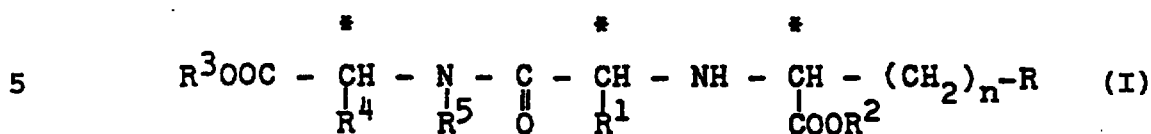


The invention relates to a method of treating cardiac insufficiency by peroral or parenteral use of angiotensin-converting enzyme inhibitors of the formula I



in which

n is 1 or 2,

R is phenyl,

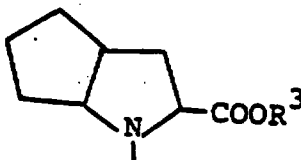
10 R¹ is hydrogen or (C₁-C₆)-alkyl, which can, where appropriate, be substituted by amino,

R² and R³ are identical or different and are hydrogen or ethyl, and

15 R⁴ and R⁵, together with the atoms carrying them, form an octahydrocyclopenta[b]pyrrole system with 5 to 15 carbon atoms.

In the case of the compounds which possess several chiral atoms, all the possible diastereomers, as racemates or enantiomers, or mixtures of various diastereomers, are suitable.

20 The possible cyclic amino acid esters have the following structural formulae:



It is particularly preferred to use compounds of the formula I in which n is 2, R = phenyl, R¹ = methyl.

25 The following compounds can be particularly advantageously used by the method according to the invention:

N-(1-S-carbethoxy-3-phenyl-propyl)-S-alanyl-cis-endo-2-azabicyclo[3.3.0]octane-3-S-carboxylic acid

N-(1-S-carbethoxy-3-phenyl-propyl)-S-lysyl-cis-endo-2-azabicyclo[3.3.0]octane-3-S-carboxylic acid

30 N-(1-S-carbethoxy-butyl)-S-alanyl-cis-endo-2-azabicyclo[3.3.0]octane-3-S-carboxylic acid

N-(1-S-carbethoxy-3-phenyl-propyl)-S-lysyl-(2S,3aR,6aS)-
octahydrocyclopenta[b]pyrrole-2-carboxylic acid

N-(1-S-carbethoxy-3-phenyl-propyl)-S-alanyl-2-
(2S,3aR,6aS)-octahydrocyclopenta[b]pyrrole-2-carboxylic
5 acid.

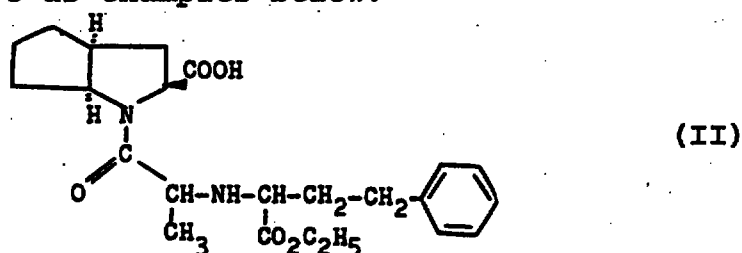
These compounds can be prepared, for example, by the
process described in German Patent Application
P 33 33 455.2, by converting the tert.-butyl or benzyl
radicals described in the Application into the mono-
10 carboxylic acid derivatives in a known manner by acid or
alkaline hydrolysis or by hydrogenolysis catalyzed by a
noble metal. The N'-benzyloxycarbonyl protective group of
the lysine derivatives is removed by hydrogenolysis
catalyzed by a noble metal. The abovementioned compounds
15 can easily be converted into the corresponding salts (for
example hydrochlorides, maleates, fumarates and the like)
with physiologically acceptable acids or bases (in the
case of mono- or dicarboxylic acids), and can be used
according to the invention in the form of salts.

20 The compounds of the formula I are inhibitors of
angiotensin-converting enzyme (ACE) or intermediates in
the preparation of such inhibitors and can also be
employed for combating hypertension of various origins.
The compounds of the formula I are known from German
25 Offenlegungsschrift 3,211,397, German Offenlegungsschrift
3,227,055, European Patent Application 46,953, European
Patent Application 79,022, European Patent Application
84,164, European Patent Application 89,637 and European
Patent Application 90,362. They are furthermore the
30 subject of German Patent Applications P 32 42 151.6,
P 32 46 503.3, P 32 46 757.5, P 33 00 774.8 and P 33 24
263.1.

In carrying out the method according to the invention,
the angiotensin-converting enzyme inhibitors described
35 above can be used on mammals, such as monkeys, dogs,
cats, rats, humans and the like. The compounds suitable

for the use according to the invention are advantageously incorporated into pharmaceutical products in the usual manner. They can be converted into the customary administration forms, such as capsules, tablets, coated tablets, solutions, ointments and emulsions and also into depot form. Where appropriate, the active compound can also be in microencapsulated form. The products can contain acceptable organic or inorganic concomitant substances, for example granulating substances, adhesives and binders, lubricants, suspending agents, solvents, antibacterial agents, wetting agents and preservatives. Oral and parenteral use forms are preferred. The compounds of the formula I can be administered in dosages of 0.1 - 50 mg per dose once to three times daily.

The efficacy of the compounds of the formula I in various forms of cardiac insufficiency can be derived from their action in various test models. The results with N-(1-S-carbethoxy-3-phenyl-propyl)-S-alanyl-cis-endo-2-azabicyclo[3,3,0]octane-3-S-carboxylic acid (formula II) may in each case serve as examples below.



It is known that converting enzyme inhibitors are capable of inhibiting the enzyme not only in the serum but also in various tissues, and especially also in the heart. This inhibition in cardiac tissue reduces the formation of angiotensin II and hence its adverse influences on various parameters of heart action.

Oral treatment of spontaneously hypertensive rats with a single dose of 1 mg/kg significantly inhibits the ACE in the heart for longer than 24 hours. In contrast, with 30 mg/kg of N-(1-carbethoxy-3-phenyl-propyl)-S-alanyl-S-proline (enalapril) perorally, already no further significant inhibition is observed after more than

6 hours. Chronic oral treatment of spontaneously hypertensive rats for two weeks with 1 mg/kg of the compound of the formula II leads to a 55 % inhibition of the ACE in the heart at the end of treatment, whilst with
5 30 mg/kg of enalapril perorally no inhibition is observed, under otherwise identical conditions. In addition, the systemic lowering of blood pressure caused by compounds of the formula I leads to a reduction in the after-load and hence to relief of the incompetent heart.

10 Postganglionic sympathetic stimulation on the isolated heart leads, via increased catecholamine release, to an increase in heart rate and contractility and to a decrease in coronary blood flow. Oral pretreatment with
15 1 mg/kg perorally of the compound of the formula I in rabbits significantly reduces the influence on heart rate and coronary blood flow, but leaves the contractility unaffected. These effects act together to protect the incompetent heart.

20 Angiotensin I decreases whilst bradykinin increases the coronary blood flow in the isolated heart of rabbits, guinea-pigs and rats. Oral pretreatment of the animals with 1 mg/kg of the compound of the formula I perorally significantly reduces the effect of angiotensin I and increases the action of bradykinin. The same effect can
25 only be achieved with 30 mg/kg of enalapril.

The following examples show the use forms for the treatment of cardiac insufficiency by the method according to the invention. The compounds of the formula I can be converted into the corresponding use forms
30 analogously to the examples.

Example 1

Preparation of the agent used according to the invention for oral administration in the treatment of cardiac insufficiency.

1,000 tablets each containing 10 mg of 1-N-(1-S-carbethoxy-3-phenyl-propyl)-S-alanyl-1S,3S,5S-2-azabicyclo[3.3.0]octane-3-carboxylic acid are prepared with the following auxiliaries:

5	N-(1-S-carbethoxy-3-phenyl-propyl)-S-alanyl-1S,3S,5S-2-azabicyclo[3.3.0]octane-3-carboxylic acid	10 g
	cornstarch	140 g
	gelatin	7.5 g
10	microcrystalline cellulose	2.5 g
	magnesium stearate	2.5 g

The N-(1-S-carbethoxy-3-phenyl-propyl)-S-alanyl-1S,3S,5S-2-azabicyclo[3.3.0]octane-3-carboxylic acid and cornstarch are mixed with an aqueous gelatin solution.

15 The mixture is dried and ground to granules. Microcrystalline cellulose and magnesium stearate are mixed with the granules. The granules formed are compressed to form 1,000 tablets, each tablet containing 10 mg of the ACE inhibitor.

20 These tablets can be used for the treatment of cardiac insufficiency.

Example 2

Gelatin capsules each containing 10 mg of N-(1-S-carbethoxy-3-phenyl-propyl)-S-alanyl-1S,3S,5S-2-azabicyclo-

25 [3.3.0]octane-3-carboxylic acid are filled with the following mixture:

	N-(1-S-carbethoxy-3-phenyl-propyl)-S-alanyl-1S,3S,5S-2-azabicyclo[3.3.0]octane-3-carboxylic acid	10 mg
30	magnesium stearate	1 mg
	lactose	214 mg

These capsules can be used for the treatment of cardiac insufficiency.

Example 3

The preparation of an injection solution for the treatment of cardiac insufficiency is described below:

N-(1-S-carboxy-3-phenyl-propyl)-S-alanyl-

5	1S,3S,5S-2-azabicyclo[3.3.0]octane-3-carboxylic acid	250 mg
	methylparaben	5 g
	propylparaben	1 g
	sodium chloride	25 g
10	water for injection purposes	5 l

The N-(1-S-carboxy-3-phenyl-propyl)-S-alanyl-1S,3S,5S-2-azabicyclo[3.3.0]octane-3-carboxylic acid, preservatives and sodium chloride are dissolved in 3 l of water for injection purposes and the solution is made up to 5 l with water for injection purposes. The solution is sterile-filtered and filled aseptically into pre-sterilized bottles, which are closed with sterilized rubber caps. Each bottle contains 5 ml of solution.

Example 4

- 20 Tablets which can be used for the treatment of cardiac insufficiency are prepared as described in Example 1, with the difference that instead of N-(1-S-carbethoxy-3-phenyl-propyl)-S-alanyl-1S,3S,5S-2-azabicyclo[3.3.0]octane-3S-carboxylic acid,
- 25 N-(1-S-carboxy-3-phenyl-propyl)-S-alanyl-1S,3S,5S-2-azabicyclo[3.3.0]octane-3-carboxylic acid or N-(1-S-carboxy-3-phenyl-propyl)-S-lysyl-1S,3S,5S-2-azabicyclo-[3.3.0]octane-3-carboxylic acid is used.

Example 5

- 30 An injection solution is prepared analogously to the instructions given in Example 3, with the difference that instead of N-(1-S-carbethoxy-3-phenyl-propyl)-S-alanyl-1S,3S,5S-2-azabicyclo[3.3.0]octane-3-carboxylic acid,

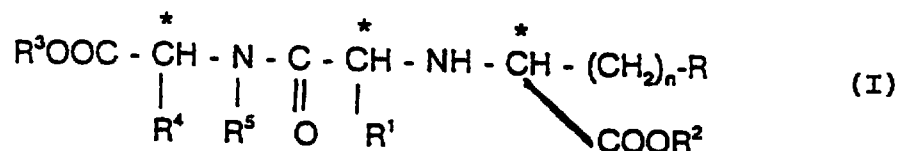
N-(1-S-carboxy-3-phenyl-propyl)-S-alanyl-1S,3S,5S-2-azabicyclo[3.3.0]octane-3-carboxylic acid or

N-(1-carboxy-3-phenyl-propyl)-S-lysyl-1S,3S,5S-2-azabicyclo[3.3.0]octane-3-carboxylic acid is used.



Patent claims

1. The use of angiotensin-converting enzyme inhibitors of the formula I



5 in which

n is 1 or 2,

R is phenyl,

R² and R³ are identical or different and are hydrogen or ethyl,

10 R¹ is hydrogen or C₁-C₆-alkyl, which can, where appropriate, be substituted by amino, and

R⁴ and R⁵, together with the atoms carrying them, are an octahydrocyclopenta[b]pyrrole system,

or their physiologically tolerated salts

15 in the preparation of a pharmaceutical for treating cardiac insufficiency in mammals.

2. The use as claimed in claim 1, wherein (S,S,S,S,S)-N-(1-carbethoxy-3-phenyl-propyl)alanyl-2-azabicyclo[3.3.0]octane-3-carboxylic acid or its physiologically tolerated salt is employed.

20 3. The use as claimed in claim 1, wherein the angiotensin-converting enzyme inhibitors are employed orally or parenterally.

25 4. The use as claimed in claim 1, wherein the angiotensin-converting enzyme inhibitors are combined with pharmaceutically appropriate vehicles or auxiliary substances for the corresponding use forms.