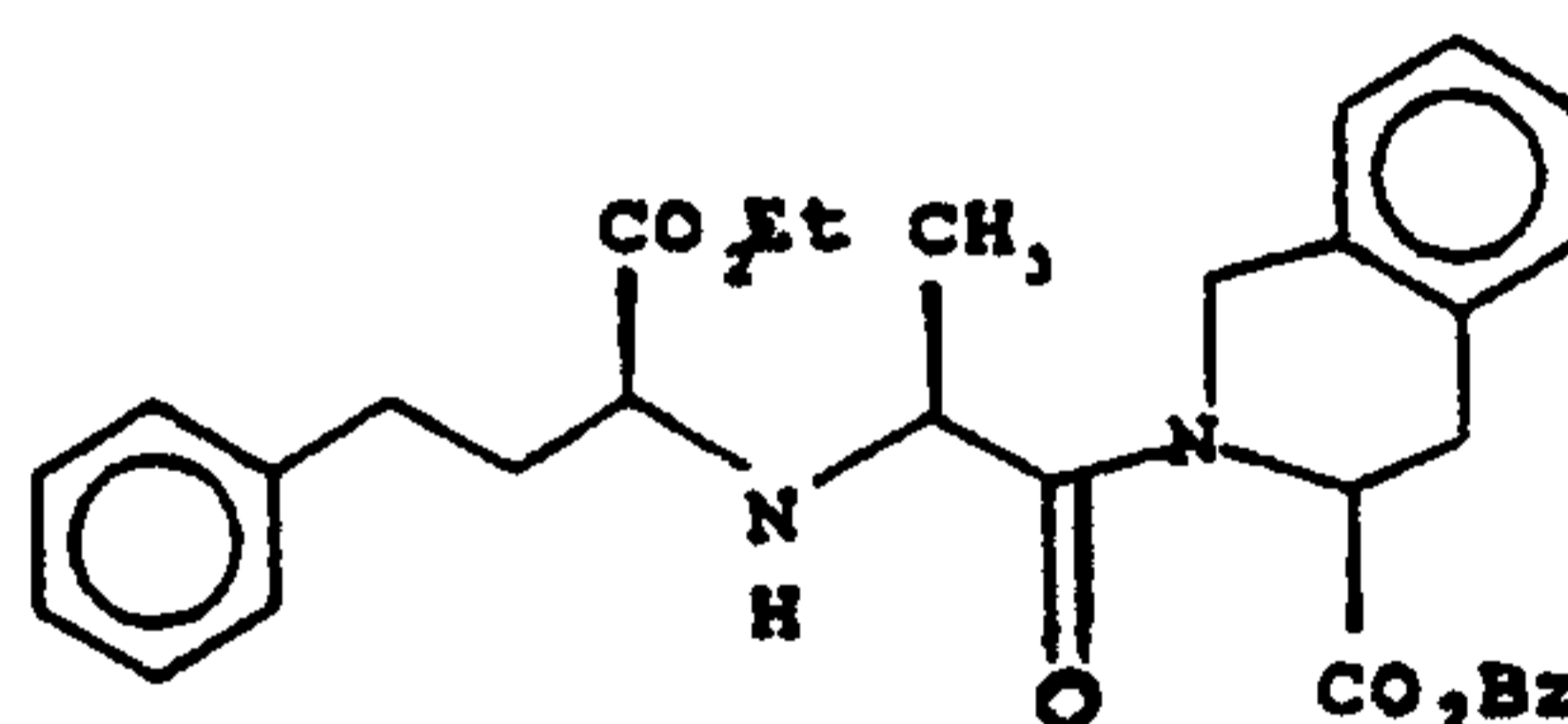
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<p>(21) Solicitud internacional: PCT/ES98/00145</p> <p>(22) Fecha de la presentación internacional: 25 de Mayo de 1998 (25.05.98)</p> <p>(30) Datos relativos a la prioridad: P 9701169 29 de Mayo de 1997 (29.05.97) ES</p> <p>(71) Solicitante (para todos los Estados designados salvo US): ESTEVE QUIMICA, S.A. [ES/ES]; Avenida Mare De Déu de Montserrat, 12, E-08024 Barcelona (ES).</p> <p>(72) Inventores; e</p> <p>(75) Inventores/solicitantes (sólo US): MONSALVATJE LLAGOSTERA, Montserrat [ES/ES]; Avenida Mare de Déu de Montserrat, 12, E-08024 Barcelona (ES). BARTRA SANMARTÍ, Martí [ES/ES]; Avenida Mare de Déu de Montserrat, 12, E-08024 Barcelona (ES). TOMAS NAVARRO, Jaime [ES/ES]; Avenida Mare de Déu de Montserrat, 12, E-08024 Barcelona (ES). PUIG TORRES, Salvador [ES/ES]; Avenida Mare de Déu de Montserrat, 12, E-08024 Barcelona (ES).</p> <p>(74) Mandatario: CARPINTERO LOPEZ, Francisco; Herrero &amp; Asociados, S.L., Alcalá, 21, E-28014 Madrid (ES).</p>	<p>(81) Estados designados: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, Patente ARIPO (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Patente euroasiática (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), Patente europea (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), Patente OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p><b>Publicada</b> <i>Con informe de búsqueda internacional. Antes de la expiración del plazo previsto para la modificación de las reivindicaciones, será publicada nuevamente si se reciben modificaciones.</i></p>	

(54) Title: PROCESS FOR OBTAINING QUINAPRYL HYDROCHLORIDE AND SOLVATES USEFUL FOR ISOLATING AND PURIFYING QUINAPRYL HYDROCHLORIDE

(54) Título: PROCEDIMIENTO PARA LA OBTENCIÓN DE QUINAPRIL CLORHIDRATO Y SOLVATOS UTILES PARA EL AISLAMIENTO Y PURIFICACIÓN DE QUINAPRIL CLORHIDRATO



(I)



(II)

**(57) Abstract**

The process for obtaining quinapril hydrochloride (I) comprises the following steps: a) hydrogenolysis of quinapril benzyl ester (II) by treatment in an alcoholic solvent, with hydrochloric acid or with a solution of hydrogen chloride in isopropanol and hydrogenation; b) removing the solvent; c) addition of toluen to precipitate the quinapril hydrochloride as toluen solvate; d) treating said solvate with a solvent of class 3 to form a solvate of quinapril hydrochloride from which it can be dry-removed without degradation; and e) drying the solvate of step b) to yield (I). These solvates are useful to isolate and purify (I), an antihypertensive agent.

**(57) Resumen**

El procedimiento para obtener quinapril clorhidrato (I) comprende las etapas de: a) hidrogenolisis del éster bencílico del quinapril (II) por tratamiento en un disolvente alcohólico, con ácido clorhídrico o con una disolución de cloruro de hidrógeno en isopropanol e hidrogenación; b) retirada del disolvente; c) adición de tolueno para precipitar el quinapril clorhidrato como solvato de tolueno; d) tratamiento de dicho solvato con un disolvente de la Clase 3 que forma un solvato de quinapril clorhidrato del que se puede eliminar por secado sin degradarlo; y e) secado del solvato de la etapa d) para rendir (I). Estos solvatos son útiles para aislar y purificar (I), un agente antihipertensivo.

PROCESS FOR OBTAINING QUINAPRIL HYDROCHLORIDE AND SOLVATES  
USEFUL FOR THE ISOLATION AND PURIFICATION OF QUINAPRIL  
HYDROCHLORIDE

5 FIELD OF THE INVENTION

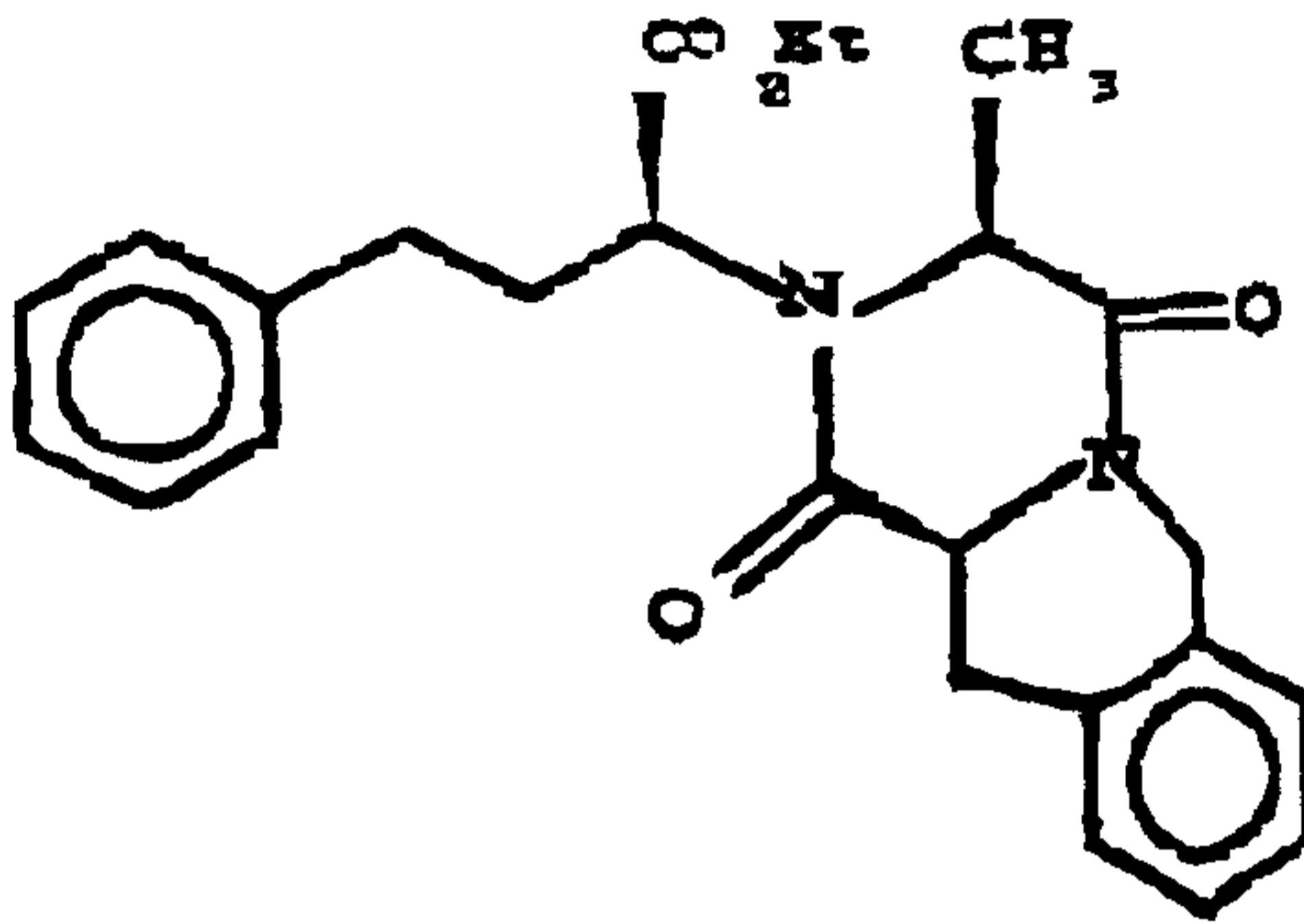
This invention refers to a procedure for obtaining  
quinapril hydrochloride, as well as new solvates of  
quinapril hydrochloride, obtained by the use of Class 3  
10 solvents, from which it is possible to eliminate the  
solvent by drying without degradation of the product, and  
which are useful for the isolation and purification of  
quinapril hydrochloride. The process can be developed at  
the industrial scale.

15 BACKGROUND OF THE INVENTION

Quinapril is the common international denomination of  
the chemical compound named (S)-2-[(S)-N-[(S)-1-  
20 (ethoxycarbonyl-3-phenylpropyl)-L-alanyl]-1,2,3,4-  
tetrahydro-3-isoquinolinecarboxylic acid]. Quinapril and  
its pharmaceutically acceptable salts are antihypertensive  
agents which act as angiotensin converting enzyme (ACE)  
inhibitors.

25 The first description of quinapril appears in the  
United States Patent No. US 4.344.949, which also describes  
its preparation starting from the ethyl ester of (S,S)- $\alpha$ -  
[(1-carboxyethyl) amino] phenylbutanoic acid and from the  
benzyl or t-butyl ester of (S)-1,2,3,4-tetrahydro-3-  
30 isoquinolinecarboxylic acid by peptide condensation with  
dicyclohexyl-carboimide (DCC) and activation with  
hydroxibenzotriazole. The benzyl or t-butyl ester of  
quinapril so obtained is unprotected by catalytic  
hydrogenation or by treatment with trifluoroacetic acid,  
35 being the final isolation of quinapril carried out (at the

laboratory scale) by precipitation with ethyl ether and by lyophilization of an aqueous solution. The isolation of quinapril is a very delicate procedure, as this product degrades very easily by intramolecular cyclisation to yield a diketopiperazine of formula



both in aqueous or organic solution as in the solid state.

The process described in said patent US 4.344.949 presents the drawbacks which are typical of the use of DCC, as the condensations carried out in the presence of DCC yield a fair amount of impurities, with the subsequent reduction in the yield (61%), thus the resulting dicyclohexylurea must be separated and, additionally, the carbodiimides are responsible for very severe allergies.

Quinapril hydrochloride is the salt which is usually employed in the manufacture medicinal products which contain quinapril.

The United States Patent No. 4.761.479 mentions that obtaining and purifying quinapril hydrochloride is hindered by its ease in degrading into by-products, essentially the diketopiperazine shown before. Said US patent No. 4.761.479 describes a process for obtaining quinapril hydrochloride which comprises unprotecting the t-butyl ester of quinapril with HCl gas in acetic acid, the isolation of the precipitation product after the addition of xylene and vacuum distillation, and the purification of the quinapril

hydrochloride by crystallisation with acetonitrile to yield a crystalline solvate of acetonitrile. The solvent of said solvate can be removed, without degradation of the quinapril hydrochloride, by drying in a vacuum oven. However, acetonitrile is a Class 2 solvent, defined by the ICH [International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use] as a "Non-mutagenic carcinogen in animals or possible cause of other irreversible toxicity such as neurotoxicity, teratogenesis or suspect of significant reversible toxicity, and, therefore, its proportion has to be limited". In the case of acetonitrile, the ICH recommends a limit not above 250 ppm (0.025%). This limit is difficult to achieve at the industrial scale due to the little stability of the product.

The Belgian Patent No. BE 892.552 describes another process for the preparation of quinapril hydrochloride starting from (S,S)- $\alpha$ -[(1-carboxyethyl) amino] phenylbutanoic acid by activation with 1,1'-carbonyldiimidazole, which yields an N-carboxyanhydride which reacts in situ, without prior isolation, with the benzyl ester of (S)-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid to yield the corresponding benzyl ester of quinapril with a yield of 56%. The resulting quinapril, protected in the form of a benzyl ester, is subsequently hydrogenated in the presence of Pd/C and it is treated with hydrochloric acid to give the quinapril hydrochloride, which is purified by chromatography and lyophilization, at a very low yield (37%). This synthetic route is also mentioned in a generic manner in the Spanish Patent ES 2.004.804, but without giving any specific conditions, nor yields, nor a description of the properties of the products obtained. Specifically, the synthesis of quinapril hydrochloride is not exemplified at all.

In general, all the processes described for obtaining quinapril hydrochloride are characterised by their difficulty or by their low yields. Only the US Patent US 4.761.479 describes a process for the industrial isolation and purification of quinapril hydrochloride, starting from the t-butyl ester of quinapril. However, said procedure has the disadvantage of using a carcinogenic solvent (acetonitrile) to obtain the corresponding solvate.

Consequently, there is a need to have a process for obtaining and purifying quinapril hydrochloride, which may be carried out at the industrial scale, and which overcomes the previously mentioned drawbacks. In order to obtain and purify quinapril hydrochloride at a high yield, the invention proposes the precipitation of said product in the form of a toluene solvate. Therefore, one of the objects of the invention is constituted by a process for obtaining quinapril hydrochloride, which comprises its isolation as the toluene solvate.

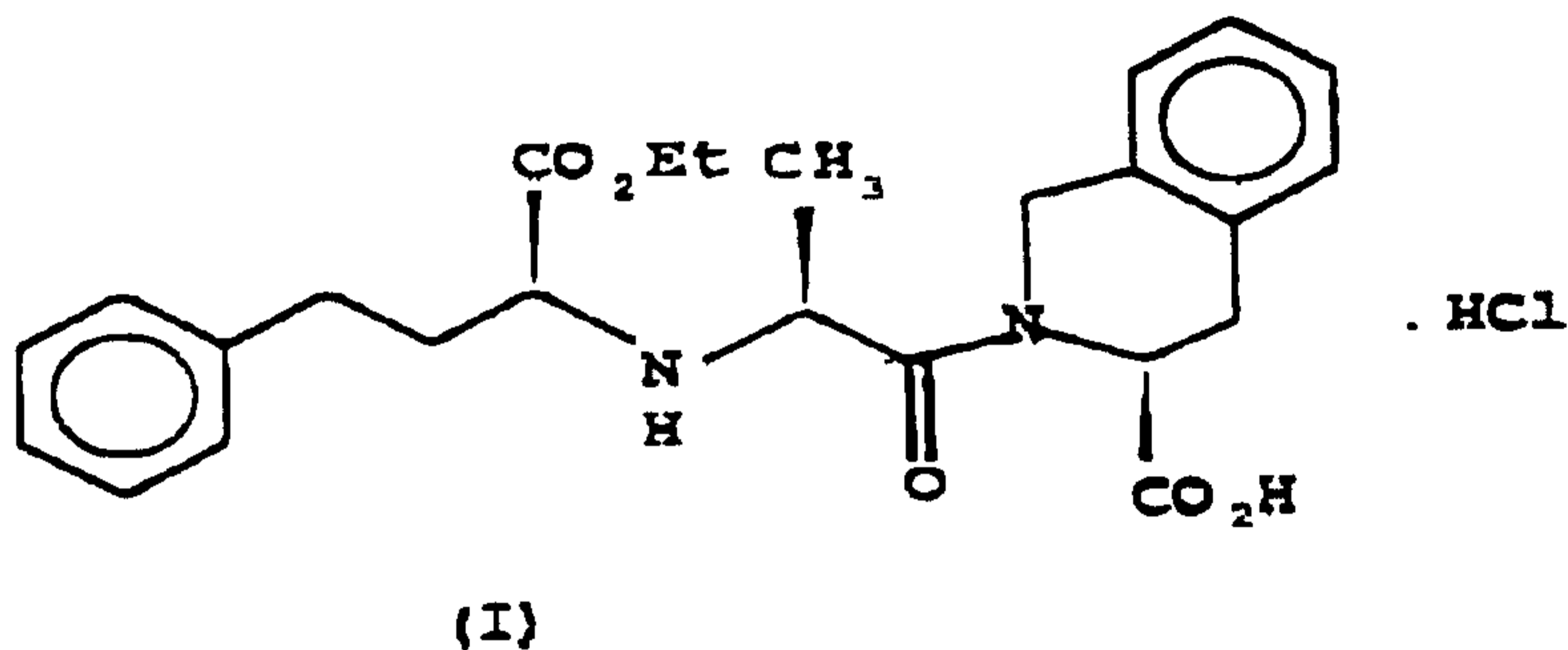
On the other hand, the solvates of quinapril hydrochloride, which are useful compounds for the purification of said product, are, in general, products from which it is extremely difficult to remove the solvent without partially degrading the quinapril hydrochloride. The only known solvate of quinapril hydrochloride which can be dried without degradation of the product is the acetonitrile solvate, but said solvate has been obtained with a carcinogenic solvent. In order to overcome these drawbacks, the invention provides solvates of quinapril hydrochloride which can be dried to remove the solvent without degrading the quinapril hydrochloride, and which have been obtained by the use of non-carcinogenic solvents. Therefore, an additional object of the invention is constituted by new solvates of quinapril hydrochloride, of solvents belonging to Class 3, from which it is possible to remove the solvent by drying without degradation of

5

quinapril hydrochloride. Class 3 solvents are defined, according to the ICH, as "Solvents with a low toxic potential to man, not being it necessary to establish an exposure limit based on health criteria. Class 3 solvents have a ADE (Allowable Daily Exposure) equal or greater than 50 mg per day".

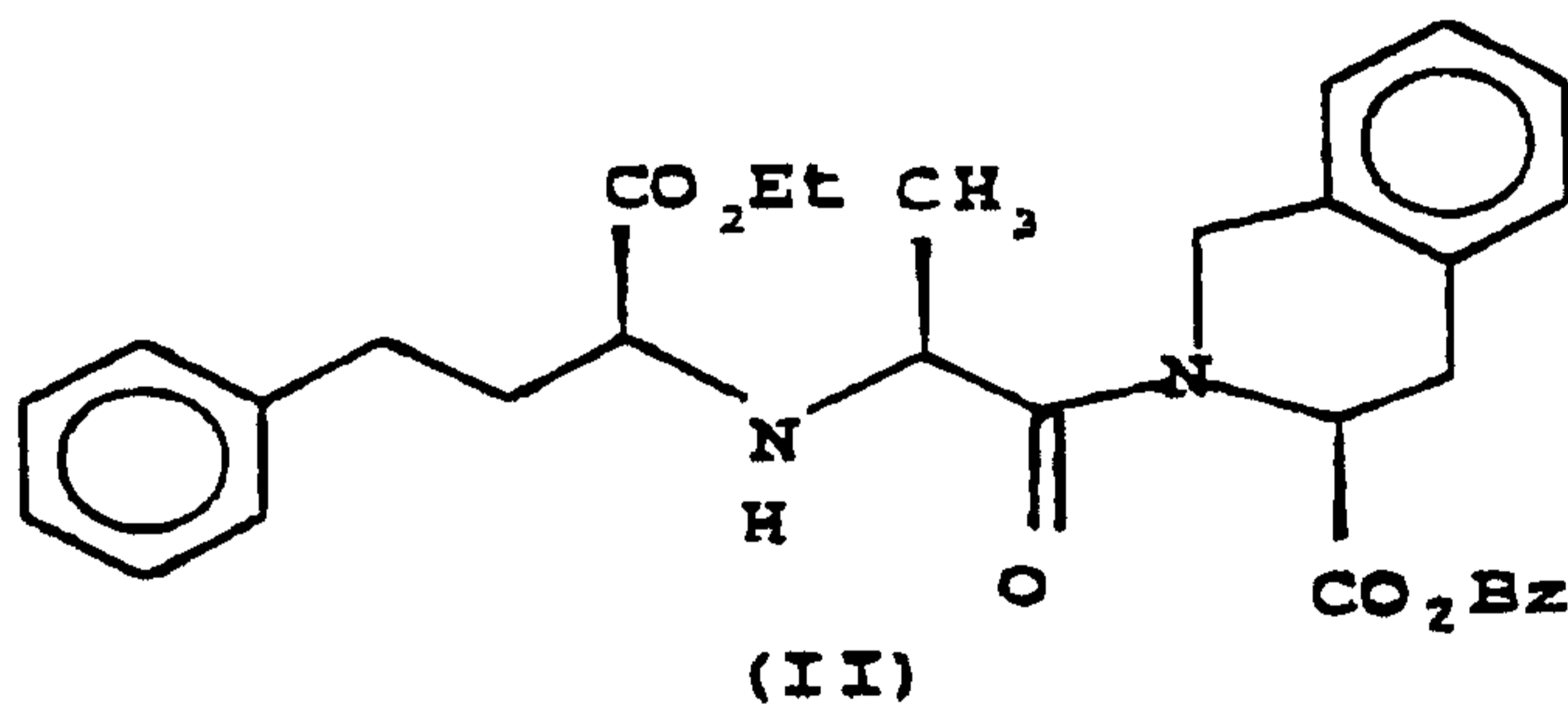
#### DETAILED DESCRIPTION OF THE INVENTION

The invention provides a process for obtaining quinapril hydrochloride of formula (I)



20 which comprises the stages of:

a) hydrogenolysis of the benzyl ester of quinapril (II)



30

where Bz is the benzyl radical;  
 b) removal of the solvent used in step a);  
 c) addition of toluene to precipitate the quinapril hydrochloride as a toluene solvate;

35

d) treatment of the toluene solvate of quinapril hydrochloride with a solvent belonging to Class 3, capable of forming a solvate of quinapril hydrochloride from which it is possible to eliminate said solvent by drying in an oven without degrading the quinapril hydrochloride; and  
5 e) drying of the solvate obtained in step d) to yield quinapril hydrochloride (I).

The benzyl ester of quinapril (II) is a known product which can be obtained by whichever of the processes described in the patents US 4.344.949 and BE 892.552, mentioned earlier, as well as in the patents EP 135181 and EP 135182 where it is described, in a general manner, the  
10 obtaining of the protected quinapril in the form of the benzyl ester starting from (S,S)- $\alpha$ - [(1- carboxyethyl) amino] phenylbutanoic acid, by activation with alkenephosphonic anhydrides.  
15

The hydrogenolysis of the benzyl ester of quinapril (II) can be carried out in an alcoholic solvent, such as ethanol or isopropanol, with concentrated hydrochloric acid or with a solution of hydrogen chloride in isopropanol, hydrogenation with hydrogen gas at a pressure comprised between approximately  $10^4$  Pa (0,1 bar) and approximately  $2 \times 10^5$  Pa (2 bar), at a temperature comprised between 10 and  
20 40 °C, in the presence of a suitable hydrogenation catalyst, for instance, Pd/C.  
25

In a specific embodiment, the hydrogenolysis reaction is carried out using ethanol as a solvent, concentrated hydrochloric acid, a pressure of  $10^5$  Pa (1 bar) and room temperature. In another specific embodiment, the  
30 hydrogenolysis reaction is carried out using isopropanol as a solvent, a solution of hydrogen chloride in isopropanol, a pressure of  $2 \times 10^5$  Pa (2 bar) and a temperature of approximately 30 °C.  
35

The molar ratio between the benzyl ester of quinapril

(II) and hydrochloric acid can be equal or slightly greater to the stoichiometric one, although preferably said molar ratio is stoichiometric as, in the event of a large defect of hydrochloric acid, quinapril tends to cyclise to form the diketopiperazine shown above, while in the event of an excess of acid, decomposition of the quinapril hydrochloride, and of the benzyl ester of quinapril itself, takes place.

Generally, hydrochloric acid is added at room temperature, and the reaction between the hydrochloric acid and the benzyl ester of quinapril (II) is virtually immediate, within minutes.

Because the solution of the benzyl ester of quinapril hydrochloride in isopropanol is more stable than the solution of the free base and, on the other hand, considering the instability of the benzyl ester of quinapril (II), the most reliable manner of preserving such product for short periods of time is maintaining it as the hydrochloride in solution in isopropanol.

Once hydrogenation is finalised, the catalyst is removed, for example, by filtration, and the solvent employed, ethanol or isopropanol, is removed, for instance, by vacuum distillation, at a temperature below 40 °C, as at greater temperatures cyclisation of the product to form the diketopiperazine is quantitatively more significant, and toluene is added. These operations involving the removal of the solvent and addition of toluene can be repeated a variable number of times. Subsequently, the bulk of the reaction is allowed to stand at room temperature for the quinapril hydrochloride to precipitate in the form of the toluene solvate.

In a specific embodiment, for the obtaining of the toluene solvate of quinapril hydrochloride starting from the raw solution in the solvent used (ethanol or isopropanol), said solution is distilled down to a defined

5 volume of approximately 1,6 ml/g of benzyl ester of  
quinapril and subsequently, an amount of toluene of  
approximately 2,25 ml of toluene per gram of benzyl ester  
of quinapril is added. After this, distillation is carried  
out again to the same volume as before, and the same amount  
of toluene is added. By working under these conditions,  
quinapril hydrochloride precipitates in the form of the  
toluene solvate within a period of time comprised between  
20 and 60 minutes. By following this precipitation process  
10 for the toluene solvate, using isopropanol as a solvent, a  
greater yield is obtained than by employing ethanol, which  
can largely be accounted for by the fact that quinapril  
hydrochloride is more soluble in ethanol than in  
isopropanol.

15 The toluene solvate of precipitated quinapril  
hydrochloride is filtered and dried, and a yield comprised  
between approximately 85% and 90% is obtained. This solvate  
is a very suitable intermediate for the subsequent  
purification of quinapril hydrochloride according to the  
20 process proposed by the present invention. The  
spectroscopic characteristics (IR, <sup>1</sup>H-NMR and <sup>13</sup>C-NMR) of  
this toluene solvate are contained in Example 2.1. The  
attempts made to remove the toluene by drying of said  
solvate, without degrading the quinapril hydrochloride,  
25 were unsuccessful.

30 Subsequently, the toluene solvate of quinapril  
hydrochloride is treated with a solvent belonging to Class  
3, i.e., non-toxic, non-carcinogenic, for example, ethyl  
formate or methyl acetate, at a temperature comprised  
between 40 °C and 45 °C, for a period of time comprised  
between 1 and 2 hours, and it is next cooled down to a  
temperature comprised between 20 °C and 25 °C, for a period  
of time comprised between 1 and 2 hours, to form the  
corresponding solvate, either of ethyl formate or of methyl  
35 acetate, which is then filtered and dried, with a yield in

any of the cases of approximately 95%. These solvates can be dried in an oven, to remove the solvent, without degrading the quinapril hydrochloride. These solvates are key intermediates for obtaining quinapril hydrochloride of a high degree of purity (99.8%) according to the process object of this invention. The spectroscopic (IR, <sup>1</sup>H-NMR and <sup>13</sup>C-NMR) and X-Ray diffraction characteristics of these solvates are contained in Examples 2.2. and 2.3.

The drying of the ethyl formate or of the methyl acetate solvates of quinapril hydrochloride obtained in this manner, in order to yield quinapril hydrochloride, can be carried out in an oven, for example in a vacuum oven, at a temperature comprised between approximately 40 and 50 °C, for a period of time comprised between 12 and 24 hours, depending on the amount of solvate to be dried. The resulting quinapril hydrochloride, the spectroscopic (IR, <sup>1</sup>H-NMR and <sup>13</sup>C-NMR), optical rotation and X-Ray diffraction characteristics of which are collected in example 2.4., is an amorphous product, the X-ray diffraction pattern of which exhibits few peaks and with a low intensity, and consequently, *a priori*, it is an amorphous product.

The hydrogenation of the product resulting after the addition of hydrochloric acid or of the solution of hydrogen chloride in isopropanol in step a) can be carried out without prior isolation of the intermediate formed. Equally, the bulk of the reaction resulting from the hydrogenolysis can be subjected to distillation in order to remove the solvent used in step a), without isolation of the product formed.

In a specific and preferred embodiment of the invention, the benzyl ester of quinapril is obtained by condensation of the N-carboxyanhydride of N-[1-(S)-ethoxycarbonyl -3-phenylpropyl]- L-alanine and of the benzyl ester of (S)-1,2,3,4-tetrahydro -3-isoquinolinecarboxylic acid. The resulting benzyl ester of

quinapril (II), without isolating, is subjected to the previously described treatment, for example, in patent BE 892.552.

The following examples serve the purpose of illustrating specific forms of embodiment of the process object of the invention, and they must not be considered as limiting to the scope of the same. All the X-ray diffraction analyses were carried out by the crystalline powder method ( $\lambda = 1,5419 \text{ \AA}$ ), the preparations of the sample were performed on a dry standard.

Material of the anode: copper  
 Wavelength,  $\lambda_1$  ( $\text{\AA}$ ) = 1,54060  
 Wavelength,  $\lambda_2$  ( $\text{\AA}$ ) = 1,54439  
 Initial angle ( $2\theta^\circ$ ) : 6,025  
 Final angle ( $2\theta^\circ$ ) : 39,9855  
 Initial d value ( $\text{\AA}$ ) = 14,65735  
 Final d value ( $\text{\AA}$ ) = 2,25302

#### EXAMPLE 1

Preparation of the benzyl ester of (S,S,S) 2-[2- [(1-ethoxycarbonyl)-3-phenylpropyl) amino] 1-oxopropyl] - 1,2,3,4- tetrahydro-3- isoquinolinecarboxylic acid [benzyl ester of quinapril (II)]

51.3 g (0.12 moles) of the para-toluenesulfonate of the benzyl ester of (S)-1,2,3,4- tetrahydro - isoquinoline-3- carboxylic acid are suspended in 150 ml of toluene. 200 ml of 10% sodium bicarbonate solution are added under stirring and the mixture is shaken until complete dissolution is achieved. The organic phase is allowed to decant and it is separated, and the same is again washed with 100 ml of 10% sodium bicarbonate solution, and it is subsequently dried with sodium sulphate and filtered. To

this toluene based solution, 36.0 g (0.12 moles) of the N-carboxyanhydride of N-[1-(S)-ethoxycarbonyl-3-phenylpropyl]-L-alanine, dissolved in 75 ml of toluene, are added, at room temperature, in 1 hour. Approximately 4 hours after the addition of said N-carboxyanhydride, the reaction is finished. The toluene phase is washed with a 5% sodium hydroxide solution, followed by water, and the solvent is vacuum-distilled until an oil is obtained, 62 g (Yield: 98%) which is the benzyl ester of quinapril.

After forming the maleate, it is characterised by:

- HPLC: the has a purity of 99.3%

- Titration: 100.2%

-  $[\alpha]^R = -12.93^\circ$  (2% methanol)

IR (KBr) ( $\nu$ ,  $\text{cm}^{-1}$ ) : 3520, 3050, 2980, 1746, 1656, 1603, 1455, 1347, 1211, 1010, 751, 697.

In solution, this compound is a mixture of two rotamers. The distribution of the rotamers is observed, in some cases, in the proton and carbon 13 nuclear magnetic resonance (NMR) spectra.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 300 MHz) ( $\delta$ (ppm)): 10,40 (wide band, 3H); 7,40-7,00 (m, 14 H); 6,29 (s, 2H); 5,43 (dd,  $J_1 = 3,9$  Hz,  $J_2 = 5,9$  Hz, 1H); 5,02 (m, 2H); 4,60 (m, 2H); 4,44 (q,  $J_1 = J_2 = J_3 = 7,1$  Hz, 1H); 4,23 (m, 2H); 3,77 ( $t_{\text{min}}$ ), 3,72 (t,  $J_1 = 6,3$  Hz, 1H); 3,45 - 3,05 (m, 2H); 2,85 - 2,65 (m, 2H); 2,30 - 2,15 (m, 2H); 1,6 ( $d_{\text{min}}$ ,  $J_1 = 6,8$  Hz), 1,45 (d,  $J_1 = 6,9$  Hz), 3H; 1,28 (t,  $J_1 = J_2 = 7,2$  Hz, 3H).

$^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ , 75 MHz) ( $\delta$ (ppm)): 170,4 (min), 170,1, 169,7 (min), 169,2 (min), 169,1, 139,6 (min), 139,5, 135,3, 135,1 (min), 134,5, 131,8, 131,3 (min), 130,9 (min), 130,7, 128,6, 128,5, 128,4, 128,3, 128,1, 128,0, 127,9, 127,8, 127,7, 127,4, 127,3, 126,6, 126,5, 126,4, 126,1, 67,9 (min), 67,2, 62,6, 62,4 (min), 59,5 (min), 58,6, 54,7 (min), 54,5 (min), 53,5, 52,6, 45,2, 44,5 (min), 32,4 (min), 32,1, 31,3 (min), 31,2, 30,5, 16,8 (min), 15,6, 14.0 (min), 13,9.

EXAMPLE 2

Preparation of (S,S,S) 2-[2- [(1-(ethoxycarbonyl)- 3-phenylpropyl) amino] 1-oxopropyl] -1,2,3,4-tetrahydroisoquinoline -3-carboxylic acid hydrochloride [Quinapril hydrochloride (I)]

2.1. Toluene solvate of quinapril hydrochloride.

62.0 g of the benzyl ester of quinapril, obtained according to Example 1, are dissolved with 400 ml of ethanol and 10 ml of concentrated hydrochloric acid, 3.1 g of 5% Pd/C (paste) catalyst are added and the mixture is hydrogenated at room temperature and at a pressure  $10^5$  Pa (1 bar) for 3 hours. After hydrogenation has concluded, the catalyst is filtered, most part of the ethanol is vacuum-distilled and 150 ml of toluene are added. Subsequently, most of the solvent is vacuum-distilled again and another 150 ml of toluene are added. Subsequently it is allowed to stand at room temperature, which leads to the precipitation of a solid which is filtered and dried under a vacuum at 40 °C. 58,5 g were obtained (Yield: 88%) of a product which corresponds to the toluene solvate of quinapril hydrochloride.

IR (KBr) ( $\nu$ ,  $\text{cm}^{-1}$ ) : 3520, 3026, 3003, 2928, 2802, 1755, 1742, 1711, 1646, 1558, 1538, 1495, 1455, 1203, 758, 737.

In solution, this compound is a mixture of two rotamers. The distribution of the rotamers is observed, in some cases, in the proton and carbon 13 nuclear magnetic resonance (NMR) spectra.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 300 MHz) ( $\delta$ (ppm)): 7,20 - 7,00 (m, 14 H); 5,15 (t wide), 4,97 ( $\text{width}_{\text{min}}$ ), 1H; 4,82 - 4,45 (m, 3H); 4,35 - 4,05 (m, 2H), 3,90 (t wide, 1H); 3,42 - 3,05 (m, 2H), 2,90 - 2,62 (m, 2H), 2,42 - 2,20 (m, 2H), 2,38 (s, 3H), 1,68 (d,  $J_1 = 6,2$  Hz); 1,60 ( $\text{d}_{\text{min}}$ ,  $J_1 = 6,2$  Hz), 3H; 1,28 ( $\text{t}_{\text{min}}$ ,  $J_1 = J_2 = 4,0$  Hz); 1,22 (t,  $J_1 = J_2 = 4,0$  Hz),

3H.

<sup>13</sup>C-NMR (CDCl<sub>3</sub>, 75 MHz) (δ(ppm)): 172,2, 171,4 (min),  
 169,2, 168,6, 168,2 (min), 168,0, 139,6 (min), 139,4,  
 137,8, 132,2, 131,4, 131,3, 131,2, 129,0, 128,6, 128,4,  
 5 128,2, 127,7, 127,1, 126,4, 126,3, 126,2, 125,2, 63,2  
 (min), 62,9, 59,1 (min), 58,9, 54,9 (min), 54,6 (min),  
 54,5, 53,1, 45,4, 44,1 (min), 31,9 (min), 31,4, 31,1, 31,0,  
 30,1 (min), 21,4, 16,2 (min), 15,2, 14,0 (min), 13,9.

10 2.2. Ethyl formate solvate of quinapril hydrochloride.

The 58.5 g of toluene solvate are shaken at 40 - 45 °C  
 with 234 ml of ethyl formate, for 2 hours, and is  
 subsequently cooled down to a temperature comprised between  
 20 and 25 °C for two additional hours. The resulting  
 15 product is filtered and dried in a vacuum oven at a  
 temperature of 30 °C, for four hours, to obtain 54 g of  
 ethyl formate solvate of quinapril hydrochloride (Yield:  
 95%).

IR (KBr) (ν, cm<sup>-1</sup>) : 3520, 3028, 3001, 2979, 2935,  
 20 2857, 1744, 1718, 1648, 1546, 1495, 1462, 1454, 1432, 1388,  
 1260, 1199, 756.

In solution, this compound is a mixture of two  
 rotamers. The distribution of the rotamers is observed, in  
 some cases, in the proton and carbon 13 nuclear magnetic  
 resonance (NMR) spectra.  
 25

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300 MHz) (δ(ppm)): 10,00 (s wide, 1H),  
 8,95 (s wide, 1H), 8,02 (s, 1H); 7,15 (m, 9H); 5,15 (J<sub>1</sub> =  
 J<sub>2</sub> = 5,6 Hz), 4,95 (width<sub>min</sub>), 1H; 4,82 - 4,62 (m, 2H); 4,60  
 - 4,42 (m, 1H); 4,20 (q, (J<sub>1</sub> = J<sub>2</sub> = J<sub>3</sub> = 7,0 Hz, 2H); 4,09  
 30 - 3,90 (m, 1H); 3,68 (q<sub>min</sub>); 3,40 - 3,05 (m, 2H), 2,97 -  
 2,59 (m, 2H); 2,42 - 2,20 (m, 2H); 1,67 (d, J<sub>1</sub> = 7,0 Hz),  
 1,56 (d<sub>min</sub>, J<sub>1</sub> = 7,0 Hz, 1H), 1,30 (t, J<sub>1</sub> = J<sub>2</sub> = 7,0 Hz),  
 1,18 (J<sub>1</sub> = J<sub>2</sub> = 7,0 Hz), 3H.

<sup>13</sup>C-NMR (CDCl<sub>3</sub>, 75 MHz) (δ(ppm)): 172,2, 171,3 (min),  
 35 169,2 (min), 168,6, 168,0, 161,0, 139,7 (min), 139,4,

14

132,2, 131,4 (min), 131,3 (min), 131,2, 128,5 (min), 128,4,  
 128,2, 127,2, 127,1, 126,3, 126,2, 126,1, 63,1 (min), 62,9,  
 59,9, 59,1 (min), 58,9, 58,2 (min), 54,8 (min), 54,6 (min),  
 54,5, 53,1, 45,4, 44,1 (min), 31,8 (min), 31,3, 31,1, 31,0,  
 5 30,8 (min), 30,1, 16,2 (min), 15,2, 14,1, 14,0 (min), 13,9.

X-Ray Diffraction (powder)Ethyl formate solvate of quinapril hydrochloride

	<u>Angle (2<math>\theta</math>)</u>	<u>Relative intensity (%)</u>
10	8,82	32,7
	10,88	23,3
	11,47	20,9
15	12,05	16,5
	13,63	34,4
	15,89	12,5
	16,08	17,2
	16,48	27,4
20	16,85	32,7
	18,05	10,4
	18,42	17,8
	18,68	24,6
	19,52	50,7
25	19,75	33,2
	20,11	45,3
	21,20	36,6
	21,86	100,0
	23,07	15,3
30	23,59	30,1
	24,50	42,5
	26,66	14,5
	27,16	22,7
	27,45	10,6
35	28,34	13,1

28,71	15,6
29,66	29,5
30,56	14,5
34,87	13,5

5

### 2.3. Methyl acetate solvate of quinapril hydrochloride

Following a similar process to that described in Example 2.2., but changing ethyl formate for methyl acetate, the corresponding methyl acetate solvate of quinapril hydrochloride (Yield: 95%) was obtained, which is characterised by the following spectroscopic data.

IR (KBr) ( $\nu$ ,  $\text{cm}^{-1}$ ) : 3500, 3084, 3003, 2860, 1746, 1735, 1706, 1648, 1545, 1495, 1455, 1259, 1196, 755.

In solution, this compound is a mixture of two rotamers. The distribution of the rotamers is observed, in some cases, in the proton and carbon 13 nuclear magnetic resonance (NMR) spectra.

$^1\text{H}$ -NMR ( $\text{CDCl}_3$ , 300 MHz) ( $\delta$  (ppm)) : 10,10 (s wide, 1H); 9,10 (s wide, 1H); 7,21 - 7,06 (m, 9H); 5,14 (t,  $J_1 = J_2 = 5,6$  Hz, 1H); 4,80 - 4,67 (m, 2H); 4,57 (m, 1H); 4,21 - 4,19 (m, 2H); 4,16 - 3,89 (m, 1H); 3,66 (s, 3H); 3,41 - 3,00 (m, 2H); 2,72 - 2,62 (m, 2H); 2,34 - 2,29 (m, 2H); 2,05 (s, 3H); 1,67 (d,  $J_1 = 6,8$  Hz), 1,57 ( $d_{\text{min}}$ ,  $J_1 = 6,8$  Hz), 3H; 1,21 ( $t_{\text{min}}$ ,  $J_1 = J_2 = 6,9$  Hz); 1,17 (t,  $J_1 = J_2 = 6,9$  Hz), 3H.

$^{13}\text{C}$ -NMR ( $\text{CDCl}_3$ , 75 MHz) ( $\delta$  (ppm)) : 172,2, 171,5 (min), 169,2 (min), 168,6, 168,3 (min), 168,1, 139,6 (min), 139,4, 132,2, 131,5 (min), 131,3 (min), 131,2, 128,6, 128,5, 128,4, 128,3 (min), 127,8 (min), 127,2, 126,4, 126,2 (min), 63,2 (min), 62,9, 58,9, 54,7 (min), 54,5, 53,2, 51,5, 45,4, 44,2 (min), 31,9 (min), 31,4, 31,1, 31,0, 30,2 20,6, 16,1 (min), 15,5, 14,0 (min), 13,9.

35

X-Ray Diffraction (powder)Methyl acetate solvate of quinapril hydrochloride

	<u>Angle (2<math>\theta</math>)</u>	<u>Relative intensity (%)</u>
5	8,86	26,0
	10,95	26,0
	11,79	19,2
	13,73	45,9
10	16,18	18,2
	16,57	37,7
	16,87	60,4
	18,76	18,6
	18,93	18,6
15	19,59	33,2
	20,16	81,9
	20,91	19,2
	21,56	30,7
	21,93	100,0
20	22,18	28,7
	23,22	14,6
	23,65	35,4
	24,62	52,6
	27,17	34,0
25	28,51	16,6
	28,93	22,9
	30,69	21,6
	30,85	14,0

## 30            2.4. Quinapril hydrochloride

The ethyl formate or methyl acetate solvates of quinapril hydrochloride, obtained according to Examples 2.2. and 2.3., can be dried directly in a vacuum oven at a temperature comprised between 40 and 50 °C for a period of

35

time comprised between 12 and 14 hours, without the need of isolating them, in order to give the quinapril hydrochloride, which is a very scarcely crystalline or an amorphous product, as evidenced by its X-ray diffraction pattern. Out of the 54 g of ethyl formate solvate of quinapril hydrochloride 46 g of quinapril hydrochloride are obtained, characterised by:

- HPLC: 99.8%
- Titration: 100.2%
- $[\alpha]_D^{25} = +15.9^\circ$  (2% methanol)

IR (KBr) ( $\nu$ ,  $\text{cm}^{-1}$ ): 3415, 3059, 2982, 2936, 1740, 1651, 1541, 1497, 1473, 1455, 1443, 1386, 1379, 1207, 751, 702.

In solution, quinapril hydrochloride is a mixture of two rotamers. The distribution of the rotamers is observed, in some cases, in the proton and carbon 13 nuclear magnetic resonance (NMR) spectra.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 300 MHz) ( $\delta$  (ppm)): 7,23, (m, 9H); 5,12 (m, 1H), 4,9 - 4,4 (m, 3H); 4,19 (m, 2H); 3,91 (m); 3,79 ( $m_{\text{min}}$ ), 1H; 3,3 - 3,1 (m, 2H); 2,77 - 2,61 (m, 2H); 2,20 (m, 2H); 1,51 (d,  $J_1 = 6,4$  Hz), 1,49 ( $d_{\text{min}}$ ,  $J_1 = 5,1$  Hz), 3H; 1,22 ( $t_{\text{min}}$ ,  $J_1 = J_2 = 7,3$  Hz), 1,17 (t,  $J_1 = J_2 = 7,3$  Hz), 3H.

$^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ , 75 MHz) ( $\delta$  (ppm)): 171,5, 171,4, 168,5, 140,2, 132,5, 132,4, 132,1 (min), 131,5 (min), 128,5, 128,4, 128,2, 128,1, 127,1, 126,7, 126,6, 126,3, 126,1, 125,4, 62,2 (min), 62,0, 57,4 (min), 57,3, 53,9 (min), 53,1 (min), 52,7, 52,0, 44,5, 43,6 (min), 31,3 (min), 30,8, 30,6 (min), 30,4, 30,0, 21,1 (min), 16,2 (min), 14,7, 13,9.

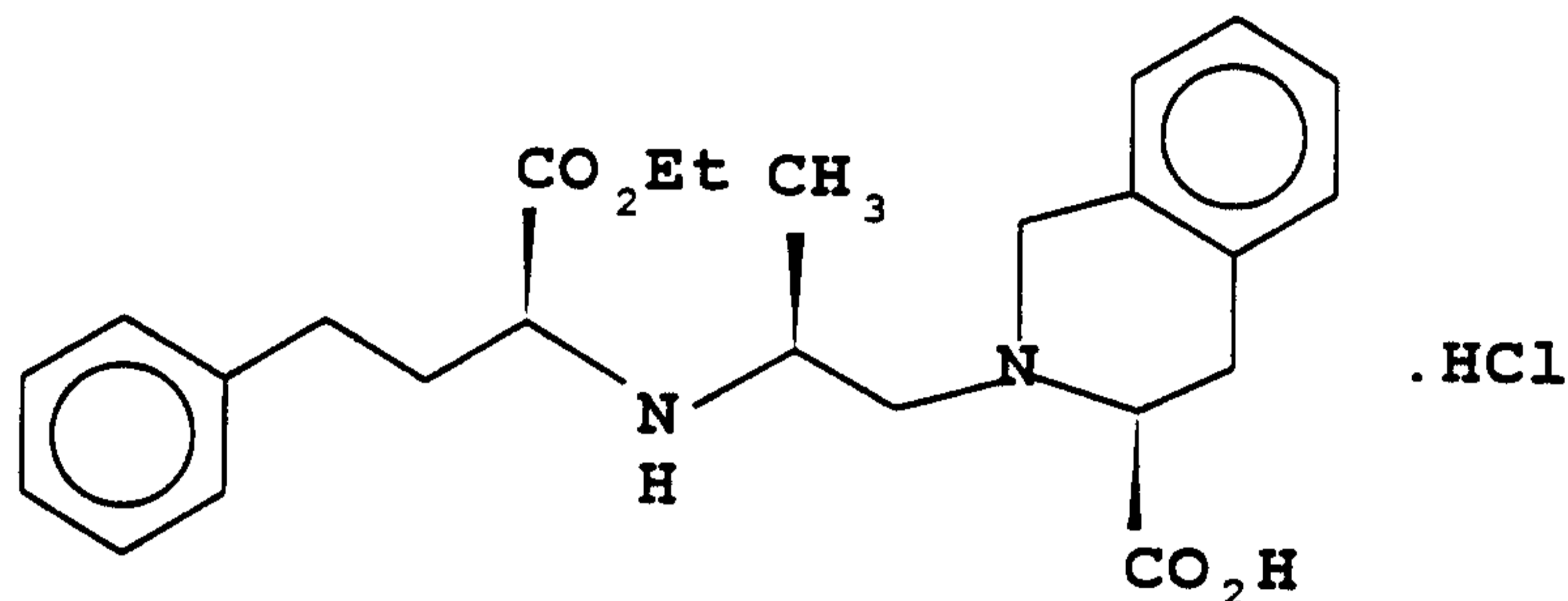
18

X-Ray Diffraction (powder)  
Quinapril hydrochloride

	<u>Angle (2<math>\theta</math>)</u>	<u>Relative intensity (%)</u>
5	11,18	31,9
	12,17	29,4
	17,38	33,9
	19,83	37,9
10	28,34	10,0
15		
20		
25		
30		
35		

## CLAIMS

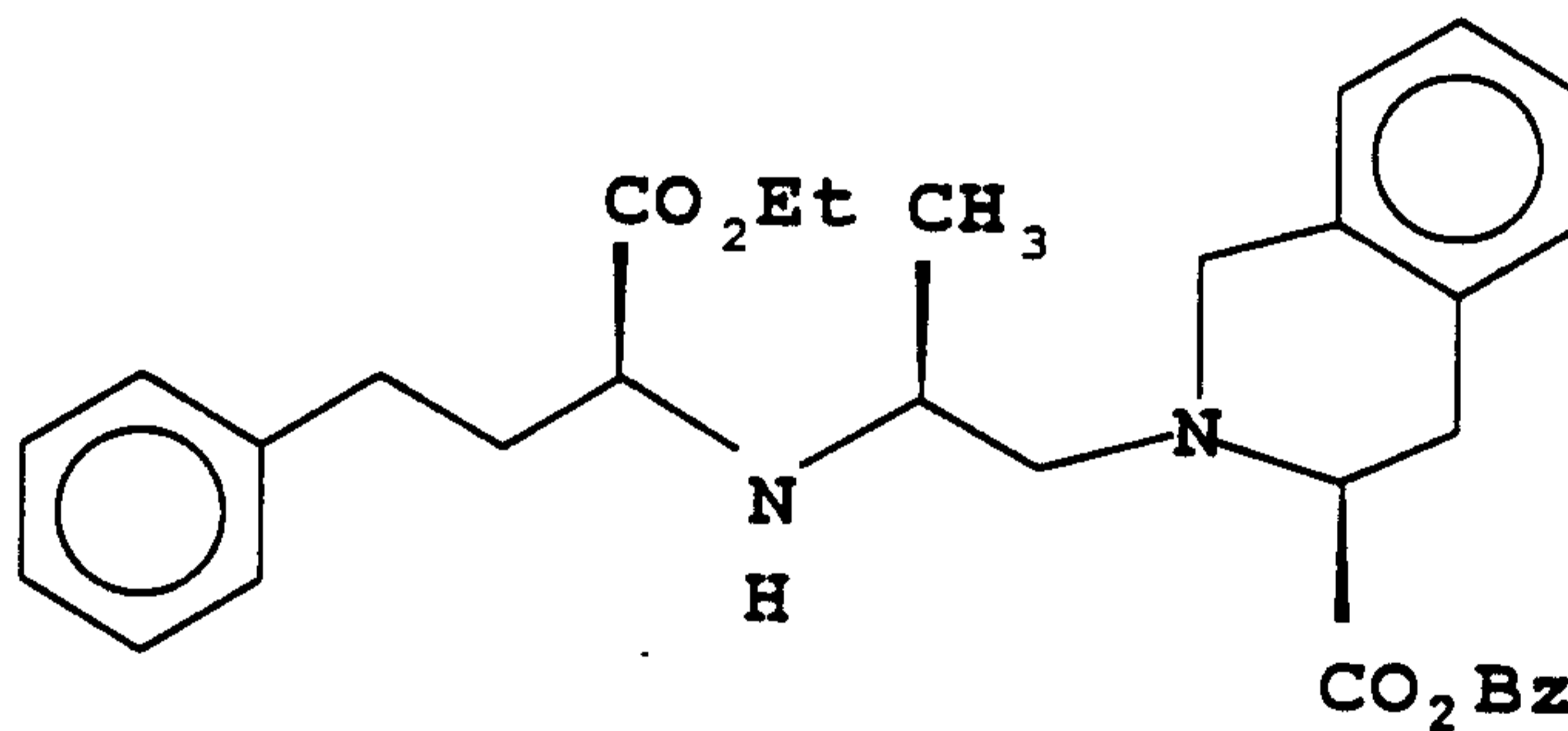
1. A process for obtaining quinapril hydrochloride of formula (I)



(I)

which comprises the stages of:

5 a) treatment of the benzyl ester of quinapril (II)



(II)

10

where Bz is the benzyl radical, with alcohol and hydrochloric acid or hydrogen chloride and hydrogenation of same through the addition of an appropriate hydrogenation catalyst;

b) removal of the solvent used in step a);

15 c) addition of toluene to precipitate the quinapril hydrochloride as a toluene solvate;

d) treatment of the toluene solvate of quinapril hydrochloride with a solvent belonging to class 3, capable of forming a solvate of quinapril hydrochloride from which it is possible to eliminate said solvent by drying in an oven without degrading the quinapril hydrochloride; and

5 e) drying of the solvate obtained in step d) at a temperature between 40°C and 50°C to yield quinapril hydrochloride (I)

2. A process according to claim 1 wherein the hydrogenolysis reaction of the benzyl ester of quinapril (II) is carried out in an alcoholic solvent, with  
10 treatment with concentrated hydrochloric acid or with a solution of hydrogen chloride in isopropanol, and hydrogenation with hydrogen gas in the presence of a hydrogenation catalyst.

3. A process according to claim 2, wherein said alcoholic solvent is chosen  
15 from between ethanol or isopropanol.

4. A process according to claim 2, wherein the hydrogenation is carried out at a pressure comprised  $10^4$  Pa and  $2 \times 10^5$  Pa.

20 5. A process according to claim 2, wherein the hydrogenation is carried out at a temperature comprised 10 and 40°C.

6. A process according to claim 2, wherein the hydrogenation catalyst is Pd/C.  
25

7. A process according to claim 2, wherein the hydrogenolysis reaction of the benzyl ester of quinapril (II) is carried out using ethanol as a solvent, concentrated hydrochloric acid, a pressure of  $1 \times 10^5$  Pa (1 bar) and room temperature.  
30

8. A process according to claim 2, wherein the hydrogenolysis reaction of the benzyl ester of quinapril (II) is carried out using isopropanol as a solvent, a

solution of hydrogen chloride in isopropanol, a pressure of  $2 \times 10^5$  Pa (1 bar) and a temperature of approximately 30 °C.

9. A process according to claim 2 wherein the molar ratio between the  
5 benzyl ester of quinapril (II) and the hydrochloric acid can be equal or greater in a proportion of 1.1 (benzyl ester of quinapril (II)) to 1 (hydrochloric acid) with respect to stoichiometric one.

10. A process according to claim 1, wherein the removal of the solvent  
10 used in stage a) is carried out by vacuum-distillation.

11. A process according to claim 1, wherein the Class 3 solvent used to  
15 treat the toluene solvate of quinapril hydrochloride is chosen from among ethyl formate and methyl acetate.

12. A process according to claim 1, wherein the treatment of the toluene  
20 solvate of quinapril hydrochloride with the class 3 solvent is carried out at a temperature comprised between 40°C and 45°C, for a period of time comprised between 1 and 2 hours, and is subsequently cooled down to a temperature comprised between 20 °C and 25 °C, for a period of time comprised between 1 and 2 hours.

13. A process according to claim 1, wherein the Class 3 solvent solvate of  
25 quinapril hydrochloride is chosen from among ethyl formate solvate of quinapril hydrochloride and the methyl acetate solvate of quinapril hydrochloride.

14. A process according to claim 1, wherein the Class 3 solvent solvate of  
quinapril hydrochloride is dried in a vacuum oven , at a temperature comprised between 40 and 50 °C for a period of time comprised between 12 and 24 hours.

15. A process according to claim 1, wherein the hydrogenation of the product resulting after the addition of hydrochloric acid or hydrogen chloride to the benzyl ester of quinapril (II) in stage a), is carried out without prior isolation of the intermediate formed.

16. A process according to claim 1, wherein the benzyl ester of quinapril (II) is obtained by condensation of the N-carboxyanhydride of N-[1-(S)-ethoxycarbonyl-3-phenylpropyl]-L-alanine and of the benzyl ester of (S)-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid, followed by hydrogenation in an acid medium.

17. A process according to claim 16, wherein the benzyl ester of quinapril (II) obtained is used without prior isolation.

18. A toluene solvate of quinapril hydrochloride characterised in that its infrared spectrum presents the following peaks:

IR (KBr) ( $\nu$ ,  $\text{cm}^{-1}$ ) : 3520, 3026, 3003, 2928, 2802, 1755, 1742, 1711, 1646, 1558, 1538, 1495, 1455, 1203, 758, 737.

19. An ethyl formate solvate of quinapril hydrochloride characterised in that its X-ray diffraction pattern presents the following characteristics:

X-Ray Diffraction (powder)

Ethyl formate solvate of quinapril hydrochloride

<u>Angle (<math>2\theta^\circ</math>)</u>	<u>Relative intensity (%)</u>
8,82	32,7
10,88	23,3

	11,47	20,9
	12,05	16,5
	13,63	34,4
	15,89	12,5
5	16,08	17,2
	16,48	27,4
	16,85	32,7
	18,05	10,4
	18,42	17,8
10	18,68	24,6
	19,52	50,7
	19,75	33,2
	20,11	45,3
	21,20	36,6
15	21,86	100,0
	23,07	15,3
	23,59	30,1
	24,50	42,5
	26,66	14,5
20	27,16	22,7
	27,45	10,6
	28,34	13,1
	28,71	15,6
	29,66	29,5
25	30,56	14,5
	34,87	13,5

20. An ethyl formate solvate of quinapril hydrochloride according to claim 19, characterised in that its infrared spectrum presents the following peaks:

IR (KBr) ( $\nu$ ,  $\text{cm}^{-1}$ ) : 3520, 3028, 3001, 2979, 2935, 2857, 1744, 1718, 1648, 1546, 1495, 1462, 1454, 1432, 1388, 1260, 1199, 756.

21. A methyl acetate solvate of quinapril

hydrochloride characterised in that its X-ray diffraction pattern presents the following characteristics:

X-Ray Diffraction (powder)

	<u>Angle (2<math>\theta</math>)</u>	<u>Relative intensity (%)</u>
5		
	<u>Methyl acetate solvate of quinapril hydrochloride</u>	
	8,86	26,0
	10,95	26,0
10	11,79	19,2
	13,73	45,9
	16,18	18,2
	16,57	37,7
	16,87	60,4
15	18,76	18,6
	18,93	18,6
	19,59	33,2
	20,16	81,9
	20,91	19,2
20	21,56	30,7
	21,93	100,0
	22,18	28,7
	23,22	14,6
	23,65	35,4
25	24,62	52,6
	27,17	34,0
	28,51	16,6
	28,93	22,9
	30,69	21,6
30	30,85	14,0

22. A methyl acetate solvate of quinapril hydrochloride according to claim 21, characterised in that its infrared spectrum presents the following peaks:

IR (KBr) ( $\nu$ ,  $\text{cm}^{-1}$ ) : 3500, 3084, 3003, 2860, 1746, 1735, 1706, 1648, 1545, 1495, 1455, 1259, 1196, 755.