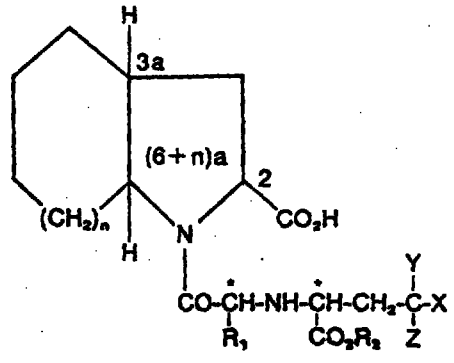
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Description

EP-A 0,038,231 discloses substituted acyl derivatives of cis,endo-octahydro-1H-indole-2-carboxylic acid and their use as inhibitors of angiotensin converting enzyme (ACE).

It has now been found that certain derivatives of bicyclic amino acids with the trans configuration have a strong ACE-inhibiting action.

The present invention therefore relates to new derivatives of the bicyclic amino acids of the formula I



I

in which the hydrogen atoms on the bridgehead C atoms 3a and (6 + n)a have the trans configuration relative to one another, and wherein

n denotes 0, 1 or 2,

r (sic) denotes methyl,

R_2 denotes hydrogen, (C_1-C_4)-alkyl or benzyl,

Y denotes hydrogen or hydroxyl,

Z denotes hydrogen or

Y and Z together denote oxygen, and

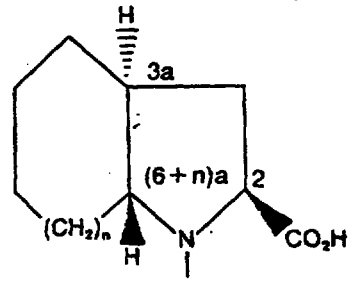
X denotes phenyl,

and their physiologically acceptable salts.

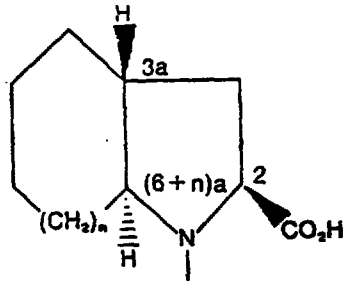
Particularly suitable salts are alkali metal and alkaline earth metal salts, salts with physiologically tolerated amines and salts with inorganic or organic acids such as, for example, CHl, HBr, H_2SO_4, maleic acid and fumaric acid.

Alkyl can be straight-chain or branched.

In the present case of the trans configuration of the H atoms on C-3a and C-(6+n)a, there are two possible configurations of the bicycle, and these are the 2β, 3aα, (6+n)aβ configuration (part-formula Ib) and the 2β, 3aβ, (6+n)aα configuration (part-formula Ic). (For the definition of α and β, see also Fieser, Steroids, page 2, 1961).



Ib



Ic

Compounds of the formula I have chiral atoms in positions (C-2, C-3a, C-(6+n)a, and in the C atoms labeled with an asterisk in the side chain. The invention relates to both the R and also the S configurations at all centers. The compounds of the formula I can thus be in the form of optical isomers, diastereomers, racemates or mixtures thereof. The compounds of the formula I are preferred in which the C atom 2 in the bicyclic ring system and the C atoms labeled with an asterisk in the side chain have the S configuration.

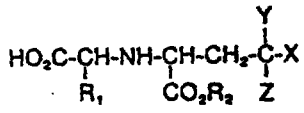
Preferred compounds of the formula I are those in which R^2 denote (sic) hydrogen or ethyl.

Compounds of the formula I to which special attention is drawn are N-(1S-carboxy-3-phenyl-propyl)-S-alanyl-2S,3aS-7aR-octahydroindole-2-carboxylic acid and N-(1S-carboethoxy-3-phenyl-propyl)-S-alanyl-2S,3aS,7aR-octahydroindole-

2-carboxylic acid, but especially N-(1S-carboethoxy-3-phenyl-propyl)-S-alanyl-2S,3aR,7aS-octahydroindole-2-carboxylic acid and N-(1S-carboethoxy-3-phenyl-propyl)-S-alanyl-2S,3aS,7aR-octahydroindole-2-carboxylic acid.

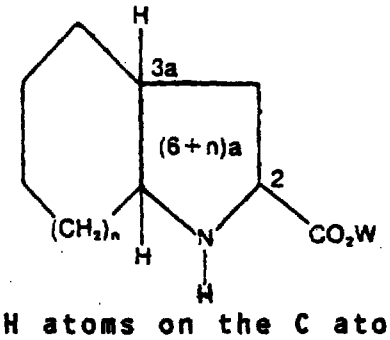
The invention further relates to a process for the preparation of the compounds of the formula I.

One variant of the process comprises reacting, by methods for amide formation known in peptide chemistry, a compound of the formula II



II

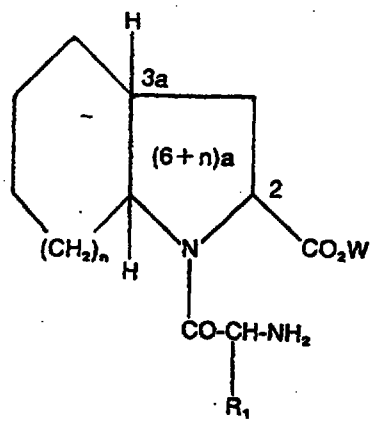
wherein R_1, R_2, X, Y and Z have the meanings as in formula I, with a compound of the formula III



III

in which the H atoms on the C atoms 3a and (6+n)a have the trans configuration relative to one another, and wherein n denotes 0, 1 or 2 and W denotes a radical which can be split off by hydrogenolysis or by acid, in particular a benzyl or a tert.-butyl radical, and the splitting off the radical W by catalytic hydrogenation or acid treatment and, where appropriate, also splitting off the radical R_2 by additional acid or base treatment, the free carboxylic acids being obtained in each case.

Further synthetic processes for the preparation of the compounds of the formula I in which Y and Z together denote oxygen comprise reacting in a known manner in a Michael reaction (Organikum, 6th edition, page 492, 1967) a compound of the formula IV



IV

wherein the H atoms on the C atoms 3a and (6+n)a have the trans configuration relative to one another, and wherein n and R_1 have the meanings as in formula I and W has the meaning as in formula III, with a compound of the formula V,

$$R_2O_2C\text{-}CH=CH\text{-}CO\text{-}X$$

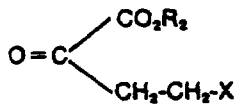
wherein R_2 and X have the meanings as in formula I, and splitting off the radical W and, if appropriate, the radical R_2 as described above, or comprise reacting in a known manner in a Mannich reaction (Bull. Soc. Chim. France 1973, page 625) a compound of the abovementioned formula IV with a compound of the general formula VI, wherein R_2 has the meaning as in formula I, and with a compound of the general formula VII

$OHC\text{-}CO_2R_2$ VI

$X\text{-}CO\text{-}CH_3$ VII

wherein X has the meaning as in formula I, and subsequently splitting off the radical W and, if appropriate, the radical R_2 as described above to form the free carboxyl groups.

Furthermore, compounds of the formula I with Y and Z each being hydrogen can also be prepared in such a manner that a compound of the abovementioned formula IV is reacted in accordance with the procedure described in J. Amer. Chem. Soc. 93 2897 (1971) with a compound of the formula VIII



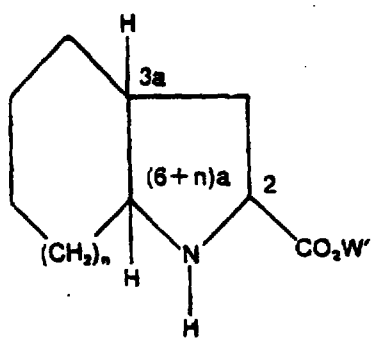
VIII

wherein R_2 and X have the meanings as in formula I, and the Schiff's bases obtained are reduced and subsequently the radical W and, if appropriate, the radical R_2 are split off as described above to form the free carboxyl groups, or that a compound of the formula I, in which Y and Z together denote oxygen, obtained according to the above procedures is reduced catalytically with hydrogen. The reduction of the Schiff's bases can be carried out catalytically, electrolytically or with reducing agents, such as, for example, sodium borohydride or sodium cyanoborohydride.

Compounds of the formula I with Y being hydroxyl and Z being hydrogen can also be obtained, for example, by reduction of a compound I with Y and Z together being oxygen obtained according to the above procedure. This reduction can be carried out catalytically with hydrogen or with another reducing agent, such as, for example, sodium borohydride.

The compounds of the formula I obtained according to the abovementioned procedure are optionally converted into their physiologically tolerated salts.

Furthermore, the invention relates to compounds of the formula III

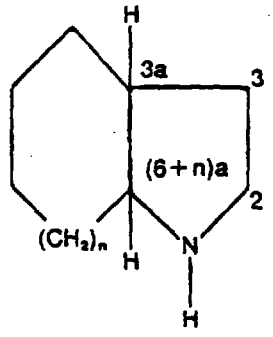


III'

in which the H atoms on the C atoms 3a and (6+n)a have the trans configuration relative to one another, and wherein n denotes 0, 1 or 2 and W' denotes hydrogen, (C_1-C_{18})-alkyl or (C_1-C_{10})-aralkyl.

According to the invention, these compounds serve as starting materials for the synthesis of compounds of the formula I and can be prepared according to the invention by the following procedures.

One synthetic variant starts with a compound of the formula IX

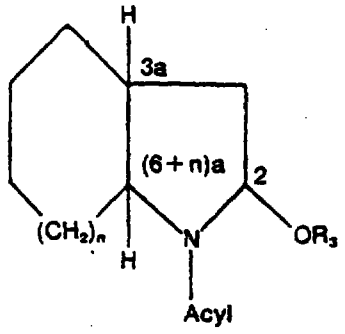


IX

wherein the H atoms on the C atoms ea and (6+n)a have the trans configuration relative to one another and wherein n denotes the number 0, 1 or 2.

Compounds of the formula IX with n being 0 are known from Booth et al., J. Chem. Soc. 1959, page 1050, those with n being 1 are known from King et al., J. Chem. Soc. 1953, pages 250 and 253 and those with n being 2 are known from Ayerst et al., J. Chem. Soc. 1960, page 3445.

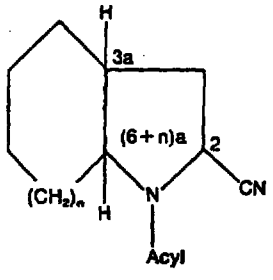
These compounds of the formula IX are acylated in a known manner, an aliphatic or aromatic acyl radical, preferably an acetyl or benzoyl radical, being bonded to the nitrogen ato, and the N-acylated compounds obtained are anodically oxidized (in analogy with Liebigs Ann. Chem. 1978 page 1719) in an aliphatic alcohol, preferably an alkanol having 1 to 4 C atoms, in particular methanol, in the presence of a conducting salt, preferably at temperatures in the range from 0° to +40°C with formation of a compound of the formula X, wherein n denotes 0, 1 or 2 and



X

R_3 denotes (C_1-C_4)-alkyl.

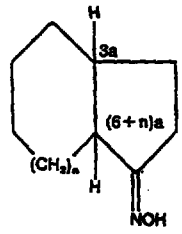
The compound of the general formula X obtained is reacted with trimethylsilyl cyanide in accordance with Tetrahedron Letters 1981, page 141 in an aprotic organic solvent, such as, for example, in a hydrocarbon, halogenated hydrocarbon, in ether or in THF at temperatures in the range from -60°C to +20°C, preferably -40°C to ±0°C in the presence of a Lewis acid, such as, for example, $ZnCl_2$, $SnCl_2$, $SnCl_4$, $TiCl_4$ or BF_3 etherate, preferably BF_3 etherate, and the compound of the formula XI obtained



XI

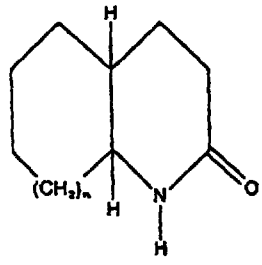
wherein the H atoms on the C atoms 3a and (6+n)a have the trans configuration relative to one another, and wherein n has the abovementioned meaning, after purification and separation from by-products by means of recrystallization or column chromatography, is hydrolyzed by the action of acids or bases in a known manner to give a compound of the formula III' having W' = hydrogen, and the latter is esterified if appropriate. In particular, in the acid hydrolysis of the nitrile group, HCl or HBr is used as the acid. In this instance as in the following, the esterification is carried out by the procedures usual in amino acid chemistry.

Compounds of the general formula III' can also be prepared by converting, in a Beckmann rearrangement analogous to Helv. Chik. Acta 46, 1190 (1963), a compound of the formula XII



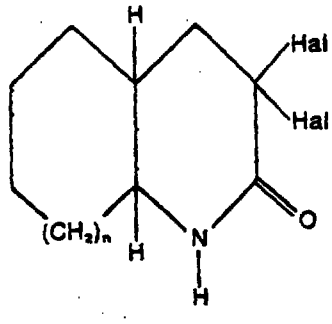
XII

wherein the H atoms on the C atoms 3a and (6+n)a have the trans configuration and n has the abovementioned meaning, into a compound of the formula XIII, wherein n has the abovementioned meaning,



XIII

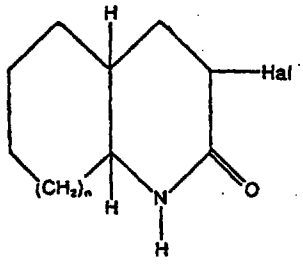
and the latter is halogenated to give a compound of the formula XIV



XIV

wherein n has the abovementioned meaning and Hal denotes a halogen atom, preferably chlorine or bromine. Examples of suitable halogenating agents are halides of inorganic acids, such as PCl_5, SO_2Cl_2, $POCl_5$, $SOCl_2$, PBr_3 or halogens, such as bromine. It is advantageous to use PCl_5 or $POCl_3$ combined with SO_2Cl_2. The intermediate initially formed is an imide halide, which, with the halogenating agents mentioned and subsequent hydrolysis under basic conditions, preferably with aqueous alkali metal carbonate, reacts further to give a compound of the formula XIV.

The compounds of the formula XIV are subsequently reduced catalytically in a polar protic solvent, such as, for example, an alcohol, preferably ethanol, or a carboxylic acid, such as, for example, acetic acid, with the addition of an acid acceptor, such as, for example, sodium acetate or triethylamine, to give a compound of the formula XV



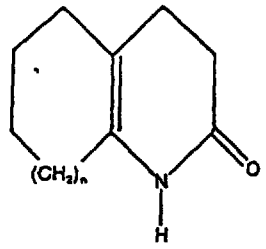
XV

wherein n and Hal have the abovementioned meanings. Examples of suitable catalysts are Raney nickel, or palladium or platinum or animal charcoal.

Compounds of the formula XV can also be prepared directly by halogenation of the compounds of the formula XIII by using smaller amounts of the abovementioned halogenating agents.

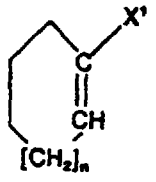
Compounds of the formula XV are converted, in accordance with the known Favorskii reaction in the presence of a base, into a compound of the formula III' with W' being hydrogen, and the latter is esterified if appropriate. The abovementioned Favorskii reaction is carried out in an alcoholic solvent, such as methanol, ethanol or tert.-butanol, or in water or in mixtures thereof at temperatures in the range from 20° to 140°C, preferably between 60° and 100°C. Bases which are expediently employed are alkali metal or alkaline earth metal hydroxides, such as sodium, potassium or barium hydroxide or alkali metal alcoholates, such as, for example, sodium methylate or potassium tert.-butanolate.

Compounds of the formula III', in which the H atoms on the C atoms 3a and (6+n)a have the trans configuration, can also be prepared from a compound of the formula XVI

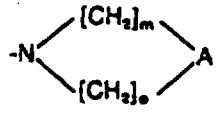


XVI

wherein n has the abovementioned meaning, by reducing the latter with sodium formate/formic acid in accordance with Bull. Soc. Chim. Belg. 85 11 (1976) to give a compound of the formula XIII and reacting the latter further in accordance with the procedures described above. 2-Aza-biocycloalkane-3-carboxylic (sic) acids with the trans configuration, of the formula III' in which n has the abovementioned meaning and W' represents hydrogen, and their alkyl and aralkyl esters can be prepared by reacting enamines of the formula XVII in which n has the previous meaning and X^1 represents dialkylamino having 2 to 10 C atoms or a radical of the formula XVIIa, wherein m and o denote a whole number from 1 to 3, (m + o) > 3 and A denotes CH_2, NH, O or S (Organikum, 6th edition, page 370, 1967),



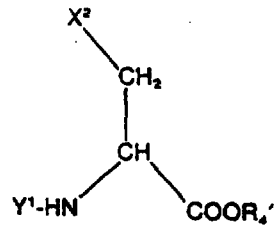
XVII



XVIIa

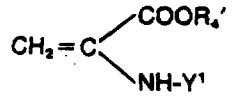
with N-acylated β-halogeno-α-aminopropionates of the formula XVIII for the free amino compound, see Helv. Chik. Acta 40, 1541 (1957)), in which X^2 represents halogen, preferably chlorine or bromine, Y^1 represents alkanoyl having 1 to 5 C atoms, aroyl having 7 to 9 C atoms or other protective groups which are customary in

peptide chemistry and which can be split off by acid, and R_4' represents alkyl having 1 to 5 C atoms or aralkyl having 7 to 9 C atoms,



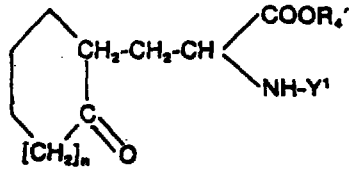
XVIII

or with acrylates of the formula XIX (Chem. Ber. 91 2427 (1958)), in which Y^1 and R_4' have the previous meaning



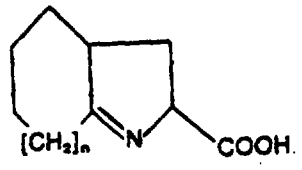
XIX

...(sic) compounds of the formula XX, in which R_4', and Y^1 have the previous meaning,

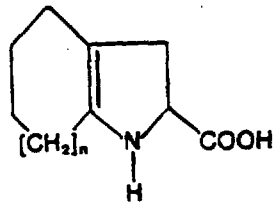


XX

cyclizing the latter, with acylamide and ester cleavage, by means of strong acids to give compounds of the formula XXIa, which can also be in the tautomeric form of the formula XXIb, and in which n has the previous meaning



XXIa



XXIb

converting the compounds of the formula XXIa or b, if appropriate after conversion into their C_1-C_{18}-alkyl or C_7-C_{10}-aralkyl esters, by catalytic hydrogenation in the presence of transition metal catalysts or by reduction with borane-amine complexes or complex borohydrides, transconfigurated into (sic) compounds of the formula III', in which n has the previous meaning and W' represents hydrogen, alkyl having 1 to 18 C atoms or aralkyl having 7 to 10 C atoms, if appropriate saponifying esters of the formula III' and, if appropriate, esterifying the latter (sic), if W' is hydrogen, to give compounds of the formula III' in which n has the previous meaning and W' represents alkyl having 1 to 18 C atoms or aralkyl having 7 to 10 C atoms.

The reaction of 3-bromopropylamine with an enamine of cyclohexanone is described in J. Amer. Chem. Soc. 81, (1956) 2596.

It is also stated that a free NH_2 group is necessary for successful alkylation. Thus it is extremely surprising that even halogenopropionic acid derivatives having an acylated amino group, as do the compounds of the formula XVIII described previously, can be employed for the alkylation of enamines. Enamines of cyclohexanone of cycloheptanone (sic) are preferably employed for this purpose. Examples of suitable amine components are diethylamine, pyrrolidine, piperidine or morpholine. However, other secondary amines are also suitable. Pyrrolidinocycloalkylenes are preferred.

Particularly suitable groups Y^1 in the β-bromo or chloro-α-amino carboxylates of the formula XVIII are formyl, acetyl, propionyl or benzoyl, or other protective groups which can be split off with acid, such as, for example, tert.-butyloxycarbonyl. The C_1-C_3-alkyl or the benzyl esters are preferably employed.

The acrylic acid derivatives of the formula XIX, which

are produced as intermediates from the β-halogeno-α-aminopropionates under the basic conditions of the experiment, are also suitable as the starting compounds. They are prepared, for example, by treatment of the halogeno-aminopropionic acid derivatives or the analogous O-tosyl-serine derivatives with bases. Tertiary organic bases, such as, for example, triethylamine are preferably used. It is advantageous to carry out the reaction with the addition of small amounts of polymerization inhibitors, such as, for example, hydroquinone in organic solvents. The acrylic acid derivatives of the formula XIX can be employed instead of the halogenopropionic acid derivatives under identical reaction conditions.

Suitable solvents for the enamine synthesis are organic solvents which cannot be alkylated, such as, for example, dimethylacetamide, DMSO, THF or toluene. Dimethylformamide is particularly suitable.

It is advisable to employ the enamines of the formula XVII in excess in order to avoid impurities of N-acyl-acrylates in the final product.

The hydrolysis of the N-acyl group necessary for cyclization is generally brought about at the same time as cleavage of the ester function by strong aqueous mineral acids, such as sulfuric acid or, preferably, hydrochloric acid. In the case of the N-tert.-butyloxycarbonyl derivatives of the formula XVII, it is possible, for example, on using dioxane/HCl or anhydrous trifluoroacetic acid, to retain the ester functionality and to isolate the esters of the dehydrocarboxylic acids XXIa or XXIb. The latter can be converted by hydrogenation in the presence of metal catalysts or reaction with borane-amine complexes or complex borohydrides into the 2-azabicyclocarboxylates of the formula III' with the trans configuration.

Noble metal or nickel catalysts are suitable for catalytic hydrogenation. The isomeric ratio occurring on catalytic

hydrogenation depends on the reaction conditions and the type of catalyst used. It is possible to shorten the reaction time by increasing the pressure of hydrogen, but the temperature should be kept low. Examples of suitable solvents for the catalytic hydrogenation are ethanol, methanol, ethyl acetate, dioxane, glacial acetic acid or mixtures of these solvents.

Compounds of the abovementioned formula III', in which n represents a whole number from 0 to 3 and W' represents hydrogen, can also be obtained by reduction of compounds of the formulae XXXIa (sic) or b, in which n has the previous meaning, with borane-amine complexes or complex borohydrides in lower alcohols.

The preferred reducing agent is sodium borohydride in alcohols, in particular in methanol, ethanol or isopropanol. Amine-borane complexes in glacial acetic acid can equally be used.

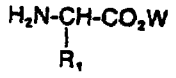
Isolation of the pure trans compounds of the formula III can, for example, be carried out by chromatographic processes or crystallization processes.

The pure trans compound of the formula III' is advantageously separated out of the mixture of diastereomers of (sic) the amine-borane-complex or boranate reduction by fractional crystallization.

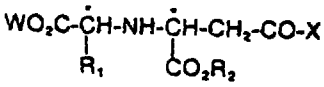
The compounds of the formula III' can, if appropriate, be converted into the (C_1-C_{18})-alkyl or (C_7-C_{10})-aralkyl esters by methods which are described, for example, in Houben-Weyl, volume VIII (1952).

The compounds of the formula II with Y and Z being hydrogen R_1 being methyl and R_2 being methyl or ethyl and X being phenyl which are used as starting materials for the preparation of the compounds of the formula I are known EP-A 0,037,231).

The compounds of the formula II can be prepared by various procedures. One synthetic variant starts from a ketone of the abovementioned formula VII, which reacts (sic) by known procedures in a Mannich reaction with a compound of the abovementioned formula VI together with amino acid esters of the formula XXII



XXII



XXIII

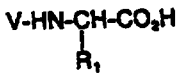
wherein R_1 and W have the abovementioned meanings, to give a compound of the formula XXIII, wherein R_1, R_2, X and W have the abovementioned meanings, with the proviso that in the case where W denotes a radical which can be split off by hydrogenolysis, in particular benzyl, R_2, may not have the meaning of W. If the radical W is split off by hydrogenolysis using, for example, palladium, compounds of the formula II with Y and Z each being hydrogen are obtained. If the radical W is split off with acids, such as, for example, trifluoroacetic acid or hydrochloric acid in an inert organic solvent, such as, for example, dioxane, compounds of the formula II with Y and Z together being oxygen are obtained.

Compounds of the formula XXIII can also be obtained by Michael addition of a compound of the abovementioned formula V with a compound of the abovementioned formula XXII by known procedures. Preferentially, this process is suitable for the preparation of those compounds of the formula XXIII in which R_1 denotes methyl, R_2 denotes ethyl and X denotes aryl.

The compounds of the formula XXIII are obtained as mixtures of diastereomers. Preferred diasteromers of the formula XXIII are those in which the chiral C atoms labeled

with an asterisk are each in the S configuration. These can be separated out by recrystallization or by chromatography, for example on silica gel. The configurations of the chiral C atoms are retained during the subsequent splitting off of the radical W.

The compounds of the abovementioned formula IV used as starting materials for the preparation of the compounds of the formula I are obtained by known procedures from the compounds of the abovementioned formula III by reaction with an N-protected 2-amino carboxylic acid of the formula XXIV



XXIV

wherein V is a protective group and R_1 has the abovementioned meaning. Examples of suitable protective groups V, which are split off again after completion of the reaction, are the groups benzyloxycarbonyl or tert.-butoxycarbonyl.

The reaction of a compound of the formula II with a compound of the formula III to prepare a compound of the formula I is carried out by a condensation reaction known in peptide chemistry, the condensing agent added being, for example, dicyclohexylcarbodiimide and 1-hydroxybenzotriazole. In the subsequent removal of the radical W by hydrogenolysis, the catalyst used is preferably palladium, while the acids employed for the acid removal of the radical W are preferably trifluoroacetic acid or hydrogen chloride.

In the reactions described above for the preparation of the compounds of the formulae III', IV and I, the configurations at the bridgehead C atoms 3a and (6+n)a in the intermediate products are retained in each case. In the case of the trans configuration of the H atoms on

the C atoms 3a and (6+n)a, the relevant compounds are obtained, in some cases, as pure diastereomers, and in other cases, as mixtures of diastereomers, which have the 2β, 3aα, (6+n)aβ or the 2β, 3aβ, (6+n)aα configuration as indicated above. These isomers can easily be separated by recrystallization or chromatography.

The compounds of the formula III' obtained according to the procedures described above are produced as racemic mixtures and can be employed as such in the further synthesis described above. However, they can also be employed as pure enantiomers after separation of the racemates into the optical antipodes by customary methods, for example, via salt formation with optically active bases or acids.

If the compounds of the formula I are produced as racemates, these can also be resolved into their enantiomers by the customary methods, such as, for example, via salt formation with optically active bases or acids.

The compounds of the formula I according to the invention are in the form of internal salts. Since they are amphoteric compounds, they can form salts with acids or bases. These salts are prepared in a customary manner by reaction with one equivalent of acid or base.

The compounds of the formula I and their salts have a long-lasting and powerful hypotensive action. They are strong inhibitors of angiotensin converting enzyme (ACE inhibitors). They can be employed to control high blood pressure of various etiologies. It is also possible to combine them with other compounds having hypotensive, vasodilator or diuretic activity. Typical representatives of these classes of active compounds are described, for example, in Erhardt-Ruschig, Arzneimittel (Drugs), 2nd edition, Weinheim, 1972. They can be used intravenously, subcutaneously or perorally.

The dosage on oral administration is 1-100 mg, preferably 1-40 mg, for a single dose for an adult patient of normal weight. This can also be increased in severe cases, since no toxic properties have been observed hitherto. A decrease in the dose is also possible and is particularly appropriate when diuretics are administered concurrently.

The compounds according to the invention can be administered orally or parenterally in an appropriate pharmaceutical formulation. For a form for oral use, the active compounds are mixed with the additives customary for this purpose, such as vehicles, stabilizers or inert diluents and converted by customary methods into suitable forms for administration, such as tablets, coated tablets, hard capsules, aqueous, alcoholic or oily suspensions or aqueous, alcoholic or oily solutions. Inert vehicles which can be used are, for example, gum arabic, magnesium carbonate, potassium phosphate, lactose, glucose or starch, particularly corn starch. In this context, the formulation can either be as dry or as wet granules. Examples of suitable oily vehicles or solvents are plant and animal oils, such as sunflower oil or fish liver oil.

For subcutaneous or intravenous administration, the active compounds or their physiologically tolerated salts are converted into solutions, suspensions or emulsions, if desired together with the substances customary for this purpose such as solubilizers, emulsifiers or other auxiliaries. Examples of suitable solvents for the new active compounds and the corresponding physiologically tolerated salts are: water, physiological saline solutions or alcohols, for example ethanol, propanediol or glycerol, additionally also sugar solutions, such as glucose or mannitol solutions, or a mixture of the various solvents mentioned.

The extremely high activity of the compounds according to formula I is demonstrated by the pharmacological data in the following table:

Intraduodenal administration to the anesthetized rat, 50 % inhibition of the pressor reaction induced by 310 ng of angiotensin I 30 min after administration in the dose .... = ED_{50}:

H atoms on C-3a and C-(6+n)a have the trans configuration; X = phenyl, R_1 = methyl

n	Y	Z	R_2	Configuration of the bicycle	ED_{50} (µg/kg)
0	H	H	H	2S, 3aR, 6aS	700
0	H	H	C_2H_5	2S, 3aR, 6aS	40
1	H	H	H	2S, 3aR, 7aS	800
1	H	H	C_2H_5	2S, 3aR, 7aS	55
1	H	H	H	2S, 3aS, 7aR	850
1	H	H	C_2H_5	2S, 3aS, 7aR	65
2	H	H	H	2S, 3aR, 8aS	1080
2	H	H	C_2H_5	2S, 3aR, 8aS	110
1	- O -		C_2H_5	2S, 3aR, 7aS	180

The symbols n, X, Y, Z, R_1 and R_2 relate to the compounds of the formula I.

The following examples serve to illustrate the invention but do not restrict it to the compounds mentioned as representative:

Example 1

Benzyl N-(1S-carboethoxy-3-oxo-3-phenylpropyl)-S-alanyl-2β, 3aβ, 8aβ-decahydrocyclopenta[b]pyrrole-2-carboxylate

10 mmol of acetophenone, 10 mmol of ethyl glyoxylate and 10 mmol of benzyl S-alanyl-2S,3aR,8aR-decahydrocyclohepta-[b]pyrrole-2-carboxylate were heated at 45°C in 30 ml of glacial acetic acid for 36 hours. After concentration in vacuo, the mixture was made alkaline with aqueous sodium bicarbonate and extracted with ethyl acetate. The ethyl acetate phase was concentrated and chromatographed on silica gel.

Example 2

N-(1S-Carboethoxy-3-phenylpropyl)-S-alanyl-2S,3aR,7aS-octahydroindole-2-carboxylic acid

a) Benzyl DL-2β,3aβ,7aα-octahydroindole-2-carboxylate hydrochloride

1.4 g of DL-2β,3aβ,7aα-octahydroindole-2-carboxylic acid were added, at -10° to 0°C, to a solution of 1.4 ml of thionyl chloride in 14 ml of benzyl alcohol prepared at -5 to 0°C. The mixture was stirred at 0°C for 1 hour and was then allowed to stand overnight at 20 to 25°C. The benzyl alcohol was distilled off at 50°C under high vacuum and the residue was triturated with diisopropyl ether. 2.5 g of colorless crystals, of m.p. 154°C, were obtained.

b) Benzyl N-(1S-carboethoxy-3-phenylpropyl)-S-alanyl-2β,3aβ,7aα-octahydroindole-2-carboxylate

1.06 g of 1-hydroxybenzotriazole, 2.2 g of benzyl DL-2β,3aβ,7aα-octahydroindole-2-carboxylate hydrochloride and 1.08 ml of N-ethylmorpholine were added to a suspension of 2.16 g of N-(1S-carboethoxy-3-phenylpropyl)-S-alanine in 8.6 ml of anhydrous dimethylformamide and then 1.7 g of dicyclohexylcarbodiimide were added at 0°C. After stirring at 20 to 25°C for 3.5 hours, the reaction mixture was diluted with 20 ml of ethyl acetate and the precipitated dicyclohexylurea was filtered off. After concentration in vacuo, the residue was taken up in ether, washed twice with saturated aqueous sodium bicarbonate, dried over sodium sulfate and evaporated. After chromatography on silica gel using ethyl acetate-cyclohexane as the eluant, 2 pale yellow oils were obtained in the ratio 1:1, and these each contain one isomer of the desired compound. ^{1}H NMR data of the isomer having the 2R, 3aR, 7aS configuration: 7.35 (s,5H); 7.2 (s,5H); 5.18 (s,2H); 4.55 (d,1H); 4.1 (q,2H); 3.4 - 2.3 (m,6H); 2.4 - 1.3 (m,12H); 1.3 (t,3H); 1.1 (d,3H). ^{1}H NMR data of the isomer having the 2S,3aS,7aR configuration : 7.35 (s,5H); 7.2 (s,5H), 5.16 (s,2H); 4.9

4.2 (m,1H); 4.2 (q,2H); 3.9 - 2.4 (m,6H); 2.4 - 1.4 (m,12H); 1.25 (d+t,6H).

c) N-(1S-Carboethoxy-3-phenylpropyl)-S-alanyl-2S,3aR,7aS-octahydroindole-2-carboxylic acid

1.7 g of the isomer having the 2S,3aS,7aR configuration obtained under b) were hydrogenated under normal pressure in 60 ml of anhydrous ethanol with the addition of 200 mg of palladium-charcoal (10%) at 20 to 25°C for 2 hours. The catalyst was filtered off and the filtrate was evaporated. 1.2 g of the title compound were obtained as a colorless foam. ^{1}H NMR data: 7.2 (s,5H); 4.4 (m,4H); 4.2 (q,2H); 3.6 - 1.3 (m,18H); 1.28 (d+t,6H).

The hydrochloride of the abovementioned compound was obtained as a colorless amorphous powder.

Examples 3 to 7

The compounds mentioned in these examples were prepared in analogy to the procedures described in Example 2.

Example 3

N-(1S-Carboethoxy-3-phenylpropyl)-S-alanyl-2S,3aS,7aR-octahydroindole-2-carboxylic acid

This compound was obtained from the mixture of products from Example 51, which were further reacted according to the procedure of Example 42. The isomers were separated by column chromatography on silica gel before hydrogenation in accordance with Example 42c. ^{1}H NMR data: 7.2 (s,5H); 4.0 - 4.6 (m,4H); 4.15 (q,2H); 3.8 - 1.2 (m,18H); 1.3 (t,3H); 1.2 (d,3H).

The hydrochloride was obtained as a colorless amorphous powder.

Example 4

N-(1S-Carboethoxy-3-phenylpropyl)-S-alanyl-2S,3aR,6aS-

octahydrocyclopenta[b]pyrrole-2-carboxylic acid

^{1}H NMR data: 7.25 (s,5H); 4.35 (m,4H); 4.2 (q,2H); 3.9 - 1.4 (m,16H); 1.35 (t,3H); 1.15 (d,3H).

The hydrochloride was obtained as a colorless amorphous powder.

Example 5

N-(1S-Carboethoxy-3-phenylpropyl)-S-alanyl-2S,3aS,6aR-octahydrocyclopenta[b]pyrrole-2-carboxylic acid

^{1}H NMR data: 7.3 (s,5H); 4.3 (m,4H); 4.2 (q,2H); 3.8 - 1.3 (m,16H); 1.3 (t+d,6H).

The hydrochloride was obtained as a colorless amorphous powder.

Example 6

N-(1S-Carboethoxy-3-phenylpropyl)-S-alanyl-2S,3aR,8aS-decahydrocyclohepta[b]pyrrole-2-carboxylic acid

^{1}H NMR data: 7.15 (s,5H); 4.4 (m,4H); 4.2 (q.2H); 3.8 - 1.3 (m, 20H); 1.3 (t+d,6H).

Example 7

N-(1S-Carboethoxy-3-phenylpropyl)-S-alanyl-2S,3aS,8aR-decahydrocyclohepta[b]pyrrole-2-carboxylic acid

^{1}H NMR data: 7.2 (s,5H); 4.4 (m,4H); 4.25 (q,2H); 3.8 - 1.2 (m,20H); 1.3 (t,3H); 1.15 (d,3H).

Example 8

2β,3aβ,7aα-Octahydroindolecarboxylic acid

a) Methyl 3-chloro-N-acetylalanine

181 g of methyl 3-chloroalanine hydrochloride were heated under reflux with 163.9 g of acetyl chloride in 1.5 l of

anhydrous toluene for about 5 hours until a clear solution was obtained. This was evaporated to dryness and the residue was crystallized from ethyl acetate/petroleum ether. 170 g of product of m.p. 104°C were obtained.

b) Methyl 3-(2-oxocyclohexyl)-N-acetylalanine

160 g of methyl 3-chloro-N-acetylalanine and 171.9 g of 1-pyrrolidinocyclohexene were dissolved in 1.2 l of absolute DMF and the mixture was allowed to stand at 20 to 25°C for 3 days.

The solution was concentrated under high vacuum, the residue obtained was taken up in 600 ml of water and the pH was adjusted to 2.0 with concentrated hydrochloric acid. The aqueous solution was extracted with ethyl acetate and the organic phase was dried over sodium sulfate and evaporated. The product was obtained as a yellow oil.

c) 3,3a,4,5,6,7-2H-Hexahydroindole-2-carboxylic acid hydrochloride

220 g of the compound obtained under b) were heated to boiling under reflux with 1 l of 2N of hydrochloric acid for 2 hours. The reaction mixture was extracted with ethyl acetate and the aqeuous phase was concentrated. Residual amounts of water were removed by evaporation in vacuo with the addition of toluene three times. 210 g of the product were obtained as a yellow oil which crystallized on being left to stand.

d) 2β,3aβ,7aα-Octahydroindole-2-carboxylic acid

128 g of 3,3a,4,5,6,7-2H-hexahydroindole-2-carboxylic acid hydrochloride were hydrogenated under normal pressure in 700 ml of glacial acetic acid with the addition of 4 g of platinum/charcoal (10 %) at room temperature. The catalyst was filtered off and the filtrate was evaporated to dryness. The residue was dissolved in 500 ml of hot ethanol and cooled down to -20°C. This caused the 2β,3aβ,7aβ-isomer of the title compound to precipitate

out. The product was obtained from the solution by concentrating and adding isopropanol, in the form of colorless crystals of m.p. 280°C.

Example 9

2β,3aβ,8aα-Decahydrocyclohepta[b]pyrrole-2-carboxylic acid

This compound was prepared in analogy to the procedures b) to d) of Example 48 starting from pyrrolidinocycloheptene.

Example 10

2β,3aβ,6aα-Octahydrocyclopenta[b]pyrrole-2-carboxylic acid

This compound was prepared in analogy to the procedures b) to d) of Example 48, starting from pyrrolidinocyclopentene.

Example 11

2β,3aα,7aβ-Octahydroindole-2-carboxylic acid

a) 3,4,5,6,7,8-Octahydro-1H-quinolin-2-one

392 g of cyclohexanone and 212 g of acrylonitrile, together with 20 g of cyclohexylamine, 4 g of glacial acetic acid and 0.4 g of hydroquinone, were heated under reflux for 4 hours up to a final temperature of 200°C. The distillate obtained after distillation at 100 to 150°C/0.5 mm Hg was heated with 10 ml of 50 % strength acetic acid at 200°C for 2 days. After cooling down, the reaction mixture was recrystallized from methanol/water. Combined with the residue from distillation, obtained previously, which was recrystallized from n-hexane, 460 g of the product of m.p. 143 to 144°C were obtained.

b) Trans-octahydro-1H-quinolin-2-one

A mixture of 25 g of the product obtained under a) and 70 g of sodium formate in 120 ml of formic acid were

heated to boiling under reflux for 18 hours. The reaction solution was made alkaline with 20 % strength aqueous sodium hydroxide and extracted with ethyl acetate. The organic phase was dried over sodium sulfate and concentrated. The residue was recrystallized from cyclohexane and the product was obtained having an m.p. of 152°C.

c) 3,3-Dichloro-trans-octahydro-1H-quinolin-2-one

A solution of 36.4 g of sulfuryl chloride in 40 ml of chloroform was added dropwise at 20 to 30°C over 30 minutes to a solution of 19.4 g of the compound obtained under b) and 24.3 g of phosphorus pentachloride in 300 ml of anhydrous chloroform. The mixture was heated to boiling for 6 hours and allowed to stand overnight at 20 to 25°C.

The mixture was neutralized with ice-cold saturated aqueous potassium carbonate, extracted with methylene chloride, and the organic phase was dried over sodium sulfate and then concentrated. After recrystallization of the product from ethanol, with the addition of active charcoal, 25 g of the product, of m.p. 195 to 198°C, were obtained.

d) 3-Chloro-trans-octahydro-1H-quinolin-2-one

15.6 g of the compound obtained under c) were hydrogenated under normal pressure in 1 l of ethanol and 9.7 ml of triethylamine, with the addition of Raney nickel, at 20 to 25°C until 1 mole-equivalent of hydrogen had been taken up.

After the catalyst had been filtered off, the filtrate was evaporated to dryness and the residue was taken up in ethyl acetate. The organic phase was washed twice with water, dried over sodium sulfate and evaporated. The residue was triturated with diisopropyl ether, filtered off with suction and dried. The product was obtained in the form of pale yellow crystals of m.p.

115 - 120°C.

e) 2β,3aα,7aβ-Octahydroindole-2-carboxylic acid

3.75 g of the compound obtained under d) were added to a boiling solution of 6.63 g of barium hydroxide octahydrate in 120 ml of water. After heating under reflux for 4 hours, 0.9 ml of concentrated sulfuric acid were added, heating under reflux was continued a further hour, the reaction solution was filtered and the filtrate was adjusted to a pH of 6.5 with 1N sodium hydroxide. After evaporation of the solution, the residue was heated in ethanol, again filtered and the filtrate was evaporated to a small volume. On cooling down, a crystalline 1:1 mixture of the title compound and the compound of Example 48, of m.p. 275-276°C was obtained.

Example 12

2β,3aβ,6aα-Octahydrocyclopenta[b]pyrrole-2-carboxylic acid

a) 1,2,3,4,6,7-Hexahydro-5H-1-pyrind-2-one (sic)

A mixture of 1 mole of cyclopentanone, 1 mole of acrylonitrile, 0.05 mole of ammonium acetate and 3 ml of 30 % strength ammonia were heated in a pressure vessel for 3 hours at 220°C. The mixture was filtered through silica gel with ethyl acetate/cyclohexane (1:1 and the residue obtained after evaporation of the filtrate was recrystallized from cyclohexane. The product melted at 118 to 120°C. ^{1}H NMR data: 9.4 (broad s,1H); 3.2 - 2.0 (m,12H).

b) Octahydro-trans-5H-1-pyrind-2-one (sic)

This compound was prepared in analogy to the procedure described in Example 51 under b). ^{1}H NMR data: 7.8 (broad s,1H); 2.9 (broad s,1H); 2.6 - 2.2 (m,2H); 2.1 - 1.0 (m,8H).

c) 3,3-Dichlorooctahydro-trans-5H-1-pyrind-2-one (sic)

This compound was prepared in analogy to the procedure

described in Example 51 under c). ^{1}H NMR data: 7.9 (broad s,1H); 3.8 (broad s,1H); 3.2 - 2.0 (m,2H); 2.1 - 1.0 (m,6H).

d) 3-Chlorooctahydro-trans-5H-1-pyrind-2-one (sic)

This compound was prepared in analogy to the procedure described in Example 51 under d). ^{1}H NMR data: 7.8 (broad s,1H); 4.6 - 4.3 (m,1H); 3.3 - 3.0 (m,1H); 2.1 (d,J = 6 Hz,2H); 1.8 - 1.1 (m,6H).

e) 2β,3aβ,6aα-Octahydrocyclopenta[b]pyrrole-2-carboxylic acid

This compound was prepared in analogy to the procedure described in Example 51 under e). ^{1}H NMR data: 4.7 - 4.4 (m,1H); 3.0 - 0.9 (m,10H).

Example 13

2β,3aβ,8aα-Decahydrocyclopenta[b]pyrrole-2-carboxylic acid

a) 1,2,3,4,5,6,7,8-Octahydrocyclohepta[b]pyrid-2-one

This compound was prepared in analogy to the procedure described in Example 51 under a), starting from cycloheptanone. ^{1}H NMR data: 9.4 (broad s,1H); 3.2 - 2.0 (m,14H).

b) trans-Decahydrocyclohepta[b]pyrid-2-one

This compound was prepared in analogy to the procedure described in Example 51 under b), starting from the compound previously mentioned under a). ^{1}H NMR data: 7.9 (broad s,1H); 2.9 (broad s,1H); 2.6 - 2,2 (m,2H); 2.1 - 1.0 (m,12H)

c) 3,3-Dichloro-trans-decahydrocyclohepta[b]pyrid-2-one

This compound was prepared in analogy to the procedure described in Example 51 under c). ^{1}H NMR data: 7.9 (broad s,1H); 3.8 (broad s,1H); 3.2 - 2.0 (m,2H); 2.1 - 1.0 (m,10H).

This compound was prepared in analogy to the procedure described in Example 51 under d). ^{1}H NMR data: 7.8 (broad s,1H); 4.6 (broad s,1H); 3.3 - 3.0 (m,1H); 2.1 (d,j = 6 Hz,2H); 1.8 - 1.1 (m,10H).

e) 2β,3aβ,8aα-Decahydrocyclohepta[b]pyrrole-2-carboxylic acid

This compound was prepared in analogy to the procedure described in Example 51 under e).
^{1}H NMR data: 4.7 - 4.4 (m,1H); 3.2 - 1.1 (m,1H).

Example 14

a) Tert.-butyl 2β,3aα,7aβ-octahydroindole-2-carboxylate hydrochloride

This compound was prepared from 2β,3aα,7aβ-octahydroindole-2-carboxylic acid in analogy to the procedure described in Example 14 b).
^{1}H NMR data: 4.7 - 4.4 (m,1H); 3.2 - 1.1 (m,12H); 1.2 (s,9H).

The compounds in the following Examples 15 to 19 were prepared in analogy to the procedure described in Example 14.

b) Tert.-butyl-2β,3aβ-7aβ-octahydroindole-2-carboxylate hydrochloride

10 ml of concentrated sulfuric acid and 50 g of isobutylene were added to a solution of 10 g of 2β,3aβ,7aβ-octahydroindole-2-carboxylic acid in 100 ml of dioxane cooled down to -10°C. The reaction mixture was slowly warmed to 20 to 25°C in an autoclave and stirred at this temperature for 20 hours.

The mixture was added to ice-cold 50 % strength aqueous sodium hydroxide and extracted with methylene chloride. The combined organic phases were washed with water, dried

with sodium sulfate and concentrated. The residue was taken up in ether and the pH was adjusted to 2.0 to 3.0 by means of ethereal hydrogen chloride. The mixture was evaporated to dryness and the product was triturated with diisopropyl ether. 7.3 g of the title compound were obtained after filtering off with suction. ^{1}H NMR data: 1.0 - 2.5 (m,11H); 1.3 (s,9H); 3.4 - 3.9 (m,1H); 4.0 - 4.5 (m,1H).

Example 15

Tert.-butyl 2β,3aβ,7aα-octahydroindole-2-carboxylate hydrochloride

^{1}H NMR data: 4.7 - 4.3 (m,1H); 3.4 - 1.1 (m,12H); 1.2 (s,9H).

Example 16

Tert.-butyl 2β,3aα,6aβ-octahydrocyclopenta[b]pyrrole-2-carboxylate hydrochloride

^{1}H NMR data: 4.8 - 4.4 (m,1H); 3.4 - 1.2 (m,10H); 1.2 (s,9H).

Example 17

Tert.-butyl 2β,3aβ,6aα-octahydrocyclopenta[b]pyrrole-2-carboxylate hydrochloride

^{1}H NMR data: 4.8 - 4.4 (m,1H); 3.5 - 1.2 (m,10H); 1.2 (s,9H).

Example 18

Tert.-butyl 2β,3aα,8aβ-decahydrocyclohepta[b]pyrrole-2-carboxylate hydrochloride

^{1}H NMR data: 4.7 - 4.4 (m,1H); 3.3 - 1.0 (m,14H); 1.2 (s,9H).

Example 19

Tert.-butyl 2β,3aβ,8aα-decahydrocyclohepta[b]pyrrole-2-carboxylate hydrochloride

^{1}H NMR data: 4.7 - 4.3 (m,1H); 3.2 - 0.8 (m,14H); 1.2 (s,9H).

Example 20

Tert.-butyl-N-(S-alanyl)-2S,3aR,7aS-octahydroindole-2-carboxylate hydrochloride

a) Tert.-butyl N-(N'-benzyloxycarbonyl-S-alanyl)-2S,3aR,-7aS-octahydroindole-2-carboxylate

This compound was prepared from Z-alanine in analogy to the procedure described in Example 36 under a), and separated from its isomer as described there. ^{1}H NMR data: 7.4 (s,5H); 5.3 - 4.8 (m,1H); 4.2 - 3.7 (m,2H); 3.1 - 1.4 (m,11H); 1.3 (d,J = 7 Hz,3H); 1.2 (s,9H).

b) The compound mentioned above under a) was hydrogenated with palladium/barium sulfate in 1N ethanolic hydrogen chloride, the desired title compound being obtained. ^{1}H NMR data: 5.2 - 4.8 (m,1H); 4.2 - 3.7 (m, 2H); 3.1 - 1.4 (m,11H); 1.3 (d,J = 7 Hz,3H); 1.2 (s,9H).

The compounds in the following Examples 21 to 25 were prepared in analogy to the procedures described in Example 20 under a) and b).

Benzyl N-tert.-butoxycarbonyl-S-alanyl-2S,3aR,7aR-octahydroindole-2-carboxylate

13 ml of N-ethylmorpholine, 13.5 g of 1-hydroxybenzotriazole and 29.6 g of benzyl 2β,3aβ,7aβ-octahydroindole-2-carboxylate hydrochloride were added to a solution of 19 g of Boc-Ala-OH in 100 ml of DMF. The mixture was cooled in an ice bath and 21 g of dicyclohexylcarbodiimide were added. The mixture was stirred at 20 to 25°C for 15 hours. The precipitated urea was filtered off with

suction, the filtrate was evaporated in vacuo and taken up in ethyl acetate. The organic phase was extracted 3 times in each case with aqueous potassium bisulfate, potassium bicarbonate and sodium chloride, dried and concentrated. The residue was chromatographed on silica gel with ethyl acetate/cyclohexane (1:3). The first fraction contained the desired product. Yield: 21 g
^{1}H NMR data: 1.3 (d,3H); 1.45 (s,9H); 1.1 - 2.4 (m,12H); 3.2 - 3.9 (m,2H); 5.3 (s,2H); 7.4 (s,5H).

Example 21
Tert.-butyl N-(S-alanyl)-2S,3aS,7aR-octahydroindole-2-carboxylate hydrochloride

^{1}H NMR data: 5.2 - 4.7 (m,1H); 4.4 - 3.8 (m,2H); 3.1 - 1.4 (m,11H); 1.25 (d,J = 7Hz,3H); 1.2 (s,9H).

Example 22
Tert.-butyl N-(S-alanyl)-2S,3aR,6aS-octahydrocyclopenta-[b]pyrrole-2-carboxylate hydrochloride

^{1}H NMR data: 5.3 - 4.7 (m,1H); 4.4 - 3.8 (m,2H); 3.1 - 1.4 (m,9H); 1.3 (d,J = 7 Hz,3H); 1.2 (2,9H).

Example 23
Tert.-butyl N-(S-alanyl)-2S,3aS,6aR-octahydrocyclopenta-[b]pyrrole-2-carboxylate hydrochloride

^{1}H NMR data: 5.3 - 4.7 (m,1H); 4.4 - 3.8 (m,2H); 3.1 - 1.4 (m,9H); 1.3 (d,J = 7 Hz,3H); 1.2 (s,9H).

Example 24
Tert.-butyl N-(S-alanyl)-2S,3aR,8aS-decahydrocyclopenta-[b]pyrrole-2-carboxylate hydrochloride

^{1}H NMR spectrum: 5.1 - 4.6 (m,1H); 4.5 - 3.7 (m,2H); 3.1 - 1.4 (m,13H); 1.3 (d,J = 7 Hz,3H); 1.2 (s,9H).

Example 25

Tert.-butyl N-(S-alanyl)-2S,3aS,8aR-decahydrocyclohepta-[b]pyrrole-2-carboxylate hydrochloride

^{1}H NMR data: 5.1 - 4.6 (m,1H); 4.5 - 3.7 (m,2H); 3.1 - 1.4 (m,13H); 1.3 (d, J - 7 Hz,3H); 1.2 (s,9H).

Example 26

a) N-(1S-Carboethoxy-3-phenylpropyl)-S-alanyl-2S,3aR,7aS-octahydroindole-2-carboxylic acid

This compound was prepared in analogy to the procedure described in Example 26 b), starting from tert.-butyl N-(S-alanyl)-2S,3aR,7aS-octahydroindole-2-carboxylate. The tert.-butyl group was split off with trifluoroacetic acid.

b) Benzyl N-(1S-carboethoxy-3-phenylpropyl)-S-alanyl-2S,3aR,7aR-octahydroindole-2-carboxylate

10 mmol of benzyl S-alanyl-2S,3aR,7aR-octahydroindole-2-carboxylate were dissolved in 30 ml of anhydrous ethanol. The solution was adjusted to a pH of 7.0 by means of ethanolic potassium hydroxide and 1 g of powdered molecular sieves (4Å) and then 10 mmol of ethyl 2-keto-4-phenyl-butyrate were added. A solution of 1 g of sodium cyano-borohydride in 10 ml of anhydrous ethanol was slowly added dropwise. After a reaction time of 20 hours at 20 to 25°C, the reaction solution was filtered and the solvent was distilled off. The residue was taken up in ethyl acetate/water. After concentration of the ethyl acetate phase, the residue was chromatographed on silica gel with ethyl acetate/cyclohexane (1:4).

Example 27

N-(1S-Carboethoxy-3-keto-3-phenylpropyl)-S-alanyl-2S,3aR,7aS-octahydroindole-2-carboxylic acid

This compound was prepared analogously to the procedure

described in Example 27 b), starting from tert.-butyl N-(S-alanyl)-2S,3aR,7aS-octahydroindole-2-carboxylate. The tert.-butyl group was split off with trifluoroacetic acid. ^{1}H NMR data: 1.2 (d+t,6H); 1.3 - 3.6 (m,16H); 4.2 (q,2H); 4.1 - 4.6 (m,4H); 7.3 - 8.1 (m,5H).

b) Benzyl N-(1S-carboethoxy-3-oxo-3-phenylpropyl)-S-alanyl-2β,3aβ,6aβ,-octahydrocyclopenta[b]pyrrole-2-carboxylate

10 mmol of benzyl S-alanyl-2S,3aR,6aR-octahydrocyclopenta[b]pyrrole-2-carboxylate were dissolved in 100 ml of anhydrous ethanol together with 10 mmol of ethyl 3-benzoylacrylate and 10 mmol of triethylamine and the mixture was stirred at 20 to 25°C for 24 hours. It was then neutralized with 1N hydrochloric acid, evaporated to dryness and the residue was taken up with ethyl acetate/water. The ethyl acetate phase was dried, evaporated and chromatographed on silica gel.

Example 28

N-(1S-Carboethoxy-3-keto-3-phenylpropyl)-S-alanyl-2S,3aS,-7aR-octahydroindole-2-carboxylic acid

This compound was prepared in analogy to the procedure described in Example 27 b), starting from tert.-butyl N-(S-alanyl)-2S,3aS,7aR-octahydroindole-2-carboxylate. The tert.-butyl group was split off with trifluoroacetic acid. ^{1}H NMR data: 1.2 (d+t,6H); 1.3 - 3.6 (m,16H); 4.2 (q,2H); 4.1 - 4.6 (m,4H); 7.3 - 8.1 (m,5H).

Example 29

N-(1S-Carboethoxy-3-keto-3-phenylpropyl)-S-alanyl-2S,3aR,6aS-octahydrocyclopenta[b]pyrrole-2-carboxylic acid

This compound was prepared in analogy to the procedure described in Example 27 b), starting from tert.-butyl

N-(S-alanyl)-2S,3aR,6aS-octahydrocyclopenta[b]pyrrole-2-carboxylate. The tert.-butyl group was split off with trifluoroacetic acid. ^{1}H NMR data: 1.1 (d,3H); 1.35 (t,3H); 1.0 - 3.7 (m,14H); 4.2 (q,2H); 4.0 - 4.7 (m,4H); 7.3 - 8.0 (m,5H).

Example 30

N-(1S-Carboethoxy-3-keto-3-phenylpropyl)-S-alanyl-2S,3aS,-6aR-octahydrocyclopenta[b]pyrrole-2-carboxylic acid

This compound was prepared in analogy to the procedure described in Example 1, followed by splitting off the tert.-butyl group with trifluoroacetic acid. ^{1}H NMR data: 1.1 (d,3H); 1.35 (t,3H); 1.0 - 3.8 (m,14H); 4.2 (q,2H); 4.0 - 4.7 (m,4H); 7.2 - 8.1 (m,5H).

Example 31

N-(1S-Carboethoxy-3-keto-3-phenylpropyl)-S-alanyl-2S,3aR,8aS-decahydrocyclohepta[b]pyrrole-2-carboxylic acid

This compound was prepared in analogy to the reaction procedure described in Example 1, followed by splitting off the tertiary butyl group with trifluoroacetic acid. ^{1}H NMR data: 1.2 (d,3H); 1.4 (t,3H); 1.2 - 3.8 (m,18H); 4.1 (q,2H); 4.0 - 4.6 (m,4H); 7.2 - 8.2 (m,5H).

Example 32

N-(1S-Carboethoxy-3-keto-3-phenylpropyl)-S-alanyl-2S,3aS,-8aR-decahydrocyclohepta[b]pyrrole-2-carboxylic acid

This compound was prepared in analogy to the procedure described in Example 1, followed by splitting off the tert.-butyl group with trifluoroacetic acid. ^{1}H NMR data: 1.2 (d+t,6H); 1.2 - 3.8 (m,18H); 4.2 (q,2H); 4.0 - 4.6 (m,4H); 7.1 - 8.1 (m,5H).

Example 33

a) N-(1S-Carboethoxy-3-hydroxy-3-phenylpropyl)-S-alanyl-2S,3aR,7aS-octahydroindole-2-carboxylic acid

This compound was prepared in analogy to the procedure described in Example 33 b). ^{1}H NMR data: 1.2 (d,3H); 1.3 (t,3H); 1.3 - 3.8 (m,16H); 4.2 (q,2H); 4.0 - 4.6 (m,4H); 4.7 (d,1H); 7.1 - 7.4 (m,5H).

Example 34

N-(1S-Carboethoxy-3-hydroxy-3-phenylpropyl)-S-alanyl-2S,3aS,6aR-octahydrocyclopenta[b]pyrrole-2-carboxylic acid

This compound was prepared in analogy to the procedure described in Example 33 b). ^{1}H NMR data: 1.2 (d+t,3H); 1.1 - 3.9 (m,14H); 4.2 (q,2H); 4.0 - 4.7 (m,4H); 4.8 (d,1H); 7.1 - 7.4 (m,5H).

Examples 35 to 48:

The compounds mentioned in these examples were prepared in analogy to the procedure described in the following example.

N-(1S-Carboxy-3-phenylpropyl)-S-alanyl-2S,3aR,7aR-octahydroindole-2-carboxylic acid

Two equivalents of potassium hydroxide and a 10 % excess of 4N potassium hydroxide were added to a solution of 1 g of N-(1S-carboethoxy-3-phenylpropyl)-S-alanyl-2S,3aR,7aR-octahydroindole-2-carboxylic acid hydrochloride in 10 ml of water. After stirring for 8 hours at 20 to 25°C, the reaction solution was adjusted to a pH of 4.0 with 2N hydrochloric acid and concentrated in vacuo. The residue was taken up in ethyl acetate and precipitated salt was filtered off. The ethyl acetate solution was concentrated and the residue was triturated with diisopropyl ether and filtered off with suction. Yield: 0.6 g

^{1}H NMR data: 1.2 (d,3H); 1.2 - 3.8 (m,18H); 4.0 - 4.6 (m,4H); 7.2 (s,5H).

Example 35

N-(1S-Carboxy-3-phenylpropyl)-S-alanyl-2S,3aR,7aS-octahydroindole-2-carboxylic acid

^{1}H NMR data: 1.2 (d,3H); 1.2 - 3.8 (m,18H); 4.0 - 4.6 (m,4H); 7.2 (s,5H).

Example 36

N-(1S-Carboxy-3-phenylpropyl)-S-alanyl-2S,3aS,7aR-octahydroindole-2-carboxylic acid

^{1}H NMR data: 1.2 (d,3H); 1.2 - 3.8 (m,18H); 4.0 - 4.6 (m,4H); 7.2 (s,5H).

Example 37

N-(1S-Carboxy-3-phenylpropyl)-S-alanyl-2S,3aR,6aS-octahydrocyclopenta[b]pyrrole-2-carboxylic acid

^{1}H NMR data: 1.2 (d,3H); 1.1 - 3.7 (m,16H); 4.0 - 4.6 (m,4H); 7.2 (s,5H).

Example 38

N-(1S-Carboxy-3-phenylpropyl)-S-alanyl-2S,3aS,6aR-octahydrocyclopenta[b]pyrrole-2-carboxylic acid

^{1}H NMR spectrum: 1.2 (d,3H); 1.1 - 3.8 (m,16H); 4.0 - 4.6 (m,4H); 7.2 (s,5H).

Example 39

N-(1S-Carboxy-3-phenylpropyl)-S-alanyl-2S,3aR,8aS-decahydrocyclohepta[b]pyrrole-2-carboxylic acid

^{1}H NMR data: 1.2 (d,3H); 0.9 - 3.6 (m,20H); 4.0 - 4.6 (m,4H); 7.2 (s,5H).

Example 40
N-(1S-Carboxy-3-phenylpropyl)-S-alanyl-2S,3aS,8aR-decahydrocyclohepta[b]pyrrole-2-carboxylic acid

^{1}H NMR data: 1.2 (d,3H); 0.8 - 3.6 (m,20H); 4.0 - 4.6 (m,4H); 7.2 (s,5H).

Example 41
N-(1S-Carboxy-3-keto-3-phenylpropyl)-S-alanyl-2S,3aR,7aS-octahydroindole-2-carboxylic acid

^{1}H NMR data: 1.2 (d,3H); 0.9 - 3.6 (m,16H); 3.9 - 4.7 (m,4H); 7.1 - 8.2 (m,5H).

Example 42
N-(1S-Carboxy-3-keto-3-phenylpropyl)-S-alanyl-2S,3aS,7aR-octahydroindole-2-carboxylic acid

^{1}H NMR data: 1.2 (d, 3H); 0.9 - 3.6 (m,16H); 3.9 - 4.7 (m,4H); 7.2 - 8.1 (m,5H).

Example 43
N-(1S-Carboxy-3-keto-3-phenylpropyl)-S-alanyl-2S,3aR-6aS-octahydrocyclopenta[b]pyrrole-2-carboxylic acid

^{1}H NMR data: 1.2 (d, 3H); 1.1 - 3.7 (m,14H); 3.9 - 4.6 (m,4H); 7.2 - 8.1 (m,5H).

Example 44
N-(1S-Carboxy-3-keto-3-phenylpropyl)-S-alanyl-2S,3aS,6aR-octahydrocyclopenta[b]pyrrole-2-carboxylic acid

^{1}H NMR data: 1.2 (d,3H); 1.1 - 3.7 (m,14H); 3.9 - 4.6 (m,4H); 7.2 - 8.1 (m,5H).

Example 45
N-(1S-Carboxy-3-keto-3-phenylpropyl)-S-alanyl-2S,3aR,8aS-decahydrocyclohepta[b]pyrrole-2-carboxylic acid

^{1}H NMR data: 1.2 (d,3H); 1.1 - 3.7 (m,18H); 3.9 - 4.6 (m,4H); 7.3 - 8.2 (m,5H).

Example 46

N-(1S-Carboxy-3-keto-3-phenyl)-alanyl-2S,3aS,8aR-decahydrocycloheptaⁿb]pyrrole-2-carboxylic acid

^{1}H NMR data: 1.2 (d,3H); 1.1 - 3.7 (m,18 H); 3.9 - 4.6 (m,4H); 7.3 - 8.2 (m,5H).

Example 47

N-(1S-Carboxy-3-hydroxy-3-phenylpropyl)-S-alanyl-2S,3aR,-7aS-octahydroindole-2-carboxylic acid

^{1}H NMR data: 1.2 (d,3H); 1.1 - 3.7 (m,16H); 3.8 - 4.6 (m,4H); 4.7 (m,1H); 7.1 - 7.4 (m,5H).

Example 48

N-(1S-Carboxy-3-hydroxy-3-phenylpropyl)-S-alanyl-2S,3aS,-6aR-octahydrocyclopentaⁿb]pyrrole-2-carboxylic acid

^{1}H NMR data: 1.2 (d,3H); 1.1 - 3.7 (m,14H); 3.9 - 4.5 (m,4H); 4.7 (d,1H); 7.1 - 7.4 (m,5H).

Example 49

2β,3aβ,7aα-octahydroindole-2-carboxylic acid

290 g of the acetylamino derivative obtained in accordance with Example 50 were heated with 2N hydrochloric acid as indicated in Example 51. The mixture was evaporated in vacuo, the residue was taken up in 1 l of isopropanol and reduced with about 35 g of $NaBH_4$ which was added in portions in the course of 30 minutes. The reaction temperature was kept at 40 - 50°C. The reaction was allowed to continue for about 4 hours, then the mixture was evaporated in vacuo, the pH was adjusted to 6.5 with dilute hydrochloric acid, solid sodium chloride was used to saturate, and the aminoacids were extracted several times with n-butanol. The residue remaining after con-

centration of the organic phase was fractionally crystallized from chloroform/diisopropyl ether as described in Example 2.

Yields: 40 - 60 g of 2β,3α,7aα-product
20 g of a mixed fraction
100 - 130 g 2β,3aβ,7aα-product.

In the same manner, 2β,3aβ,7aα-2-azabicyclo(5.3.0)-decane-3-carboxylic acid and 2β,3aβ,7aα-2-azabicyclo(6.3.0)-undecane-3-carboxylic acid can be prepared.

Example 50

2β,3aβ,7aβ-Octahydroindole-2-carboxylic acid

a) N-Acetyl-3aβ,7aβ-octahydroindole

3.5 g of platinum oxide were added to a solution of 77 g of indole in 700 ml of glacial acetic acid. The compound was initially hydrogenated under 100 atmospheres at 20 to 25°C for 16 hours and then at 20 to 25°C under normal pressure until the uptake of hydrogen was complete. The catalyst was filtered off with suction and the solvent was distilled off in vacuo. The residue was taken up in water and made alkaline with saturated potassium carbonate solution. After saturation with sodium chloride, the aqueous phase was extracted four times with methylene chloride and the organic phase was dried and evaporated.

The residue was taken up in 250 ml of pyridine, 93 ml of acetic anhydride were added and the mixture was allowed to react at 20 to 25°C for 12 hours. After distilling off the pyridine, water was added to the residue and the mixture was made alkaline with concentrated aqueous sodium hydroxide. The aqueous phase was extracted with methylene chloride, the organic phase obtained was washed with 2N hydrochloric acid and with water. After drying and concentrating the solution, the residue was distilled.
Yield: 85 g; b.p.: 91 to 95°C/0.2 mm Hg

b) N-Acetyl-2-methoxy-3aβ,7aβ-octahydroindole

54 g of N-acetyl-3aβ,7aβ-octahydroindole were anodically oxidized in methanol, with the addition of tetramethylammonium tetrafluoroborate, according to the details in Liebigs Ann. Chem. 1978, page 1790. The solvent was distilled off and the residue was filtered through 500 g of silica gel by means of ethyl acetate. 53.6 g of the abovementioned product were obtained from the ethyl acetate solution after evaporation. R_f value (thin-layer chromatogram): 0.33 (silica gel, ethyl acetate).

c) N-Acetyl-2β,3aβ,7aβ-octahydroindole-2-carbonitrile

25 g of trimethylsilyl cyanide in 50 ml of methylene chloride were added dropwise to a solution of 49.8 g of N-acetyl-2-methoxy-3aβ,7aβ-octahydroindole in 250 ml of methylene chloride at -40°C. Subsequently, 35.9 g of boron trifluoride etherate were added dropwise so that the temperature of the reaction mixture did not exceed -20°C. After 2 hours of reaction at -20°C, the temperature was slowly raised to 0°C, the mixture was stirred overnight at 0°C and then for one hour at 20 to 25°C. Water was added to the mixture and this was stirred for 10 min. The aqueous phase was extracted three times with methylene chloride. The combined organic extracts were dried, concentrated and the residue was triturated with diisopropyl ether.
Yield: 47 g; m.p. 128° to 130°C.

d) 2β,3aβ,7aβ-Octahydroindole-2-carboxylic acid

10 g of N-acetyl-2β,3aβ,7aβ-octahydroindole-2-carbonitrile in 30 ml of concentrated hydrogen bromide were heated to boiling for 2 hours. After distilling off the hydrogen bromide, the residue was stirred with a little acetone and filtered off with suction.

An aqueous solution of the product was adjusted to a pH

of 6.0 with a weakly basic ion exchanger. After filtration, the solution was evaporated and the residue was filtered through silica gel with a mixture of methylene chloride, methanol, glacial acetic acid and water in the ratio 20:10:0.5:0.5. The eluate was concentrated and the residue was triturated with diisopropyl ether.
Yield: 7.6 g
^{1}H NMR spectrum*: 1.0-2.5 (m,11H); 3.4-3.9(m,1H); 4.0-4.5(m,1H); 7.5-8.3 (broad s, exchangeable with D_2O)

When the process was carried out in analogy to the procedures described under Example 50, the compounds mentioned under Example 51 in the following text were obtained:

Example 51
2β,3aβ,6aβ-Octahydrocyclopenta[b]pyrrole-2-carboxylic acid
a) N-Acetyl-cis-octahydrocyclopenta[b]pyrrole
^{1}H NMR data: 1.0 to 2.3 (m 9H); 2.0 (d,3H); 3.3 to 4.2 (m,3H)

b) Acetyl-2-methoxy-cis-octahydrocyclopenta[b]pyrrole
^{1}H NMR data: 0.9 to 2.6 (m,9H); 2.1 (s,3H); 3.3 (s,3H); 3.8 - 4.3 (m,1H); 4.7 - 5.5 (m,1H).

c) N-Acetyl-2-cyano-cis-octahydrocyclopenta[b]pyrrole
^{1}H NMR data: 1.0 - 3.0 (m,9H); 2.1 (d,3H): 3.5 - 4.1 (m,1H); 4.4 - 4.7 (m,1H).

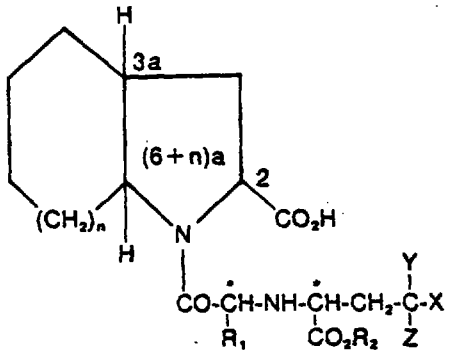
d) 2β,3aβ,6aβ-Octahydrocyclopenta[b]pyrrole-2-carboxylic acid
^{1}H NMR data: 1.0 - 2.3 (m,9H); 3.5 - 3.9)m,1H); 4.0 - 4.6 (m,1H); 7.7 - 8.4 (broad s, exchangeable with D_2O)

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* Here, as in the other examples, the ^{1}H NMR data were obtained in $CDCl_3$ and are reported in ppm.

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 bridgehead C atoms 3a and (6+n)a have the trans configuration relative to one another and wherein
n denotes 0, 1 or 2,
R_1 denotes methyl,
R_2 denotes hydrogen, (C_1-C_4)-alkyl or benzyl,
Y denotes hydrogen or hydroxyl,
Z denotes hydrogen or
Y and Z together denote oxygen and
X denotes phenyl,
and its physiologically acceptable salts.

2. A compound of the formula I as claimed in claim 1, characterized in that the C atom in position 2 of the bicyclic ring system and the C atoms labeled with an asterisk in the side chain have the S configuration, and its physiologically acceptable salts.

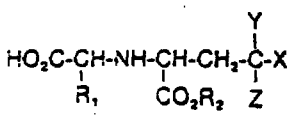
3. A compound of the formula I as claimed in claim 1 or 2, characterized in that R_2 denotes hydrogen or ethyl, and its physiologically acceptable salts.

4. N-(1-S-Carboethoxy-3-phenyl-propyl)-S-alanyl-2S,3aR,-7aS-octahydroindole-2-carboxylic acid,
and its physiologically acceptable salts.

* C L M S *

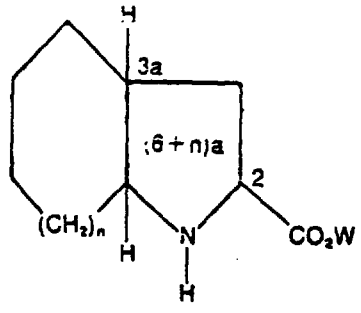
5. N-(1-S-Carboethxy-3-phenyl-propyl)-S-alanyl-2S,3aS,-7aR-octahydroindole-2-carboxylic acid,
and its physiologically acceptable salts.

6. A process for the preparation of the compounds of the formula I as claimed in any of claims 1 to 5, which
a) comprises reacting a compound of the formula II



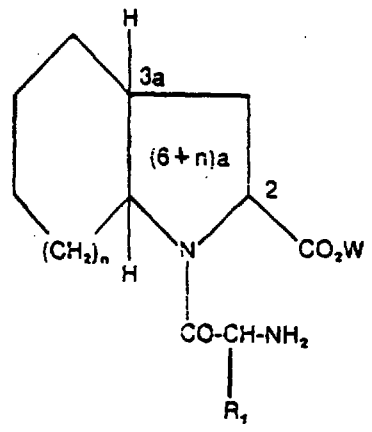
II

wherein R_1, R_2, X, Y and Z have the meanings as in formula I, with a compound of the formula III



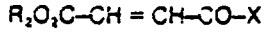
III

in which the H atoms on the C atoms 3a and (6+n)a have the trans configuration relative to one another, wherein
n denotes 0, 1 or 2 and
W denotes a radical which can be split off by hydrogenolysis or by acid, and then splitting off the radical W and, if appropriate, the radical R_2 to form the free carboxyl groups, or
b) for the preparation of compounds of the formula I, in which Y and Z together denote oxygen, comprises
b_1) reacting a compound of the formula IV
in which the H atoms on the C atoms 3a and (6+n)a



IV

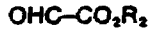
have the trans configuration relative to one another and wherein n and R_1 have the meanings as in formula I and W has the meaning as in formula III, with a compound of the formula V,



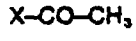
V

wherein R_2 and X have the meanings as in formula I, and subsequently splitting off the radical W and, if appropriate, also the radical R_2 to form the free carboxyl groups, or,

b_2) reacting a compound of the formula IV mentioned under b_1) with a compound of the general formula VI, wherein R_2 has the meaning as in formula I, and with a compound of the general formula VII



VI



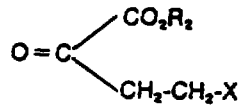
VII

wherein X has the meaning as in formula I, subsequently splitting off the radical W and, if appropriate, the radical R_2 to form the free carboxyl group, or

c) for the preparation of compounds of the formula I, in which Y and Z each denote hydrogen, comprises

c_1) reacting a compound of the formula IV mentioned under b_1) with a compound of the formula VIII

* C L M S *



VIII

wherein R_2 and X have the meanings as in formula I, reducing the Schiff's bases obtained and subsequently splitting off the radical W and, if appropriate, the radical R_2 to form the free carboxyl groups, or

c_2) catalytically reducing a compound of the formula I in which Y and Z together denote oxygen, with hydrogen, or

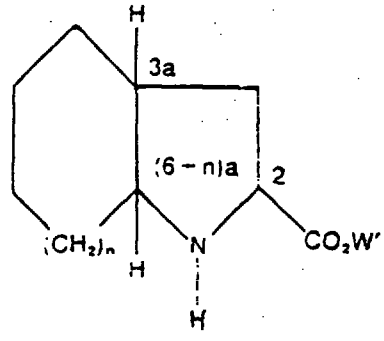
d) for the preparation of compounds of the formula I, in which Y denotes hydroxyl and Z denotes hydrogen, comprises reducing a compound of the formula I, in which Y and Z together denote oxygen, catalytically with hydrogen or with a reducing agent, such as sodium borohydride, and, if appropriate, converting the compounds obtained according to (a)-(d) into their physiologically acceptable salts.

7. A compound as claimed in any of claims 1 to 5 for use as a medicine.

8. A compound as claimed in claim 7 for use as a medicine for treating high blood pressure.

9. A compound as claimed in claim 7 or 8 for use in combination with a diuretic.

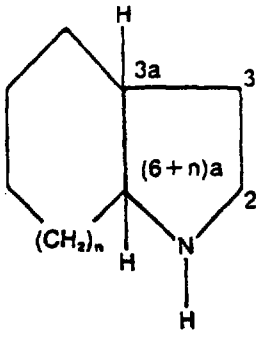
10. A compound of the formula III',



III'

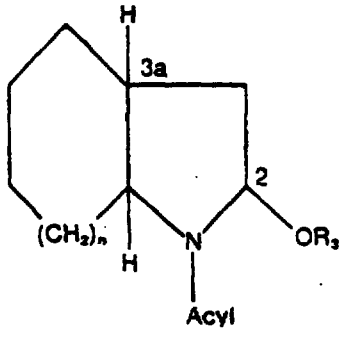
in which the H atoms on the C atoms 3a and (6+n)a have the trans configuration relative to one another and wherein n denotes 0, 1 or 2,
W' denotes hydrogen, (C_1-C_{18})-alkyl or (C_7-C_{10})-aralkyl.

11. A process for the preparation of the compounds of the formulae (sic) III' as claimed in claim 10, which comprises a) acylating a compound of the formula IX



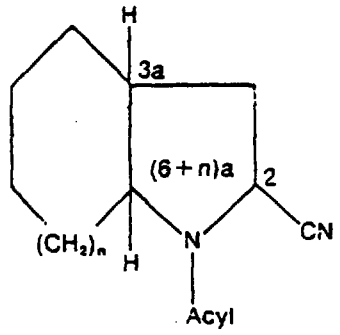
IX

wherein the H atoms on the C atomns 3a and (6+n)a have the trans configuration relative to one another and wherein n denotes the number 0, 1 or 2, subsequently anodically oxidizing the compound obtained with an aliphatic alcohol in the presence of a conducting salt to give a compound of the formula X



X

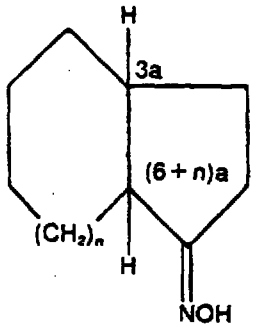
wherein n has the abovementioned meaning, acyl is an aliphatic or aromatic acyl radical and R_3 denotes (C_1-C_4)-alkyl, reacting this product with trimethylsilyl cyanide in an aprotic organic solvent in the presence of a Lewis acid to give a compound of the formula XI



XI

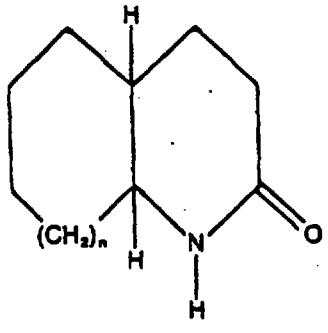
wherein the H atoms on the C atoms 3a and (6+n)a have the trans configuration relative to one another and wherein n has the abovementioned meaning, and (sic) hydrolyzing the latter by the action of acids or bases to give a compound of the formula III' with W' = hydrogen and if appropriate, esterifying the latter, or

b) reacting a compound of the formula XII



XII

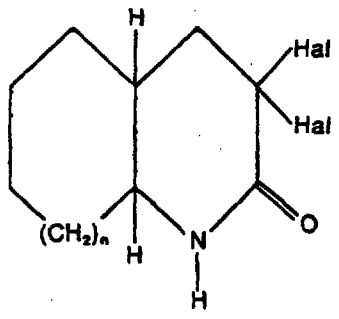
wherein the H atoms on the C atoms 3a and (6+n)a have the trans configuration and n has the abovementioned meaning, in a Beckmann rearrangement to give a compound of the formula XIII



XIII

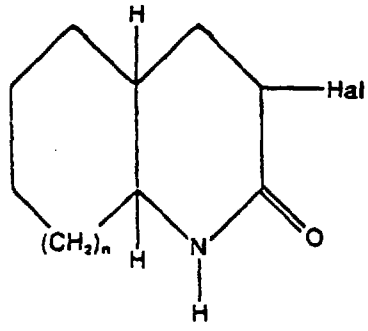
* C L M S *

wherein n has the abovementioned meaning, halogenating the latter to give a compound of the formula XIV



XIV

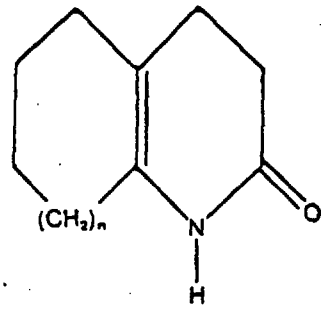
wherein n has the abovementioned meaning and Hal denotes a halogen atom, catalytically reducing the latter in a polar protic solvent with addition of an acid acceptor to give a compound of the formula XV



XV

wherein n and Hal have the abovementioned meanings, and subsequently reacting the latter in an alcoholic solvent under the action of a base to give a compound of the formula III' with W' = hydrogen and optionally esterifying the latter, or

c) of reducing a compound of the formula XVI

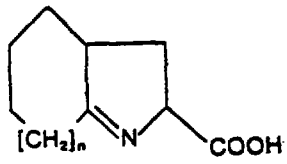


XVI

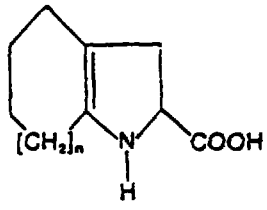
* C L M S *

wherein n has the abovementioned meaning, with sodium formate and formic acid to give a compound of the formula XIII mentioned under b), and further reacting the latter as described under b), or

d) converting compounds of the formula XXIa or b, in which n has the previous meaning,



XXIa



XXIb

after conversion into their (C_1-C_{18}-alkyl) or (C_7-C_{10}-) aralkyl esters, by catalytic hydrogenation in the presence of transition metal catalysts or by reduction with borane-amine complexes or complex borohydrides, into compounds of the formula III', in which W' represents hydrogen, alkyl having 1 to 18 C atoms or aralkyl having 7 to 10 C atoms, if appropriate, saponifying esters of the formula III' which have been obtained and if appropriate esterifying, if W' is hydrogen, to give compounds of the formula III' in which W' represents alkyl having 1 to 18 C atoms or aralkyl having 7 to 10 C atoms.

12. A pharmaceutical agent containing a compound as claimed in any of claims 1 to 5.

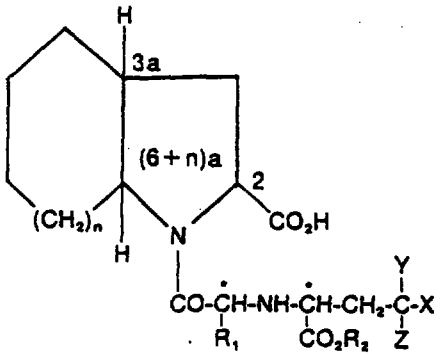
13. An agent as claimed in claim 12, characterized in that it additionally contains a diuretic.

* C L M S *

As printed.

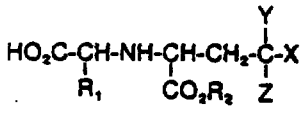
Patentansprüche für den Vertragsstaat: Österreich

1. Verfahren zur Herstellung der Verbindungen der Formel I,



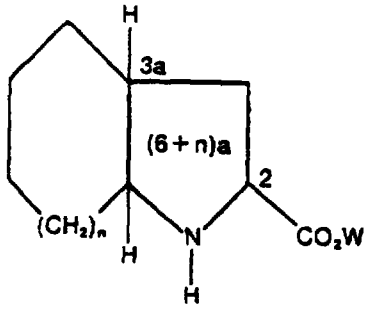
I

in der die Wasserstoffatome an den Brückenkopf-C-Atomen 3a und (6+n)a zueinander trans-konfiguriert sind und worin
n = 0, 1 oder 2,
R_1 = Methyl,
R_2 = Wasserstoff, (C_1–C_4)-Alkyl oder Benzyl,
Y = Wasserstoff oder Hydroxy,
Z = Wasserstoff oder
Y und Z = zusammen Sauerstoff und
X = Phenyl bedeuten, sowie
deren physiologisch unbedenklichen Salzen, dadurch gekennzeichnet,
a) dass man eine Verbindung der Formel II,



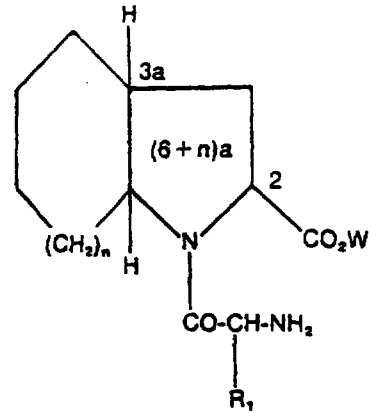
II

worin R_1, R_2, X, Y und Z die Bedeutungen wie in Formel I haben, mit einer Verbindung der Formel III



III

in der die H-Atome an den C-Atomen 3 a und (6+n)a zueinander trans-konfiguriert sind und wobei
n = 0, 1 oder 2 und
W = einen hydrogenolytisch oder sauer abspaltbaren Rest bedeuten, umsetzt und anschliessend den Rest W und gegebenenfalls den Rest R_2 unter Bildung der freien Carboxygruppen abspaltet, oder,
b) dass man zur Herstellung der Verbindungen der Formel I, in der Y und Z zusammen Sauerstoff bedeuten,
b_1) eine Verbindung der Formel IV,



IV

in der die H-Atome an den C-Atomen 3a und (6+n)a zueinander trans-konfiguriert sind und worin n und R_1 die Bedeutungen wie in Formel I und W die Bedeutung wie in Formel III besitzen, mit einer Verbindung der Formel V,

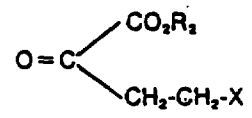
$$R_2O_2C–CH=CH–CO–X \qquad V$$

worin R_2 und X die Bedeutungen wie in Formel I haben, umsetzt und anschliessend den Rest W und gegebenenfalls auch den Rest R_2 unter Bildung der freien Carboxygruppen abspaltet, oder
b_2) eine Verbindung der unter b_1) genannten Formel IV mit einer Verbindung der allgemeinen Formel VI, worin R_2 die Bedeutung wie in Formel I hat, und mit einer Verbindung der allgemeinen Formel VII,

$$OHC–CO_2R_2 \qquad X–CO–CH_3$$

VI VII

worin X die Bedeutung wie in Formel I hat, umsetzt und anschliessend den Rest W und gegebenenfalls den Rest R_2 unter Bildung der freien Carboxygruppen abspaltet, oder
c) dass man zur Herstellung von Verbindungen der Formel I, in der Y und Z jeweils Wasserstoff bedeuten,
c_1) eine Verbindung der unter b_1) genannten Formel IV mit einer Verbindung der Formel VIII,



VIII

worin R_2 und X die Bedeutungen wie in Formel I besitzen, umsetzt, die erhaltenen Schiff-Basen reduziert und anschliessend den Rest W und gegebenenfalls den Rest R_2 unter Bildung der freien Carboxygruppen abspaltet, oder
c_2) eine Verbindung der Formel I, in der Y und Z zusammen Sauerstoff bedeuten, katalytisch mit Wasserstoff recuziert, oder

d) dass man zur Herstellung von Verbindungen der Formel I, in der Y = Hydroxy und Z = Wasserstoff bedeuten, eine Verbindung der Formel I, in der Y und Z zusammen Sauerstoff bedeuten, katalytisch mittels Wasserstoff oder mit einem Reduktionsmittel wie Natriumborhydrid reduziert, und die nach (a)–(d) erhaltenen Verbindungen gegebenenfalls in ihre physiologisch verträglichen Salze überführt.

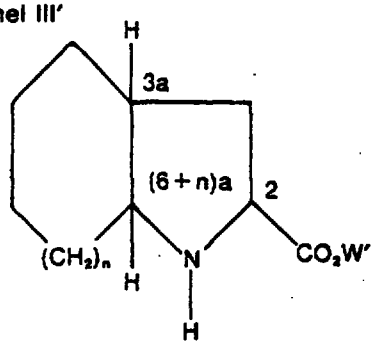
2. Verfahren zur Herstellung von Verbindungen der Formel I gemäss Anspruch 1, dadurch gekennzeichnet, dass das C-Atom in Position 2 des bicyclischen Ringsystems sowie die mit einem Stern markierten C-Atome der Seitenkette S-Konfiguration aufweisen.

3. Verfahren zur Herstellung von Verbindungen der Formel I gemäss Anspruch 1 oder 2, dadurch gekennzeichnet, dass R_2 = Wasserstoff oder Ethyl bedeutet.

4. Verfahren gemäss einem der Ansprüche 1 bis 3, dadurch gekennzeichnet, dass
N-(2-S-Carbethoxy-3-phenyl-propyl)-S-alanyl-2S,
3aR,7aS-octahydroindol-2-carbonsäure
oder deren physiologisch verträgliches Salz hergestellt wird.

5. Verfahren gemäss einem der Ansprüche 1 bis 3, dadurch gekennzeichnet, dass
N-(1-S-Carbethoxy-3-phenyl-propyl)-S-alanyl-2S,
3aS,7aR-octahydroindol-2-carbonsäure
oder deren physiologisch verträgliches Salz hergestellt wird.

6. Verfahren zur Herstellung der Verbindungen der Formel III'



III'

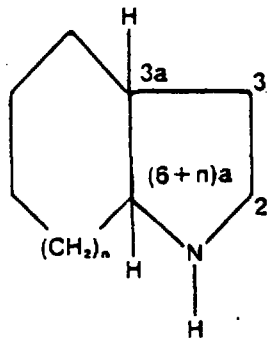
in der die H-Atome an den C-Atomen 3 a und (6+n)a zueinander trans-konfiguriert sind und worin

n = 0, 1 oder 2

W' = Wasserstoff, (C_1–C_{18})-Alkyl oder (C_7–C_{10})-Aralkyl bedeutet,

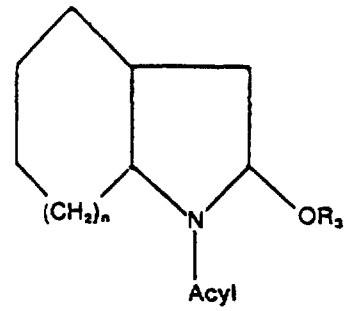
dadurch gekennzeichnet,

a) dass man eine Verbindung der Formel IX,



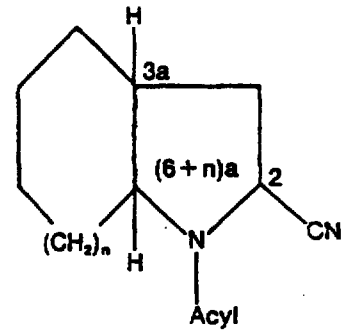
IX

worin die H-Atome an den C-Atomen 3 a und (6+n)a zueinander trans-konfiguriert sind und worin n die Zahl 0, 1 oder 2 bedeutet, acyliert, anschliessend mit einem aliphatischen Alkohol in Gegenwart eines Leitsalzes zu einer Verbindung der Formel X,



X

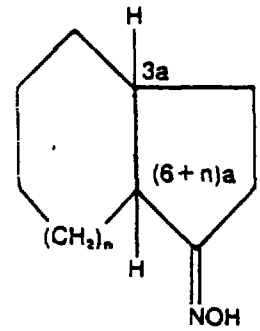
worin n die oben genannte Bedeutung hat, Acyl ein aliphatischer oder aromatischer Acylrest ist und R_3 (C_1–C_4)-Alkyl bedeutet, anodisch oxydiert, diese mit Trimethylsilylcyanid in einem aprotischen organischen Lösemittel in Gegenwart einer Lewis-Säure zu einer Verbindung der Formel XI,



XI

worin die H-Atome an den C-Atomen 3 a und (6+n)a zueinander trans-konfiguriert sind und worin n die oben genannte Bedeutung hat, umsetzt und diese durch Einwirkung von Säuren oder Basen zu einer Verbindung der Formel II' mit W' = Wasserstoff hydrolysiert und letztere gegebenenfalls verestert, oder

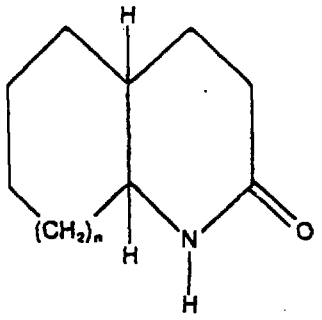
b) dass man eine Verbindung der Formel XII,



XII

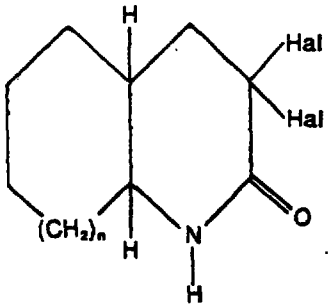
worin die H-Atome an den C-Atomen 3 a und (6+n)a trans-konfiguriert sind und n die oben genannte Bedeutung besitzt in einer Beckmann-Umlagerung zu einer Verbindung der Formel XIII

* C L M S *



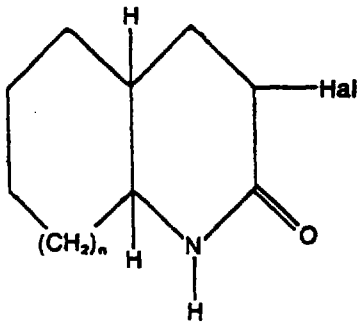
XIII

worin n die obengenannte Bedeutung besitzt, umsetzt, diese zu einer Verbindung der Formel XIV,



XIV

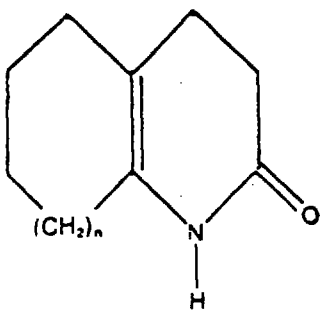
worin n die obengenannte Bedeutung besitzt und Hal ein Halogenatom bedeutet, halogeniert, diese zu einer Verbindung der Formel XV,



XV

worin n und Hal die oben genannten Bedeutungen besitzen, in einem polaren protischen Lösungsmittel unter Zusatz eines Säureakzeptors katalytisch reduziert, und diese anschliessend unter Einwirkung einer Base in einem alkoholischen Lösungsmittel zu einer Verbindung der Formel III' mit W' = Wasserstoff umsetzt und diese gegebenenfalls verestert, oder

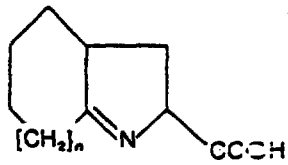
c) dass man eine Verbindung der Formel XVI,



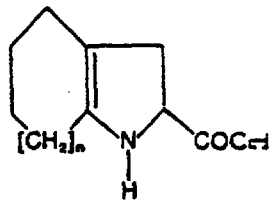
XVI

worin n die obengenannte Bedeutung besitzt mit Natriumformiat und Ameisensäure zu einer Verbindung der unter b) genannten Formel XIII reduziert, und diese, wie unter b) beschrieben, weiter umsetzt, oder

d) dass man Verbindungen der Formel XXIa oder b, in welcher n vorstehende Bedeutung hat,



XXIa



XXIb

gegebenenfalls nach Überführung in ihre C_1–C_{18}-Alkyl- oder C_7–C_{10}-Aralkylester durch katalytische Hydrierung in Gegenwart von Übergangsmetallkatalysatoren oder durch Reduktion mit Boran-Amin-Komplexen oder komplexen Borhydriden in Verbindungen der Formel III' in welcher

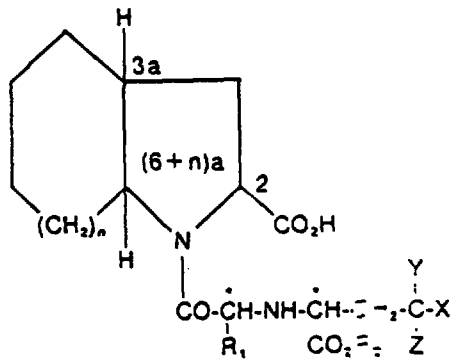
W' für Wasserstoff, Alkyl mit 1 bis 18 C-Atomen oder Aralkyl mit 7 bis 10 C-Atomen steht, überführt, gegebenenfalls erhaltene Ester der Formel III' verseift und, falls W' Wasserstoff ist, gegebenenfalls zu Verbindungen der Formel III', worin W' für Alkyl mit 1 bis 18 C-Atomen oder Aralkyl mit 7 bis 10 C-Atomen steht, verestert.

7. Verfahren zur Herstellung eines pharmazeutischen Mittels enthaltend eine Verbindung der Formel I gemäss einem der Ansprüche 1 bis 5, dadurch gekennzeichnet, dass man diese in eine geeignete Darreichungsform bringt.

8. Verfahren gemäss Anspruch 7, dadurch gekennzeichnet, dass man ein Diuretikum zusetzt.

Claims for the Contracting states: BE, CH, DE, FR, GB, IT, LI, Lu, NL, SE

1. A compound of the formula I



in which the hydrogen atoms on the bridgehead C atoms 3a and (6+n)a have the trans configuration relative to one another and wherein
n denotes 0, 1 or 2,
R_1 denotes methyl,
R_2 denotes hydrogen, (C_1–C_4)-alkyl or benzyl,
Y denotes hydrogen or hydroxyl,
Z denotes hydrogen or
Y and Z together denote oxygen and
X denotes phenyl,
and its physiologically acceptable salts.

2. A compound of the formula I as claimed in claim 1, characterized in that the C atom in position 2 of the bicyclic ring system and the C atom in the side chain labeled with an asterisk have the S configuration, and its physiologically acceptable salts.

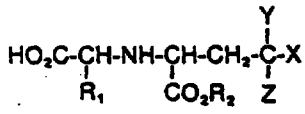
3. A compound as claimed in claim 1 or 2, characterized in that R_2 denotes hydrogen or ethyl, and its physiologically acceptable salts.

4. N-(1-S-Carboethoxy-3-phenyl-propyl)-S-alanyl-2S,3aR,7aS-octahydroindole-2-carboxylic acid,
and its physiologically acceptable salts.

5. N-(1-S-Carboethoxy-3-phenyl-propyl)-S-alanyl-2S,3aS,7aR-octahydroindole-2-carboxylic acid,
and its physiologically acceptable salts.

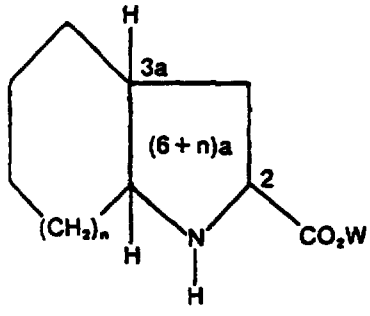
6. A process for the preparation of the compounds of the formula I as claimed in any of claims 1 to 5, which

a) comprises reacting a compound of the formula II



II

wherein R_1, R_2, X, Y and Z have the meanings as in formula I, with a compound of the formula III

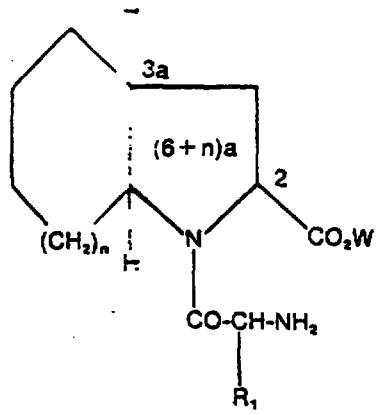


III

in which the H atoms on the C atoms 3a and (6+n)a have the trans configuration relative to one another and wherein
n denotes 0, 1 or 2 and
W denotes a radical which can be cleaved off by hydrogenolysis or by acid, and subsequently splitting off the radical W and, if appropriate, the radical R_2 to form the free carboxyl groups, or

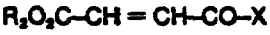
b) for the preparation of compounds of the formula I, in which Y and Z together denote oxygen, comprises

b_1) reacting a compound of the formula IV



IV

in which the H atoms on the C atoms 3a and (6+n)a have the trans configuration relative to one another and wherein n and R_1 have the meanings as in formula I and W has the meaning as in formula III, with a compound of the formula V,



V

wherein R_2 and X have the meanings as in formula I, and subsequently splitting off the radical W and, if appropriate, also the radical R_2 to form the free carboxyl groups, or,

b_2) reacting a compound of the formula IV mentioned under b_1) with a compound of the general formula VI, wherein R_2 has the meaning as in formula I, and with a compound of the general formula VII

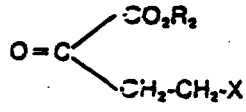


VI VII

wherein X has the meaning as in formula I, subsequently splitting off the radical W and, if appropriate, the radical R_2 to form the free carboxyl group, or

c) for the preparation of compounds of the formula I, in which Y and Z each denote hydrogen, comprises

c_1) reacting a compound of the formula IV mentioned under b_1) with a compound of the formula VIII



VIII

wherein R_2 and X have the meanings as in formula I, reducing the Schiff's bases obtained and subsequently splitting off the radical W and, if appropriate, the radical R_2 to form the free carboxyl groups, or

c_2) catalytically reducing a compound of the formula I in which Y and Z together denote oxygen, with hydrogen, or

d) for the preparation of compounds of the formula I, in which Y denotes hydroxyl and Z denotes hydrogen, comprises reducing a compound of the formula I, in which Y and Z together denote oxy-

* C L M S *

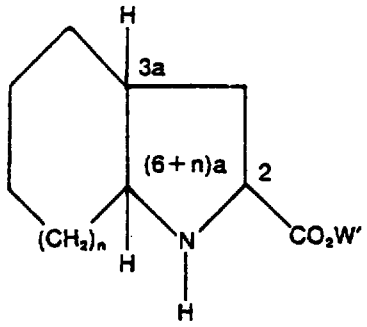
gen, catalytically with hydrogen or with a reducing agent, such as sodium borohydride,
and, if appropriate, converting the compounds obtained according to (a)–(d) into their physiologically acceptable salts.

7. A compound as claimed in any of claims 1 to 5 for the use as a medicine.

8. A compound as claimed in claim 7 for the use as a medicine for treating high blood pressure.

9. A compound as claimed in claim 7 or 8 for the use in combination with a diuretic.

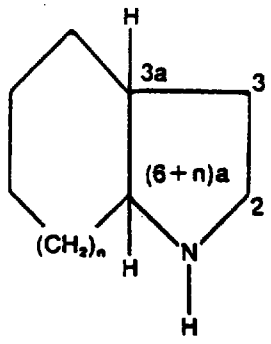
10. A compound of the formula III',



III'

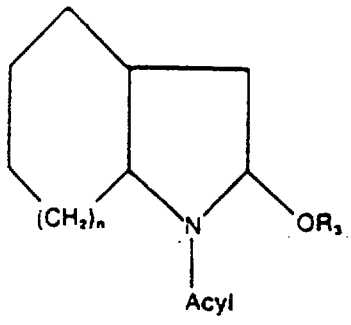
in which the H atom on the C atoms 3a and (6+n)a have the trans configuration relative to one another and in which
n denotes 0, 1 or 2,
W' denotes hydrogen, (C_1–C_{18})-alkyl or (C_7–C_{10})-aralkyl.

11. A process for the preparation of the compounds of the formula III' as claimed in claim 10 which comprises
a) acylating a compound of the formula IX



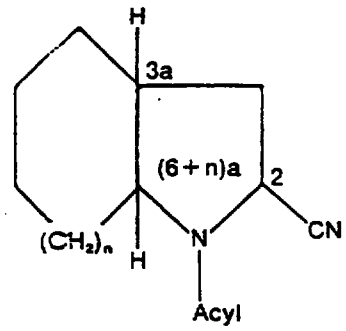
IX

wherein the H atom on the C atoms 3a and (6+n)a have the trans configuration relative to one another and wherein n denotes the number 0, 1 or 2, subsequently anodically oxidizing the compound obtained with an aliphatic alcohol in the presence of a conducting salt to give a compound of the formula X



X

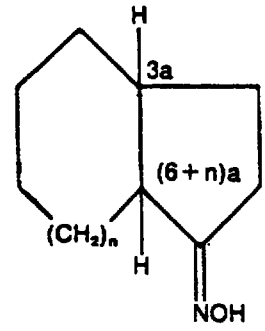
wherein n has the above-mentioned meaning, Acyl is an aliphatic or aromatic acyl radical and R_3 denotes (C_1–C_4)-alkyl, reacting this product with trimethylsilyl cyanide in an aprotic solvent in the presence of a Lewis acid to give a compound of the formula XI



XI

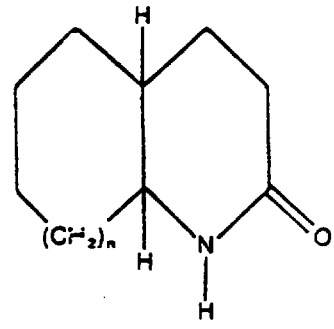
wherein the H atoms on the C atoms 3a and (6+n)a have the trans configuration relative to one another and wherein n has the above-mentioned meaning and hydrolyzing the latter by the action of acids or bases to give a compound of the formula III' with W' = hydrogen and if appropriate, esterifying the latter, or

b) reacting a compound of the formula XII



XII

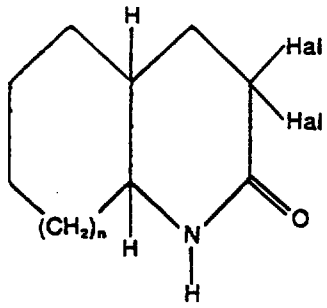
wherein the H atoms on the C atoms 3a and (6+n)a have the trans configuration and n has the above-mentioned meaning, in a Beckmann rearrangement to give a compound of the formula XIII



XIII

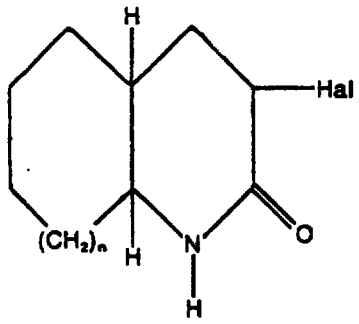
wherein n has the above-mentioned meaning, halogenating the latter to give a compound of the formula XIV

* C L M S *



XIV

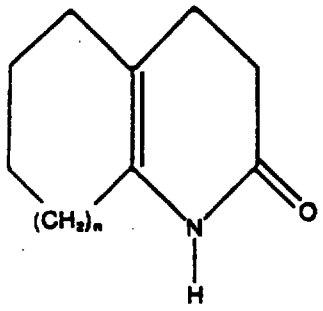
wherein n has the above-mentioned meaning and Hal denotes a halogen atom, catalytically reducing the latter in a polar protic solvent with addition of an acid acceptor to give a compound of the formula XV



XV

wherein n and Hal have the above-mentioned meanings, and subsequently reacting the latter in an alcoholic solvent under the action of a base to give a compound of the formula III' with W' = hydrogen and optionally esterifying the latter, or

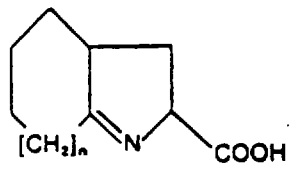
c) reducing a compound of the formula XVI



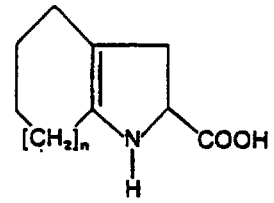
XVI

wherein n has the above-mentioned meaning, with sodium formate and formic acid to give a compound of the formula XIII mentioned under b), and further reacting the latter as described under b), or

d) converting compounds of the formula XXIa or b, in which n has the previous meaning,



XXIa



XXIb

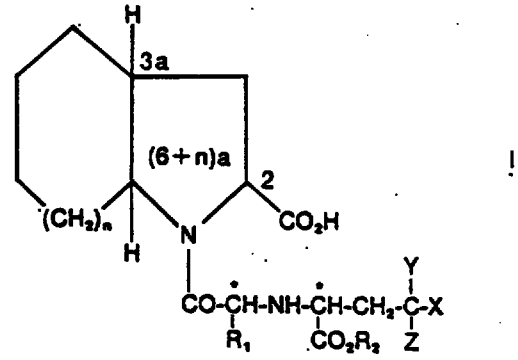
optionally after conversion into their C_1–C_{16}-alkyl or C_7–C_{16}-aralkyl esters, by catalytic hydrogenation in the presence of transition metal catalysts or by reduction with borane-amine complexes or complex borohydrides, into compounds of the formula III', in which W' represents hydrogen, alkyl having 1 to 18 C atoms or aralkyl having 7 to 10 C atoms, saponifying, if appropriate, esters of the formula III' and, if W' is hydrogen, optionally esterifying to give compounds of the formula III', in which n has the previous meaning and W' represents alkyl having 1 to 18 C atoms or aralkyl having 7 to 10 C atoms.

12. A pharmaceutical composition containing a compound as claimed in any of claims 1 to 5.

13. A composition as claimed in claim 12, characterized in that it additionally contains a diuretic.

Claims for the Contracting state: Austria

1. A process for the preparation of the compounds of the formula I



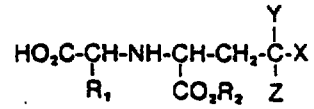
I

in which the hydrogen atoms on the bridgehead C atoms 3a and (6+n)a have the trans configuration relative to one another and wherein

n denotes 0, 1 or 2,
R_1 denotes methyl,
R_2 denotes hydrogen, (C_1–C_4)-alkyl or benzyl,
Y denotes hydrogen or hydroxyl,
Z denotes hydrogen or
Y and Z together denote oxygen and
X denotes phenyl,

and its physiologically acceptable salts, which

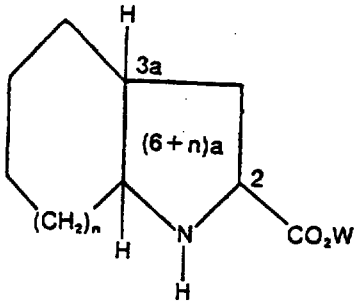
a) comprises reacting a compound of the formula II



II

wherein R_1, R_2, X, Y and Z have the meanings as in formula I, with a compound of the formula III

* C L M S *



III

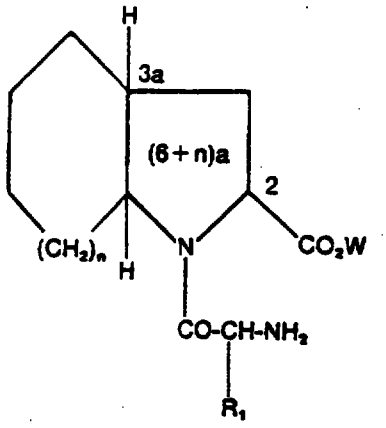
in which the H atoms on the C atoms 3a and (6+n)a have the trans configuration relative to one another and wherein

n denotes 0, 1 or 2 and

W denotes a radical which can be cleaved off by hydrogenolysis or by acid, and subsequently splitting off the radical W and, if appropriate, the radical R_2 to form the free carboxyl groups, or

b) for the preparation of compounds of the formula I, in which Y and Z together denote oxygen, comprises

b_1) reacting a compound of the formula IV



IV

in which the H atoms on the C atoms 3a and (6+n)a have the trans configuration relative to one another and wherein n and R_1 have the meanings as in formula I and W has the meaning as in formula III, with a compound of the formula V.

$$R_2O_2C-CH=CH-CO-X \qquad V$$

wherein R_2 and X have the meanings as in formula I, and subsequently splitting off the radical W and, if appropriate, also the radical R_2 to form the free carboxyl groups, or,

b_2) reacting a compound of the formula IV mentioned under b_1) with a compound of the general formula VI, wherein R_2 has the meaning as in formula I, and with a compound of the general formula VII

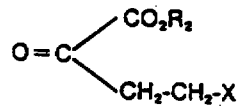
$OHC-CO_2R_2$ VI

$X-CO-CH_3$ VII

wherein X has the meaning as in formula I, subsequently splitting off the radical W and, if appropriate, the radical R_2 to form the free carboxyl group, or

c) for the preparation of compounds of the formula I, in which Y and Z each denote hydrogen, comprises

c_1) reacting a compound of the formula IV mentioned under b_1) with a compound of the formula VIII



VIII

wherein R_2 and X have the meanings as in formula I, reducing the Schiff's bases obtained and subsequently splitting off the radical W and, if appropriate, the radical R_2 to form the free carboxyl groups, or

c_2) catalytically reducing a compound of the formula I in which Y and Z together denote oxygen, with hydrogen, or

d) for the preparation of compounds of the formula I, in which Y denotes hydroxyl and Z denotes hydrogen, comprises reducing a compound of the formula I, in which Y and Z together denote oxygen, catalytically with hydrogen or with a reducing agent, such as sodium borohydride,

and, if appropriate, converting the compounds obtained according to (a)–(d) into their physiologically acceptable salts.

2. A process for the preparation of compounds of the formula I as claimed in claim 1, characterized in that the C atom in position 2 of the bicyclic ring system and the C atom in the side chain labeled with an asterisk have the S configuration.

3. A process for the preparation of compounds as claimed in claim 1 or 2, characterized in that R_2 denotes hydrogen or ethyl, and its physiologically acceptable salts.

4. A process as claimed in any of claims 1 to 3, characterized in that

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

2S,3aR,7aS-octahydroindole-2-carboxylic acid

or its physiologically acceptable salt is prepared.

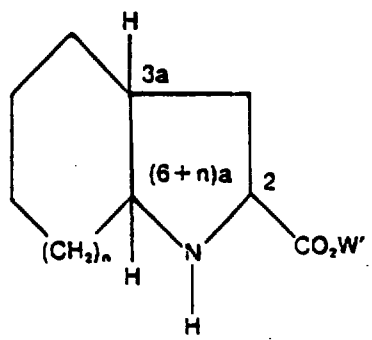
5. A process as claimed in any of claims 1 to 3, characterized in that

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

2S,3aS,7aR-octahydroindole-2-carboxylic acid

or and its physiologically acceptable salt is prepared.

6. A process for the preparation of compounds of the formula III',



III'

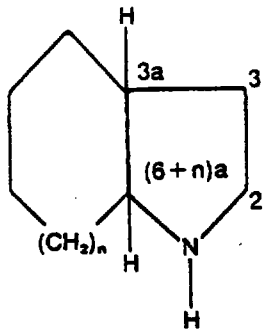
* C L M S *

in which the H atom on the C atoms 3a and (6+n)a have the trans configuration relative to one another and in which

n denotes 0, 1 or 2,

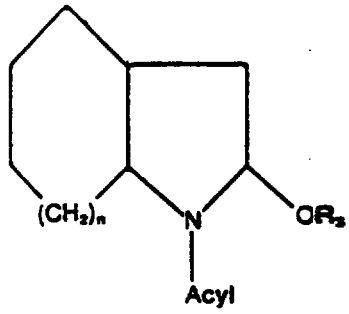
W' denotes hydrogen, (C_1–C_{16})-alkyl or (C_7–C_{10})-aralkyl, which comprises

a) acylating a compound of the formula IX



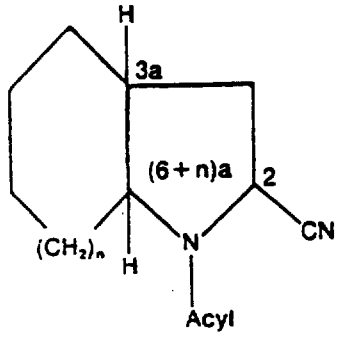
IX

wherein the H atom on the C atoms 3a and (6+n)a have the trans configuration relative to one another and wherein n denotes the number 0, 1 or 2, subsequently anodically oxidizing the compound obtained with an aliphatic alcohol in the presence of a conducting salt to give a compound of the formula X



X

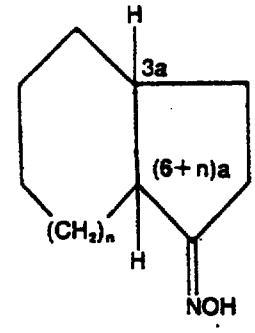
wherein n has the above-mentioned meaning, Acyl is an aliphatic or aromatic acyl radical and R_3 denotes (C_1–C_4)-alkyl, reacting this product with trimethylsilyl cyanide in an aprotic solvent in the presence of a Lewis acid to give a compound of the formula XI



XI

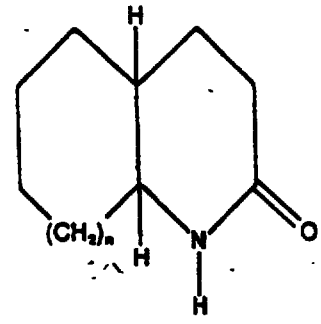
wherein the H atoms on the C atoms 3a and (6+n)a have the trans configuration relative to one another and wherein n has the above-mentioned meaning and hydrolyzing the latter by the action of acids or bases to give a compound of the formula III' with W' = hydrogen and if appropriate, esterifying the latter, or

b) reacting a compound of the formula XII



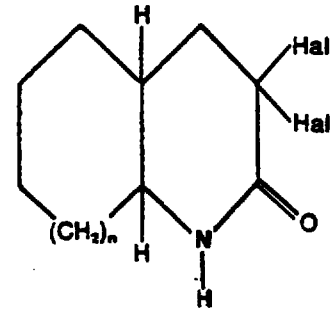
XII

wherein the H atoms on the C atoms 3a and (6+n)a have the trans configuration and n has the above-mentioned meaning, in a Beckmann rearrangement to give a compound of the formula XIII



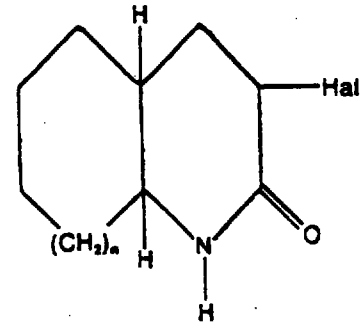
XIII

wherein n has the above-mentioned meaning, halogenating the latter to give a compound of the formula XIV



XIV

wherein n has the above-mentioned meaning and Hal denotes a halogen atom, catalytically reducing the latter in a polar protic solvent with addition of an acid acceptor to give a compound of the formula XV

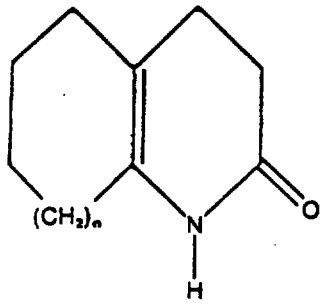


XV

* C L M S *

wnerein n and Hal have the above-mentioned meanings, and subsequently reacting the latter in an alcoholic solvent under the action of a base to give a compound of the formula III' with W' = hydrogen and optionally esterifying the latter, or

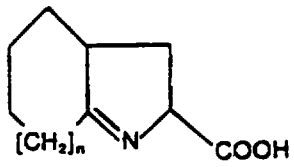
c) reducing a compound of the formula XVI



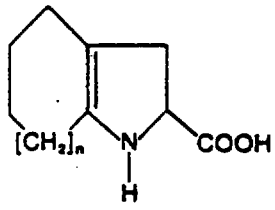
XVI

wherein n has the above-mentioned meaning, with sodium formate and formic acid to give a compound of the formula XIII mentioned under b), and further reacting the latter as described under b), or

d) converting compounds of the formula XXIa or b, in which n has the previous meaning,



XXIa



XXIb

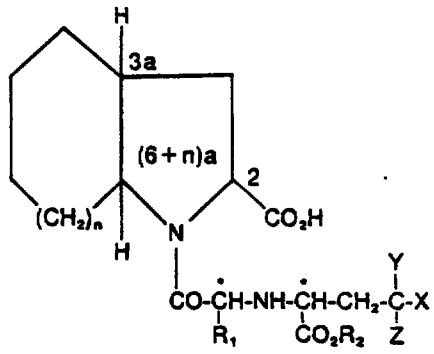
optionally after conversion into their C_1–C_{18}-alkyl or C_7–C_{10}-aralkyl esters, by catalytic hydrogenation in the presence of transition metal catalysts or by reduction with borane-amine complexes or complex borohydrides, into compounds of the formula III', in which W' represents hydrogen, alkyl having 1 to 18 C atoms or aralkyl having 7 to 10 C atoms, saponifying, if appropriate, esters of the formula III' and, if W' is hydrogen, optionally esterifying to give compounds of the formula III', in which n has the previous meaning and W' represents alkyl having 1 to 18 C atoms or aralkyl having 7 to 10 C atoms.

7. A process for the preparation of a pharmaceutical composition containing a compound of the formula I as claimed in any of claims 1 to 5, characterized in that this compound is brought in a suitable form for administration.

8. A process as claimed in claim 7, characterized in that a diuretic is added.

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 sur les atomes de carbone de tête de pont 3a et (6+n)a sont en configuration trans l'un par rapport à l'autre, et dans laquelle

n = 0, 1 ou 2,

R_1 représente le groupe méthyle,

R_2 représente un atome d'hydrogène, un groupe alkyle en C_1–C_4 ou benzyle,

Y représente un atome d'hydrogène ou le groupe hydroxy,

Z représente un atome d'hydrogène, ou

Y et Z représentent ensemble un atome d'oxygène, et

X représente le groupe phényle,

et les sels physiologiquement acceptables de celui-ci.

2. Composé de formule I selon la revendication 1, caractérisé en ce que l'atome de carbone en position 2 du système bicyclique, ainsi que les atomes de carbone de la chaîne latérale qui sont marqués par un astérisque, présentent la configuration S, et les sels physiologiquement acceptables de celui-ci.

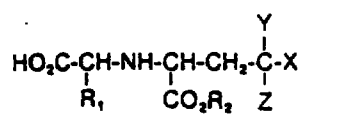
3. Composé de formule I selon la revendication 1 ou 2, caractérisé en ce que R_2 représente un atome d'hydrogène ou le groupe éthyle, et les sels physiologiquement acceptables de celui-ci.

4. Acide N-(1-S-carbéthoxy-3-phényl-propyl)-S-alanyl-2S,3aR,7aS-octahydro-indole-2-carboxylique, et les sels physiologiquement acceptables de celui-ci.

5. Acide N-(1-S-carbéthoxy-3-phényl-propyl)-S-alanyl-2S,3aS,7aR-octahydro-indole-2-carboxylique, et les sels physiologiquement acceptables de celui-ci.

6. Procédé pour la préparation des composés de formule I selon une des revendications 1 à 5, caractérisé en ce que

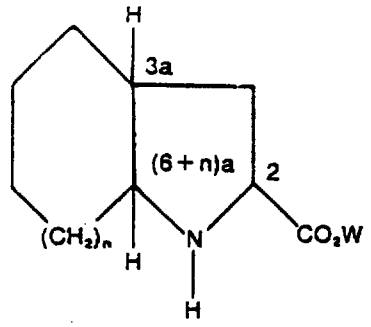
a) on fait réagir un composé de formule II



II

dans laquelle R_1, R_2, X, Y et Z ont les mêmes significations que dans la formule I, avec un composé de formule III

* C L M S *



III

dans laquelle les atomes d'hydrogène sur les atomes de carbone 3a et (6+n)a sont en configuration trans l'un par rapport à l'autre,

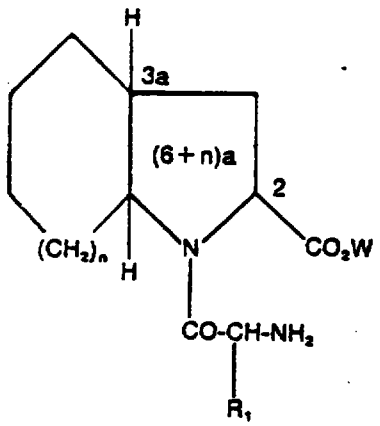
n = 0, 1 ou 2, et

W représente un reste séparable par hydrogénolyse ou par voie acide,

et on sépare ensuite le reste W et, éventuellement, le reste R_2 pour obtenir les groupes carboxy libres, ou

b) on fait réagir, pour la préparation des composés de formule I dans lesquels Y et Z représentent ensemble un atome d'oxygène,

b_1) un composé de formule IV



IV

dans laquelle les atomes d'hydrogène sur les atomes de carbone 3a et (6+n)a sont en configuration trans l'un par rapport à l'autre, et dans laquelle n et R_1 ont les mêmes significations que dans la formule I et W a la même signification que dans la formule III, avec un composé de formule V

$$R_2O_2C-CH=CH-CO-X \qquad V$$

dans laquelle R_2 et X ont les mêmes significations que dans la formule I, et on sépare ensuite le reste W et, éventuellement, aussi le reste R_2, pour former les groupes carboxy libres, ou

b_2) un composé de formule IV indiquée en b_1) avec un composé de formule générale VI

$$CHC-CO_2R_2 \qquad VI$$

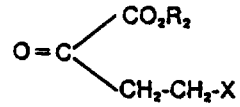
dans laquelle R_2 a la même signification que dans la formule I, et avec un composé de formule générale VII

$$X-CO-CH_3 \qquad VII$$

dans laquelle X a la même signification que dans la formule I, et on sépare ensuite le reste W et éventuellement le reste R_2, en formant les groupes carboxy libres, ou

c) pour la préparation des composés de formule I dans lesquels Y et Z représentent chacun un atome d'hydrogène,

c_1) on fait réagir un composé de formule IV indiquée en b_1) avec un composé de formule VIII



VIII

dans laquelle R_2 et X ont les mêmes significations que dans la formule I, on réduit les bases de Schiff obtenues et on sépare ensuite le reste W et éventuellement le reste R_2 en formant les groupes carboxy libres, ou

c_2) on réduit avec de l'hydrogène, par voie catalytique, un composé de formule I dans lequel Y et Z représentent ensemble un atome d'oxygène, ou

d) pour la préparation des composés de formule I dans lesquels Y représente un groupe hydroxy et Z représente un atome d'hydrogène, on réduit au moyen d'hydrogène, par voie catalytique, ou avec un réducteur tel que le borohydrure de sodium, un composé de formule I dans lequel X et Y représentent ensemble un atome d'oxygène,

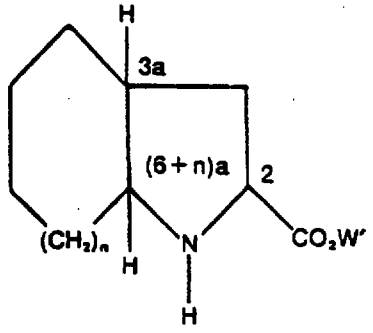
et on transforme éventuellement les composés obtenus selon (a)–(d) en leurs sels physiologiquement acceptables.

7. Composé selon l'une des revendications 1 à 5, pour utilisation comme médicament.

8. Composé selon la revendication 7, pour utilisation comme médicament dans le traitement de l'hypertension.

9. Composé selon la revendication 7 ou 8, pour utilisation en association avec un diurétique.

10. Composé de formule III'



III'

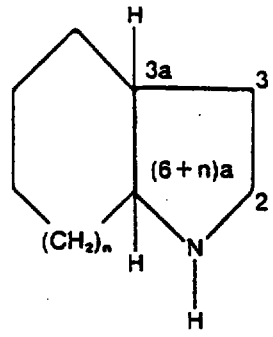
dans laquelle les atomes d'hydrogène sur les atomes de carbone 3a et (6+n)a sont en configuration trans l'un par rapport à l'autre, et dans laquelle

n = 0, 1 ou 2,

W' représente un atome d'hydrogène, un groupe alkyle en C_1–C_{18} ou un groupe aralkyle en C_7–C_{18}.

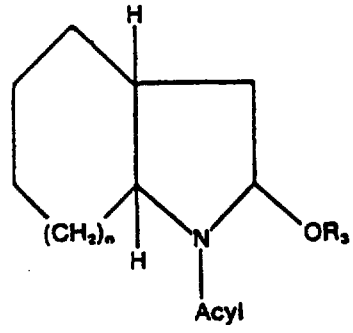
11. Procédé pour la préparation des composés de formule III' selon la revendication 10, caractérisé en ce que

a) on soumet à une acylation un composé de formule IX



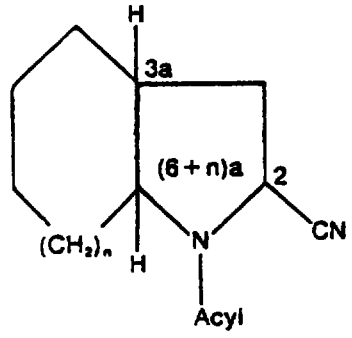
IX

dans laquelle les atomes d'hydrogène sur les atomes de carbone 3a et (6+n)a sont en configuration trans l'un par rapport à l'autre, et dans laquelle n représente 0, 1 ou 2, on le soumet ensuite à une oxydation anodique avec un alcool aliphatique, en présence d'un sel conducteur, pour obtenir un composé de formule X



X

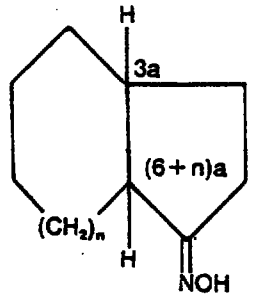
dans laquelle n a la signification donnée plus haut, «acyle» étant un radical acyle aliphatique ou aromatique, et R_3 représente un groupe alkyle en C_1–C_4, on fait réagir ce composé avec du cyanure de triméthylsilyle dans un solvant organique aprotique, en présence d'un acide de Lewis, pour aboutir à un composé de formule XI



XI

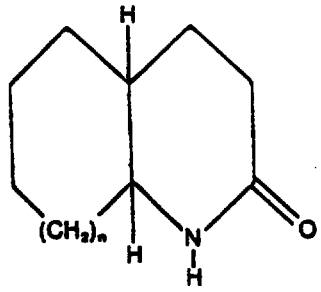
dans laquelle les atomes d'hydrogène sur les atomes de carbone 3a et (6+n)a sont en configuration trans l'un par rapport à l'autre, et dans laquelle n a la signification donnée plus haut, puis on hydrolyse celui-ci sous l'action d'acides ou de bases, pour aboutir à un composé de formule III' dans lequel W' est un atome d'hydrogène, et on estérifie éventuellement ce dernier, ou

b) on fait réagir un composé de formule XII



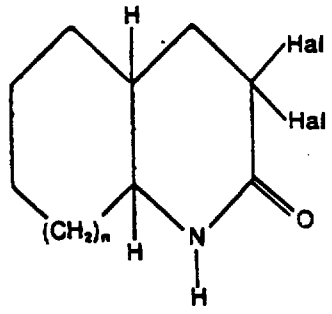
XII

dans laquelle les atomes d'hydrogène sur les atomes de carbone 3a et (6+n)a sont en configuration trans et n a la signification donnée plus haut, dans une transposition de Beckmann, pour aboutir à un composé de formule XIII



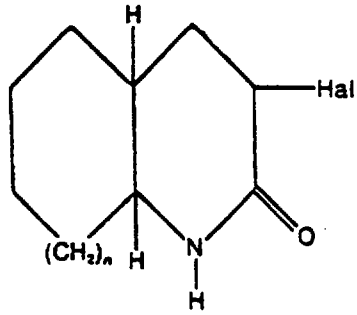
XIII

dans laquelle n a la signification donnée plus haut, on soumet celui-ci à une halogénation pour aboutir à un composé de formule XIV,



XIV

dans laquelle n a la signification donnée plus haut et Hal représente un atome d'halogène, on réduit ce composé par voie catalytique, dans un solvant polaire protique, en utilisant un accepteur d'acide, pour aboutir à un composé de formule XV

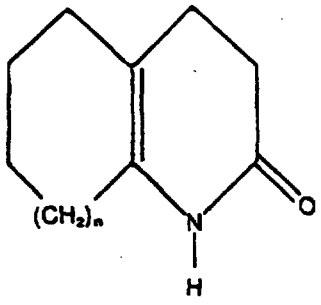


XV

dans laquelle n et Hal ont les significations données plus haut, et on transforme ensuite celui-ci, sous l'effet d'une base, dans un solvant alcoolique, en un composé de formule III' dans lequel W' est un atome d'hydrogène, puis on estérifie éventuellement celui-ci, ou

c) on réduit avec du formiate de sodium et de l'acide formique un composé de formule XVI

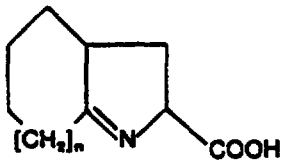
* C L M S *



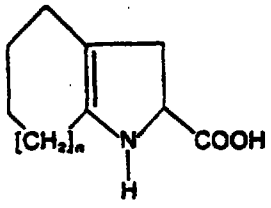
XVI

dans laquelle n a la signification donnée plus haut, pour aboutir à un composé de formule XIII indiquée en b), et on poursuit la transformation de celui-ci comme décrit en b), ou

d) on transforme des composés de formule XXIa ou b



XXIa



XXIb

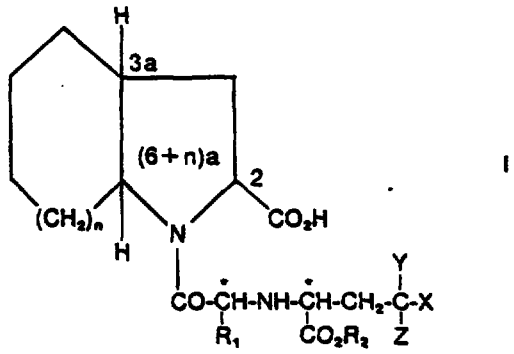
dans lesquelles n a la signification donnée plus haut, éventuellement après conversion en leurs esters d'alkyle en C_1–C_{18} ou d'aralkyle en C_7–C_{10}, par hydrogénation catalytique en présence de catalyseurs à base de métaux de transition, ou par réduction avec des complexes borane-amine ou des borohydrures complexes, en composés de formule III' dans lesquels W' représente un atome d'hydrogène, un groupe alkyle ayant de 1 à 18 atomes de carbone ou un groupe aralkyle ayant de 7 à 10 atomes de carbone, on saponifie éventuellement les esters de formule III' obtenus et, au cas où W' est un atome d'hydrogène, on les estérifie éventuellement, pour aboutir à des composés de formule III' dans lesquels W' représente un groupe alkyle ayant de 1 à 18 atomes de carbone ou un groupe aralkyle ayant de 7 à 10 atomes de carbone.

12. Produit pharmaceutique contenant un composé selon l'une des revendications 1 à 5.

13. Produit selon la revendication 12, caractérisé en ce qu'il contient en outre un diurétique.

Revendications pour l'Etat contractant: AT

1. Procédé pour la préparation des composés de formule I



I

dans laquelle les atomes d'hydrogène sur les atomes de carbone de tête de pont 3a et (6+n)a sont en configuration trans l'un par rapport à l'autre, et dans laquelle

n = 0, 1 ou 2,

R_1 représente le groupe méthyle,

R_2 représente un atome d'hydrogène, un groupe alkyle en C_1–C_4 ou benzyle,

Y représente un atome d'hydrogène ou le groupe hydroxy,

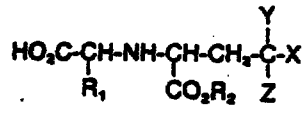
Z représente un atome d'hydrogène, ou

Y et Z représentent ensemble un atome d'oxygène, et

X représente le groupe phényle,

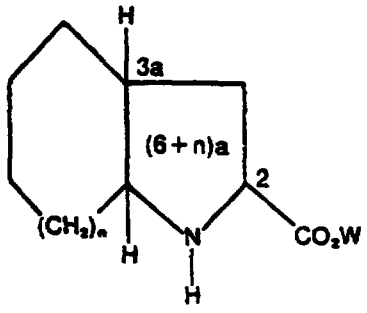
et des sels physiologiquement acceptables de ceux-ci, caractérisé en ce que

a) on fait réagir un composé de formule II



II

dans laquelle R_1, R_2, X, Y et Z ont les mêmes significations que dans la formule I, avec un composé de formule III



III

dans laquelle les atomes d'hydrogène sur les atomes de carbone 3a et (6+n)a sont en configuration trans l'un par rapport à l'autre,

n = 0, 1 ou 2, et

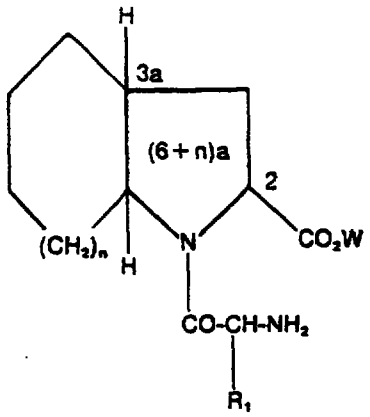
W représente un reste séparable par hydrogénolyse ou par voie acide,

et on sépare ensuite le reste W et, éventuellement, le reste R_2 pour obtenir les groupes carboxy libres, ou

b) on fait réagir, pour la préparation des composés de formule I dans lesquels Y et Z représentent ensemble un atome d'oxygène,

b_1) un composé de formule IV

* C L M S *



IV

dans laquelle les atomes d'hydrogène sur les atomes de carbone 3a et (6+n)a sont en configuration trans l'un par rapport à l'autre, et dans laquelle n et R_1 ont les mêmes significations que dans la formule I et W a la même signification que dans la formule III, avec un composé de formule V

$$R_2O_2C\text{–}CH = CH\text{–}CO\text{–}X \qquad V$$

dans laquelle R_2 et X ont les mêmes significations que dans la formule I, et on sépare ensuite le reste W et, éventuellement, aussi le reste R_2, pour former les groupes carboxy libres, ou

b_2) un composé de formule IV indiquée en b_1) avec un composé de formule générale VI

$$OHC\text{–}CO_2R_2 \qquad VI$$

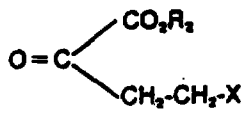
dans laquelle R_2 a la même signification que dans la formule I, et avec un composé de formule générale VII

$$X\text{–}CO\text{–}CH_3 \qquad VII$$

dans laquelle X a la même signification que dans la formule I, et on sépare ensuite le reste W et éventuellement le reste R_2, en formant les groupes carboxy libres, ou

c) pour la préparation des composés de formule I dans lesquels Y et Z représentent chacun un atome d'hydrogène,

c_1) on fait réagir un composé de formule IV indiquée en b_1) avec un composé de formule VIII



VIII

dans laquelle R_2 et X ont les mêmes significations que dans la formule I, on réduit les bases de Schiff obtenues et on sépare ensuite le reste W et éventuellement le reste R_2 en formant les groupes carboxy libres, ou

c_2) on réduit avec de l'hydrogène, par voie catalytique, un composé de formule I dans lequel Y et Z représentent ensemble un atome d'oxygène, ou

d) pour la préparation des composés de formule I dans lesquels Y représente un groupe hydroxy et Z représente un atome d'hydrogène, on réduit au moyen d'hydrogène, par voie catalytique, ou avec un réducteur tel que le borohydrure de sodium, un composé de formule I dans lequel X et Y représentent ensemble un atome d'oxygène, et on transforme éventuellement les composés obtenus selon (a)–(d) en leurs sels physiologiquement acceptables.

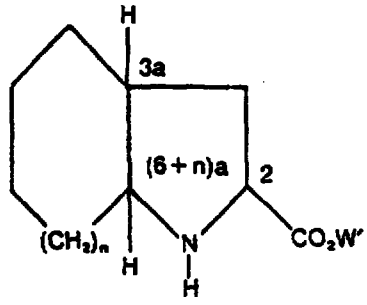
2. Procédé pour la préparation de composés de formule I selon la revendication 1, caractérisé en ce que l'atome de carbone en position 2 du système bicyclique, ainsi que les atomes de carbone de la chaîne latérale qui sont marqués par un astérisque, présentent la configuration S.

3. Procédé pour la préparation de composés de formule I selon la revendication 1 ou 2, caractérisé en ce que R_2 représente un atome d'hydrogène ou le groupe éthyle.

4. Procédé selon l'une des revendications 1 à 3, caractérisé en ce que l'on prépare l'acide N-(1-S-carbéthoxy-3-phényl-propyl)-S-alanyl-2S,3aR,7aS-octahydro-indole-2-carboxylique ou un sel physiologiquement acceptable de celui-ci.

5. Procédé selon l'une des revendications 1 à 3, caractérisé en ce que l'on prépare l'acide N-(1-S-carbéthoxy-3-phényl-propyl)-S-alanyl-2S,3aS,7aR-octahydro-indole-2-carboxylique ou un sel physiologiquement acceptable de celui-ci.

6. Procédé pour la préparation des composés de formule III'



III'

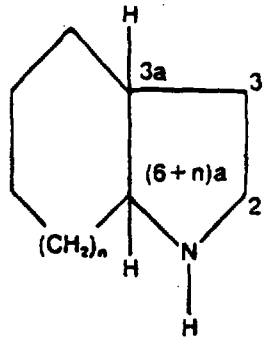
dans laquelle les atomes d'hydrogène sur les atomes de carbone 3a et (6+n)a sont en configuration trans l'un par rapport à l'autre, et dans laquelle

n = 0, 1 ou 2,

W' représente un atome d'hydrogène, un groupe alkyle en C_1–C_{12} ou un groupe aralkyle en C_7–C_{16},

caractérisé en ce que

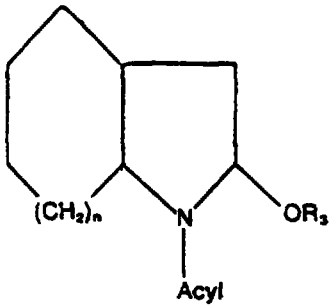
a) on soumet à une acylation un composé de formule IX



IX

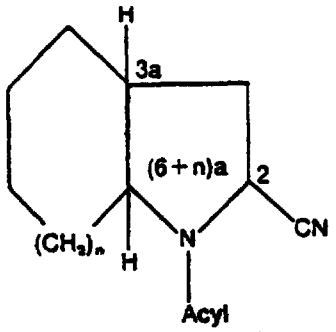
* C L M S *

dans laquelle les atomes d'hydrogène sur les atomes de carbone 3a et (6+n)a sont en configuration trans l'un par rapport à l'autre, et dans laquelle n représente 0, 1 ou 2, on le soumet ensuite à une oxydation anodique avec un alcool aliphatique, en présence d'un sel conducteur, pour obtenir un composé de formule X



X

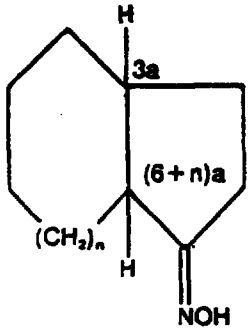
dans laquelle n a la signification donnée plus haut, acyle étant un radical acyle aliphatique ou aromatique, et R_3 représente un groupe alkyle en C_1–C_4, on fait réagir ce composé avec du cyanure de triméthylsilyle dans un solvant organique aprotique, en présence d'un acide de Lewis, pour aboutir à un composé de formule XI



XI

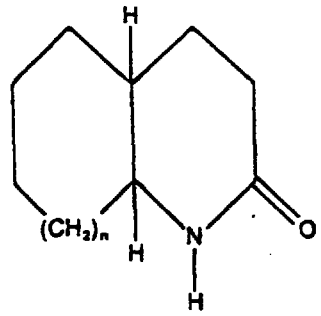
dans laquelle les atomes d'hydrogène sur les atomes de carbone 3a et (6+n)a sont en configuration trans l'un par rapport à l'autre, et dans laquelle n a la signification donnée plus haut, puis on hydrolyse celui-ci sous l'action d'acides ou de bases, pour aboutir à un composé de formule III' dans lequel W' est un atome d'hydrogène, et on estérifie éventuellement ce dernier, ou

b) on fait réagir un composé de formule XII



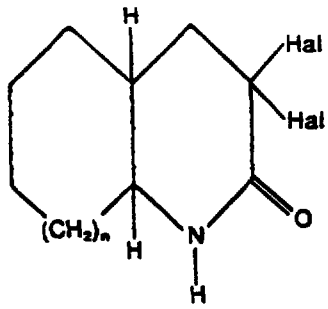
XII

dans laquelle les atomes d'hydrogène sur les atomes de carbone 3a et (6+n)a sont en configuration trans et n a la signification donnée plus haut, dans une transposition de Beckmann, pour aboutir à un composé de formule XIII



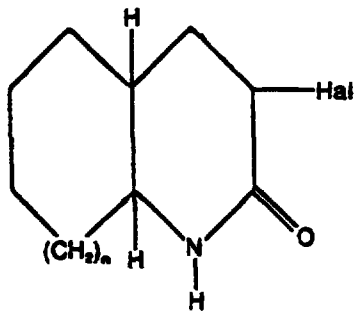
XIII

dans laquelle n a la signification donnée plus haut, on soumet celui-ci à une halogénation pour aboutir à un composé de formule XIV,



XIV

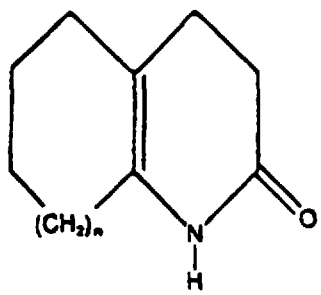
dans laquelle n a la signification donnée plus haut et Hal représente un atome d'halogène, on réduit ce composé par voie catalytique, dans un solvant polaire protique, en utilisant un accepteur d'acide, pour aboutir à un composé de formule XV



XV

dans laquelle n et Hal ont les significations données plus haut, et on transforme ensuite celui-ci, sous l'effet d'une base, dans un solvant alcoolique, en un composé de formule III' dans lequel W' est un atome d'hydrogène, puis on estérifie éventuellement celui-ci, ou

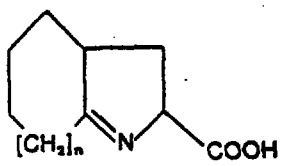
c) on réduit avec du formiate de sodium et de l'acide formique un composé de formule XVI



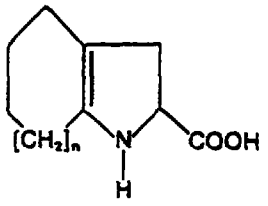
XVI

dans laquelle n a la signification donnée plus haut, pour aboutir à un composé de formule XIII indiquée en b), et on poursuit la transformation de celui-ci comme décrit en b), ou

d) on transforme des composés de formule XXIa ou b



XXIa



XXIb

dans lesquelles n a la signification donnée plus haut, éventuellement après conversion en leurs esters d'alkyle en C_1–C_{18} ou d'aralkyle en C_7–C_{10}, par hydrogénation catalytique en présence de catalyseurs à base de métaux de transition, ou par réduction avec des complexes borane-amine ou des borohydrures complexes, en composés de formule III' dans lesquels W' représente un atome d'hydrogène, un groupe alkyle ayant de 1 à 18 atomes de carbone ou un groupe aralkyle ayant de 7 à 10 atomes de carbone, on saponifie éventuellement les esters de formule III' obtenus et, au cas où W' est un atome d'hydrogène, on les estérifie éventuellement, pour aboutir à des composés de formule III' dans lesquels W' représente un groupe alkyle ayant de 1 à 18 atomes de carbone ou un groupe aralkyle ayant de 7 à 10 atomes de carbone.

7. Procédé pour la préparation d'un produit pharmaceutique contenant un composé de formule I selon une des revendications 1 à 5, caractérisé en ce que l'on met celui-ci sous une forme d'administration appropriée.

8. Procédé selon la revendication 7, caractérisé en ce que l'on ajoute un diurétique.

* C L M S *