Process for preparing enantiomerically pure N-methyl-N-[(1S)-1-phenyl-2-((3S)-3-hydroxypyrrolidin-1-yl)ethyl]-2,2-diphenylacetamide

The invention relates to a novel process for alternatively preparing N-methyl-N-[(1S)-1-phenyl-2-((3S)-3-hydroxypyrrolidin-1-yl)ethyl]-2,2-diphenylacetamide or N-methyl-N-[(1R)-1-phenyl-2-((3R)-3-hydroxypyrrolidin-1-yl)ethyl]-2,2-diphenylacetamide, and to the novel compounds N-methyl-N-[(1S)-1-phenyl-2-((3S)-3-hydroxypyrrolidin-1-yl)ethane] and N-methyl-N-[(1R)-1-phenyl-2-((3R)-3-hydroxypyrrolidin-1-yl)ethane] which are prepared as intermediates.

As described by Barber et al. (B.J. Pharmacol. (1994), **113**, 1317-1327), both the compound N-methyl-N-[(1S)-1-phenyl-2-((3S)-3-hydroxypyrrolidin-1-yl)ethyl]-2,2-diphenylacetamide and its physiologically acceptable salts have pharmacological properties such as an analgesic, anti-inflammatory, and aquaretic effect so that they are suitable in particular for preparing medicaments.

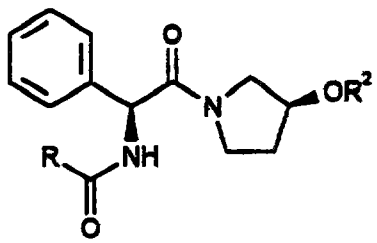
As described in the Patent Application DE 1 95 23 502 or EP 752 246, it has been found that this compound is a particularly effective compound which is very particularly suitable for use as a medicament for the treatment of inflammatory bowel disease. This compound can be used and is effective for this indication in particular because it simultaneously alleviates the pain associated with this disease and, in the acute case of ileus caused by or imminent owing to inflammatory bowel disease, renormalizes or restarts bowel motoricity without causing any noticeable side effects. The compound can also be used for non-inflammatory intestinal disorders such as IBS (irritable bowel syndrome).

The patent applications DE 40 34 785 A1 and DE 42 15 213 A1 or EP 0 569 802 A1 describe the preparation of N-methyl-N-[(1S)-1-phenyl-2-((3S)-3-hydroxypyrrolidin-1-yl)ethyl]-2,2-diphenylacetamide by reacting (2S)-2-N-carboxyethyl-2-phenylglycine-N,N-[(3S)-3-hydroxytetramethylamide with diphenylacetyl chloride. As described in DE 42 15 213, the starting material (2S)-2-N-carboxyethyl-2-phenylglycine-N,N-[(3S)-3-hydroxytetramethyleneamide, also referred to as (1S)-[1-N-methylamino-1-phenyl-2-((3S)-3-hydroxypyrrolidino)ethane can be prepared by reacting (1S)-1-amino-1-phenyl-2-chloroethane with (3S)-3-hydroxypyrrolidine, followed by methylation with methyl iodide. However, this preparation method is problematic owing to the solubility of the starting materials and the fact that the racemic product mixture obtained after the synthesis is contaminated by byproducts and has to be separated in a complicated manner. Thus, the known process for preparing N-methyl-N-[(1S)-1-phenyl-2-((3S)-3-hydroxypyrrolidin-1-yl)-ethyl]-2,2-diphenylacetamide is complicated and expensive and leads to low yields, based on the starting materials employed.

It was therefore an object of the present invention to provide a process which is inexpensive and can be carried out in a simple manner, for the preparation of N-methyl-N-[(1S)-1-phenyl-2-((3S)-3-hydroxypyrrolidin-1-yl)ethyl]-2,2-diphenylacetamide or, using the enantiomeric starting materials, of N-methyl-N-[(1R)-1-phenyl-2-((3R)-3-hydroxypyrrolidin-1-yl)ethyl]-2,2-diphenylacetamide which employs inexpensive, readily soluble starting materials which afford a product that is as enantiomerically pure as possible and which can subsequently be isolated and purified in a simple manner.

This object is achieved by a process according to Claim 1 where either the hitherto unknown compound N-methyl-N-[(1S)-1-phenyl-2-((3S)-3-hydroxypyrrolidin-1-yl)-ethane] is employed as novel intermediate for preparing N-methyl-N-[(1S)-1-phenyl-2-((3S)-3-hydroxypyrrolidin-1-yl)ethyl]-2,2-diphenylacetamide or N-methyl-N-[(1R)-1-phenyl-2-((3R)-3-hydroxypyrrolidin-1-yl)ethane] is employed as novel intermediate for preparing N-methyl-N-[(1R)-1-phenyl-2-((3R)-3-hydroxypyrrolidin-1-yl)ethyl]-2,2-diphenylacetamide.

It has been found that compounds of the formula (III)



(III)

in which R and R^2 are as defined below,

R is H, OR^1 or SR^1,

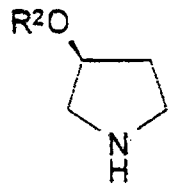
R^1 is A, aryl, heteroaryl, $Si(R^3)_3$ or COR^3,

R^2 is H, A, aryl, heteroaryl and $Si(R^3)_3$ or COR^3,

R^3 is H, A, aryl or heteroaryl,

A is a straight-chain or branched alkyl radical having 1 to 6 carbon atoms,

can be prepared in high yields and enantiomerically pure by hermetic coupling off, depending on the desired end product, (3S)-3-hydroxypyrrolidines or (3R)-3-hydroxypyrrolidines of the formula (II)



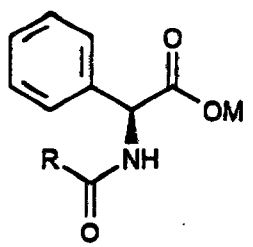
(II)

in which

R^2 is H, A, aryl, heteroaryl and $Si(R^3)_3$ or COR^3 and
R^3 is H, A, aryl or heteroaryl

or salts thereof formed with HCl, HBr, HI, H_2SO_4, H_3PO_4 or suitable organic acids

with appropriate (S)- or (R)-enantiomeric forms of N-substituted phenylglycines of the formula (I)



(I)

in which

R is H, OR^1 or SR^1,
R^1 is A, aryl, heteroaryl, $Si(R^3)_3$ or COR^3,
R^3 is H, A, aryl or heteroaryl,
M is H or a cation from the group consisting of alkali metals, alkaline earth metals, ammonium or alkylammonium.

Alkyl has 1 to 6, preferably 1, 2, 3 or 4, C atoms. Alkyl is preferably methyl, furthermore ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl or tert-butyl, furthermore also pentyl, 1-, 2- or 3-methylbutyl, 1,1-, 1,2- or 2,2-dimethylpropyl, 1-ethylpropyl, hexyl, 1-, 2-, 3- or 4-methylpentyl, 1,1-, 1,2-, 1,3-, 2,2-, 2,3- or 3,3-dimethylbutyl, 1- or 2-ethylbutyl, 1-ethyl-1-methylpropyl, 1-ethyl-2-methylpropyl, 1,1,2- or 1,2,2-trimethylpropyl.

Aryl is preferably unsubstituted phenyl or phenyl which is mono- or disubstituted by Hal, OA or alkyl, furthermore, for example, biphenyl or naphthyl.

Heteroaryl is preferably, for example, furanyl, thiophenyl, pyridinyl, pyrrolyl or thiazolyl.

$Si(R^3)_3$ is preferably, for example, $Si(CH_3)_3$.

COR^3 is preferably, for example, acetyl or benzoyl.

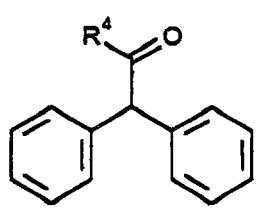
R is preferably, in particular, for example, methoxy or ethoxy.

R^1 is in particular, for example, methyl, ethyl, propyl, butyl, phenyl, $Si(CH_3)_3$ or acetyl.

R^2 is, in particular, for example, H, tert-butyl, $Si(CH_3)_3$, acetyl, benzyl or benzoyl, very particularly preferably it is H.

The prepared amides of the formula (III) can be converted reductively in a simple manner, if appropriate by cleaving off the protective group of the hydroxyl group of the pyrrolidine, into N-methyl-N-[(1S)-1-phenyl-2-((3S)-3-hydroxypyrrolidin-1-yl)ethane] or N-methyl-N-[(1R)-1-phenyl-2-((3R)-3-hydroxy-pyrrolidin-1-yl)ethane] of the formula (IV).

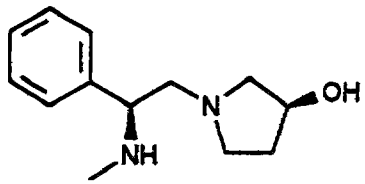
By reaction with activated carboxylic acids of the formula (V)



(V)

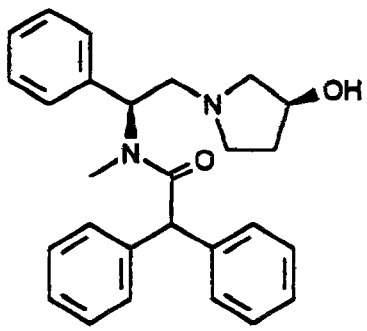
in which
R^4 is F, Cl, Br, I, OA or O-CO-A,

it is possible to prepare, from the free bases of the compounds of the formula (IV)



(IV)

or from its salts, formed with HCl, HBr, HI, H_2SO_4, H_3PO_4 or suitable organic acids, the enantiomeric compounds of the formula (VI)



(VI)

in pure form. These compounds are preferably prepared as hydrochlorides, the compound N-methyl-N-[(1S)-1-phenyl-2-((3S)-3-hydroxypyrrolidin-1-yl)ethyl]-2,2-diphenylacetamide being the known form EMD 61753; but it is also possible to prepare, in a similar manner, the corresponding salts with the other abovementioned acids.

In particular, by the last-mentioned reaction with diphenylacetyl chloride, it is possible to prepare N-methyl-N-[(1S)-1-phenyl-2-((3S)-3-hydroxypyrrolidin-1-yl)ethyl]-2,2-diphenylacetamide in this manner.

The compounds of the formula (IV) synthesized as intermediates can generally be obtained by reacting

compounds of the formula (I) with those of the formula (II). In this reaction, preference is given to using compounds of the formula (I), in which R is OR^1 where R^1 is A, aryl, heteroaryl, $Si(R^3)_3$ or COR^2 and R^2 is H, alkyl, aryl or heteroalkyl, having the preferred meanings given above. Surprisingly, in contrast to when the corresponding formyl compound is employed, this gives enantiomerically pure reaction products of the formula (III). In this manner, the resolution of the racemate can advantageously be dispensed with.

The reaction of the compounds (I) and (II) can be carried out in any aprotic solvent. Particularly suitable are polar aprotic solvents from the group consisting of diethyl ether, petroleum ether, acetone, nitrobenzene, dimethylformamide, dimethyl sulphoxide, or other appropriate solvents. Here, the starting materials are taken up in an exceptional amount of solvent that a from 10 to 30 per cent solution results. The reaction is preferably thoroughly mixed [sic] in the solvent tetrahydrofuran.

The reactions of the compounds (I) and (II) are carried out under suitable conditions at temperatures between 0 and 50°C. However, particularly good results are obtained at room temperatures between 20 and 30°C and at atmospheric pressure.

To activate the starting materials, the presence of an auxiliary reagent is required. These can be auxiliaries which are also used as peptide coupling reagents. Suitable compounds are, for example, phosphorus oxytrichloride, phosphorus halides of the valency III and V, phosgene, dicyclohexylcarbodiimide, tributylammonium salt of pyridine, phenyl dichlorophosphate, 2-chloro-1,2,3-trinitrobenzene, phosphoric acid esters, chlorosulphonyl isocyanate, CH_3SO_2Cl-$(C_2H_5)_3N$, $(C_6H_5)_3P$-CCl_4-$(C_2H_5)_3N$,N,N'-

carbonyldiimidazole, N-(alkylcarbonyl)imidazoles, acid anhydrides or acyl chlorides and in particular alkyl chloroformates, such as ethyl chloroformate. Other suitable auxiliary reagents are described in various technical books such as, for example, in C. Ferri "Reaktionen der organischen Synthese" [Reactions of organic synthesis]; R.C. Larock "Comprehensive Organic Transformations; A Guide to Functional Group Preparations", Verlag Chemie, 1989.

Furthermore the presence of a base is required. Suitable bases are likewise quoted in the abovementioned technical books. Such bases are, for example, tertiary amines, such as, for example, triethylamine. However, it is also possible to add inorganic bases. Suitable inorganic bases are, in particular, carbonates. When using alkali metal hydroxides, such as NaOH or KOH, exact dosage has to be ensured in particular, since undesirable side reactions may otherwise occur. However, to simplify work-up, it is also possible to employ an excess of hydroxypyrrolidine, so that it itself acts as base.

The work-up of the resulting reaction product (III) can, after the precipitate which is obtained has been filtered off, be carried out with customary laboratory methods from the filtrate. In a customary and suitable method, for example, the solvent is distilled off, the crude product is again taken up in an organic solvent, the resulting solution is extracted repeatedly with water, the solvent is once more distilled off and the resulting product is recrystallized [sic] by recrystallization from a suitable solvent, such as, for example, from methanol. However, it is also possible to employ other variants for work-up known to the person skilled in the art, such as, for example, those which include chromatographic purification.

Depending on the reaction conditions, the reaction product (III) is obtained as a free base or as acid additions salt of the acids HCl, HBr, HI, H_2SO_4 or an organic carboxylic acid from an aqueous solvent mixture. In the last-mentioned cases, isolation by customary laboratory methods can be carried out after phase separation.

Aliphatic, alicyclic, araliphatic, aromatic or heterocyclic, mono- or polybasic carboxylic, sulphonic or sulphuric acids, for example formic acid, acetic acid, propionic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, lactic acid, tartaric acid, malic acid, citric acid, gluconic acid, ascorbic acid, nicotinic acid, isonicotinic acid, methane- or ethanesulphonic acid, ethanedisulphonic acid, 2-hydroxyethanesulphonic acid, benzenesulphonic acid, p-toluenesulphonic acid, naphthalenemono- and disulphonic acids, laurylsulphuric acid, in particular, may be used as suitable organic carboxylic acids.

The reduction of the compounds of the formula (III) is carried out under an atmosphere of protective gas, for example under an atmosphere of nitrogen, in the presence of a hydride transfer reagent. Suitable hydride transfer reagents are those from the group of the metal aluminium hydrides, preferably lithium aluminium hydride, metal alkoxyaluminohydrides, such as, for example, lithium triethoxyaluminohydride, metal borohydrides, preferably $NaBH_4$, or borane, where additionally the presence of a Lewis acid, such as, for example, boron trifluoride, is required.

The reduction is preferably carried out in a polar aprotic and hydride-inert solvent. Suitable solvents are those which have already been mentioned above.

Particularly suitable are, for example, diethyl ether or tetrahydrofuran.

To carry out the hydrogenation, a compound of the formula (III) is dissolved in a suitable solvent and added with heating to a solution which contains equimolar amounts or a slight excess of the hydride transfer reagent. However, it is also possible to initially charge the starting material to be hydrogenated and to add an appropriate amount of the hydrogenating agent in a suitable manner so that a reaction mixture is obtained in which the starting material has a concentration of from 10 to 25% by weight, based on the solvent. To bring the reaction to completion, the reaction mixture is stirred under reflux conditions for several hours. The reaction solution is subsequently worked up by methods known to the person skilled in the art, inter alia by decomposing the excess of hydride transfer reagent and liberating the reaction product by addition of a solvent mixture comprising a proton-donating and an aprotic solvent. Suitable proton-donating solvents are, for example, water or alcohols, such as ethanol or methanol. Suitable aprotic solvents are the polar aprotic solvents which have already been mentioned above, in particular tetrahydrofuran. The latter is used preferably, since it is available as a technical-grade anhydrous product.

After the phase separation, the product can be worked up by customary laboratory methods. The crude product obtained can be worked up by crystallization methods, or it is taken up for work-up, for example, in an organic water-immiscible solvent and admixed with an excess of an inorganic acid, preferably hydrochloric acid. The salt formed in this manner can subsequently be separated off in crystalline form.

The further reaction of N-methyl-N-[(1S)-1-phenyl-2-((3S)-3-hydroxypyrrolidin-1-yl)ethane or its dihydrochloride with a suitable diphenylacetic acid derivative, preferably the acid chloride, to give the desired end product N-methyl-N-[(1S)-1-phenyl-2-((3S)-3-hydroxypyrrolidin-1-yl)ethyl]-2,2-diphenylacetamide (formula VI, EMD 61753) is carried out by the methods described in DE-A1-40 34 785 and DE-A1-42 15 213 or EP 0 569 802 A1.

The examples given hereinbelow are to illustrate the present invention, but they cannot serve to limit the claimed invention to these, since various variations of the examples are possible which lead to the desired product N-methyl-N-[(1S)-1-phenyl-2-((3S)-3-hydroxypyrrolidin-1-yl)ethane [formula (IV)] which can be used as intermediate for preparing N-methyl-N-[(1S)-1-phenyl-2-((3S)-3-hydroxypyrrolidin-1-yl)ethyl]-2,2-diphenylacetamide.

EXAMPLES

N-substituted (2S)-2-phenylglycine-N,N-[(3S)-3-hydroxy-tetramethyleneamides] of the formula III from (2S)-2-phenylglycines of the formula I

Example 1

(2S)-N-formyl-2-phenylglycine-N,N-[(3S)-3-hydroxytetra-methyleneamide]

From (2S)-N-formyl-2-phenylglycine (obtainable from (S)-(+)-alpha-aminophenylacetic acid and acetic anhydride/formic acid, for example according to Huszthy, Peter; Oue, Masatoshi; Bradshaw, Jerald S.; Zhu, Cheng Y.; Wang, Tingmin; et al., J. Org. Chem., EN, 57 (20) [1992] 5383-5394)

and

(3S)-3-hydroxypyrrolidine (obtainable from commercial (S)-1-benzyl-3-pyrrolidinol, for example according to Bhat, Krishna L.; Flanagan, Denise M.; Joullie, Madeleine M., Synth.Commun., EN, 15(7)[1985] 587-598 or Naylor, Alan; Judd, Duncan B.; Scopes, David I.C.; Hayes, Ann G.; Birch, Philip J., J. Med. Chem., EN, 37 (14) [1994] 2138-2144):

Under an atmosphere of nitrogen and at -15°C, 4.8 ml of ethyl chloroformate in 10 ml of tetrahydrofuran and, after an interval of 10 minutes, a solution of 6.2 g of (3S)-3-hydroxypyrrolidine hydrochloride and 7 ml of triethylamine in 50 ml of dimethylformamide are added with stirring to 9 g of (2S)-N-formyl-2-phenylglycine and 5.5 ml of N-methylmorpholine in 250 ml THF. The mixture is stirred for 18 hours, after which the resulting precipitate is separated off, and the (2S)-N-formyl-2-phenylglycine-N,N-[(3S)-3-hydroxytetramethyleneamide formed is isolated from the filtrate by concentration and subsequent chromatographic purification using customary laboratory methods.

1H-NMR: D_6-DMSO; 3.0-3.8 (m), 4.25 (d), 5.0 (s,brd), 5.7 (dd), 7.4 (ArH), 8.0 (ArH), 8.8 (CHO):

MS-FAB: $(M+1)^{\oplus}$ 221, 205;

Crystals m.p.: 97-101°C;

$[\alpha]_D^{20}$ =+ 208 , c=1 in methanol .

Example 2

(2S)-N-carboxybenzyl-2-phenylglycine-N,N-[(3S)-3-hydroxytetramethyleneamide]

From (2S)-N-carboxybenzyl-2-phenylglycine (from (S)-(+)-alpha-aminophenylacetic acid and benzyl chloroformate, for example according to Jones, Raymond CF; Turner, Ian; Howard, Kevin J., Tetrahedron Lett., 34 (39) [1993] 6329-6332)

and

(3S)-3-hydroxypyrrolidine (obtainable from commercial (S)-1-benzyl-3-pyrrolidinole for example according to Bhat, Krishna L.; Flanagan, Denise M.; Joullie, Madeleine M., Synth. Commun., EN, 15 (7) [1985] 587-598 or Naylor, Alan; Judd, Duncan B.; Scopes, David I. C.; Hayes, Ann G.; Birch, Philip J., J. Med. Chem., EN, 37 (14) [1994] 2138-2144):

Under an atmosphere of nitrogen, 14.3 g of (2S)-N-carboxybenzyl-2-phenylglycine in 100 ml of tetrahydrofuran are mixed in the cold with 5.5 ml of 4-methylmorpholine and a solution of 4.8 ml of ethyl chloroformate and 10 ml of tetrahydrofuran, and the mixture is then stirred for 30 min. A solution of 4.36 g of (3S)-3-hydroxypyrrolidine and 10 ml of tetrahydrofuran is then added. The mixture is stirred for 18 hours and the resulting precipitate is then separated off and the (2S)-N-carboxybenzyl-2-phenylglycine-N,N-[(3S)-3-hydroxytetramethyleneamide formed is then isolated from the filtrate by concentration, taken up in an organic solvent, washing with an aqueous phase, renewed concentration and crystallization, using customary laboratory methods.

1H-NMR: D_6-DMSO+TFA; 5.1 (s), $PhCH_2R$;

FAB-MS: 355 $(M+1)^{\oplus}$, 311, 196, 176;

Consistency: oil;

$[\alpha]_D^{20}$ =+ 108, c=1 in methanol.

Example 3

(2S)-N-carboxyethyl-2-phenylglycine-N,N-[(3S)-3-hydroxytetramethyleneamide]

3.a)

From (2S)-N-carboxyethyl-2-phenylglycine (from (S)-(+)-alphaaminophenylacetic acid and ethyl chloroformate, for example according to Bodurow, C.C.; Boyer, B.D.; Brennan, J.; Bunnell, C.A.; Burks, J. E.; et al., Tetrahedron Lett., EN, 30 (18) [1989] 2321-2324)

and

(3S)-3-hydroxypyrrolidine (obtainable from commercial (S)-1-benzyl-3-pyrrolidinole for example according to Bhat, Krishna L.; Flanagan, Denise M.; Joullie, Madeleine M., Synth. Commun., EN, 15 (7) [1985] 587-598 or Naylor, Alan; Judd, Duncan B.; Scopes, David I. C.; Hayes, Ann G.; Birch, Philip J., J. Med. Chem., EN, 37 (14) [1994] 2138-2144)

Under an atmosphere of nitrogen, 16.7 g of (2S)-N-carboxyethyl-2-phenylglycine in 100 ml of tetrahydrofuran are admixed in the cold with 8.3 ml of 4-methylmorpholine and a solution of 7.1 ml of ethyl chloroformate and 20 ml of tetrahydrofuran, and the mixture is then stirred for 60 min. A solution of 6.5 g of (3S)-3-hydroxypyrrolidine and 30 ml of

tetrahydrofuran is then added. The mixture is stirred for 18 hours, after which the resulting precipitate is separated off and the (2S)-N-carboxyethyl-2-phenylglycine-N,N-[(3S)-3-hydroxytetramethyleneamide is isolated from the filtrate by concentration, taken up in an organic solvent, washing with an aqueous phase, renewed concentration and crystallization, using customary laboratory methods.

3.b)

From (2S)-N-carboxyethyl-2-phenylglycine (see above) and (3S)-3-hydroxypyrrolidine hydrochloride (commercially available): at approximately -10°C, a mixture of 24 g of (2S)-N-carboxyethyl-2-phenylglycine with 10 g of methylmorpholine in 100 ml of THF are metered into 11 g of ethyl chloroformate in 100 ml of THF. The mixture is stirred for some time, and a mixture of 12 g of (3S)-3-hydroxypyrrolidine hydrochloride in 10 ml of deionized water and a mixture of 10 g of methylmorpholine in 20 ml of THF are then added. The mixture is stirred for several hours, after which the phases are separated, and the (2S)-N-carboxyethyl-2-phenylglycine-N,N-[(3S)-3-hydroxytetramethyleneamide is isolated by concentration, taken up in an organic solvent, washing with an aqueous phase, renewed concentration and crystallization, using customary laboratory methods.

The analytical data for variants 3a and 3b correspond to one another:

1H-NMR: D_6-DMSO; 1.2 (t), 3 - 3.8 (m, brd), 4.05 (q), 4.25 (s, brd), 7.25-7.45 (m);

MS: 293 $(M+1)^{\oplus}$, 247, 178, 106;

Crystals m.p.: 124-126°C;

$[\alpha]_D^{20}$ =+ 137 C=1 in methanol.

N-methyl-N-[(1S)-1-phenyl-2-((3S)-3-hydroxypyrrolidin-1-yl)ethanes of the formula IV

Example 4

N-methyl-N-[(1S]-1-phenyl-2-((3S)-3-hydroxypyrrolidin-1-yl)ethane = 1-[(3S)-3-hydroxypyrrolidin-1-yl]-(2S)-2-methylamino-2-phenylethane

Under nitrogen, 2200 ml of a 1.08 molar solution of lithium aluminium hydride in tetrahydrofuran are heated gently, and a solution of 264 g of (2S)-N-carboxyethyl-2-phenylglycine-N,N-[(3S)-3-hydroxytetramethyleneamide] and 1400 ml of tetrahydrofuran are metered in with stirring. After the end of the addition, the mixture is refluxed for 3 hours and the cold reaction solution is hydrolyzed using a water/tetrahydrofuran mixture. After treatment with sodium carbonate and removal of inorganic components, the product is isolated from the filtrate using customary laboratory methods. The oily crude product forms, after purification by crystallization or chromatography, a solid.

1H-NMR: D_6-DMSO; 2.1-3.1(m), 3.6(dd), 4.3(m), 7.15-7.35 (m);

MS: 220($M^{\oplus}$), 205, 120, 100, 91;

Appearance: yellowish oil which, depending on the batch, crystallizes;
$[\alpha]_D^{20}$ =+ 66.8;c=0.0938 g in 10 ml methanol.

Example 5

N-methyl-N-[(1S)-1-phenyl-2-((3S)-3-hydroxypyrrolidin-1-yl)ethane dihydrochloride =

1-[(3S)-3-hydroxypyrrolidin-1-yl]-(2S)-2-methylamino-2-phenylethane dihydrochloride

Under nitrogen, 2200 ml of a 1.08 molar solution of lithium aluminium hydride in tetrahydrofuran are heated gently, and a solution of 264 g of (2S)-N-carboxyethyl-2-phenylglycine-N,N-[(3S)-3-hydroxytetramethyleneamide] and 1400 ml of tetrahydrofuran are metered in with stirring. After the end of the addition, the mixture is refluxed for 3 hours and then cooled and the reaction solution is hydrolyzed using a mixture of 80 ml of water and 400 ml of tetrahydrofuran. After treatment with sodium carbonate and removal of inorganic components, the product is isolated from the filtrate using customary laboratory methods. The oily crude product is taken up in an organic water-immiscible solvent and admixed with an excess of hydrochloric acid. The crystalline product is isolated and dried.

1H-NMR: D_6-DMSO; 3.4(m), 3.8(m), 4.2(m), 4.4(m), 4.9(m), 7.5 and 7.8 (ArH);

Melting point: 240-242°C;

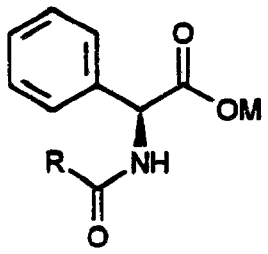
$[\alpha]_D^{20} = -22.4$; c=1 in water.

Patent Claims

1. Process for alternatively preparing N-methyl-N-[(1S)-1-phenyl-2-((3S)-3-hydroxypyrrolidin-1-yl)ethyl]-2,2-diphenylacetamide or N-methyl-N-[(1R)-1-phenyl-2-((3R)-3-hydroxypyrrolidin-1-yl)ethyl]-2,2-diphenylacetamide, characterized in that

a) an N-substituted phenylglycine derivative of the formula I

This Sheet Has Been Replaced



(I)

in which

R is H, OR^1 or SR^1,

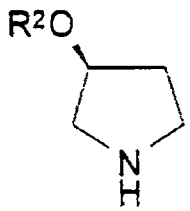
R^1 is A, aryl, heteroaryl, $Si(R^3)_3$ or COR^3,

R^3 is H, A, aryl or heteroaryl,

A is a straight-chain or branched alkyl radical having 1 to 6 carbon atoms,

M is H or a cation from the group consisting of alkali metal ammonium [sic], alkaline earth metal ammonium [sic], ammonium ammonium [sic] or alkylammonium

is reacted with a compound of the formula II



(II)

in which

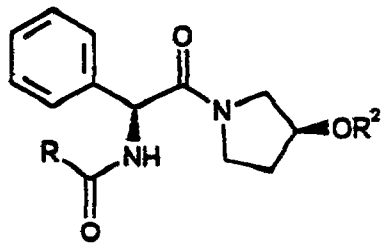
R^2 is H, A, aryl, heteroaryl, $Si(R^3)_3$ or COR^3

and

R^3 is H, A, aryl or heteroaryl

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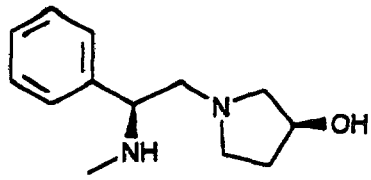
or an acid addition salt of the compound of the formula (II), of the acids HCl, HBr, HI, H_2SO_4, H_3PO_4 or an organic carboxylic acid, to give a compound of the formula III



(III)

in which R and R^2 are as defined above,

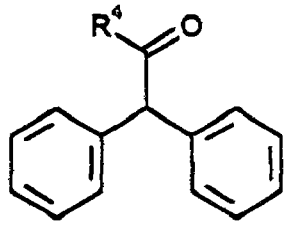
b) which is subsequently reduced to a compound of the formula (IV)



(IV)

which is optionally converted into a corresponding acid addition salts [sic] of the acids HCl, HBr, HI, H_2SO_4, H_3PO_4 or into a salt of an organic carboxylic acid, and

c) the resulting compound of the formula (IV) is reacted with an activated carboxylic acid of the formula (V)



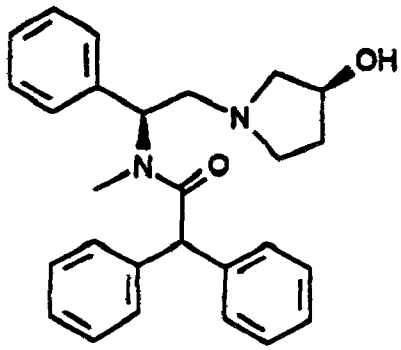
(V)

in which

R^4 is F, Cl, Br, I, OA or O-CO-A,

to give the compound of the formula (VI)

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(VI)

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which is optionally converted with an inorganic acid from the group consisting of HCl, HBr, HI, sulphuric acid, sulphaminic acid, nitric acid, phosphoric acid, orthophosphoric acid, or with an organic acid, into the corresponding acid addition salt,
where the starting materials employed for step a) depend on the enantiomer desired as end product.

2. N-methyl-N-[(1S)-1-phenyl-2-((3S)-3-hydroxypyrrolidin-1-yl)ethane],
N-methyl-N-[(1R)-1-phenyl-2-((3R)-3-hydroxypyrrolidin-1-yl)-ethane].

3. N-methyl-N-[(1S)-1-phenyl-2-((3S)-3-hydroxypyrrolidin-1-yl)ethane] as intermediate for preparing N-methyl-N-[(1S)-1-phenyl-2-((3S)-3-hydroxypyrrolidin-1-yl)ethyl]-2,2-diphenylacetamide.

4. N-methyl-N-[(1R)-1-phenyl-2-((3R)-3-hydroxypyrrolidin-1-yl)ethane] as intermediate for preparing N-methyl-N-[(1R)-1-phenyl-2-((3R)-3-hydroxypyrrolidin-1-yl)ethyl]-2,2-diphenylacetamide.

5. Process according to Claim 1, characterized in that compounds of the formula (I) are employed in which R has the meaning OR^1 where R^1 is A, aryl,

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heteroaryl, $SI(R^3)_3$ or COR^3 and R^3 is H, A, aryl or heteroaryl.

6. Process according to Claims 1 and/or 5, characterized in that the reaction of the compounds (I) and (II) is carried out in an aprotic, preferably polar aprotic, solvent at a temperature of from 0 to 50°C, preferably at temperatures between 20 and 30°C.

7. Process according to one or more of Claims 1, 5 and 6, characterized in that the reaction of the compounds (I) and (II) is carried out in a solvent from the group consisting of diethyl ether, petroleum ether, acetone, nitrobenzene, dimethylformamide, dimethyl sulphoxide, tetrahydrofuran, where the starting materials in the solvent are present in a concentration of from 10 to 30%.

8. Process according to one or more of Claims 1, 5 to 7, characterized in that the reaction of the compounds (I) and (II) is carried out in the presence of an auxiliary reagent from the group consisting of phosphorus oxytrichloride, phosphorus halides of the valency III and V, phosgene, dicyclohexylcarbodiimide, tributylammonium salt of pyridine, phenyl dichlorophosphate, 2-chloro-1,2,3-trinitrobenzene, phosphoric acid esters, chlorosulphonyl isocyanate, CH_3SO_2Cl-$(C_2H_5)_3N$, $(C_6H_5)_3P$-CCl_4-$(C_2H_5)_3N$,N,N'-carbonyldiimidazole, N-(alkylcarbonyl)imidazoles, acetic anhydride, acetyl chloride and ethyl chloroformate and an organic or inorganic base.

9. Process according to one or more of Claims 1, 5 to 8, characterized in that the reaction of the

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compounds (I) and (II) is carried out in the presence of a base from the group consisting of triethylamine, sodium carbonate, potassium carbonate, calcium carbonate, NaOH, KOH.

10. Process according to one or more of Claims 1, 5 to 9, characterized in that the reduction of the compounds of the formula (III) is carried out in the presence of a hydride transfer reagent from the group consisting of the metal aluminium hydrides, preferably lithium aluminium hydride, the metal alkoxyaluminohydrides, preferably lithium triethoxyaluminohydride, the metal borohydrides, preferably $NaBH_4$, or borane, and, if appropriate, in the presence of a Lewis acid, such as boron trifluoride, in a polar aprotic solvent from the group consisting of diethyl ether, petroleum ether, acetone, nitrobenzene, dimethylformamide, dimethyl sulphoxide, tetrahydrofuran.

11. Process according to Claims 1 and/or 10, characterized in that a compound of the formula (III) as starting material is dissolved in a solvent in a concentration of from 10 to 25% and the hydrogenation product is set free by addition of a proton-donating solvent in a mixture with an aprotic solvent.

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