(CONVENTION. By one or more persons and/or a Company.) Form 4

COMMONWEALTH OF AUSTRALIA

Patents Act 1952-1969

CONVENTION APPLICATION FOR A PATENT

~~618752~~

(1) Here insert (in full) Name or Names of Applicant or Applicants, followed by Address (es).

I/We (1) ADIR ET CIE

of 22 Rue Garnier, F-92201 Neuilly Sur Seine, France

(2) Here insert Title of Invention.

hereby apply for the grant of a Patent for an invention entitled: (2)

PROCESS FOR THE INDUSTRIAL SYNTHESIS OF (2S, 3aS, 7aS) 2-CARBOXY PERHYDROINDOLE. APPLICATION TO THE INDUSTRIAL SYNTHESIS OF CARBOXYALKYL DIPEPTIDES

(3) Here insert number(s) of basic application(s)

which is described in the accompanying complete specification. This application is a Convention application and is based on the application numbered (3)

8712900

(4) Here insert Name of basic Country or Countries, and basic date or dates

for a patent or similar protection made in (4) France

on 17th September 1987

My/Our address for service is Messrs. Edwd. Waters & Sons, Patent Attorneys, 50 Queen Street, Melbourne, Victoria, Australia.

DATED this 15th day of September 19 88

(5) Signature (s) of Applicant (s) or Seal of Company and Signatures of its Officers as prescribed by its Articles of Association.

(5)

ADIR ET CIE

by Louis C. Gebhardt

Registered Patent Attorney

M002873 16/09/88

To:

THE COMMISSIONER OF PATENTS.

(CONVENTION: Company.)

COMMONWEALTH OF AUSTRALIA

Patents Act 1952-1969

DECLARATION IN SUPPORT OF A CONVENTION APPLICATION FOR A PATENT OR PATENT OF ADDITION

(1) Here insert (in full) Name of Company.

In support of the Convention Application made by(1) ADIR ET CIE
22 RUE GARNIER, F-92201 NEUILLY SUR SEINE

(hereinafter referred to as the applicant) for a Patent

(2) Here insert title of Invention.

for an invention entitled:(2) Process for the industrial synthesis of (2S, 3aS, 7aS) 2 - carboxy perhydroindole. Application to the industrial synthesis of carboxyalkyl dipeptides.

(3) Here insert full Name and Address, of Company official authorized to make declaration.

I,(3) GERARD ADAM
of ADIR ET CIE
22 RUE GARNIER, F-92201 NEUILLY SUR SEINE

do solemnly and sincerely declare as follows:

1. I am authorised by the applicant for the patent to make this declaration on its behalf.

2. The basic application as defined by Section 141 of the Act was made in(4)

(4) Here insert basic Country or Countries followed by date or dates and basic Applicant or Applicants.

on the 17th day of SEPTEMBER 1987, by ADIR ET CIE
under N° 87.12900
or~~dxx~~ ~~dxxxxx~~ ~~19xxxxxxx~~

(5) Here insert (in full) Name and Address of Actual Inventor or Inventors.

3.(5) MICHEL VINCENT, 8 allée du Prunier Hardy, F-92220 BAGNEUX
JEAN BALIARDA, 25 avenue Jeanne d'Arc, F-92160 ANTHONY
BERNARD MARCHAND, 71 rue Laveau, F-45430 CHECY
GEORGES REMOND, 9 avenue des Etats-Unis, 78000 VERSAILLES

is~~X~~are the actual inventors of the invention and the facts upon which the applicant is entitled to make the application are as follow:

The applicant is the assignee of MICHEL VINCENT, JEAN BALIARDA, BERNARD MARCHAND, GEORGES REMOND

4. The basic application referred to in paragraph 2 of this Declaration was the first application made in a Convention country in respect of the invention the subject of the application.

DECLARED at NEUILLY, France
this 23rd day of August 1988

(6) Signature.

(6) GERARD ADAM PROXY FOR ADIR ET CIE

To: THE COMMISSIONER OF PATENTS.

Edwd. Waters & Sons, Melbourne.

(12) PATENT ABRIDGMENT (11) Document No. AU-B-22361/88
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 618752

(54) Title
PROCESS FOR THE INDUSTRIAL SYNTHESIS OF (2S, 3AS, 7AS) 2-CARBOXY PERHYDROINDOLE. APPLICATION TO THE INDUSTRIAL SYNTHESIS OF CARBOXYALKYL DIPEPTIDES

International Patent Classification(s)
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(71) Applicant(s)
ADIR ET CIE

(72) Inventor(s)
MICHEL VINCENT; JEAN BALIARDA; BERNARD MARCHAND; GEORGES REMOND

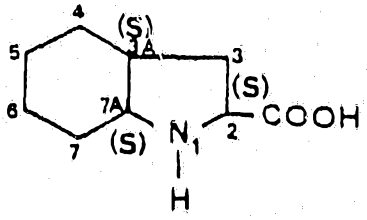
(74) Attorney or Agent
WATERMARK PATENT & TRADEMARK ATTORNEYS , Locked Bag 5, HAWTHORN VIC 3122

(56) Prior Art Documents
AU 608363 22362/88 C07K 5/06 C07D 209/42 C07C 101/20

(57) The Applicant Company has now found an original process for the synthesis of (2S,3aS,7aS)-2-carboxyperhydroindole, which also offers the advantage of employing 2-carboxyindole as starting material, but which does not offer the disadvantage of this arduous separation of the two 2S,3aS,7aS and 2R,3aR,7aR isomers of carboxyperhydroindole, since, in a first step, the carboxyindole is reduced to carboxyindoline to give a mixture of (2R) and (2S)-2-carboxyindolines which are easily separated in a single stage by fractional crystallization; the (2S) isomer being then subjected to catalytic hydrogenation, to lead stereoselectively to (2S,3aS,7aS)-2-carboxyperhydroindole, after crystallization from a strictly chosen polar solvent.

CLAIM

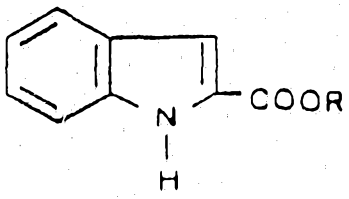
1. A process for the industrial preparation of (2S,3aS,7aS)-2-carboxyperhydroindole of formula (IIIaS):



(IIIaS)

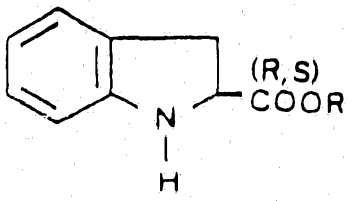
.../2

wherein the starting material employed is 2-carboxy-indole or one of its esters of formula (IV):



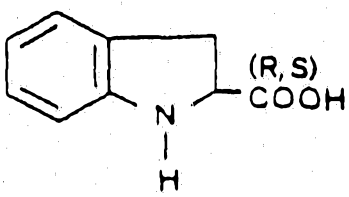
(IV)

optionally converted into a salt with an acid, ~~addition~~,
in which formula R denotes a hydrogen atom or a lower alkyl group,
which is subjected to reduction by a process such as the use of the tin-hydrochloric acid couple,
to lead to (R,S)-2-carboxyindoline or to one of its esters of formula (V):



(V)

in which R has the same meaning as in the formula (IV),
which, when R = H, is the (R,S)-2-carboxyindoline of formula (VI);
which, when R is other than H, is converted by alkaline hydrolysis into (R,S)-2-carboxyindoline of formula (VI):



(VI)

consisting, in fact, of a mixture of two isomers according to whether the carbon bearing the carboxyl is:

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

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

.../3

a precipitate of the salt of (S)-2-carboxyindoline with (+)-α-methylbenzylamine,
which, after filtration, is dissolved in water, the solution obtained being then acidified to permit the liberation of (S)-2-carboxyindoline,
which is subjected to catalytic hydrogenation, the catalyst being chosen from nickel, platinum, palladium or rhodium, mixed with a support such as charcoal, so as to make it possible to obtain a maximum proportion of (2S,3aS,7aS)-2-carboxyperhydroindole, the latter being separated from the (2S,3aR,7aR) isomer obtained in a low proportion by a single crystallization in a polar solvent carefully chosen from lower aliphatic alcohol, acetonitrile, dioxane or ethyl acetate, by itself or mixed with each other or mixed with water, provided that the mixture forms a single phase.

3. An industrially usable process for the separation of the 2S isomer of carboxyindoline from the mixture of its two 2S and 2R isomers, wherein the mixture is added to a solution of (+)-α-methylbenzylamine in a lower aliphatic alcohol medium, to form a precipitate of the salt of (S)-2-carboxyindoline with (+)-α-methylbenzylamine,
which is crystallized in a solvent chosen preferably from lower aliphatic alcohol,
the (S)-2-carboxyindoline being liberated from its salt merely by dissolving in water, acidifying the solution obtained and filtering off.

4. An industrially usable process for the separation of the 2R isomer of carboxyindoline from the mixture of its two 2R and 2S isomers, wherein the mixture is added to a solution of (-)-α-methylbenzylamine in a lower aliphatic alcohol medium to form a precipitate of the salt of (S)-2-carboxyindoline with (-)-α-methylbenzylamine,
which is crystallized from a solvent chosen preferably from lower aliphatic alcohol,

.../4

the (R)-2-carboxyindoline being liberated from its salt merely by dissolving in water, acidifying the solution obtained and filtering off.

10. The salt of α-methylbenzylamine with (S)-2-carboxyindoline.

11. The salt of (+)-α-methylbenzylamine with (S)-2-carboxyindoline.

12. The salt of (-)-α-methylbenzylamine with (R)-2-carboxyindoline.

Form 10

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952-69

COMPLETE SPECIFICATION

(ORIGINAL)

618752

Class Int. Class

Application Number:
Lodged:

Complete Specification Lodged:
Accepted:
Published:

Priority :

Related Art :

Name of Applicant : ADIR ET CIE

Address of Applicant : 22 rue Garnier, F-92201 Neuilly Sur Seine, France

Actual Inventor: MICHEL VINCENT, JEAN BALIARDA, BERNARD MARCHAND and GEORGES REMOND

Address for Service : EDWD. WATERS & SONS,
50 QUEEN STREET, MELBOURNE, AUSTRALIA, 3000.

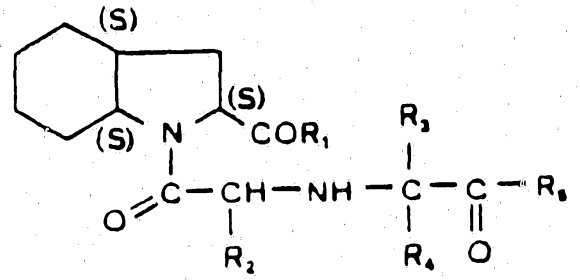
Complete Specification for the invention entitled:

PROCESS FOR THE INDUSTRIAL SYNTHESIS OF (2S, 3aS, 7aS) 2-CARBOXY PERHYDROINDOLE. APPLICATION TO THE INDUSTRIAL SYNTHESIS OF CARBOXYALKYL DIPEPTIDES

The following statement is a full description of this invention, including the best method of performing it known to :- us

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

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



(I)

and their pharmaceutically acceptable salts,
in which formula:

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

R_2 is hydrogen, lower alkyl, aryl-lower alkyl, aminomethylphenyl-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 linear or branched alkyl with 1 to 10 carbon atoms, a lower alkyl substituted by one or more substituents chosen from halo, hydroxy, lower alkoxy, aryloxy, substituted aryloxy, heteroaryloxy, substituted heteroaryloxy, amino, lower alkylamino, lower dialkylamino, acylamino, arylamino, substitued arylamino, guanidino, imidazolyl, indolyl, lower alkylthio, arylthio, substituted arylthio,

carboxy, carbamoyl, lower alkoxy-carbonyl, or else R_3 is aryl, substituted aryl, lower aralkyl, lower aralkenyl, substituted lower aralkyl, substituted lower aralkenyl, lower heteroaralkyl, substituted lower heteroaralkyl, lower heteroaralkenyl, substituted lower heteroaralkenyl, aralkyloxy, substituted aralkyloxy, heteroaralkyloxy, substituted heteroaralkyloxy, aralkylthio, substituted aralkylthio, heteroaralkylthio or substituted heteroaralkylthio, the aryl or heteroaryl moiety of the abovementioned substituted aryloxy, heteroaryloxy, arylamino, arylthio, aryl, aralkyloxy, heteroaralkyloxy, aralkylthio, heteroaralkylthio, lower aralkyl, lower aralkenyl, lower heteroaralkenyl or lower heteroaralkyl being substituted by one or more groups chosen from halo, lower alkyl, hydroxy, lower alkoxy, amino, acylamino, lower alkylamino, lower dialkylamino, carboxyl, cyano or sulfamoyl; the alkyl moiety of the abovementioned substituted aralkyloxy, aralkylthio, lower aralkyl, lower heteroaralkyl, heteroaralkyloxy or heteroaralkylthio being substituted by one or more groups also chosen from halo, lower alkyl, hydroxy, lower alkoxy, amino, acylamino, lower alkylamino, lower dialkylamino, carboxyl, cyano or sulfamoyl;

R_4 is hydrogen or a lower alkyl group.

It should be stated that, among the abovementioned values, the term "acyl" includes the radicals $-\overset{\overset{O}{\|}}{C}-R_6$ in which R_6 denotes lower alkyl, lower alkenyl or aryl.

The terms lower alkyl and lower alkenyl also denote any hydrocarbon radical with 1 to 6 carbon atoms, be they linear or branched, such as methyl, ethyl, n-propyl, isopropyl n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, vinyl, allyl, and the like.

The term aryl means, unless stated otherwise, phenyl or naphthyl, optionally substituted by one or more lower alkyl or alkyloxy groups, such as toluyl, xylyl, and the like.

The term heteroaryl may be illustrated by pyridyl, thienyl, furyl, pyrrolyl, benzothienyl, benzofuryl, indolyl, thiazolyl, imidazolyl, oxazolyl, benzimidazolyl,

benziothiazolyl or benzoxazolyl radicals, as well as by one of the preceding resulting from the substitution of one or more -CH- chain units by an -N- chain unit.

Among the compounds of formula (I), the preferred ones are those in which:

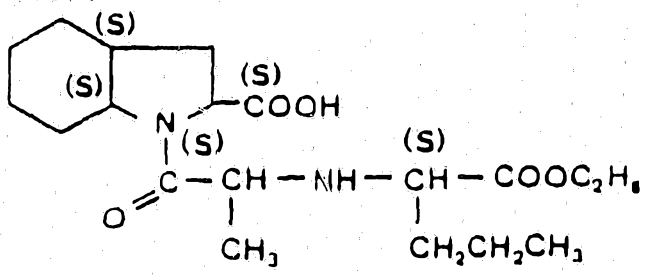
R_1 and R_5 are, independently of each other, a hydroxy or linear or branched lower alkoxy group,

R_2 is a linear or branched lower alkyl group optionally substituted by an amino group,

R_3 is a linear or branched lower alkyl group optionally substituted by a cycloalkyl or aryl radical such as phenyl, and among these, the n-propyl, n-butyl and phenylethyl groups are preferred,

R_4 is a hydrogen atom.

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



(II)

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

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

in the case of which the process of the present invention may be applied more particularly.

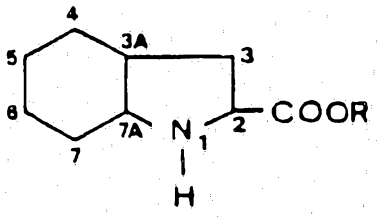
The compounds of formula (I) as well as their salts have interesting pharmacological properties. In particular, they exert an inhibiting activity on certain enzymes, such as carboxypolypeptidases, enkephalinases or kininase II. In particular, they inhibit the conversion of the angiotensin I decapeptide to angiotensin II octapeptide, responsible in certain cases for arterial hypertension, by acting on the conversion enzyme.

The use of these compounds in therapeutics makes it possible, therefore, to reduce or even to suppress the activity of these enzymes, which are responsible for the hypertensive disorder or for cardiac insufficiency. The

action on kininase II results in an increase in the circulating bradykinin and also in a lowering of the arterial pressure via this route.

Compounds of formula (I), their preparation, and their use in therapeutics have been described in European Patents No. 0,049,658, No. 0.088,341 and in European Patent Applications No. 0,154,886 and No. 0,046,953. The derivative of formula (II), its preparation and its use in therapeutics have been described in European Patent No. 0,049,658.

In particular, one of the starting materials which can be employed for the preparation of the compounds of formula (I) is 2-carboxyperhydroindole, described in European Patent Application No. 0,037,231, as well as its esters of formula (III):



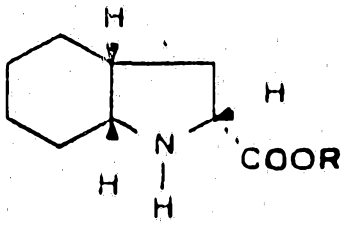
(III)

where R denotes a lower alkyl or benzyl group, or a hydrogen atom.

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

the two cis IIIa and IIIb epimers,

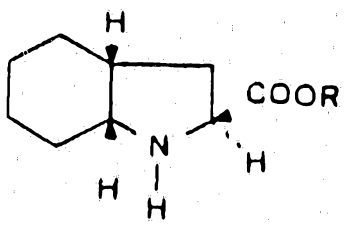
the two trans IIIc and IIId epimers,



(±) IIIa

cis, endo

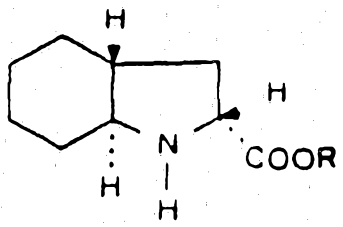
2S, 3aS, 7aS ou 2R, 3aR, 7aR



(±) IIIb

cis, exo

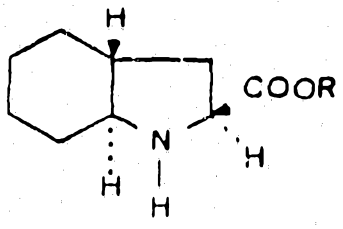
2S, 3aR, 7aR ou 2R, 3aS, 7aS



(±) IIIc

trans α

2S, 3aS, 7aR ou 2R, 3aR, 7aS



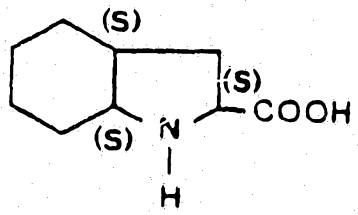
(±) IIId

trans β

2R, 3aS, 7aR ou 2S, 3aR, 7aS

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

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



(IIIaS)

It is known, in fact (EP 37,231, EP 49,658, EP 88,341 and EP 154,886), that the compounds of formula (I) in which the configuration of the bicyclic system is 2S,3aS,7aS have an activity which is markedly higher than that of the compounds in the case of which the cis configuration of the bicyclic system is different.

The preparation of (2S,3aS,7aS)-2-carboxyperhydroindole may be carried out according to 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 these employ 2-carboxyindole as starting material, which has the advantage of being a starting material which is readily available and relatively inexpensive (EP 0,037,231), and which is subjected to

catalytic reduction on rhodized charcoal to give a mixture of both cis endo isomers of 2S,3aS,7aS and 2R,3aR,7aR configuration respectively.

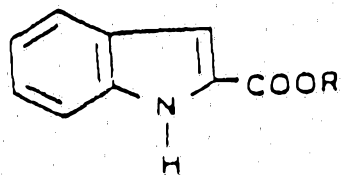
However, the separation of the 2S,3aS,7aS isomer, which is used in the synthesis of the carboxyalkyl dipeptides of formula (I), from the 2R,3aR,7aR isomer generally requires the use of methods which are particularly arduous to employ.

Thus, to perform this separation of the 2S,3aS, 7aS and 2R,3aR,7aR (cis, endo racemic) isomers, Patent No. 0,037,231 employs many stages requiring the synthesis of the N-benzoyl derivative, fractional crystallization of the salt of the diastereoisomer with S-α-phenylethylamine, the liberation of the two N-benzoyl SSS and RRR derivatives, and then the removal of the benzoyl group, followed by a pass through an ion exchange column and a recrystallization.

For this same separation, European Patent Application No. 0,115,345 employs several stages requiring the esterification of the carboxylic acid group with benzyl alcohol, conversion of the amino ester into a salt with (S)-N-benzyloxycarbonylphenylalanine, separation of the S,S,S isomer by fractional crystallization, and the liberation of the amino group, optionally followed by the liberation of the carboxylic acid group.

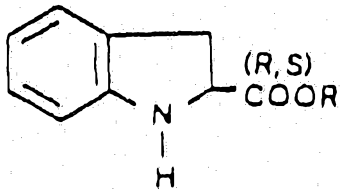
The Applicant Company has now found an original process for the synthesis of (2S,3aS,7aS)-2-carboxyperhydroindole, which also offers the advantage of employing 2-carboxyindole as starting material, but which does not offer the disadvantage of this arduous separation of the two 2S,3aS,7aS and 2R,3aR,7aR isomers of carboxyperhydroindole, since, in a first step, the carboxyindole is reduced to carboxyindoline to give a mixture of (2R) and (2S)-2-carboxyindolines which are easily separated in a single stage by fractional crystallization; the (2S) isomer being then subjected to catalytic hydrogenation, to lead stereoselectively to (2S,3aS,7aS)-2-carboxyperhydroindole, after crystallization from a strictly chosen polar solvent.

More particularly, the synthesis of (2S,3aS,7aS)-2-carboxyperhydroindole, which has now been found by the Applicant Company, employs as starting material 2-carboxyindole or one of its esters of formula (IV):



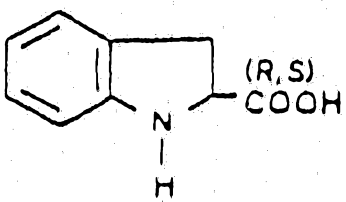
(IV)

optionally converted into a salt with an acid, in which R denotes a lower alkyl or benzyl group or a hydrogen atom, which is subjected to reduction by a process such as the use of the tin/hydrochloric acid couple, preferably at ambient temperature in a lower aliphatic alcohol medium, to (R,S)-2-indoline acid or to 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)-2-carboxyindoline of formula (VI); which, when R is other than H, is converted by alkaline hydrolysis into (R,S)-2-carboxyindoline of the formula (VI):



(VI)

consisting, in fact, of a mixture of two isomers according to whether the carbon bearing the carboxyl is:

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

from which mixture 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)-2-carboxyindoline with α-methylbenzylamine, which, after filtration, is dissolved in water, the solution obtained being then acidified to permit the liberation of (S)-2-carboxyindoline,

which is subjected to catalytic hydrogenation, the catalyst being chosen from platinum, nickel, palladium or rhodium, mixed with a support such as charcoal, so as to make it possible to obtain a maximum proportion of (2S,3aS,7aS)-2-carboxyperhydroindole, the latter being separated from the (2S,3aR,7aR) isomer obtained in a low proportion by a single crystallization, by means of a solvent strictly selected from lower aliphatic alcohol, acetonitrile, dioxane and ethyl acetate, by itself or mixed with each other or mixed with water, provided that the mixture forms a single phase.

It should be noted that (R)-2-carboxyindoline can be separated from (R,S)-2-carboxyindoline by employing the same procedure as in the case of (S)-2-indoline acid; it then suffices to employ (-)-α-methylbenzylamine.

The invention also extends to the original products obtained while this process is performed and, more particularly, to the salts formed by α-methylbenzylamine with the isomers of 2-carboxyindoline, and more particularly with (S)-2-carboxyindoline.

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

EXAMPLE: (2S,3aS,7aS)-2-CARBOXYOCTAHYDROINDOLE

STAGE A: 2-Ethoxycarbonylindole

Heat 5 kg of 2-carboxyindole suspended in ethanol in the presence of sulfuric acid to boiling for 8 hours. Evaporate off the ethanol, then take up with 40 liters of ethyl acetate and wash the organic solution with an aqueous sodium hydroxide solution and dry.

Evaporate off the ethyl acetate, take up the crystalline mass with hexane. After filtering off 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

Spectrometry in the infrared:

2150 cm^{-1} (NH)

1680 cm^{-12} (carboxylic acid)

STAGE B: (R,S)-2-Ethoxycarbonyl indoline

Suspend 10 kg of 2-ethoxycarbonylindoline obtained earlier in 110 liters of hydrochloric ethanol in a reactor. Next, add 20 kg of granulated tin. Keep stirring for approximately 2 days at ambient temperature.

Evaporate off the ethanol, take up the residue with water and add 110 liters of toluene. Stir for approximately 20 minutes. Alkalify with aqueous ammonia. Separate off the aqueous phase and extract it once again with 150 liters of toluene.

Combine the toluene phases and wash them with water. Separate off the toluene phases, filter.

Remove the water by distilling the water-toluene azeotrope. Cool and pass through a stream of anhydrous HCl gas.

Cool. Evaporate and wash with pure toluene.

Weight obtained: 10.11 kg

Yield: 84 %

Thin layer chromatography:

Solvent: toluene: 10

ethyl acetate: 5

Support: Merck silica 60 F 254

Developer: UV

R_f: 0.55

STAGE C: (R,S)-2-Carboxyindoline

2.15 kg of (R,S)-2-ethoxycarbonylindoline dissolved in ethanol are saponified with 12.5 liters of N sodium hydroxide, with stirring for 24 hours. After washing the alkaline solution, neutralize with concentrated hydrochloric acid. After filtering off, washing and drying, 1.57 kg of white crystals of the expected product are obtained.

Yield: 86 %.

Melting point: 188-189°C

Spectrometry in the infrared:

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

STAGE 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 filtering off, is digested in refluxing isopropanol. After cooling, the solid is filtered off and washed with a little isopropanol; the white crystals obtained are dried: 3.68 kg.

Rotatory power:

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

(S)-2-Carboxyindoline is prepared in a quantitative yield by dissolving 1 kg of the above salt in 5 liters of water and neutralizing with an aqueous hydrochloric acid solution. This precipitate is filtered off, washed with water and dried.

STAGE E: (2S,3aS,7aS)-2-Carboxyoctahydroindole

Place 25 kg of (S)-2-carboxyindoline obtained previously in 110 liters of methanol in a vessel. Keep stirred. Charge the rhodium catalyst (5 % dry) into a mixer.

In a hydrogenator, start up the stirring, and charge the methanolic suspension of (S)-2-carboxyindoline by making it flow through the mixer and rinse the assembly with water. Heat to 60°C and pressurize with hydrogen.

Filter off the catalyst on a single-plate filter. Collect the hydroalcoholic liquors in a reactor and evaporate off the methanol under vacuum.

After concentrating, charge approximately 300 kg of dioxane. Heat to boiling and add water until a solution is obtained. Allow to cool. Filter off and dry.

22.3 kg of crystals are obtained.

Yield: 86.1 %

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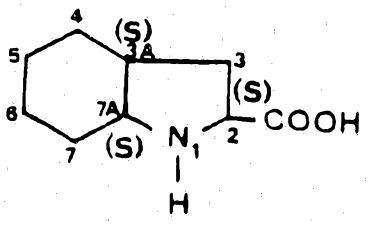
THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

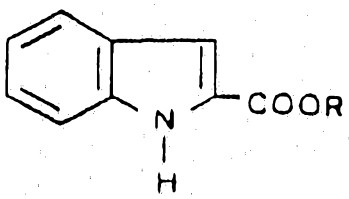
CLAIMS

1. A process for the industrial preparation of (2S,3aS,7aS)-2-carboxyperhydroindole of formula (IIIaS):



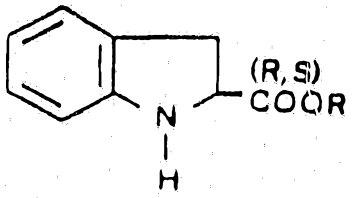
(IIIaS)

wherein the starting material employed is 2-carboxyindole or one of its esters of formula (IV):



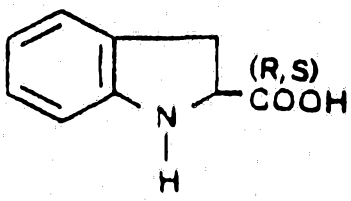
(IV)

optionally converted into a salt with an acid,
in which formula R denotes a hydrogen atom or a lower alkyl group,
which is subjected to reduction by a process such as the use of the tin-hydrochloric acid couple,
to lead to (R,S)-2-carboxyindoline or to one of its esters of formula (V):



(V)

in which R has the same meaning as in the formula (IV),
which, when R = H, is the (R,S)-2-carboxyindoline of formula (VI);
which, when R is other than H, is converted by alkaline hydrolysis into (R,S)-2-carboxyindoline of formula (VI):



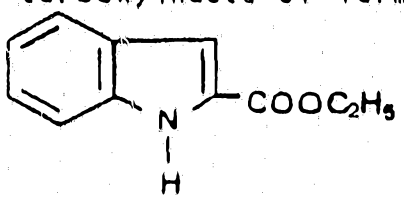
(VI)

consisting, in fact, of a mixture of two isomers according to whether the carbon bearing the carboxyl is:

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

from which mixture 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)-2-carboxyindoline with (+)-α-methylbenzylamine,
which, after filtration, is dissolved in water, the solution obtained being then acidified to permit the liberation of (S)-2-carboxyindoline,
which is subjected to catalytic hydrogenation, the catalyst being chosen from nickel, platinum, palladium or rhodium, mixed with a support such as charcoal, so as to make it possible to obtain a maximum proportion of (2S,3aS,7aS)-2-carboxyperhydroindole, the latter being separated from the (2S,3aR,7aR) isomer obtained in a low proportion by a single crystallization in a polar solvent carefully chosen from lower aliphatic alcohol, acetonitrile, dioxane or ethyl acetate, by itself or mixed with each other or mixed with water, provided that the mixture forms a single phase.

2. A process for the industrial synthesis of (2S, 3aS,7aS)-2-carboxyperhydroindole as claimed in claim 1, wherein the starting material employed is the ethyl ester of 2-carboxyindole of formula (IVo):



(IVo)

itself obtained by esterification of 2-carboxyindole with ethanol in the presence of an esterification catalyst such as sulfuric acid.

3. An industrially usable process for the separation of the 2S isomer of carboxyindoline from the mixture of its two 2S and 2R isomers, wherein the mixture is added to a solution of (+)-α-methylbenzylamine in a lower aliphatic alcohol medium, to form a precipitate

of the salt of (S)-2-carboxyindoline with (+)-α-methylbenzylamine,
which is crystallized in a solvent chosen preferably from lower aliphatic alcohol,
the (S)-2-carboxyindoline being liberated from its salt merely by dissolving in water, acidifying the solution obtained and filtering off.

4. An industrially usable process for the separation of the 2R isomer of carboxyindoline from the mixture of its two 2R and 2S isomers, wherein the mixture is added to a solution of (-)-α-methylbenzylamine in a lower aliphatic alcohol medium to form a precipitate of the salt of (S)-2-carboxyindoline with (-)-α-methylbenzylamine,
which is crystallized from a solvent chosen preferably from lower aliphatic alcohol,
the (R)-2-carboxyindoline being liberated from its salt merely by dissolving in water, acidifying the solution obtained and filtering off.

5. A process as claimed in any one of claims 1 to 3, wherein the precipitation of (S)-2-carboxyindoline with (+)-α-methylbenzylamine is performed in ethanol.

6. A process as claimed in any one of claims 1 to 3, wherein the reduction of the carboxyindole or of one of its esters of formula (VI), which are optionally converted into a salt, to (R,S)-2-carboxyindoline is performed by means of the tin-hydrochloric acid couple in a lower aliphatic alcohol medium, and at ambient temperature.

7. A process as claimed in one of claims 1 to 3, 5 and 6, wherein the reduction of (S)-2-carboxyindoline to 2-carboxyperhydroindole is performed using rhodium on charcoal as catalyst.

8. A process as claimed in any one of claims 1 to 3, 5, 6 and 7, wherein the recrystallization for the purpose of isolating the (2S,3aS,7aS)-2-carboxyperhydroindole from the reaction mixture obtained after catalytic reduction of (S)-2-carboxyindoline is performed using a dioxane-water mixture as a solvent.

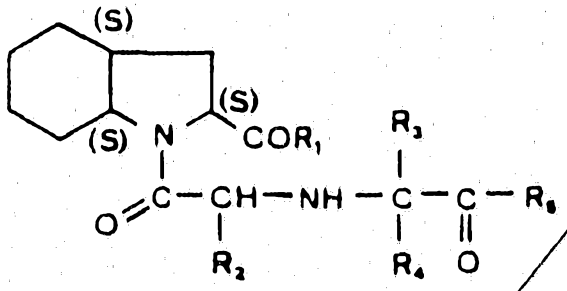
9. A process as claimed in one of claims 1 to 3, wherein the crystallization of the salt of (S)-2-carboxyindoline with (+)-α-methylbenzylamine is carried out in isopropanol.

10. The salt of α-methylbenzylamine with (S)-2-carboxyindoline.

11. The salt of (+)-α-methylbenzylamine with (S)-2-carboxyindoline.

12. The salt of (-)-α-methylbenzylamine with (R)-2-carboxyindoline.

13. A use of (2S,3aS,7aS)-2-carboxyperhydroindole obtained as claimed in any one of claims 1, 2, 3, 5 to 9 for the preparation of carboxyalkyl dipeptides of formula (I):



(I)

as well as their pharmaceutically acceptable salts, in which formula:

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

R_2 is hydrogen, lower alkyl, aryl-lower alkyl, aminomethylphenyl-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 linear or branched alkyl with 1 to 10 carbon atoms, a lower alkyl substituted by

~~one or more substituents chosen from halo, hydroxy,~~ lower alkoxy, aryloxy, substituted aryloxy, heteroaryloxy, substituted heteroaryloxy, amino, lower alkylamino, lower dialkylamino, acylamino, arylamino, substituted arylamino, guanidino, imidazolyl, indolyl, lower alkylthio, arylthio, substituted arylthio, carboxy, carbamoyl, lower alkoxycarbonyl, or else R_3 is aryl, substituted aryl, lower aralkyl, lower aralkenyl, substituted lower aralkyl, substituted lower aralkenyl, lower heteroaralkyl, substituted lower heteroaralkyl, lower heteroaralkenyl, substituted lower heteroaralkenyl, aralkyloxy, substituted aralylkyloxy, heteroaralkyloxy, substituted heteroaralkyloxy, aralkylthio, substituted aralkylthio, heteroaralkylthio or substituted heteroaralkylthio, the aryl or heteroaryl moiety of the abovementioned substituted aryloxy, heteroaryloxy, arylamino, arylthio, aryl, aralkyloxy, heteroaralkyloxy, arylkylthio, heteroaralkylthio, lower aralkyl, lower alkenyl, lower heteroaralkenyl or lower heteroaralkyl being substituted by one or more groups chosen from halo, lower alkyl, hydroxy, lower alkoxy, amino, acylamino, lower alkylamino, lower dialkylamino, carboxyl, cyano or sulfamoyl; the alkyl moiety of the abovementioned substituted aralkyloxy, aralkylthio, lower aralkyl, lower heteroaralkyl, heteroaralkyloxy or heteroaralkylthio being substituted by one or more groups which are also chosen from halo, lower alkyl, hydroxy, lower alkoxy, amino, acylamino, lower alkylamino, lower dialkylamino, carboxyl, cyano or sulfamoyl;

R_4 is hydrogen or a lower alkyl group.

14. A use as claimed in claim 13 of (2S,3aS,7aS)-2-carboxyperhydroindole for the industrial preparation of (2S,3aS,7aS)-1-{2-[1-(ethoxycarbonyl)-(S)-butylamino]-(S)-propionyl}octahydroindole-2-carboxylic acid from its tert-butylamine salt.

DATED this 15th day of September 1988.
ADIR ET CIE

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