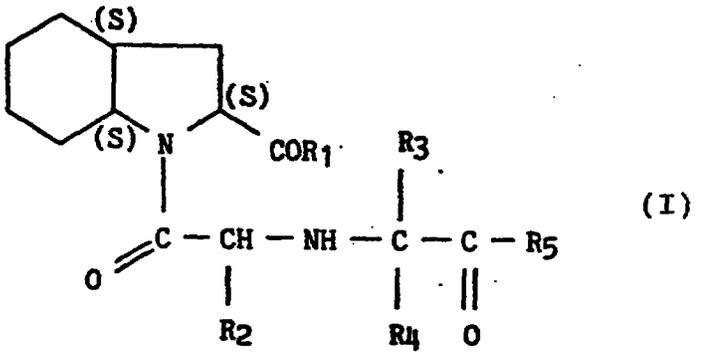
The present invention relates to a new process for the industrial synthesis of (2S,3aS,7aS)-perhydroindole-2-carboxylic acid and its application in the industrial synthesis of carboxyalkyl dipeptides.

More specifically, the present invention relates to a process for the industrial synthesis of perhydro-indole-2-carboxylic acid and its application in the synthesis of carboxyalkyl dipeptides of formula (I) :



(I)

and their pharmaceutically acceptable salts,
in which:
R_1 and R_5, which are the same or different, represent hydroxy, lower alkoxy, lower alkenyloxy, di-lower alkylamino-lower alkoxy, acylamino-lower alkoxy, acyloxy-lower alkoxy, aryloxy, aryl-lower alkoxy, amino, lower alkylamino, di-lower alkylamino, hydroxyamino, aryl-lower alkylamino or substituted aryloxy or substituted aryl-lower alkoxy wherein the substituent is methyl, halo or methoxy;

R_2 is hydrogen, lower alkyl, aryl-lower alkyl, amino-methylphenyl-lower alkyl, hydroxyphenyl-lower alkyl, hydroxy-lower alkyl, acylamino-lower alkyl, amino-lower alkyl, dimethylamino-lower alkyl, guanidino-lower alkyl, imidazolyl-lower alkyl, indolyl-lower alkyl or lower alkylthio-lower alkyl;

R_3 is hydrogen, a straight-chain or branched alkyl having

from 1 to 10 carbon atoms, a lower alkyl substituted by one or more substituents selected from halo, hydroxy, lower alkoxy, aryloxy, substituted aryloxy, heteroaryloxy, substituted heteroaryloxy, amino, lower alkylamino, di-lower alkylamino, acylamino, arylamino, substituted arylamino, guanidino, imidazolyl, indolyl, lower alkylthio, arylthio, substituted arylthio, carboxy, carbamoyl and lower alkoxycarbonyl, or R_3 is aryl, substituted aryl, aryl-lower alkyl, aryl-lower alkenyl, substituted aryl-lower alkyl, substituted aryl-lower alkenyl, heteroaryl-lower alkyl, substituted heteroaryl-lower alkyl, heteroaryl-lower alkenyl, substituted heteroaryl-lower alkenyl, aralkoxy, substituted aralkoxy, heteroaralkoxy, substituted heteroaralkoxy, aralkylthio, substituted aralkylthio, heteroaralkylthio or substituted heteroaralkylthio, the aryl or heteroaryl moiety of the above substituted aryloxy, heteroaryloxy, arylamino, arylthio, aryl, aralkoxy, heteroaralkoxy, aralkylthio, heteroaralkylthio, aryl-lower alkyl, aryl-lower alkenyl, heteroaryl-lower alkenyl and heteroaryl-lower alkyl being substituted by one or more groups selected from halo, lower alkyl, hydroxy, lower alkoxy, amino, acylamino, lower alkylamino, di-lower alkylamino, carboxy, cyano and sulphamoyl; the alkyl moiety of the said substituted aralkoxy, aralkylthio, aryl-lower alkyl, heteroaryl-lower alkyl, heteroaralkoxy and heteroaralkylthio being substituted by one or more groups also selected from halo, lower alkyl, hydroxy, lower alkoxy, amino, acylamino, lower alkylamino, di-lower alkylamino, carboxy, cyano and sulphamoyl;

and

R_4 is hydrogen or a lower alkyl group.

Among the meanings mentioned above, it should be

noted that the term "acyl" includes the radicals $-\overset{\overset{O}{\|}}{C}-R_6$ in which R_6 represents lower alkyl, lower alkenyl or aryl.

The terms lower alkyl and lower alkenyl denote any hydrocarbon radical having from 1 to 6 carbon atoms, either straight-chain or branched, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec.-butyl, tert.-butyl, pentyl, vinyl, allyl etc..

Unless specified otherwise, the term aryl denotes phenyl or naphthyl optionally substituted by one or more lower alkyl or lower alkoxy groups, such as tolyl, xylyl etc..

The term heteroaryl may be illustrated by the radicals pyridyl, thienyl, furyl, pyrrolyl, benzothienyl, benzofuryl, indolyl, thiazolyl, imidazolyl, oxazolyl, benzimidazolyl, benzothiazolyl, benzoxazolyl and also one of the afore-mentioned in which one or more -CH- chain members is replaced by an -N- chain member.

Preferred compounds of formula (I) are those in which :

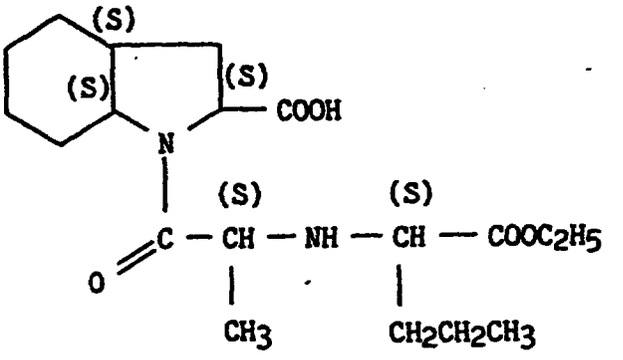
R_1 and R_5 are each independently of the other a hydroxy group or a straight-chain or branched lower alkoxy group,

R_2 is a straight-chain or branched lower alkyl group optionally substituted by an amino group,

R_3 is a straight-chain or branched lower alkyl group optionally substituted by a cycloalkyl or aryl radical, such as phenyl, and among those n-propyl,

n-butyl and phenylethyl groups are preferred, and R_4 is a hydrogen atom.

The preferred compound of formula (I) is perindopril of formula (II) :



(II)

or (2S,3aS,7aS)-1-{2(S)-[1(S)-(ethoxycarbonyl)butyl-amino]propionyl}-octahydroindole-2-carboxylic acid,

as well as the addition salts thereof with a pharmaceutically acceptable acid or base,

for which the process of the present invention may be more especially applied.

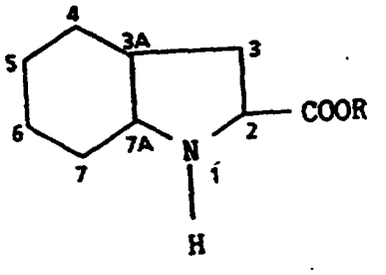
The compounds of formula (I) and their salts possess valuable pharmacological properties. In particular they exert an inhibiting activity on certain enzymes, such as the carboxypolypeptidases, the enkephalinases or kininase II. They inhibit especially the transformation of the decapeptide angiotensin I into the octapeptide angiotensin II, responsible in certain cases for arterial hypertension, by acting on the converting enzyme.

The therapeutic use of those compounds thus makes it possible to reduce or even suppress the activity of those enzymes responsible for hypertension or cardiac defic-

iency. The action on kininase II results in an increase in circulating bradykinin and also in a reduction in arterial tension by that means.

Compounds of formula (I), their preparation and their therapeutic use have been described in European Patents Nos. 0 049 658 and 0 088 341 and in European Patent Applications Nos. 0 154 886 and 0 046 953. The compound of formula (II), its preparation and its therapeutic use have been described in European Patent No. 0 049 658.

In particular, one of the starting materials that may be used for the preparation of compounds of formula (I) is perhydroindole-2-carboxylic acid described in European Patent Application No. 0 037 231, and also its esters of formula (III):

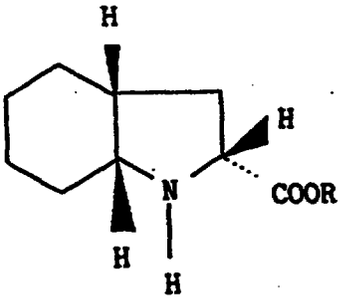


(III)

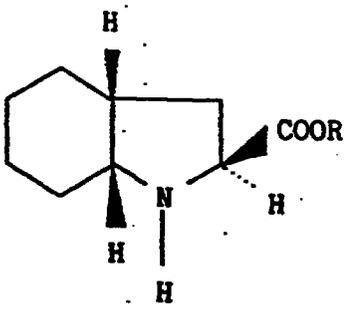
wherein R represents a lower alkyl group, a benzyl group or a hydrogen atom.

The compounds of formula (III) exist in the form of four pairs of racemates :

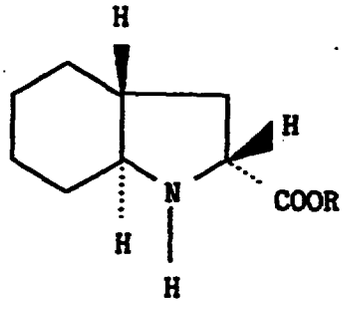
the two cis epimers IIIa and IIIb
the two trans epimers IIIc and IIId



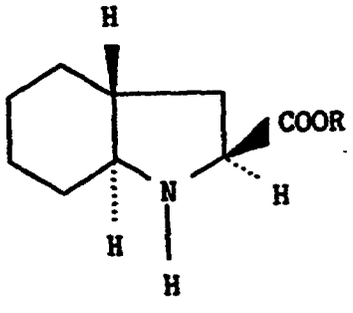
(±) IIIa
cis, endo
2S,3aS,7aS or 2R,3aR,7aR



(±) IIIb
cis, exo
2S,3aR,7aR or 2R,3aS,7aS



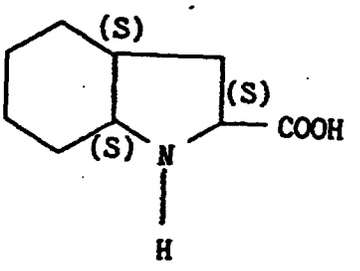
(±) IIIc
trans α
2S,3aS,7aR or 2R,3aR,7aS



(±) IIId
trans ß
2S,3aS,7aR or 2S,3aR,7aS

The preparation of those compounds of formula (III) can be carried out by well-known methods from the prior art (EP 0 037 231, EP O 084 164, EP 0 115 345, EP 0 173 199, EP 0 132 580).

However, the isomer specifically used in the synthesis of compounds of formula (I) is (2S,3aS,7aS)-perhydroindole-2-carboxylic acid as well as its esters of formula (IIIaS) :



(IIIaS).

It is in fact known (EP 37231, EP 49658, EP 88341, EP 154 886) that the compounds of formula (I) of which the configuration of the bicyclic system is 2S,3aS,7aS have an activity that is distinctly superior to that of the compounds in which the cis configuration of the bicyclic system is different.

The preparation of (2S,3aS,7aS)-perhydroindole-2-carboxylic acid can be carried out in accordance with the methods described in the prior art (EP 0 037 231, EP 0 115 345, EP 0 173 199, EP 0 132 580).

Some of them use indole-2-carboxylic acid as starting material, which has the advantage of being a readily available starting material and of posing relatively few problems (EP 0 037 231), which is subjected to catalytic reduction on rhodium-on-carbon to yield a mixture of the two cis and endo isomers of the configurations 2S,3aS,7aS and 2R,3aR,7aR.

The separation of the 2S,3aS,7aS isomer, however, which is used in the synthesis of the carboxyalkyl dipeptides of formula (I), from the 2R,3aR,7aR isomer generally requires the use of methods that are particularly laborious.

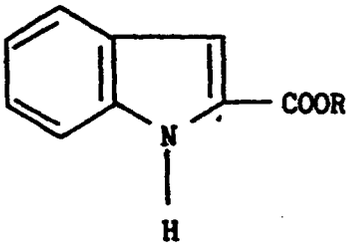
Thus, in order to carry out this separation of the 2S,3aS,7aS and 2R,3aR,7aR isomers (racemic cis, endo), Patent no. 0 037 231 uses numerous steps requiring the

synthesis of the N-benzoylated derivative, fractional crystallisation of the salt of the diastereoisomer with S-α-phenylethylamine, liberation of the two N-benzoylated derivatives SSS and RRR, then removal of the benzoyl group followed by passage through an ion exchange column and recrystallisation.

European Patent Application No. 0 115 345 uses, for that same separation, several steps requiring the esterification of the carboxylic acid function by benzyl alcohol, conversion of the amino ester into a salt by (S)-N-benzyloxycarbonylphenylalanine, removal of the S,S,S-isomer by fractional crystallisation, and liberation of the optionally aminated function followed by liberation of the carboxylic acid grouping.

The Applicant has now discovered a novel process for the synthesis of (2S,3aS,7aS)-perhydroindole-2-carboxylic acid that also has the advantage of using indole-2-carboxylic acid as starting material but does not have the drawback of laborious separation of the two isomers 2S,3aS,7aS and 2R,3aR,7aR of perhydroindolecarboxylic acid, since the indolecarboxylic acid is in a first step reduced to indolinecarboxylic acid to give a mixture of (2R)- and (2S)-indoline-2-carboxylic acid which are easily separated in a single step by fractional crystallisation, the (2S) isomer then being subjected to catalytic hydrogenation to yield stereoselectively, after crystallisation from a carefully selected polar solvent, (2S,3aS,7aS)-perhydroindole-2-carboxylic acid.

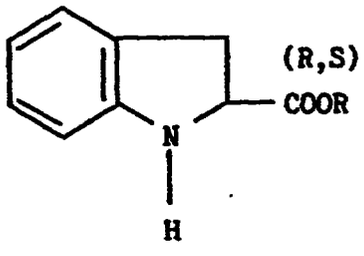
More especially, the synthesis of (2S,3aS,7aS)-perhydroindole-2-carboxylic acid discovered by the Applicant uses as starting material indole-2-carboxylic acid or one of its esters of formula (IV) :



(IV),

in which R represents a lower alkyl group, a benzyl group or a hydrogen atom,

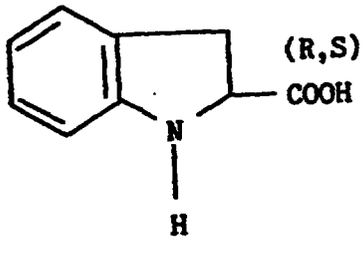
which is subjected to reduction by a process using the couple tin/hydrochloric acid, at room temperature in a lower aliphatic alcohol medium, to yield (R,S)-indoline-2-carboxylic* acid or one of its esters of formula (V) :



(V)

in which R has the same meaning as in formula (IV), which, when R = H, is the (R,S)-indoline-2-carboxylic acid of formula (VI);

which, when R is other than H, is converted by alkaline hydrolysis into (R,S)-indoline-2-carboxylic acid of formula (VI) :



(VI)

* Translator's note: "carboxylic" has been inserted by the translator as it is assumed "carboxylique" was omitted from the French text in error.

which, in fact, comprises a mixture of two isomers according to how the carboxy-carrying carbon atom is configured :

- in the R configuration (R isomer),
- in the S configuration (S isomer),

a mixture from which the S isomer is isolated by adding the said mixture to a solution of (+)-α-methylbenzylamine in a lower aliphatic alcohol, to obtain a precipitate of the salt of (S)-indoline-2-carboxylic acid with α-methylbenzylamine,

which, after filtration, is dissolved in water, the solution obtained then being acidified to allow the (S)-indoline-2-carboxylic acid to be liberated,

which acid is subjected to catalytic hydrogenation, the catalyst being selected from platinum, nickel, palladium and rhodium in admixture with a support such as carbon, so as to obtain (2S,3aS,7aS)-perhydroindole-2-carboxylic acid, the latter being separated from the small proportion of (2S,3aR,7aR)-isomer by a single crystallisation in a solvent carefully selected from a lower aliphatic alcohol, acetonitrile, dioxan and ethyl acetate, alone, or mixed with one another or with water provided the mixture is monophasic.

It should be noted that the (R)-indoline-2-carboxylic acid can be separated from the (R,S)-indoline-2-carboxylic acid using the same process as for (S)-indoline-2-carboxylic* acid : it is thus sufficient to

* Translator's note: "carboxylic" has been inserted by the translator as it is assumed "carboxylique" was omitted from the French text in error.

use (-)-α-methylbenzylamine.

The invention extends also to novel products obtained during the course of the execution of this process.

The following Example illustrates the invention but does not limit it in any way.

EXAMPLE : (2S,3aS,7aS)-OCTAHYDROINDOLE-2-CARBOXYLIC ACID

Heat to the boil 5 kg of 2-carboxyindole, suspend in ethanol in the presence of sulphuric acid for 8 hours. Evaporate the ethanol, then take up in 40 litres of ethyl acetate and wash the organic solution with an aqueous sodium hydroxide solution and dry.

Evaporate the ethyl acetate, and take up the crystalline mass in hexane. After suction-filtering and drying, 5.3 kg of crystals are obtained.

Melting point : 123-125°C.

Microanalysis :

Calculated :	C % 69.83	H % 5.86	N % 7.40
Found :	C % 69.56	H % 5.74	N % 7.30

Infrared spectrometry :
2150 cm^{-1} (NH)
1680 cm^{-1} (carboxylic acid)

STEP B : (R,S)-2-ethoxycarbonylindoline

In a reactor, suspend 10 kg of 2-ethoxycarbonyl-

hydroxide, with stirring, for 24 hours. After washing the alkaline solution, neutralise with concentrated hydrochloric acid. After suction-filtering, washing and drying, 1.57 kg of white crystals of the desired product are obtained.

Yield : 86 %

Melting point : 188-189°C

Infrared spectrometry :

NH_2^+ : 2500-2000 cm^{-1}
COO^- : 1620 cm^{-1}

STEP D : (S)-2-carboxyindoline

6.05 kg of (R,S)-2-carboxyindoline are added to a solution of 4.49 kg of (+)-α-methylbenzylamine in anhydrous ethanol. A white precipitated product is obtained which, after suction-filtering, is digested in isopropanol heated at reflux. After cooling, suction-filtering is carried out, followed by washing with a small amount of isopropanol, and the resulting white crystals are dried : 3.68 kg.

Rotatory power :

$[\alpha]_D^{21} = -5.3$ (c = 1 % ethanol)

The (S)-2-carboxyindoline is prepared in a quantitative yield by dissolving 1 kg of the above salt in 5 litres of water and neutralising with an aqueous hydrochloric acid solution. This precipitate is suction-filtered, washed with water and dried.

STEP E : (2S,3aS,7aS)-octahydroindole-2-carboxylic acid

In a vat, place 25 kg of (S)-indoline-2-carboxylic acid obtained above in 110 litres of methanol. Maintain stirring. In a mixer, add the rhodium catalyst (5 % dry).

In a hydrogenator, commence stirring, introduce the methanolic suspension of (S)-indoline-2-carboxylic acid making it pass through the mixer, and rinse the whole with water. Heat to 60°C and place under hydrogen pressure.

Filter off the catalyst using a monoplate filter. Collect the aqueous alcoholic liquids in a reactor and evaporate the methanol in vacuo.

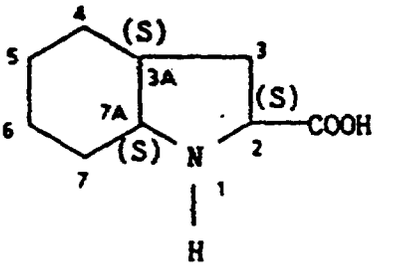
After concentration, introduce approximately 300 kg of dioxan. Bring to the boil and add water until a solution is obtained. Allow to cool. Suction-filter and dry.

22.3 kg of crystals are obtained.

Yield : 86.1 %.

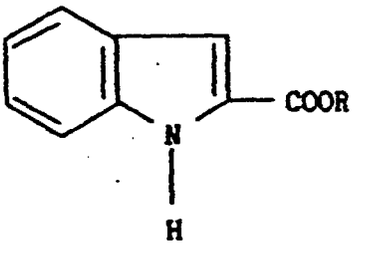
CLAIMS for the Contracting States: AT BE CH DE FR GB IT LI LU NL SE

1/ A process for the industrial preparation of (2S,3aS,7aS)-perhydroindole-2-carboxylic acid of formula (IIIaS) :



(IIIaS)

characterised in that there is used as starting material an indole-2-carboxylic acid or one of its esters of formula (IV) :



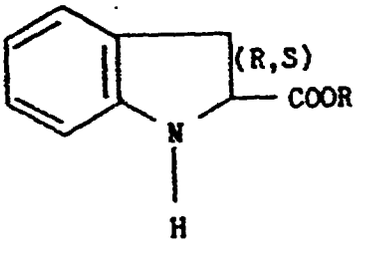
(IV),

optionally converted into a salt by an acid AH,

in which R represents a hydrogen atom or a lower alkyl group,

which is subjected to reduction by a process using the couple tin/hydrochloric acid,

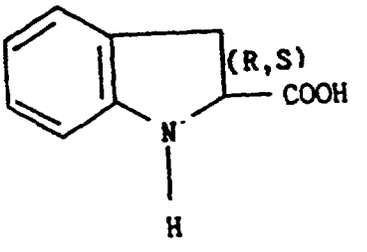
to yield (R,S)-indoline-2-carboxylic acid or one of its esters of formula (V) :



(V)

in which R has the same meaning as in formula (IV), which, when R = H, is the (R,S)-indoline-2-carboxylic acid of formula (VI);

which, when R is other than H, is converted by alkaline hydrolysis into (R,S)-indoline-2-carboxylic acid of formula (VI) :



(VI)

which, in fact, comprises a mixture of two isomers according to how the carboxy-carrying carbon atom is configured :

- in the R configuration (R isomer),
- in the S configuration (S isomer),

a mixture from which the S isomer is isolated by adding the said mixture to a solution of (+)-α-methylbenzylamine in a lower aliphatic alcohol, to obtain

a precipitate of the salt of (S)-indoline-2-carboxylic acid with (+)-α-methylbenzylamine,

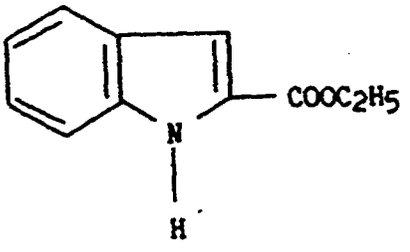
which, after filtration, is dissolved in water, the solution obtained then being acidified to allow the (S)-indoline-2-carboxylic acid to be liberated,

which acid is subjected to catalytic hydrogenation, the catalyst being selected from nickel, platinum, palladium and rhodium in admixture with a support such as carbon, so as to obtain (2S,3aS,7aS)-perhydroindole-2-carboxylic acid, the latter being separated from the small propor-

* C L M S *

tion of (2S,3aR,7aR)-isomer by a single crystallisation in a polar solvent carefully selected from a lower aliphatic alcohol, acetonitrile, dioxan and ethyl acetate, alone, or mixed with one another or with water provided the mixture is monophasic.

2/ A process for the industrial synthesis of (2S,3aS,7aS)-perhydroindole-2-carboxylic acid according to claim 1, characterised in that there is used as starting material the ethyl ester of indole-2-carboxylic acid of formula (IVo) :



(IVo)

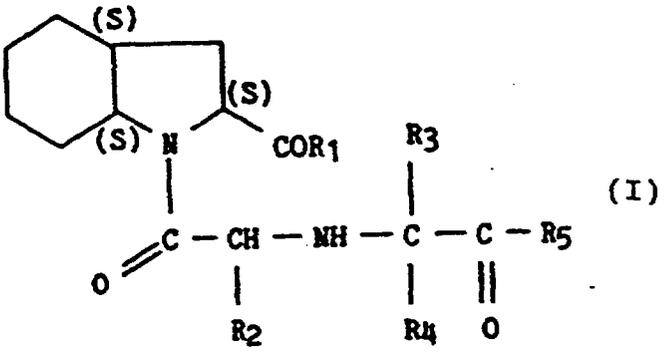
which is itself obtained by esterifying indole-2-carboxylic acid with ethanol in the presence of an esterification catalyst, such as sulphuric acid.

3/ A process according to either claim 1 or claim 2, characterised in that the reduction of the (S)-indoline-2carboxylic acid to perhydroindole-2-carboxylic acid is carried out using rhodium-on-carbon as catalyst.

4/ A process according to any one of claims 1 to 3, characterised in that the recrystallisation for the purpose of isolating (2S,3aS,7aS)-perhydroindole-2-carboxylic acid from the reaction mixture obtained after the catalytic reduction of (S)-indoline-2-carboxylic acid is carried out using a dioxan/water mixture as solvent.

5/ The use of the (2S,3aS,7aS)-perhydroindole-2-carboxylic acid obtained according to any one of claims 1

to 4 for the preparation of carboxyalkyl dipeptides of formula (I)



(I)

and their pharmaceutically acceptable salts,
in which:

R_1 and R_5, which are the same or different, represent hydroxy, lower alkoxy, lower alkenyloxy, di-lower alkylamino-lower alkoxy, acylamino-lower alkoxy, acyloxy-lower alkoxy, aryloxy, aryl-lower alkoxy, amino, lower alkylamino, di-lower alkylamino, hydroxyamino, aryl-lower alkylamino or substituted aryloxy or substituted aryl-lower alkoxy wherein the substituent is methyl, halo or methoxy;

R_2 is hydrogen, lower alkyl, aryl-lower alkyl, amino-methylphenyl-lower alkyl, hydroxyphenyl-lower alkyl, hydroxy-lower alkyl, acylamino-lower alkyl, amino-lower alkyl, dimethylamino-lower alkyl, guanidino-lower alkyl, imidazolyl-lower alkyl, indolyl-lower alkyl or lower alkylthio-lower alkyl;

R_3 is hydrogen, a straight-chain or branched alkyl having from 1 to 10 carbon atoms, a lower alkyl substituted by one or more substituents selected from halo, hydroxy, lower alkoxy, aryloxy, substituted aryloxy, heteroaryl-oxy, substituted heteroaryloxy, amino, lower alkylamino, di-lower alkylamino, acylamino, arylamino, substituted arylamino, guanidino, imidazolyl, indolyl, lower alkyl-thio, arylthio, substituted arylthio, carboxy, carbamoyl and lower alkoxycarbonyl, or R_3 is aryl, substituted

* C L M S *

aryl, aryl-lower alkyl, aryl-lower alkenyl, substituted aryl-lower alkyl, substituted aryl-lower alkenyl, heteroaryl-lower alkyl, substituted heteroaryl-lower alkyl, heteroaryl-lower alkenyl, substituted heteroaryl-lower alkenyl, aralkoxy, substituted aralkoxy, heteroaralkoxy, substituted heteroaralkoxy, aralkylthio, substituted aralkylthio, heteroaralkylthio or substituted heteroaralkylthio, the aryl or heteroaryl moiety of the above substituted aryloxy, heteroaryloxy, arylamino, arylthio, aryl, aralkoxy, heteroaralkoxy, aralkylthio, heteroaralkylthio, aryl-lower alkyl, aryl-lower alkenyl, heteroaryl-lower alkenyl and heteroaryl-lower alkyl being substituted by one or more groups selected from halo, lower alkyl, hydroxy, lower alkoxy, amino, acylamino, lower alkylamino, di-lower alkylamino, carboxy, cyano and sulphamoyl; the alkyl moiety of the said substituted aralkoxy, aralkylthio, aryl-lower alkyl, heteroaryl-lower alkyl, heteroaralkoxy and heteroaralkylthio being substituted by one or more groups also selected from halo, lower alkyl, hydroxy, lower alkoxy, amino, acylamino, lower alkylamino, di-lower alkylamino, carboxy, cyano and sulphamoyl;

and

R_4 is hydrogen or a lower alkyl group.

6/ The use according to claim 5 of (2aS,3aS,7aS)-perhydroindole-2-carboxylic acid for the industrial preparation of (2S,3aS,7aS)-1-(2(S)-[1(S)-(ethoxycarbonyl)butylamino]propionyl}octahydroindole-2-carboxylic acid from its tert.-butylamine salt.