(12) PATENT ABRIDGMENT (11) Document No. AU-B-82094/87
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 609754

(54) Title
DERIVATIVES OF BICYCLIC AMINOCARBOXYLIC ACIDS, A PROCESS AND INTERMEDIATES FOR THEIR PREPARATION, AND THEIR USE

International Patent Classification(s)
(51)[4] **C07D 401/12** **C07C 103/46** **C07C 103/84** **C07D 209/42**
C07D 209/52 **C07D 213/89**

(21) Application No. : **82094/87** (22) Application Date : **04.12.87**

(30) Priority Data

(31) Number (32) Date (33) Country
3641451 **04.12.86** **DE FEDERAL REPUBLIC OF GERMANY**

(43) Publication Date : **09.06.88**

(44) Publication Date of Accepted Application : **09.05.91**

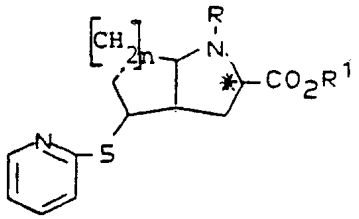
(71) Applicant(s)
HOECHST AKTIENGESELLSCHAFT

(72) Inventor(s)
DEREK BARTON; PIERRE POTIER; YOLANDE HERVE; JOSIANE THIERRY

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

(57) Claim

1. A compound of the formula I



I

in which

n = 1, 2 or 3,

R denotes (C_1-C_{17})-acyl, and

R^1 denotes (C_1-C_6)-alkyl, (C_3-C_7)-cycloalkyl, (C_7-C_{11})-aralkyl or another carboxyl-protecting group.

Form 10

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952-69

COMPLETE SPECIFICATION

(ORIGINAL)

609754

Class Int. Class

Application Number:
Lodged:

Complete Specification Lodged:
Accepted:
Published:

Priority :

Related Art :

This document contains the amendments made under Section 49 and is correct for printing.

Name of Applicant : HOECHST AKTIENGESELLSCHAFT

Address of Applicant : 45 Bruningstrasse, D-6230 Frankfurt/Main 80, Federal Republic of Germany

Actual Inventor: DEREK BARTON, PIERRE POTIER, YOLANDE HERVE, JOSIANE THIERRY

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

Complete Specification for the invention entitled:

DERIVATIVES OF BICYCLIC AMINOCARBOXYLIC ACIDS, A PROCESS AND INTERMEDIATES FOR THEIR PREPARATION, AND THEIR USE

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

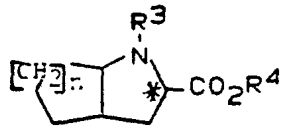
HOECHST AKTIENGESELLSCHAFT HOE 86/F 297 Dr. WS/MW

Description

Derivatives of bicyclic aminocarboxylic acids, a process and intermediates for their preparation, and their use.

Acyl derivatives of octahydroindole-2-carboxylic acid, octahydrocyclopenta [b]pyrrole-2-carboxylic acid or decahydrocyclohepta [b]pyrrole-2-carboxylic acid are disclosed, for example, in EP-A-79,022, EP-A-50,800, EP-A-84,164, EP-A-111,873, EP-A-37,231, US Patent 4,350,704 or US Patent 4,587,258. Many of these compounds exhibit a notable biological activity. For example, they inhibit, highly effectively, the angiotensin-converting enzyme or are distinguished by a nootropic action.

Compounds of the formula IV



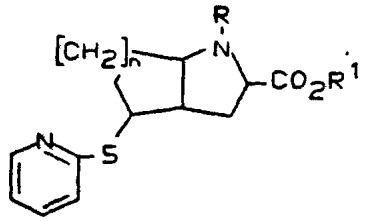
(IV)

in which R^3 denotes hydrogen or an acyl radical, and R^4 denotes hydrogen, an ester group or another carboxyl-protecting group, play a key role in the synthesis of the acyl derivatives mentioned initially.

It is often advantageous for carbon atom C-2 in position 2 of the bicyclic ring system of these active compounds to have a certain absolute configuration, preferably the S configuration. Their synthesis therefore preferably starts from intermediates of the formula IV which already have this desired configuration at C-2.

In the preparation processes which are already known for compounds of the formula IV, a racemate resolution was unavoidable if compounds having a defined configuration at C-2 were desired.

It has now been found that thiohydroxamic acid derivatives, in particular N-hydroxy-2-thiopyridone derivatives, of appropriately substituted and configured aspartic acids can be converted into optically uniform compounds of the formula IV having the desired configuration at C-2 through cyclization and subsequent removal of a 2-thioxo-2H-[1]-pyridyl radical, without a racemate resolution being necessary in any of the steps in this novel process. Compounds of the formula I



(I)

are important intermediates in this process.

The invention therefore relates to compounds of the formula I
in which
N = 1, 2 or 3,
R denotes (C_1-C_{12})-acyl and
R^1 denotes (C_1-C_6)-alkyl, (C_3-C_7)-cycloalkyl, (C_7-C_{11})-aralkyl or another carboxyl-protecting group, the hydrogen atoms on the bridgehead carbon atoms 3a and (5+n)a preferably having a cis-configuration.

The carbon atom in position 2 of the bicyclic ring system can have either the R or the S configuration; the S configuration is preferred.

R is preferably (C_1-C_6)-alkanoyl, (C_6-C_{10})-aryl-(C_1-C_4)-alkanoyl, (C_6-C_{10})-aroyl, (C_1-C_6)-alkoxycarbonyl or (C_7-C_{11})-aralkyloxy-carbonyl, but in particular (C_1-C_4)-alkanoyl, such as acetyl or propionyl, or benzoyl or substituted benzoyl.

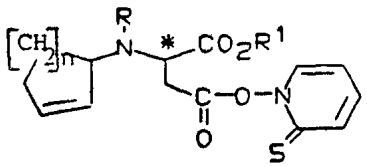
In addition, R, if not already covered by the definitions above, may represent a urethane type amine-protecting group which is conventional in peptide chemistry (cf.,

for example, Hubbuch, Kontakte Merck 3/79, 14-22). Urethane type protecting groups are, for example, Pyoc, Fmoc, Tcboc, Z, Boc, Ddz, Bpoc, Adoc, Msc, Moc, $Z(NO_2)$, $Z(Hal_n)$, Dobz, Iboc, Adpoc, Mboc and 1,4-dimethylpyridyloxycarbonyl.

R^1 is preferably (C_1-C_4)-alkyl, such as, for example, methyl, ethyl or tert.-butyl, or (C_7-C_{11})-aralkyl, such as, for example, benzyl.

In addition, R^1, if not already covered by the definitions above, may represent a carboxyl-protecting group which is conventional in peptide chemistry (cf., for example, the abovementioned article by Hubbuch). Carboxyl-protecting groups are, for example, the abovementioned alkyl radicals or benzyl. Furthermore, modified benzyl radicals, such as p-nitrobenzyl, p-methoxybenzyl, p-bromobenzyl, p-chlorobenzyl and radicals such as 4-picolyl or benzoylmethyl, are suitable. Above and below, alkyl is taken to mean straight-chain or branched alkyl. In a corresponding fashion, the same applies to radicals derived therefrom, such as, for example, alkanoyl and aralkyl. Lower alkyl preferably has up to 6 carbon atoms. (C_8-C_{10})-aryl is, for example, phenyl or naphthyl, phenyl is preferred. In a corresponding fashion, the same applies to radicals derived therefrom, such as, for example, aroyl and aralkyl.

The invention furthermore relates to a process for the preparation of compounds of the formula I, wherein a compound of the formula II



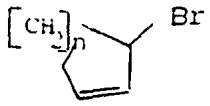
(II)

in which n, R and R^1 are as defined above, is subjected to free-radical decarboxylation.

Free-radical decarboxylation can be carried out, for example, by warming the compound to 40-190°C, preferably 80-130°C, in a suitable solvent, or alternatively without solvent, if appropriate in the presence of a free-radical initiator. Suitable solvents here are, in particular, aprotic solvents, such as benzene, toluene or xylene. Suitable intiators are, for example, organic peroxides, such as tert.-butyl peroxide, and substituted azoacetonitriles.

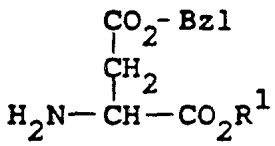
In addition, the free-radical decarboxylation can be carried out photolytically or radiolytically in a suitable dipolar aprotic solvent between -20°C and the boiling point of the reaction mixture, preferably between 10 and 50°C. Photolytic decarboxylation is preferred. Suitable dipolar aprotic solvents are, for example, ethers, such as diethyl ether, tetrahydrofuran and dioxane.

The compounds of the formula II are prepared starting from cycloalkenyl bromides of the formula V



(V)

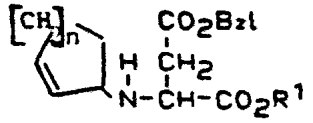
in which n is 1, 2 or 3. The latter compounds are reacted with aspartic acid derivatives of the formula VI



(VI)

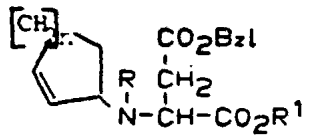
in which R^1 is as defined above, but preferably denotes (C_1-C_6)-alkyl, such as tert. butyl, and which preferably have the L configuration, in the presence of a base, such as K_2CO_3, in a dipolar aprotic solvent, such as acetonitrile, between 0°C and the boiling point of the reaction mixture, preferably at room temperature, to form compounds of the formula VII in which

n and R^1 are as defined above.



(VII)

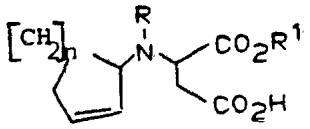
The latter are acylated to form compounds of the formula VIII



(VIII)

in which n, R and R^1 are as defined above. The acylation is expediently carried out in a dipolar aprotic solvent, such as acetone, in between -20°C and the boiling point of the reaction mixture, preferably at room temperature, preferably in the presence of a base. Suitable acylating agents are, for example, chlorides of the formula RCl or anhydrides of the formula R_2O. Suitable bases are tertiary amines, such as triethylamine, and inorganic bases, such as K_2CO_3.

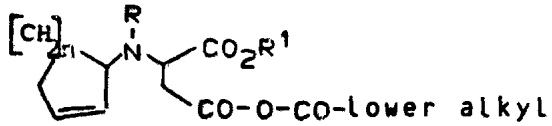
Hydrolysis of the diester VII using an alkali, preferably NaOH, in DMF at room temperature gives the compound of the formula IX



(IX)

in which n, R and R^1 are as defined above.

The latter compound is activated at -30 to 0°C in a dipolar aprotic solvent, such as tetrahydrofuran, by adding a lower alkyl chloroformate, preferably isobutyl chloroformate, and a base such as n-methylmorpholine, giving intermediate compounds of the formula X

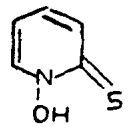


(x)

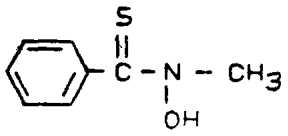
in which n, R and R^1 have the meaning above.

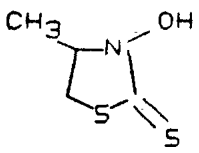
While maintaining the temperature, the alkali metal salt, preferably the sodium salt, of thiohydroxamic acids, preferably n-hydroxy-2H-pyridine-2-thione, is now added, forming the compound of the formula II.

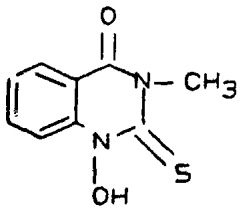
Besides N-hydroxy-2H-pyridine-2-thione



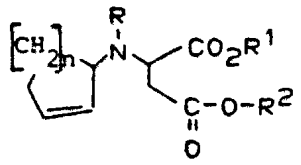
the following thiohydroxamic acids are also suitable, for example:







The invention also relates to compounds of the formula III



(III)

in which n, R and R^1 are as defined above, and R^2 denotes, in particular, 2-thioxo-2H-[1]pyridyl or (C_1-C_6)-alkoxycarbonyl, which are intermediates in the abovementioned process.

In addition, the invention relates to the use of compounds of the formula I in a process for the preparation of a compound of the formula IV in which R^3 denotes hydrogen or is as defined for R, and R^4 denotes hydrogen or is as defined for R^1, through treatment of a compound of the formula I with Raney nickel in a suitable solvent, preferably a lower alcohol, water or dioxane, 1 or 2 of the radicals R^3 and/or R^4 which do not denote hydrogen subsequently being replaced, if appropriate, by hydrogen with the aid of acids and/or bases and/or hydrogenolytically, and a compound of the formula IV being converted, if desired, into an ester of the formula IV in which R^4 is as defined for R by esterification or transesterification. Bromine substituents on R = aroyl are replaced by hydrogen in this process. Lower alcohol is taken to mean an aliphatic alcohol having 1 to 4 carbon atoms; ethanol is preferred. The reaction is preferably carried out between $-20^{\circ}C$ and the boiling point of the reaction mixture, in particular between 10 and $40^{\circ}C$. Besides Raney nickel, other desulfurizing agents, such as, for example, nickel boride, can also be used.

The examples below serve to illustrate the invention without representing a limitation.

Example 1

β-Benzyl α-tert.butyl N-(2-cyclohexen-1-yl)-L-aspartate

A solution of 3.22 g (20 mmol) of 3-bromocyclohexene in 20 ml of acetonitrile is introduced into a 250 ml flask containing 4.324 g (15.5 mmol) of β-benzyl α-tert.butyl L-aspartate and 6.417 g (46.5 mmol) of potassium carbonate in 65 ml of anhydrous acetonitrile. The mixture is stirred vigorously at room temperature for 48 hours. The K_2CO_3 is filtered off and rinsed with plenty of acetonitrile. The solvent is evaporated at reduced pressure, and the amine is purified over silica gel (eluent: diethyl ether/hexane 1:1).

Yield: 5.02 g (89 % of theory) of a slightly yellowish oil,

$[\alpha]_D^{R.T.} = + 5.1^o$ (c=1, methanol)

IR: ν = 3320; 1735; 1500; 1455 cm^{-1}

^1H NMR: δ[ppm]=

1.49 (9H, S, OtBu); 1.24 - 2.12 (yH, m, $-(CH_2)_3-$ + NH)

3.12 (1H, m, -CH-NH-); 2.63 (2H, d, J=6Hz, $-CH_2-COOBzl$);

3.62 (1H, t, J=6Hz, -CH t); 5.09 (2H, s, $-CH_2-Ph$);

5.6 (2H, m, -CH=CH-); 7.28 (5H, s, Ph).

Elemental analysis ($C_{21}H_{29}NO_4$:359):

calculated: % C 70.17 H 8.13 O 17.80

found: % C 69.99 H 7.99 O 17.86

Mass spectrum: m/e; 360 (M^++1) 259 (M^+-COOtBu).

(R.T. in the optical rotation value represents "room temperature").

Example 2

β-Benzyl α-tert.butyl N-acetyl-N-(2-cyclohexen-1-yl)-L-aspartate

1.1 g (3.06 mmol) of the amine from Example 1 are dissolved in 12 ml of acetone, and 1.1 g (3.06 mmol) of potassium carbonate are added. 0.43 ml of acetyl chloride

(2 equivalents) dissolved in 3 ml of ether is then added, and the mixture is stirred vigorously at room temperature for 2 days. The carbonate is filtered off and rinsed with plenty of acetone, and the solvent is evaporated at reduced pressure. The polar amide is purified over a silica gel column (eluent: diethyl ether/hexane 1:1, then 2:1).

Yield: 1.19 g (97 % of theory) of a colorless oil;

$[\alpha]_D^{R.T.} = -44.4^{\circ}$ (c=1, methanol)

IR: δ = 1740; 1730; 1675; 1650; 1500 cm^{-1}

^1H NMR: [ppm] =

1.41 (9H, s, OtBu); 1.85 (6H, m)

2.06 (3H, s, $COC\underline{H}_3$); 3.62 (2H, m, $-C\underline{H}_2-COOBzl$);

4.19 (1H, dd, J_1=9Hz, J_2=3Hz, CH_2)

4.35 (1H, m, $-C\underline{H}-N$); 5.1 (2H, s, $-C\underline{H}_2-Ph$);

5.82 (2H, m, $-C\underline{H}=C\underline{H}-$); 7.3 (5H, s, -Ph).

Elemental analysis ($C_{23}H_{31}O_5N$: 401)

calculated: % C 68.80 H 7.78 O 19.93

found: % C 68.71 H 7.85 O 19.95

Mass spectrum

m/e = 401 (M^+); 358 ($M^+ - COCH_3$)

Example 3

α-Tert.butyl N-acetyl-N-(2-cyclohexen-1-yl)-L-aspartate

1.3 g (3.24 mmol) of the amide from Example 2 are dissolved in 5 ml of DMF and hydrolysed at room temperature for 2 1/2 days using 2 ml (1.2 equivalents) of 2N sodium hydroxide solution. The solvent is evaporated, and the residue is dissolved in 2 ml of water. It should be ensured that the pH is alkaline. This aqueous phase is washed with ether in order to remove the benzyl alcohol, and then acidified to a pH of 4 using solid citric acid. The mixture is then extracted with ethyl acetate. The organic phase is washed with saturated aqueous NaCl solution, dried over Na_2SO_4, filtered and evaporated on a rotary evaporator. The acid thus obtained is purified over a silica gel column (40 g of SiO_2 60-200µm; eluent

CH_2Cl_2/methanol 98:2).
Yield: 910 mg (90 % of theory) of a foam,
$[\alpha]_D^{R.T.} = -108.9^\circ$ (c=1.94; methanol)
IR: ν = 3350; 1740; 1700 cm^{-1}
^1H NMR δ [ppm] =
1.42 (9H, s, OtBu); 1.92 (6H, m);
2.12 (3H, s, $-COCH_3$); 3.56 (2H, m, $-CH_2-$);
4.16 (1H, dd, J_1=9Hz, J_2=3Hz, $-CH_2$);
4.35 (1H, m, $-CH-N-$); 5.51-5,86 (2H, m, $-CH=CH-$)
Mass spectrum
m/e: 311 (M^+); 212 (M^+-COOtBu); 268 M^+ - 43)

Example 4

β-Benzyl α-tert.butyl N-(p-bromobenzoyl)-N-(2-cyclohexen-1-yl)-L-aspartate

2.5 g (6.9 mmol) of β-benzyl α-tert.butyl L-aspartate are added to a suspension of 3.86 g (28 mmol) of potassium carbonate in 32 ml of acetone, and the solution of 2.26 g (10.3 mmol) of p-bromobenzoyl chloride in 10 ml of ether is added. The mixture is then stirred vigorously at room temperature for 2 days, the carbonate is filtered off and rinsed with plenty of acetone, and the solvent is evaporated at reduced pressure. The oil which remains is purified over a silica gel column (eluent: diethyl ether/hexane 1:3).
Yield: 3.046 g (81 % of theory); m.p.: 100-101°C (from diethyl ether/hexane); $[\alpha]_D^{R.T.} = -49.8^\circ$ (c=1.8; methanol)
IR (Nujol): ν = 1730; 1635; 1590; 1420 cm^{-1}
^1H-NMR (200 MHz): [ppm] =
1.45 (9H, s, OtBu); 1.32-2.15 (6H, m, $-CH_2-$); O
2.47 (1H, dt, J_1=3Hz; J_2=12Hz; $-CH_2-$); $-C-R$
3.73 (1H, m, 1H of CH_2); 4.23 (2H, m, $-CH-N-CH$);
5.13 (2H, m, $-CH_2$-ph); 5.7 (2H, m, $-CH=CH-$);
7.28 (9H, m, Ar).

Elemental analysis ($C_{28}H_{32}NO_5Br$: 542)
calculated: % C 61.99 H 5.94 N 2.59 O 14.74
found: % C 61.87 H 5.78 N 2.46 O 14.47

Example 5

α-Tert.butyl N-(p-bromobenzoyl)-N-(2-cyclohexen-1-yl)-L-aspartate

1 g (1.8 mmol) of the amide from Example 4 is hydrolysed by adding 2 ml (1.1 equivalents) of 1 N sodium hydroxide solution, the mixture is stirred at room temperature for 1 day, and the dioxane is then evaporated. The aqueous phase is washed with ether, its pH is adjusted to 4 using solid citric acid, and the mixture is then extracted with ethyl acetate.

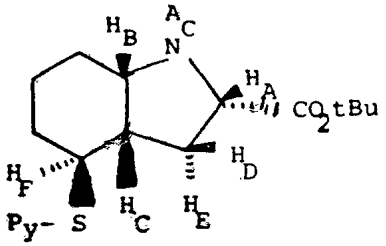
The acid thus obtained is purified over a silica gel column (30 g of SiO_2 70-200 µm; eluent) CH_2Cl_2/methanol 98:2)
Yield: 685 mg (84 % of theory) of a foam.
IR: ν = 3450; 1730; 1680; 1585; cm^{-1}
^1H NMR: [ppm] =
1.47 (9H, s, OtBu); 1,3-2,62 (6H, m);
3.65 (2H, m, -C<u>H</u>$_2$-COOH); 4.22 (2H, m, -C<u>H</u>-N-C<u>H</u>-);
5.84 (2H, m, -C<u>H</u>=C<u>H</u>-); 7.16 (2H, d, J=8Hz);
7.47 (2H, d, J=8Hz, Ar); 8.1 (1H, s, -COOH).

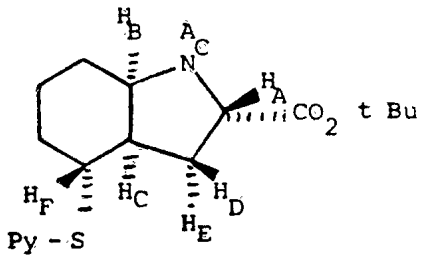
Microanalysis was carried out on the dicyclohexylamine salt, and similarly the melting point and optical rotation were determined for the dicyclohexylamine salt.
Elemental analysis: ($C_{33}H_{49}N_2O_5Br$: 633)
calculated: % C 62.55 H 7.79 N 4.42 O 12.62
found: % C 62.32 H 7.68 N 4.25 O 12.47
$[\alpha]_D^{R.T.}$ = -9.1° (c=0.76; methanol)
m.p.: 156-157°C [from ethyl acetate/petroleum ether].

Example 6

Tert.butyl 1-acetyl-4-(2'-pyridyl)-mercaptoperhydroindole-2-L-carboxylate 0.28 ml (2.5 mmol) of N-methylmorpholine and 0.36 ml (2.5 mmol) of isobutyl chloroformate are added while stirring to a solution of 776 mg (2.5 mmol) of the acid from Example 3 in 13 ml of THF under argon at -15°C. After an activation time of 5 minutes, 484 mg (1.3 equivalents) of the sodium salt of N-hydroxy-2H-pyridine-2-thione are added, and the mixture is stirred for 1.5 hours at -15°C under argon while excluding light. The mixture is then diluted with 20 ml of THF and allowed to stand at room temperature for 2 hours. The THF is evaporated under reduced pressure, and the residue is purified over silica gel (eluent: diethyl ether/hexane 2:1, 3:1, then 4:1 and, as soon as the first diastereoisomer has been removed, diethyl ether must be used as the eluent.

Balance: diastereomer 1	263 mg
Mixture of diastereomers 1 a. 2	160 mg
Diastereomer 2	151 mg
Total yield	574 mg (56 % of theory)





diasteromer 1 diasteromer 2

(Py = 2'-pyridyl; Ac = acetyl; tBu = tert.butyl)

The 160 mg of the diastereomeric mixture above were separated by means of preparative thin-layer chromatography (SiO_2; mobile phase: diethyl ether/hexane 1:1), a further 17 mg of diastereomer 1 and 125 mg of diastereomer 2 being obtained.

Diastereomer 1

Pale yellow oil; $[\alpha]_D^{R.T.}$ = -67.9° (c=0.6; methanol)

IR: ν = 1740; 1720; 1640; 1585; 1560 cm^{-1}

^1H NMR (200 MHz): δ[ppm] =

1.53 (9H, s, OtBu); 2.18 (3H, s, $-COOH_3$);
1.43-2.35 (7H, m, $-CH_2-$); 2.5 (1H, m, H_D or H_E,
2.72 (1H,m H_C); 4.15 (1H, m, H_B); 4.45 (1H, t, J=10Hz,
H_F);
4.58 (1H, m, H_A); 7.23-7.93 (3H, m, -S-Py);
8,8 (1H, m, -S-Py)

Mass spectrum

m/e = 376 (M^+), 320 (M^+- ≮), 276 (M^+-COOtBu)
265 (M^+-S-Py)

Diastereomer 2:

m.p.: 163-165°C [from diethyl ether/hexane];

$[\alpha]_D^{R.T.}$ = +19.3° (c=0.7; methanol)

^1H NMR (400 MHz); δ[ppm] =

1.5 (9H, s, OtBu);	2.12 (3H, S, $-COCH_3$);
1.16-2.29 (7H, m);	2.39 (1H, m, H_D or H_E);
2.63 (1H, m, H_C);	3.97 (1H, m, H_B);
4.26 (1H, t, J=9Hz, H_F);	4.36 (1H, m, H_A);
6.88-7.58 (3H, m, S-Py);	8.38 (1H, m).

IR: ν =1740; 1720; 1640; 1585; 1560 cm^{-1}

Mass spectrum:

m/e= 376 (M^+), 320 (M^+- ≮), 276 (M^+-COOtBu),
265 (M^+-S-Py)

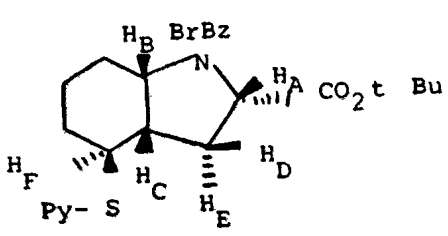
Example 7

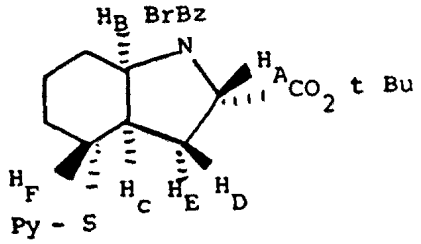
Tert.-butyl 1-(p-bromobenzoyl)-4-[(2'-pyridyl)-mercapto]-perhydroindole-2-L-carboxylate

The title compound was prepared in a fashion analogous to Example 6 starting from 600 mg (1.3 mmol) of the acid from Example 5.

Separation by column chromatography (SiO_2, eluent diethyl ether/hexane 1:2, later 1:1) led to resolution of the diastereomers.

Balance:	diastereomer 1'	205 mg
	mixture of diastereomers 1' and 2'	135 mg
	diastereomer 2'	125 mg
	total yield	465 mg(69 % of theory)





diastereomer 1' diastereomer 2'

(Py = 2'-pyridyl; BrBz = p-bromobenzoyl; tBu=tert.butyl)

Diastereomer 1':

m.p.: 164-165°C [from ethanol],

$[\alpha]_D$ = -170.0° (c=1.09; methanol)

IR: ν =1740; 1640; 1600; 1580; 1560; 1450; cm^{-1}

^1H NMR (200 MHz): δ[ppm] =

1.48 (9H, m); 1.1-2.33 (7H, m, - CH_2);

2.48 (2H, m, H_C + H_D or (H_E)); 3.76 (1H, m, H_B);

4.31 (1H, m, H_F)); 4.45 (1H, m, H_A));

6.86-7.68 (8H, Ar); 8.36 (1H, m).

Elementary analysis ($C_{25}H_{29}N_2O_3Br$:517)

calculated: % C 58.01 H 5.64 N 5.44 O 9.27

found: % C 57.88 H 5.48 N 5.49 O 9.08

Diastereomer 2':

foam; $[\alpha]_D^{R.T.}$ = +63.9° (c=0.8; methanol)

^1H NMR (400 MHz): δ [ppm] =

1.44 (9H, s, -OtBu); 0.8-1.91 (6H, m, -$(CH_2)_3$-);

2.09 (1H, dd, J_{EA}=0, J_{ED}=13Hz, J_{EC}=7Hz, H_E);

2.36 (1H, dt, J_{DE}=J_{DC}=13Hz, J_{DA}=10Hz, H_D);

2.83 (1H, m, H_C); 4.03 (1H, m, H_B);

4.27 (1H, m, H_F); 4.6 (1H, d, J_{DA}=10Hz, H_A);

6.90-7.68 (7H, m); 8.32 (1H, m).

Mass spectrum:

m/e: 515, 517, 518, (M^+), 461 (M^+-≺)

317 (M^+-COOtBu), 406 (M^+-S-Py).

Example 8:

Tert.butyl cis, exo-N-benzoyl-perhydroindole-2-L-carboxylate

150 mg (0.29 mmol) of diastereomer 1' from Example 7 are dissolved in 2 ml of absolute ethanol and reduced overnight at room temperature using Raney nickel (®Prolabo, 50 % shrink in water). The mixture is subsequently filtered, the catalyst is rinsed with plenty of an ethanol/water mixture, and the solvent is evaporated on a rotary evaporator.
Yield: 100 mg of crude product.

Example 9:

Cis,exo-N-benzoyl-perhydroindole-2-L-carboxylic acid

The crude product from Example 8 is hydrolyzed for one hour at room temperature in a mixture of 0.2 ml of a trifluoroacetic acid and 0.2 ml of CH_2Cl_2. The mixture is subsequently evaporated, and the oily residue (87 mg) is washed with pentane.

Example 10;

Ethyl cis, exo-N-benzoyl-perhydroindole-2-L-carboxylate

The acid from Example 9 is dissolved in 1.2 ml of DMF and neutralized using 52 mg (0.6 mmol) of $NaHCO_3$. A solution of 0.1 ml (1.25 mmol) of ethyl bromide in 1.2 ml of DMF is now added, and the mixture is stirred at room temperature for 24 hours. The DMF is evaporated under reduced pressure, and the residue is taken up in 1.5 ml of a 10 % strength aqueous citric acid solution. The title compound is extracted with ethyl acetate and then purified by chromatography (preparative TLC, SiO_2; mobile phase: diethyl ether/hexane 1:1).
Yield 57 mg (65 % of theory) of a colorless oil;
$[\alpha]_D = -41.1^\circ$ (c=0.48, methanol).

IR: ν = 1750; 1640; 1600; 1570 cm^{-1}.

^1H NMR (400 MHz): δ[ppm] =

1.30 (3H, m, -CO-CH_2-$\underline{CH_3}$); 0.85-1.94 (8H, m, -$(CH_2)_4$);

2.07 (1H, dt, $J_{ED}=J_{EC}=13Hz$, $J_{EA}=8Hz$, H_E);

2.23 (1H, m, H_D); 2.38 (1H, m, H_C);

3.57 (1H, m, H_B); 4.24 (2H, m, -CO-$\underline{CH_2}$-CH_3);

4.62 (1H, dd, $J_{AE}=8Hz$, $J_{AD}=6Hz$, H_A);

7.31 (2.5H,Ar); 5.87 (2.5 H, Ar).

[numbering of the H atoms as for diastereomers 1' and 2']

Mass spectrum:

m/e = 301 (M^+), 237 (M^+-COOEt), 196 (M^+-CO-Ph).

Example 11:

Ethyl cis, endo-N-benzoyl-perhydroindole-2-L-carboxylate

The procedure described above under Examples 8-10 is carried out using 120 mg (0.23 mmol) of diastereomer 2' from Example 7.

Yield: 46 mg (66 % of theory) of white crystals;

m.p.: 111-112°C [from diethyl ether/pentane];

$[\alpha]_D^{R.T.}$ = -91.9° (c=0.47; methanol)

IR: ν = 1750; 1640; 1600; 1570 cm^{-1}.

^1H NMR (400 MHz): δ[ppm] =

1.3 (3H, t, J=7Hz, CH_3-); 0.83-1,78 (8H, m, -$(CH_2-)_4$);

1.87 (1H, dd, $J_{EA}=0$, $J_{EB}=13Hz$, $J_{EC}=6,5Hz$, H_E);

2.23 (1H, dt, $J_{DA}=10Hz$, $J_{DE}=J_{DC}=13Hz$, H_D);

2.67 (1H, m, H_C); 3.26 (1H, m, H_B);

4.22 (2H, q, J=7Hz, -$\underline{CH_2}$-CH_3);

4.69 (1H, d, $J_{AD}=10Hz$, H_A);

7.37 (2.5H, m, Ar); 7.48 (2.5H, m, Ar).

[numbering of the H atoms as for diastereomers 1' and 2']

Mass spectrum:

m/e = 301 (M^+), 237 (M^+-COOEt),

196 (M^+-COPh).

Example 12:

Tert.butyl cis,exo-N-acetyl-perhydroindole-2-L-carboxylate

150 mg (0.4 mmol) of diastereomer 1 from Example 6 are dissolved in 3 ml of ethanol and reduced overnight while stirring at room temperature using a raney nickel. The nickel is filtered off and rinsed with a water/ethanol mixture, and the filtrate is evaporated in vacuo.

Crude yield: 130 mg

Example 13:

Cis, exo-perhydroindole-2-L-carboxylic acid hydrochloride

The crude product from Example 12 is refluxed for one hour with 4 ml of 6 N hydrochloric acid. After evaporation in vacuo, the hydrochloride remains in the form of an oil.

Example 14:

Ethyl cis, exo-perhydroindole-2-L-carboxylate hydrochloride

Hydrogen chloride is passed into a solution of the hydrochloride from Example 13 in 3 ml of absolute ethanol for 5 minutes at room temperature and for 10 minutes at 0°C. After evaporation of the ethanol, the residue remains as the hydrochloride of the ethyl ester (100 mg).

Example 15:

Ethyl cis, exo-N-(p-bromobenzoyl)-perhydroindole-2-L-carboxylate

The ester hydrochloride from Example 14 is dissolved in a mixture of 3 ml of THF and 1 ml of CH_2Cl_2, and, at 0°C, 0.07 ml (0.5 mmol) of triethylamine is added. 151 mg (0.75 mmol) of p-bromobenzoic acid, 115 mg (0.75 mmol) of hydroxybenzotriazole and 155 mg (0.75 mmol) of dicyclohexylcarbodiimide are then added successively at 0°C, and the mixture is stirred vigorously at room temperature

for 24 hours. The dicyclohexylurea is filtered off and rinsed with THF, and the solvent is evaporated from the filtrate.

The residue is dissolved in 5 ml of ethyl acetate, and the organic phase is washed successively with 0.1 N aqueous $NaHCO_3$ solution, water, 0.5 N hydrochloric acid, again with water and a saturated aqueous NaCl solution. The organic phase is then dried over Na_2SO_4, filtered and evaporated in vacuo. The derivative thus obtained is now purified by means of preparative thin-layer chromatography (SiO_2; eluent diethyl ether/hexane 1:1).

Yield: 62 mg (41 % of theory) of a colorless oil;
$[\alpha]_D^{R.T.} = -39.1^o$ (c=0.6; ethanol).
IR: ν = 1745; 1635; 1595; 1490 cm^{-1}.
^1H NMR (200 MHz): δ [ppm] =
1.3 (3H, m, CH_3); 0.83-1.95 (8H, m, $-(CH_2)_4-$);
2.17 (1H, m, H_E); 2.37 (1H, dt, $J_{DC}=J_{DA}=8Hz$, $J_{DE}=16Hz$, H_D)
2.71 (1H, m, H_C); 3.6 (1H, m, H_B);
4.27 (2H, m, $-COOCH_2-CH_3$); 4.67 (1H, m, H_A);
7.37 (2H, d, J=9Hz); 7.6 (2H, d, J=9Hz).
[numbering of the H atoms as for diastereomers 1 and 2]
Mass spectrum:
m/e = 320 (M^+), 307 (M^+-COOEt), 196 (M^+-COAr).

Example 16

Ethyl cis, endo-N-(p-bromobenzoyl)-perhydroindole-2-L-carboxylate

Starting from 120 mg (0.32 mmol) of diastereomer 2 from Example 6, 55 mg (45 % of theory) of the title compound are obtained, in the form of an oil, analogously to Examples 12-15.
$[\alpha]_D^{R.T.} = -54.4^o$ (c=1.1; ethanol).
IR: ν = 1745; 1635; 1595; 1495; cm^{-1}.
^1H NMR (200 MHz); δ [ppm]
1.32 (3H, t, J=7Hz, $-Ch_3$); 0.83-1.8 (8H, m, $-(CH_2)_4-$);

1.88 (1H, dd, J_{ED}=13Hz, J_{EC}=6,5Hz, H_E);
2.37 (1H, dt, J_{DE}=J_{DC}=13Hz; J_{DA}=9Hz, H_D); 2.6
(1H, m, H_C);
3.87 (1H, ddd ($^{J}BH_1$=16Hz, $^{J}BH_2$=10.5Hz, J_{BC}=5Hz)H_B);
4.2 (2H, q, J=7Hz, -O-C$\underline{H_2}$-CH_3);
4.68 (1H, d, J=9Hz, H_A); 7.38 (2H, d, J=9Hz);
7.55 (2H, d, J=9Hz).
[numbering of the H atoms as for diastereomers 1 and 2]
Mass spectrum:
m/e = 380 (M^+), 307 (M^+-COOEt), (M^+-COAr).

Example 17:

Tert.butyl cis,exo-N-benzoyl-perhydroindole-2-L-carboxylate

The title compound is obtained starting from diastereomer 1' from Example 7 through treatment with Raney nickel in ethanol. Purification is effected by means of preparative thin-layer chromatography (SiO_2; mobile phase diethyl ether/hexane 1:1).

m.p.: 114-115°C [from ethanol];
$[\alpha]_D^{R.T.}$ = -44.2° (c=0.9; methanol).
IR: ν = 1740; 1640; 1600; 1420 cm^{-1}
^1H NMR (200MHz): δ[ppm] =
1.58 (9H, m, OtBu); 0.96-1.96 (8H, m,-(CH_2-)$_4$);
2.18 (2H, m, H_D, H_E); 2.43 (1H, m, H_C);
3.73 (1H, m, H_B); 4.7 (1H, m, H_A);
7.7 (5H, m, Ar).
[numbering of the H atoms as for diastereomers 1' and 2']
Mass spectrum:
m/e = 329 (M^+), 229 (M^+-COOtBu), 224 (M^+-CO-Ph).

Example 18:

Tert.butyl cis, endo-N-benzoyl-perhydroindole-2-L-carboxylate

The title compound is obtained starting from the diastereomer

2' from example 7 to treatment with Raney nickel in ethanol. Purification is effected by means of preparative thin-layer chromatography (SiO_2; mobile phase diethyl ether/hexane 1:1).

m.p.: 111-112°C [from ethanol];

$[\alpha]_D^{R.T.} = -96.6^\circ$ (c=1.05; methanol).

IR: ν = 1740; 1640; 1600; 1420 cm^{-1}.

^1H NMR (400 MHz): δ [ppm] =

1.5 (9H, s, OtBu); 0.82-1.7 (8H, m, $-(CH_2)_4$;

1.84 (1H, dd, J_{EA}=0, J_{ED}=13Hz, J_{EC}=6.5Hz, H_E);

2.31 (1H, dt, J_{DA}=10Hz, J_{DE}-J_{DC}=13Hz, H_D);

2.67 (1H, m, H_C); 3.86 (1H, m, H_B);

4.56 (1H, d, J=10Hz, H_A); 7.42 (5H, m, Ar).

[numbering of the H atoms as for diastereomers 1' and 2']

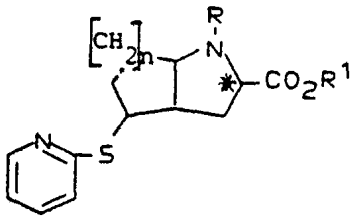
Elemental analysis ($C_{20}H_{27}NO_3$):

calculated: % C 72.91 H 8.26 O 14.57

found: % C 72.83 H 8.38 O 14.81

Patentxxclaims
THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A compound of the formula I



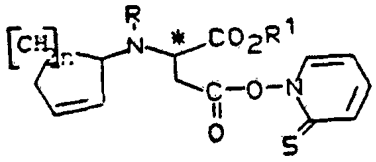
I

in which
n = 1, 2 or 3,
R denotes (C_1-C_{12})-acyl, and
R^1 denotes (C_1-C_6)-alkyl, (C_3-C_7)-cycloalkyl, (C_7-C_{11})-aralkyl or another carboxyl-protecting group.

2. A compound of the formula I as claimed in claim 1, in which the hydrogen atoms on the bridgehead carbon atoms 3a and (5+n)a have a cis configuration.

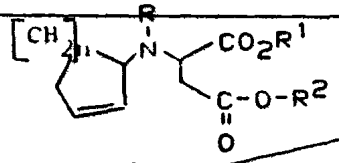
3. A compound of the formula I as claimed in claim 1 or 2, in which the carbon atom in position 2 has the S configuration.

4. A process for the preparation of a compound of the formula I as claimed in claim 1, wherein a compound of the formula II



II

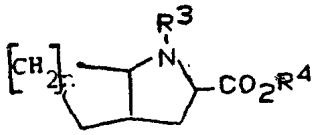
in which n, R and R^1 are as defined in claim 1, is subjected to free-radical decarboxylation.



(III)

in which n, R and R^1 are as defined in claim 1, and R^2 denotes 2-thioxo-2H-[1]pyridyl or ~~(C_1-C_6)-alkoxycarbonyl.~~

5. The use of a compound of the formula I as claimed in one or more of claims 1-3 in a process for the preparation of a compound of the formula IV



(IV)

in which
R^3 denotes hydrogen or is as defined for R in claim 1, and
R^4 denotes hydrogen or is as defined for R^1 in claim 1, through treatment of a compound of the formula I with Raney nickel in a suitable solvent, 1 or 2 of the radicals R^3 and/or R^4 which do not denote hydrogen subsequently being replaced, if appropriate, by hydrogen with the aid of acids and/or bases and/or hydrogenolytically, and a compound of the formula IV being converted, if desired, into an ester of the formula IV in which R^4 is as defined for R in Claim 1 by esterification or transesterification.

DATED this 3rd day of December 1987.

HOECHST AKTIENGESELLSCHAFT

EDWD. WATERS & SONS
PATENT ATTORNEYS
50 QUEEN STREET
MELBOURNE. VIC. 3000.