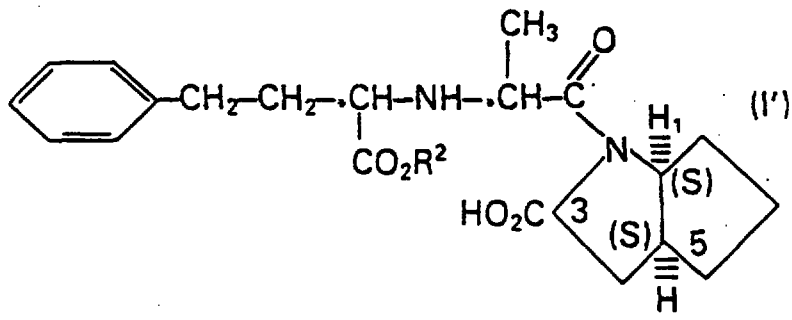
Description 0079022

Substituted acyl derivatives of octahydro-1H-indole-2-carboxylic acid and their use as inhibitors of the angiotensin-converting enzyme (ACE) are known from EP-A2-37,231.

Surprisingly, it has now been found that derivatives of cis,endo-2-azabicyclo-[3.3.0]-octane-3-carboxylic acid are powerful ACE inhibitors.

The invention therefore relates to compounds of the formula I'



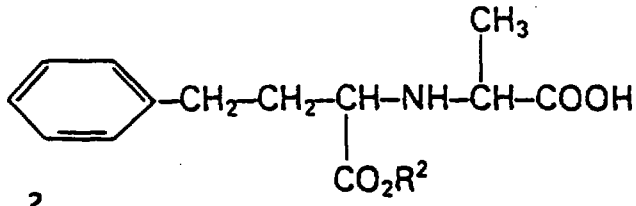
(I')

in which the hydrogen atoms on the bridge-head C atoms 1 and 5 are in the cis-configuration relative to one another and the carboxyl groups (sic) on C atom 3 is orientated in the endo-position relative to the bicyclic ring system (i.e., it faces the cyclopentane ring), and the chirality centers on both C atoms labeled with a star (*) in the chain and on C atom 3 of the bicycle have the S-configuration, and in which R^2 = hydrogen, methyl, ethyl or benzyl, and the physiologically acceptable salts thereof.

Preferred compounds are:
N-(1-S-carbethoxy-3-phenyl-propyl)-S-alanyl-cis,endo-2-azabicyclo-[3.3.0]-octane-3-S-carboxylic acid and N-(1-S-carboxy-3-phenyl-propyl)-S-alanylcis, endo-2-azabicyclo-[3.3.0]-octane-3-S-carboxylic acid and in each case the physiologically acceptable salts thereof.

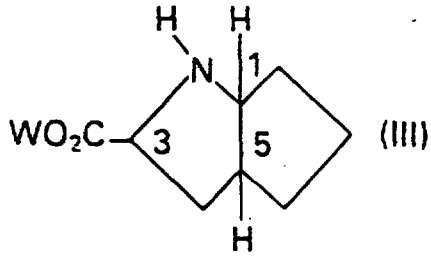
Possible salts are, in particular, the hydrochlorides, maleates and tartrates, and the alkali metal, Ca, Mg and Zn salts.

The invention furthermore relates to a process for the preparation of the compounds of the formula I', which is characterized in that a compound of the formula II'



(II')

in which R^2 has the meaning defined above, with the exception of R^2 = hydrogen, is reacted, according to methods of amide formation known in peptide chemistry, with a compound of the formula III

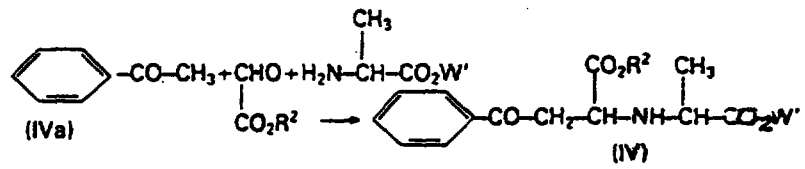


(III)

in which the hydrogen atoms on the bridge-head C atoms 1 and 5 are in the cis-configuration relative to one another and the CO_2W group on C atom 3 is orientated in the endo-position relative to the bicyclic ring system (i.e. it faces the cyclopentane ring), and in which W denotes a carboxyl-esterifying group preferably tert.-butyl or benzyl, and the product is then hydrogenated or treated with an acid or a base, and the compound thus obtained is optionally converted into its physiologically acceptable salt.

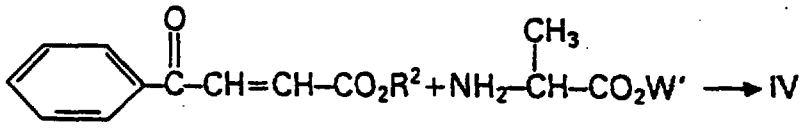
Compounds of the formula II' in which R^2 = CH_3 or C_2H_5 are known for example from EP-A2-37,231, and are accessible in various ways. The benzyl esters (R^2 = benzyl) can be prepared analogously.

It has furthermore been found that the Mannich reaction of acetophenone of the formula IVa with glyoxylic acid esters and alanine esters leads to compounds of the formula IV. In formula IV, W' denotes a radical which can be split off by basic or acidic hydrogenolysis, preferably benzyl or tert.-butyl, and R^2 has the above-defined meanings. However, in the case of the benzyl ester (W' = benzyl), R^2 may not be benzyl. Hydrogenolysis of these compounds with Pd gives the compounds of the formula II'



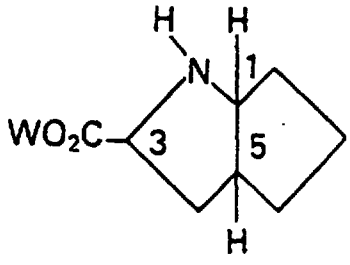
(IVa) (IV)

Compounds of the formula IV can also be obtained in high yields by Michael addition of corresponding keto-acrylic acid esters with alanine esters. Ester cleavage leads to the same products as the Mannich reaction.



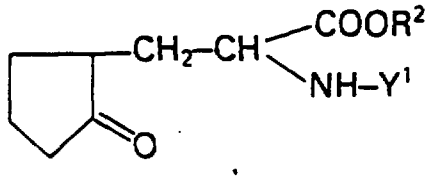
When L-alanine esters are used, the diastereomers with the preferred S,S-configuration are predominantly formed, and can be isolated by crystallization or by chromatographic separation of the esters II' on silica gel.

The invention furthermore relates to compounds of the formula III



III)

in which the hydrogen atoms on the bridge-head C atoms 1 and 5 are in the cis-configuration relative to one another and the CO_2W group on C atom 3 is orientated in the endo-position relative to the bicyclic ring system (i.e. it faces the cyclopentane ring), and in which W denotes hydrogen or a carboxyl-esterifying group preferably tert.-butyl or benzyl, which can be split off by hydrogenation or treatment with an acid or a base, and the salts thereof, and to a process for the preparation of these compounds, which is characterized in that the compound which is obtained by cyclization of a compound of the formula X

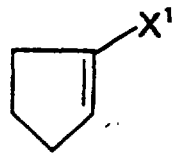


(X)

in which R^2 denotes an ester group which can be split off by an acid and Y^1 denotes an acyl radical, under acidic conditions, is converted into compounds of the formula III

in which W denotes hydrogen, by catalytic hydrogenation in the presence of noble metal catalysts or by reduction with complex hydrides, this compound is optionally esterified to give compounds of the formula III in which W has the meanings as above with the exception of hydrogen, and the compounds obtained are optionally converted into their salts.

The starting compounds for the process for preparing compounds of the formula III are obtained by reacting an enamine of the formula VI in which X^1 represents dialkylamine with 2 to 10 carbon atoms or a radical of the formula VII, in which m and o denote an integer from 1 to 3, (m + o) $\geq$3 and A denotes CH_2, NH, O or S,



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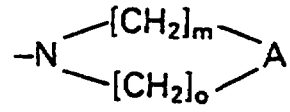
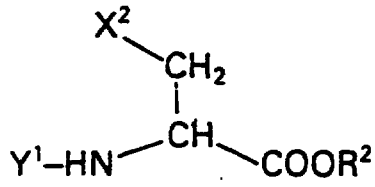


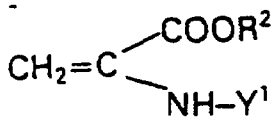
(VII)

with an N-acylated β-halogeno-α-amino-carboxylic acid ester of the formula VIII, in which X_2 (sic) represents a nucleofugic group, Y^1 represents alkanoyl with 1 to 5 carbon atoms, aroyl with ... (sic) to 9 carbon atoms or other protective groups which are customary in peptide chemistry and can be split off under acid conditions, and R^2 represents alkyl with 1 to 5 carbon atoms or aralkyl with 7 to 9 carbon atoms



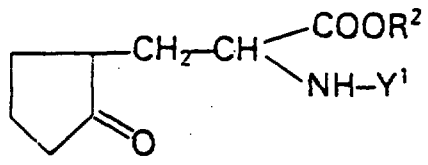
(VIII)

or with an acrylic acid ester of the formula IX, in which Y^1 and R^2 have the above meanings,



(IX)

to give a compound of the formula X, in which R^2 and Y^1 have the above meaning,



(X)

and cyclizing this compound with the aid of strong acids, and acylamide and ester cleavage.

The bicyclic compounds of the formula III have the cis,endo-configuration, i.e. the $-CO_2W$ group faces the cyclopentane ring. They are preferably all in the S-configuration. All the other 2-azabicyclo-[3.3.0]-octane-3-carboxylic acid derivatives mentioned in the present invention are also in the cis,endo-condifuration (sic).

Examples of preferred enamines are pyrrolidino-cyclopentene and morpholinocyclopentene. Cyclization of the alkylation products of the formula X is preferably carried out with aqueous hydrochloric acid. The compounds of the formula III (in which W = H) can be esterified by the methods customary for amino acids (cf. for example, Houben-Weyl, Methoden der organischen Chemie (Methods of Organic Chemistry), Volume VIII (1952), for example with thionyl chloride/benzyl alcohol or isobutylene/sulfuric acid. They give, after appropriate working up, compounds of the formula III in the form of the free base or of a salt.

The new compounds of the formula I' have a long-lasting, intense hypotensive action. They are powerful inhibitors of the angiotensin-converting enzyme (ACE inhibitors) and can be used for controlling high blood pressure of various origins. They can also be combined with other hypotensive, vasodilating or diuretic compounds. Typical representatives of these classes of active compounds are described in, for example, Erhardt-Ruschig, Arzneimittel (Medicaments), 2nd edition, Weinheim, 1972.

They can be administered intravenously, subcutaneously or perorally.

The dosage for oral administration is 1 - 100 mg per individual dose. In severe cases, it can also be increased, since no toxic properties have as yet been observed. It is also possible to reduce the dose, which is appropriate, above all, if diuretic agents are administered at the same time.

The compounds according to the invention can be administered orally or parenterally in an appropriate pharmaceutical formulation. For an oral use form, the active compounds are mixed with the additives customary for this form, such as excipients, stabilizers or inert diluents, and the mixture is converted to suitable administration forms, such as tablets, dragees, push-fit capsules, aqueous alcoholic or oily suspensions or aqueous alcoholic or oily solutions, by customary methods. Examples of inert carriers which can be used are gum arabic, magnesium carbonate, potassium phosphate, lactose, glucose and starch, especially maize starch. The formulation may be prepared in the form of either dry or moist granules. Examples of possible oily excipients or solvents are vegetable and animal oils, such as sunflower oil or cod-liver oil.

For subcutaneous or intravenous administration, the active compounds or physiologically acceptable salts thereof are dissolved, suspended or emulsified, if desired with the substances customary for this purpose, such as solubilizing agents, emulsifiers or other auxiliaries. Examples of possible solvents for the new active compounds and the corresponding physiologically acceptable salts are: water, physiological sodium chloride solutions or alcohols, for example ethanol, propanediol or glycerol, and in addition also sugar solutions, such as glucose or mannitol solutions, or a mixture of the various solvents mentioned.

The exceptionally powerful activity of the compounds according to formula I' - even when administered orally - is demonstrated by the following pharmacological

data.

Intravenous administration to anesthetized rats, 50% inhibition of the pressor reaction induced by 310 ng of angiotensin I, 30 minutes after administration of the dose ... ED_{50}

R^2	ED_{50} (µg/kg)
C_2H_5	8.3
H	2.7

R^2	ED_{50} (µg/kg)
C_2H_5	50
H	600

On oral administration to conscious rats, a dosage of 1 mg/kg of, for example, the compound of the formula I' in which R^2 = ethyl exhibits over 90% inhibition, lasting over 6 hours, of the pressor reaction triggered off by intravenous administration of angiotensin I.

The examples which follow are intended to illustrate the procedures according to the invention, without restricting the invention to the substances mentioned here as representatives.

Example I

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

(1) Methyl 2-acetylamino-3-(2-oxo-cyclopentyl)-propionate

269 g of methyl 3-chloro-2-acetylamino-propionate and 257 g of cyclopentenopyrrolidine in 1.5 liters of DMF were kept at room temperature for 24 hours. The mixture was concentrated in vacuo, the residue was taken up in a little water and the aqueous mixture was adjusted to pH 2 with concentrated hydrochloric acid and extracted twice with 4-liter portions of ethyl acetate. On concentration of the organic phase, a light yellow oil remained.

Yield: 290 g.

NMR: 2.02 (s,3H); 3.74 (s,3H); 4.4-4.8 (m,1H) ($CDCl_3$)

Analysis:	C	H	N
calculated	58.1	7.54	6.16
found	58.5	7.2	6.5

(2) cis,endo-2-Azabicyclo-[3.3.0]-octane-3-carboxylic acid hydrochloride

270 g of the acetylamino derivative prepared under (1) were boiled under reflux in 1.5 liters of 2 N hydrochloric acid for 45 minutes. The mixture was concentrated in vacuo, the residue was taken up in glacial acetic acid, 5 g of Pt/C (10% of Pt) were added and hydrogenation was carried out under 5 bar. After filtration, the mixture was concentrated and the residue was crystallized from chloroform/diisopropyl ether.

Melting point: 205 - 209°C,

Yield: 150 g

(3) Benzyl cis,endo-2-azabicyclo-[3.3.0]-octane-3-carboxylate hydrochloride

40 g of the carboxylic acid prepared under (2) were added to an ice-cold mixture of 390 g of benzyl alcohol and 65 g of thionyl chloride and the mixture was left to stand at room temperature for 24 hours. After concentration in vacuo, 47 g of the benzyl ester were crystallized from chloroform/isopropanol.

Melting point: 175°C (hydrochloride)

(4) Benzyl N-(1-S-carbethoxy-3-phenyl-propyl)-S-alanyl-cis,endo-2-azabicyclo-[3.3.0]-octane-3-S-carboxylate

14 g of the benzyl ester prepared according to (3) were reacted with 6.7 g of HOBt, 13.8 g of N-(1-S-carbethoxy-3-phenyl-propyl)-S-alanine and 10.2 g of dicyclohexylcarbodiimide in 200 ml of dimethylformamide. After the mixture had been stirred for 3 hours at room temperature, the dicyclohexylurea which had precipitated was filtered off with suction, the filtrate was concentrated, the residue was taken up in 1 liter of ethyl acetate and the mixture was extracted by shaking with 3 x 500 ml of 5% strength $NaHCO_3$ solution. The organic phase was concentrated and the residue was chromatographed over a column of 1 kg of silica gel using ethyl acetate/petroleum ether in the ratio 2 : 1. The isomer eluted first was the S,S,S-compound, and concentration of a later eluate gave the S,S,R-compound.

In each case 8.0 g of product were obtained as an

oil.

NMR: of the S,S,S-compound: characteristic signals: 1.20 (d,3H), 1.27 (t,2H), 4.17 (q,3H), 5.13 (s,2H), 7.18 (s,5H) and 7.32 (s,5H) ($CDCl_3$)

Analysis		C	H	N
$C_{30}H_{38}N_2O_5$				
	calculated	71.1	7.56	5.53
	found	70.8	7.8	5.7

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

8.0 g of the S,S,S-benzyl ester from (4) were dissolved in 100 ml of ethanol and were debenzylated hydrogenolytically under normal pressure, with addition of 0.5 g of 10% Pd/C. This reaction could also have been carried out under pressure, together with a shortening of the reaction time. After the calculated amount of hydrogen had been taken up, the catalyst was filtered off and the residue was concentrated in vacuao. The zwitter ion crystallized from ether, in almost quantitative yield:

Melting point: 110 - 112°C (decomposition)

A hydrochloride (decomposition from 120°C) can be obtained by addition of an equivalent amount of hydrochloric acid, or a zinc complex salt which is particularly stable to heat (decomposition above 160°C) can be obtained by addition of aqueous zinc salts to a concentrated methanolic solution of the title compound.

Analysis		C	H	N
$C_{23}H_{32}N_2O_5$				
	calculated	66.3	7.7	6.73
	found	66.1	7.8	6.6

The NMR and mass spectra obtained are in agreement with the given structure.

$[\alpha]_d$ = + 15.6° (c = 1, methanol).

Example II

(1) tert.-Butyl cis,endo-2-azabicyclo-[3.3.0]-octane-3-carboxylate

25 g of azabicyclo-[3.3.0]-octane-carboxylic acid hydrochloride from Example I (2) were reacted with 250 ml of isobutylene and 25 ml of concentrated sulfuric acid in

250 ml of dioxane. After 14 hours at room temperature, the mixture was rendered alkaline with sodium hydroxide solution and concentrated in vacuo, 100 ml of water were added and the ester was extracted with ether. Evaporation of the ether gave 15 g of a colorless oil.

Analysis		C	H	N
$C_{12}H_{21}NO_2$	calculated:	68.2	10.2	6.63
	found:	67.9	10.1	6.3

Example III

General method: Hydrolysis of esters to prepare compounds of the formula I' in which R^2 = H.

10 g of the corresponding ethyl or benzyl ester of the formula I' were dissolved in 200 ml of dimethoxyethane. One drop of a dilute indicator solution, for example bromothymol blue, was added, and an equivalent amount of 4 N KOH (aqueous) was added in the course of 5 minutes, while stirring vigorously, so that at the end of the reaction the indicator indicated a pH value of 9 - 10. The mixture was then adjusted to pH 4 with hydrochloric acid and concentrated to dryness in vacuo, the residue was taken up in 250 ml of ethyl acetate and the mixture was filtered. On concentration of the ethyl acetate, the dicarboxylic acids precipitated as solid, crystalline or amorphous compounds.

The yields were between 80 and 95%.

Example IIIa

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

1 g of N-(1-S-carbethoxy-3-phenyl-propyl)-S-alanyl-2-azabicyclo-[3.3.0]-octane-S-S-carboxylic acid from Example I (5) was hydrolyzed (1 hour) and the mixture was worked up, as described under Example III.

Yield: 0.85 g

m/e: 388

Example IV

N-(1-S-Carbethoxy-3-oxo-3-phenyl-propyl)-S-alanine benzyl ester

65.7 g of ethyl 3-phenyl-3-oxo-1-carboxylate (ethyl benzoylacrylate) were dissolved in 225 ml of

ethanol, and 1 ml of triethylamine was added. A solution of 70 g of S-alanine benzyl ester in 90 ml of ethanol was rapidly added to this solution dropwise at room temperature. The mixture was stirred at room temperature for 2 hours and the solution was then cooled. The S,S-isomer crystallized out.

Yield 94.3 g

Melting point: 83 - 74°C

$[\alpha]_D^{20}$ = + 17.8° (c = 1, CH_3OH)

Example V

N-(1-S-Carbethoxy-3-oxo-3-phenyl-propyl)-S-alanine

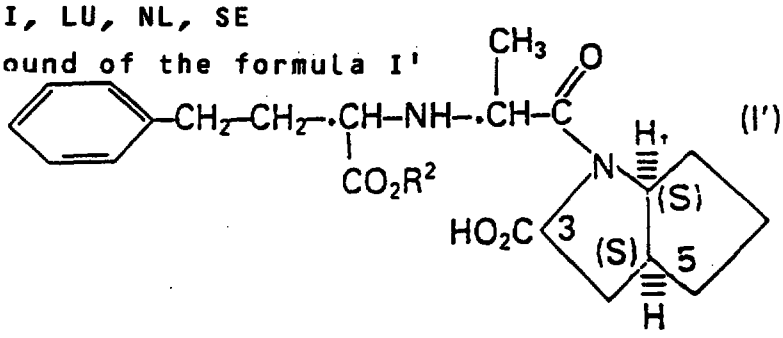
0.5 g of the compound from Example IV was dissolved in 40 ml of ethanol, 0.1 g of 10% Pd/C was added and hydrogenation was carried out at room temperature and under normal pressure.

Yield: 300 mg melting point: 210 - 220°C

^{1}H-NMR (DMSO-d_6): 1.0-1.4 (t,6H); 3.2-5.0 (m,8H); 7.2-8.2 (m,5H)

Patent claims for the contracting states: BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. A compound of the formula I'



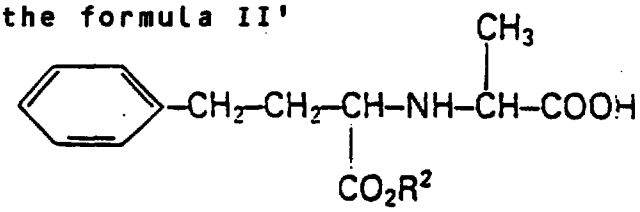
(I')

in which the hydrogen atoms on the bridge-head C atoms 1 and 5 are in the cis-configuration relative to one another and the carboxyl groups [sic] on C atom 3 is orientated in the endo-position relative to the bicyclic ring system (i.e. it faces the cyclopentane ring), and the chirality centers on both C atoms labeled with a star (*) in the chain and on C atom 3 of the bicycle have the S-configuration, and in which R^2 = hydrogen, methyl, ethyl or benzyl, and the physiologically acceptable salts thereof.

2. N-(1-S-Carbethoxy-3-phenyl-propyl)-S-alanyl-cis,endo-2-azabicyclo-[3.3.0]-octane-3-S-carboxylic acid and the physiologically acceptable salts thereof.

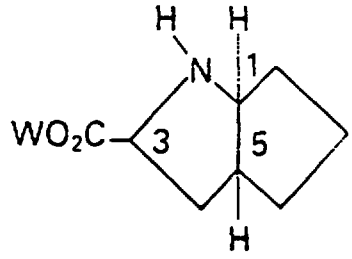
3. N-(1-S-Carboxy-3-phenyl-propyl)-S-alanyl)-cis,endo-2-azabicyclo-[3.3.0]-octane-3-S-carboxylic acid and the physiologically acceptable salts thereof.

4. A process for the preparation of a compound according to any of claims 1 - 3, characterized in that a compound of the formula II'



(II')

in which R^2 has the meaning given in claim 1, with the exception of R^2 = hydrogen, is reacted with a compound of the formula III



(III)

in which the hydrogen atoms on the bridge-head C atoms 1

and 5 are in the cis-configuration relative to one another and the CO_2W group on C atom 3 is orientated in the endo-position relative to the bicyclic ring system (i.e. it faces the cyclopentane ring), and in which W denotes a carboxyl-esterifying group, and the product is then hydrogenated or treated with an acid or a base, and the compound thus obtained is optionally converted into its physiologically acceptable salt.

5. A process according to claim 4, characterized in that a compound of the formula III, wherein W denotes tert.-butyl or benzyl, is reacted.

6. A pharmaceutical composition containing a compound according to any of claims 1 to 3 and customary additives.

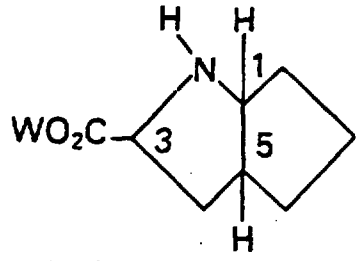
7. A compound according to any of claims 1 to 3 for use as a medicine.

8. A compound according to any of claims 1 to 3 for use as a medicine for the treatment of hypertension.

9. A composition according to claim 6, characterized in that it contains a diuretic agent.

10. A compound according to claim 7 or 8 for the said use in combination with a diuretic agent.

11. A compound of the formula III



(III)

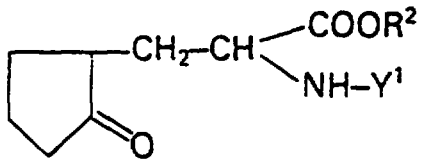
in which the hydrogen atoms on the bridge-head C atoms 1 and 5 are in the cis-configuration relative to one another and the CO_2W group on C atom 3 is orientated in the endo-position relative to the bicyclic ring system (i.e. it faces the cyclopentane ring), and in which W denotes hydrogen or a carboxyl-esterifying group, which can be split off by hydrogenation or treatment with an acid or a base, and the salts thereof.

12. A compound according to claim 11, characterized in that its chirality centers all have the S-configuration.

13. A compound according to claim 11 or 12, characterized in that W denotes hydrogen, tert.-butyl or benzyl.

* C L M S *

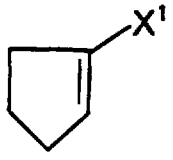
14. A process for the preparation of a compound of the formula III according to claim 11, characterized in that the compound which is obtained by cyclization of a compound of the formula X



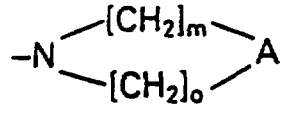
(X)

in which R^2 denotes an ester group which can be split off by an acid and Y^1 denotes an acyl radical, under acidic conditions, the compound obtained is converted into a compound of the formula III in which W denotes hydrogen, by catalytic hydrogenation in the presence of noble metal catalysts or by reduction with complex hydrides, this compound is optionally esterified to give compounds of the formula III in which W has the meanings as in claim 11 with the exception of hydrogen, and the compounds obtained are optionally converted into their salts.

15. A process according to claim 14, characterized in that the starting compound for the process for preparing compounds of the formula III is obtained by reacting an enamine of the formula VI in which X^1 represents dialkylamino with 2 to 10 carbon atoms or a radical of the formula VII, in which m and o denote an integer from 1 to 3, $(m+o) \geq 3$ and A denotes CH_2, NH, O or S,



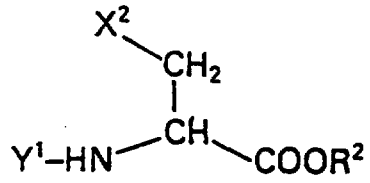
(VI)



(VII)

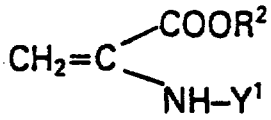
with an N-acylated β-halogeno-α-amino-carboxylic acid ester of the formula VIII, in which X^2 represents a nucleofugic group, Y^1 represents alkanoyl with 1 to 5 carbon atoms, aroyl with 7 to 9 carbon atoms or other protective groups which are customary in peptide chemistry and can be split off under acid conditions, R^2 represents alkyl with 1 to 5 carbon atoms or aralkyl with 7 to 9

carbon atoms



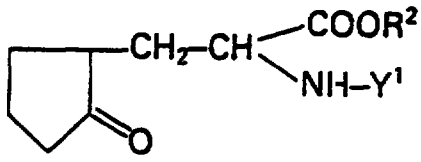
(VIII)

or with an acrylic acid ester of the formula IX, in which Y^1 and R^2 have the above meaning



(IX)

to give a compound of the formula X, in which R^2 and Y^1 have the above meaning



(X)

and cyclizing this compound with the aid of strong acids, with acylamide and ester cleavage.

* C L M S *

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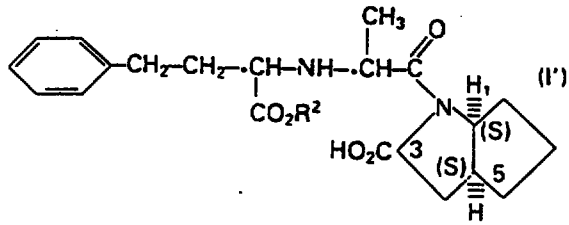
As printed.

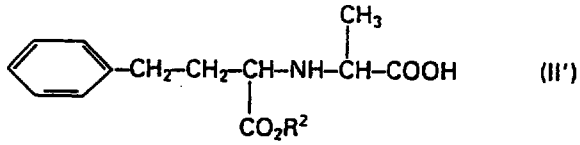
Patentansprüche für den Vertragsstaat AT

1. Verfahren zur Herstellung einer Verbindung der Formel I'



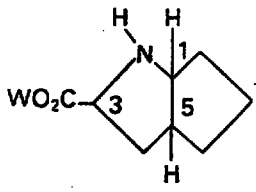
(I')

in der die Wasserstoffatome an den Brückenkopf-C-Atomen 1 und 5 zueinander cis-konfiguriert sind, die Carboxygruppen am C-Atom 3 endoständig zum bicyclischen Ringsystem orientiert (d. h. dem Cyclopentanring zugewandt) ist, und die Chiralitätszentren an den mit einem Stern (*) markierten beiden C-Atomen der Kette und am C-Atom 3 des Bicyclus in der S-Konfiguration vorliegen und in der R^2 = Wasserstoff, Methyl, Ethyl oder Benzyl bedeutet sowie deren physiologisch unbedenklichen Salze, dadurch gekennzeichnet, dass man eine Verbindung der Formel II'



(II')

in der R^2 die oben definierte Bedeutung mit Ausnahme von R^2 = Wasserstoff hat, mit einer Verbindung der Formel III



(III)

in der die Wasserstoffatome an den Brückenkopf-C-Atomen 1 und 5 zueinander cis-konfiguriert sind und die CO_2W-Gruppe am C-Atom 3 endoständig zum bicyclischen Ringsystem orientiert (d. h. dem Cyclopentanring zugewandt) ist und in der W eine Carboxy veresternde Gruppe bedeutet, umsetzt und anschliessend das Produkt hydriert oder mit einer Säure oder einer Base behandelt und die erhaltene Verbindung gegebenenfalls in ihr physiologisch verträgliches Salz überführt.

2. Verfahren gemäss Anspruch 1, dadurch gekennzeichnet, dass N-(1-S-Carbethoxy-3-phenylpropyl)-S-alanyl-cis, endo-2-azabicyclo-[3.3.0]-octan-3-S-carbonsäure oder deren physiologisch verträgliches Salz hergestellt wird.

3. Verfahren gemäss Anspruch 1, dadurch gekennzeichnet, dass N-(1-S-Carboxy-3-phenyl-propyl)-S-alanyl-cis, endo-2-azabicyclo-[3.3.0]-octan-3-S-carbonsäure oder deren physiologisch verträgliches Salz hergestellt wird.

4. Verfahren gemäss einem der Ansprüche 1 bis 3, dadurch gekennzeichnet, dass eine Verbindung der Formel III umgesetzt wird, worin W tert. Butyl oder Benzyl bedeutet.

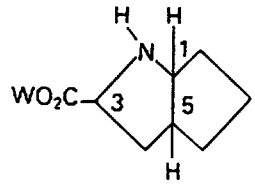
5. Verfahren zur Herstellung eines pharmazeutischen Mittels, enthaltend eine Verbindung der Formel I' gemäss einem der Ansprüche 1 bis 3, dadurch gekennzeichnet, dass man diese zusasmmen mit den üblichen Zusätzen in eine geeignete Darreichungsform bringt.

6. Verfahren gemäss Anspruch 1 zur Herstellung einer Verbindung der Formel I' zur Anwendung als Heilmittel.

7. Verfahren gemäss Anspruch 1 zur Herstellung einer Verbindung der Formel I' zur Anwendung bei der Behandlung des Bluthochdrucks.

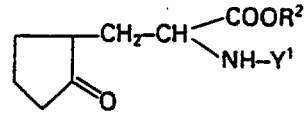
8. Verfahren gemäss Anspruch 5, dadurch gekennzeichnet, dass man ein Diuretikum zusetzt.

9. Verfahren zur Herstellung einer Verbindung der Formel III



(III)

in der die Wasserstoffatome an den Brückenkopf-C-Atomen 1 und 5 zueinander cis-konfiguriert sind und die CO_2W-Gruppe am C-Atom 3 endoständig zum bicyclischen Ringsystem orientiert (d. h. dem Cyclopentanring zugewandt) ist und in der W Wasserstoff oder eine Carboxy veresternde Gruppe, die durch Hydrieren oder durch Behandeln mit einer Säure oder Base abspaltbar ist, bedeutet sowie deren Salze, dadurch gekennzeichnet, dass man jene Verbindung, die erhalten wird, indem man eine Verbindung der Formel X



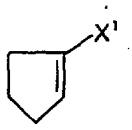
(X)

in welcher R^2 eine sauer abspaltbare Estergruppe und Y^1 einen Acylrest bedeuten, unter sauren Bedingungen cyclisiert, durch katalytische Hydrierung in Gegenwart von Edelmetallkatalysatoren oder durch Reduktion mit komplexen Hydriden in eine Verbindung der Formel III, in welcher W für Wasserstoff steht, überführt, diese gegebenenfalls zu Verbindungen der Formel III, in welcher W nicht Wasserstoff bedeutet, verestert und die erhaltenen Verbindungen gegebenenfalls in ihre Salze überführt.

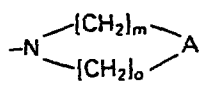
10. Verfahren gemäss Anspruch 9, dadurch gekennzeichnet, dass eine Verbindung der Formel III hergestellt wird, deren Chiralitätszentren alle die S-Konfiguration aufweisen.

11. Verfahren gemäss Anspruch 9 oder 10, dadurch gekennzeichnet, dass eine Verbindung der Formel III hergestellt wird, in der W Wasserstoff, tert. Butyl oder Benzyl bedeutet.

12. Verfahren gemäss Anspruch 9, dadurch gekennzeichnet, dass die Ausgangsverbindung des Herstellungsverfahrens für Verbindungen der Formel III erhalten wird durch Umsetzung eines Enamins der Formel VI, in welcher X^1 für Dialkylamino mit 2 bis 10 C-Atomen oder für einen Rest der Formel VII, worin m und o eine ganze Zahl von 1 bis 3, (m+o) ≥3 und A CH_2, NH, O oder S bedeuten, steht,

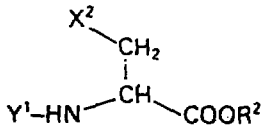


(VI)



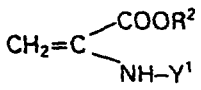
(VII)

mit einem N-acylierten β-Halogen-α-amino-carbonsäureester der Formel VIII, in welcher X^2 für eine nucleofuge Gruppe, Y^1 für Alkanoyl mit 1 bis 5 C-Atomen, Aroyl mit 7 bis 9 C-Atomen oder andere, in der Peptidchemie übliche, sauer abspaltbare Schutzgruppen und R^2 für Alkyl mit 1 bis 5 C-Atomen oder Aralkyl mit 7 bis 9 C-Atomen steht



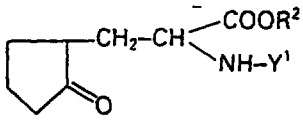
(VIII)

oder mit einem Acrylsäureester der Formel IX, in welcher Y^1 und R^2 vorstehende Bedeutung haben



(IX)

zu einer Verbindung der Formel X, in welcher R^2 und Y^1 vorstehende Bedeutung haben

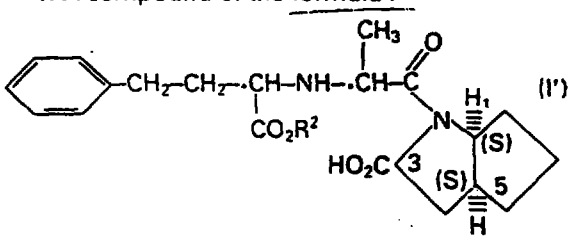


(X)

und Cyclisierung dieser Verbindung mit Hilfe starker Säuren unter Acylamid- und Esterspaltung.

Claims for the contracting States: BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. A compound of the formula I'



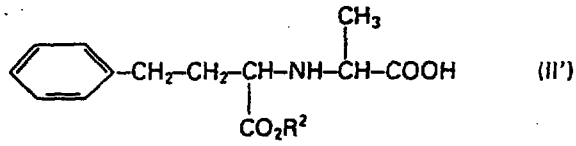
(I')

in which the hydrogen atoms on the bridge-head C atoms 1 and 5 are in the cis-configuration relative to one another and the carboxyl group on C atom 3 is orientated in the endo-position relative to the bicyclic ring system (i.e. it faces the cyclopentane ring), and the chirality centers on both C atoms labeled with a star (*) in the chain and on C atom 3 of the bicycle all have the S-configuration, and in which R^2 denotes hydrogen, methyl, ethy or benzyl, and physiologically acceptable salts thereof.

2. N-(1-S-Carbethoxy-3-phenyl-propyl)-S-alanyl-cis, endo-2-azabicyclo-[3.3.0]-octane-3-S-carboxylic acid and physiologically acceptable salts thereof.

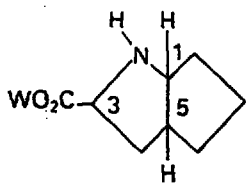
3. N-(1-S-Carboxy-3-phenyl-propyl)-S-alanylcis, endo-2-azabicyclo-[3.3.0]-octane-3-S.carboxylic acid and physiologically acceptable salts thereof.

4. A process for the preparation of a compound according to any of claims 1 to 3, characterized in that a compound of the formula II'



(II')

in which R^2 has the meaning given in claim 1, with the exception of R^2 = hydrogen, is reacted with a compound of the formula III



(III)

in which the hydrogen atoms on the bridge-head C atoms 1 and 5 are in the cis-configuration relative to one another and the CO_2W group on C atom 3 is orientated in the endo-position relative to the bicyclic ring system (i. e. it faces the cyclopentane ring), and in which W denotes a carboxyl-esterifying group, and the product is hydrogenated or treated with an acid or a base, and the compound thus obtained is optionally converted into its physiologically acceptable salt.

5. A process according to claim 4, characterized in that a compound of the formula III, wherein W denotes tert.-butyl or benzyl, is reacted.

6. A pharmaceutical composition containing a compound according to any of claims 1 to 3 and customary additives.

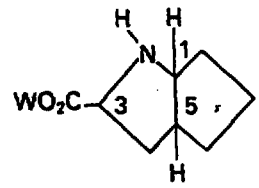
7. A compound according to any of claims 1 to 3 for the use as a medicine.

8. A compound according to any of claims 1 to 3 for the use as a medicine for the treatment of hypertension.

9. A composition according to claim 6, characterized in that it contains a diuretic agent.

10. A compound according to claim 7 or 8 for the said use in combination with a diuretic agent.

11. A compound of the formula III



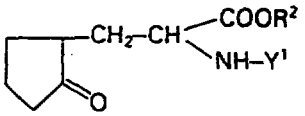
(III)

in which the hydrogen atoms on the bridge-head C atoms 1 and 5 are in the cis-configuration relative to one another and the CO_2W group on C atom 3 is orientated in the endo-position relative to the bicyclic ring system (i. e. it faces the cyclopentane ring), and in which W denotes hydrogen or a carboxyl-esterifying group, which can be cleaved by hydrogenation or treatment with an acid or a base, and the salts thereof.

12. A compound according to claim 11, characterized in that its chirality centers all have the S-configuration.

13. A compound according to claim 11 or 12, characterized in that W denotes hydrogen, tert.-butyl or benzyl.

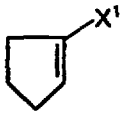
14. A process for the preparation of a compound of the formula III according to claim 11, characterized in that the compound with is obtained by cyclization of a compound of the formula X



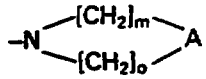
(X)

in which R^4 denotes an ester group which can be cleaved by an acid and Y^1 denotes an acyl radical, under acidic conditions, the compound obtained is converted into a compound of the formula III in which W denotes hydrogen, by catalytic hydrogenation in the presence of nobel metal catalysts or by reduction with complex hydrides, this compound is optionally esterified to give compounds of the formula III in which W has the meanings as in claim 11 with the exception of hydrogen, and the compounds obtained are optionally converted into their salts.

15. A process according to claim 14, characterized in that the starting compounds for the process for preparing compounds of the formula III are obtained by reacting an enamine of the formula VI in which X^1 represents dialkylamino with 2 to 10 carbon atoms or a radical of the formula VII, in which m and o denote integers from 1 to 3, (m+o) ≥3 and A denotes CH_2, NH, O or S,

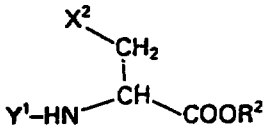


(VI)



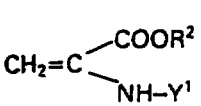
(VII)

with an N-acylated β-halogeno-α-amino-carboxylicacidester for the formula VIII, in which X^2 represents a nucleofugic group, Y^1 represents alkanoyl with 1 to 5 carbon atoms, aroyl with 7 to 9 carbon atoms or another protective group which is customary in peptide chemistry and can be split off under acid conditions, and R^2 represents alkyl with 1 to 5 carbon atoms or aralkyl with 7 to 9 carbon atoms,



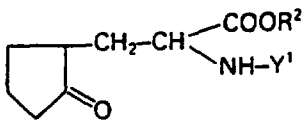
(VIII)

or with an acrylic acid ester of the formula IX, in which Y^1 and R^2 have the above meanings



(IX)

to give a compound of the formula X, in which R^2 and Y^1 have the above meanings,

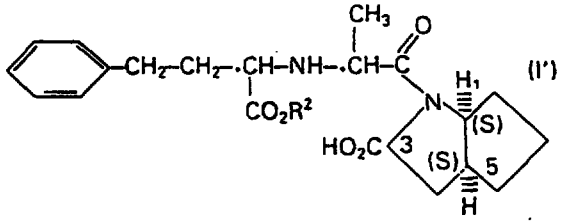


(X)

and cyclizing this compound with the aid of a strong acid, with acylamide and ester cleavage.

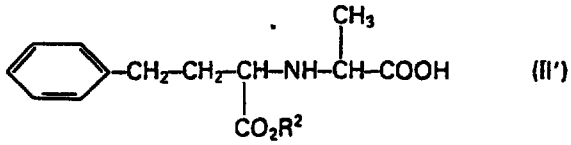
Claims for the contracting State: AT

1. A process for the preparation of a compound of the formula I'



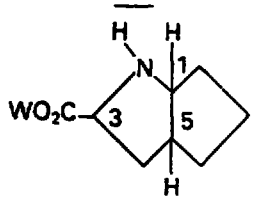
(I')

in which the hydrogen atoms on the bridge-head C atoms 1 and 5 are in the cis-configuration relative to one another and the carboxyl group on C atom 3 is orientated in the endo-position relative to the bicyclic ring system (i.e. it faces the cyclopentane ring), and the chirality centers on both C atoms labeled with a star (*) in the chain and on C atom 3 of the bicycle all have the S-configuration, and in which R^2 denotes hydrogen, methyl, ethy or benzyl, and physiologically acceptable salts thereof, characterized in that a compound of the formula II'



(II')

in which R^2 has the meaning given above, with the exception of R^2 = hydrogen, ist reacted with a compound of the formula III



(III)

in which the hydrogen atoms on the bridge-head C atoms 1 and 5 are in the cis-configuration relative to one another and the CO_2W group on C atom 3 is orientated in the endo-position relative to the bicyclic ring system (i. e. it faces the cyclopentane ring), and in which W denotes a carboxyl-esterifying group, and then the product is hydrogenated or treated with an acid or a base, and the compound thus obtained is optionally converted into its physiologically acceptable salt.

2. A process according to claim 1, characterized in that N-(1-S-carbethoxy-3-phenyl-propyl)-S-alanyl-cis, endo-2-azabicyclo-[3.3.0]-octane-3-S-carboxylic acid or a physiologically acceptable salt thereof is prepared.

3. A process according to claim 1, characterized in that N-(1-S-carboxy-3-phenyl-propyl)-S-alanyl-cis, endo-2-azabicyclo-[3.3.0]-octane-3-S-carboxylic acid or a physiologically acceptable salt thereof is prepared.

4. A process according to any of claims 1 to 3, characterized in that a compound of the formula III, wherein W denotes tert.-butyl or benzyl, is reacted.

* C L M S *

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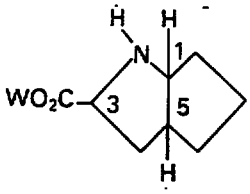
5. A process for the preparation of a pharmaceutical composition containing a compound according to any of claims 1 to 3, characterized in that this compound together with the customary additives is brought into a suitable form for administration.

6. A process according to claim 1 for the preparation of a compound of the formula I' for the use as a medicine.

7. A process according to claim 1 for the preparation of a compound of the formula I' for the use as a medicine for the treatment of hypertension.

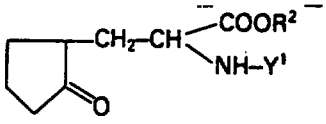
8. process according to claim 5 characterized in that a diuretic agent is added.

9. A process for the preparation of a compound of the formula III



(III)

in which the hydrogen atoms on the bridge-head C atoms 1 and 5 are in the cis-configuration relative to one another and the CO_2W group on C atom 3 is orientated in the endo-position relative to the bicyclic ring system (i. e. it faces the cyclopentane ring), and in which W denotes hydrogen or a carboxyl-esterifying group, which can be cleaved by hydrogenation or treatment with an acid or a base, and the salts thereof, characterized in that the compound which is obtained by cyclization of a compound of the formula X



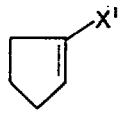
(X)

in which R^2 denotes an ester group which can be cleaved by an acid and Y^1 denotes an acyl radical, under acidic conditions, the compound obtained is converted into a compound of the formula III in which W denotes hydrogen, by catalytic hydrogenation in the presence of nobel metal catalysts or by reduction with complex hydrides, this compound is optionally esterified to give compounds of the formula III in which has the above meanings with the exception of hydrogen, and the compounds obtained are optionally converted into their salts.

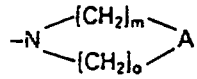
10. A process according to claim 9, characterized in that a compound of the formula III is prepared wherein the chirality centers all have the S-configuration.

11. A process according to claim 9 or 10, characterized in that a compound of the formula III is prepared wherein W denotes hydrogen, tert.-butyl or benzyl.

12. A process according to claim 9, characterized in that the starting compounds for the process for preparing compounds of the formula III are obtained by reacting an enamine of the formula VI in which X^1 represents dialkylamino with 2 to 10 carbon atoms or a radical of the formula VII, in which m and o denote integers from 1 to 3, (m+o) ≥3 and A denotes CH_2, NH, O or S,

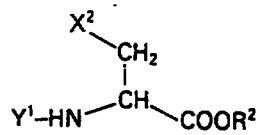


(VI)



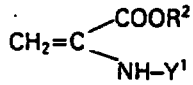
(VII)

with an N-acylated β-halogeno-α-amino-carboxylicacidester for the formula VIII, in which X^2 represents a nucleofugic group, Y^1 represents alkanoyl with 1 to 5 carbon atoms, aroyl with 7 to 9 carbon atoms or another protective group which is customary in peptide chemistry and can be split off under acid conditions, and R^2 represents alkyl with 1 to 5 carbon atoms or aralkyl with 7 to 9 carbon atoms,



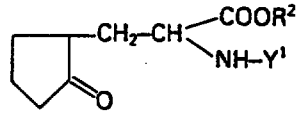
(VIII)

or with an acrylic acid ester of the formula IX, in which Y^1 and R^2 have the above meanings



(IX)

to give a compound of the formula X, in which R^2 and Y^1 have the above meanings,

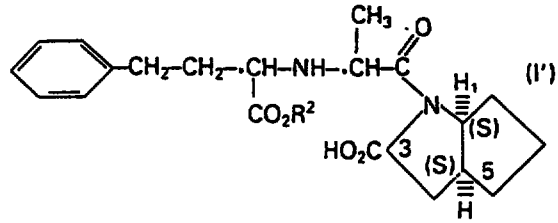


(X)

and cyclizing this compound with the aid of a strong acid, with acylamide and ester cleavage.

Revendications pour les Etats contractants: BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Composé de formule I'



(I')

dans laquelle les atomes d'hydrogène fixés aux atomes de carbone 1 et 5 de la tête de pont ont la configuration cis l'un par rapport à l'autre, le groupe carboxylique fixé à l'atome de C en 3 est orienté en position endo par rapport au système bicyclique (c'est-à-dire qu'il est tourné vers le cycle cyclopentane), et les centres de chiralité sur les deux atomes de C de la chaîne marquée d'un astérisque (*) et sur l'atome de C en 3 du double cycle se trouvent dans la configuration S et dans laquelle R^2 représente l'hydrogène, un radical mé-

* C L M S *

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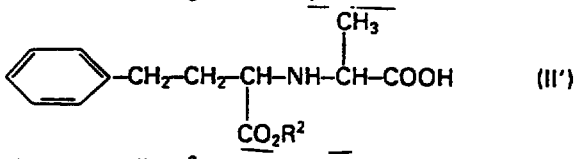
thyle, éthyle ou benzyle, ainsi que leurs sels physiologiquement acceptables.

2. Acide N-(1-S-carbéthoxy-3-phényl-propyl)-S-alanyl-cis, endo-2-azabicyclo-[3.3.0]-octane-3-S-carboxylique ainsi que ses sels physiologiquement acceptables.

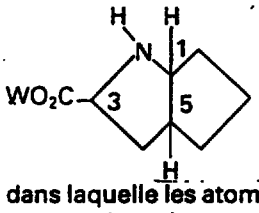
3. Acide N-(1-S-arboxy-3-phényl-propyl)-S-alanyl-cis, endo-2-azabicyclo-[3.3.0]-octane-3-S-carboxylique ainsi que ses sels physiologiquement acceptables.

4. Procédé de préparation d'un composé selon l'une des revendications 1 à 3, caractérisé en ce que l'on fait réagir un composé de formule II'



(II')

dans laquelle R^2 a la signification définie dans la revendication 1, à l'exception de R^2 = hydrogène, avec un composé de formule III



(III)

dans laquelle les atomes d'hydrogène fixés sur les atomes de carbone 1 et 5 de la tête de pont ont la configuration cis l'un par rapport à l'autre et le groupe CO_2W sur l'atome de C en 3 est orienté en position endo par rapport au système bicyclique (c'est-à-dire est tourné vers le cycle cyclopentane) et dans laquelle W désigne un groupe estérifiant le groupe carboxylique et en ce qu'ensuite, on hydrogène le produit ou on le traite par un acide ou par une base et on convertit éventuellement le composé obtenu en l'un de ses sels physiologiquement acceptables.

5. Procédé selon la revendication 4, caractérisé en ce que l'on fait réagir un composé de formule III dans laquelle W désigne le radical tertiobutyle ou benzyle.

6. Médicament contenant un composé selon l'une quelconque des revendications 1 à 3 et les additifs habituels.

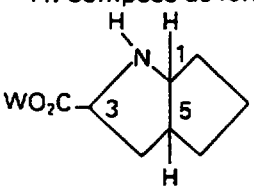
7. Composé selon l'une quelconque des revendications 1 à 3, destiné à l'emploi comme médicament.

8. Composé selon l'une quelconque des revendications 1 à 3, destiné à l'emploi comme médicament dans le traitement de l'hypertension.

9. Médicament selon la revendication 6, caractérisé en ce qu'il contient un diurétique.

10. Composé selon la revendication 7 ou 8, destiné à l'emploi en association avec un diurétique.

11. Composé de formule III



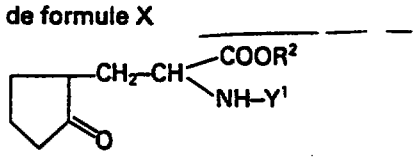
(III)

dans laquelle les atomes d'hydrogène fixés sur les atomes de carbone 1 et 5 de la tête de pont ont la configuration cis l'un par rapport à l'autre et le groupe CO_2W fixé sur l'atome de C en 3 est orienté en position endo par rapport au système bicyclique (c'est-à-dire tourné vers le cycle cyclopentane) et dans laquelle W représente l'hydrogène ou un groupe estérifiant le groupe carboxylique, qui peut être séparé par hydrogénation ou par traitement avec un acide ou avec une base ainsi que ses sels.

12. Composé selon la revendication 11, caractérisé en ce que ses centres de chiralité présentent tous la configuration S.

13. Composé selon la revendication 11 ou 12, caractérisé en ce que W représente l'hydrogène, le radical tertiobutyle ou le radical benzyle.

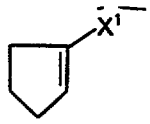
14. Procédé de préparation d'un composé de formule III selon la revendication 11, caractérisé en ce que l'on part du composé obtenu par cyclisation dans des conditions acides d'un composé de formule X



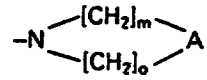
(X)

dans laquelle R^2 représente un groupe ester séparable par action d'un acide et Y^1 représente un radical acyle, que l'on convertit le composé ainsi obtenu, par hydrogénation catalytique, en présence de catalyseurs à base de métaux nobles ou par réduction par des hydrures complexes, en un composé de formule III, dans laquelle W représente l'hydrogène, que l'on estérifie éventuellement celui-ci pour donner des composés de formule III dans laquelle W a les significations indiquées dans la revendication 11 à l'exception de l'hydrogène, et que l'on convertit éventuellement les composés obtenus en leurs sels.

15. Procédé selon la revendication 14, caractérisé en ce que l'on obtient le composé de départ du procédé de préparation des composés de formule III en faisant réagir une énamine de formule VI, dans laquelle X^1 représente un groupe dialkylamino ayant de 2 à 10 atomes de carbone ou un radical de formule VII dans laquelle m et o sont des nombres entiers de 1 à 3, (m+o) ≥3 et A représente CH_2, NH, O ou S,



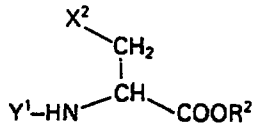
(VI)



(VII)

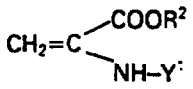
avec un ester N-acylé d'un acide β-halogéno-α-amino-carboxylique de formule VIII, dans laquelle X^2 représente un groupe nucléofuge, Y^1 représente un groupe alcanoyle ayant 1 à 5 atomes de C, un groupe aroyle ayant 7 à 9 atomes de C ou d'autres groupes protecteurs séparables par action d'un acide et usuels dans la chimie des peptides et R^2 représente un groupe alkyle ayant 1 à 5

atomes de carbone ou un groupe aralkyle ayant 7 à 9 atomes de carbone



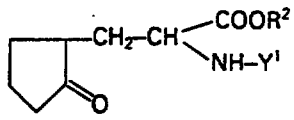
(VIII)

ou avec un ester d'acide acrylique de formule IX, dans laquelle Y^1 et R^2 ont la signification ci-dessus



(IX)

pour donner un composé de formule X, dans laquelle R^2 et Y^1 ont la signification ci-dessus,

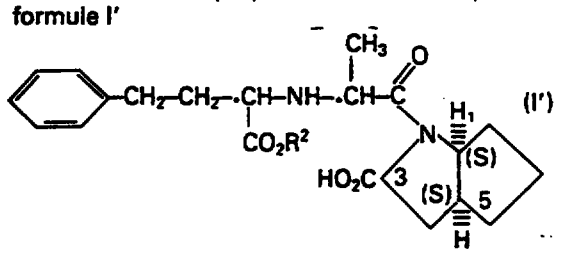


(X)

et en cyclisant ce composé à l'aide d'acides forts avec séparation des groupes acylamide et ester.

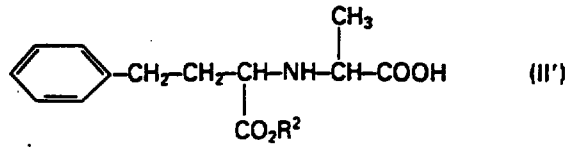
Revendications pour l'Etats contractant: AT

1. Procédé de préparation d'un composé de formule I'



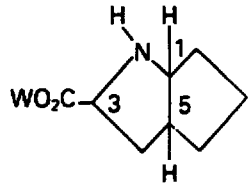
(I')

dans laquelle les atomes d'hydrogène fixés sur les atomes de carbone 1 et 5 de la tête de pont ont une configuration cis l'un par rapport à l'autre, le groupe carboxylique fixé à l'atome de C en 3 est orienté en position endo par rapport au système bicyclique (c'est-à-dire tourné vers le cycle cyclopentane), et les centres de chiralité sur les deux atomes de C de la chaîne marqués d'un astérisque (*) et sur l'atome de C en 3 du double cycle ont la configuration S et dans laquelle R^2 représente l'hydrogène, un radical méthyle, éthyle ou benzyle, ainsi que leurs sels physiologiquement acceptables, caractérisé en ce que l'on fait réagir un composé de formule II'



(II')

dans laquelle R^2 a la signification définie ci-dessus, à l'exception de R^2 = hydrogène, avec un composé de formule III



(III)

dans laquelle les atomes d'hydrogène fixés sur les atomes de carbone 1 et 5 de la tête de pont ont la configuration cis l'un par rapport à l'autre et le groupe CO_2W fixé sur l'atome de C en 3 est orienté en position endo par rapport au système bicyclique (c'est-à-dire tourné vers le cycle cyclopentane) et dans laquelle W représente un groupe estérifiant le groupe carboxylique, et en ce qu'ensuite, on hydrogène le produit ou on le traite par un acide ou par une base et on convertit éventuellement le composé obtenu en l'un de ses sels physiologiquement acceptables.

2. Procédé selon la revendication 1, caractérisé en ce que l'on prépare l'acide N-(1-S-carbéthoxy-3-phényl-propyl)-S-alanyl-cis, endo-2-azabicyclo-[3.3.0]-octane-3-S-carboxylique ou un de ses sels physiologiquement acceptables.

3. Procédé selon la revendication 1, caractérisé en ce que l'on prépare l'acide N-(1-S-carboxy-3-phényl-propyl)-S-alanyl-cis, endo-2-azabicyclo-[3.3.0]-octane-3-S-carboxylique ou un de ses sels physiologiquement acceptables.

4. Procédé selon l'une quelconque des revendications 1 à 3, caractérisé en ce que l'on fait réagir un composé de formule III dans laquelle W représente le radical tertiobutyle ou benzyle.

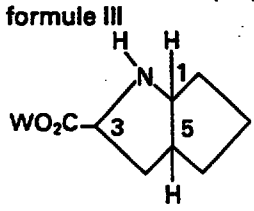
5. Procédé de préparation d'un médicament contenant un composé de formule I' selon l'une des revendications 1 à 3, caractérisé en ce que l'on met celui-ci, avec les additifs habituels, sous une forme d'administration appropriée.

6. Procédé selon la revendication 1 pour la préparation d'un composé de formule I' destiné à l'emploi comme médicament.

7. Procédé selon la revendication 1 pour la préparation d'un composé de formule I' destiné au traitement de l'hypertension.

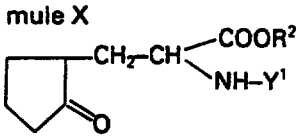
8. Procédé selon la revendication 5, caractérisé en ce que l'on ajoute un diurétique.

9. Procédé de préparation d'un composé de formule III



(III)

dans laquelle les atomes d'hydrogène fixés sur les atomes de carbone 1 et 5 de la tête de pont ont la configuration cis l'un par rapport à l'autre et le groupe CO_2W fixé sur l'atome de C en 3 est orienté en position endo par rapport au système bicyclique (c'est-à-dire tourné vers le cycle cyclopentane) et dans laquelle W représente l'hydrogène ou un groupe estérifiant le groupe carboxylique, qui peut être séparé par hydrogénation ou par traitement avec un acide ou une base, ainsi que les sels de ce composé, caractérisé en ce que l'on part du composé que l'on obtient en cyclisant dans des conditions acides un composé de formule X



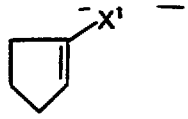
(X)

dans laquelle R^2 représente un groupe ester séparable par action d'un acide et Y^1 représente un radical acyle, que l'on convertit le composé ainsi obtenu, par hydrogénation catalytique, en présence de catalyseurs à base de métaux nobles ou par réduction par des hydrures complexes, en un composé de formule III, dans laquelle W représente l'hydrogène, que l'on estérifie éventuellement celui-ci pour donner des composés de formule III dans laquelle W est défini comme ci-dessus, mais ne représente par l'hydrogéne, et en ce que l'on convertit éventuellement les composés obtenus en leurs sels.

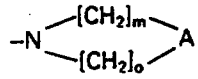
10. Procédé selon la revendication 9, caractérisé en ce que l'on prépare un composé de formule III dont les centres de chiralité présentent tous la configuration S.

11. Procédé selon la revendication 9 ou 10, caractérisé en ce que l'on prépare un composé de formule III dans laquelle W représente l'hydrogène, un radical tertiobutyle ou un radical benzyle.

12. Procédé selon la revendication 9, caractérisé en ce que le composé de départ du procédé de fabrication des composés de formule III est obtenu par réaction d'une énamine de formule VI, dans laquelle X^1 représente un groupe dialkylamino ayant de 2 à 10 atomes de C ou un radical de formule VII dans lequel m et o sont des nombres entiers de 1 à 3, $(m+o) \geq 3$ et A représente CH_2, NH, O ou S,

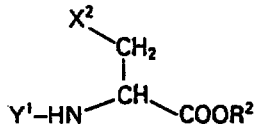


(VI)



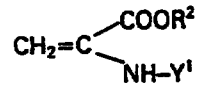
(VII)

avec un ester N-acylé d'un acide β-halogéno-α-amino-carboxylique de formule VIII, dans laquelle X^2 représente un groupe nucléofuge, Y^1 représente un groupe alcanoyle ayant 1 à 5 atomes de C, un groupe aroyle ayant 7 à 9 atomes de C ou d'autres groupes protecteurs séparables par action d'un acide et usuels dans la chimie des peptides et R^2 représente un groupe alkyle ayant 1 à 5 atomes de carbone ou un groupe aralkyle ayant 7 à 9 atomes de carbone



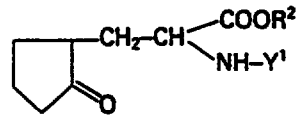
(VIII)

ou avec un ester d'acide acrylique de formule IX, dans laquelle Y^1 et R^2 ont la signification ci-dessus



(IX)

pour donner un composé de formule X, dans laquelle R^2 et Y^1 ont la signification ci-dessus,



(X)

et en cyclisant ce composé à l'aide d'acides forts avec séparation des groupes acylamide et ester.