

Description

The present invention concerns a process for preparing pyrrolidinone derivatives, more specifically 2-oxo-1-pyrrolidineacetamide derivatives, which may also be called 1-carbamoylmethyl-2-pyrrolidinone derivatives.

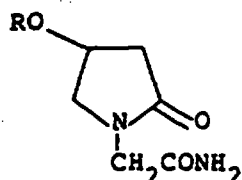
It is known that 4-substituted derivatives of 2-oxo-1-pyrrolidineacetamide are valued psychotropic agents that, in animals and man, restore cognitive function that has been damaged as a result of various pathologies. These drugs are described for example in Pharm. Res. Commun. 16, 67 (1984) by Banfi et al, or in Drug Development Res. 2, 447 (1982) by TM Itil et al.

Known processes for preparing the above pyrrolidinone derivatives which are described in GB 1588074 and 1588075 start from gamma-amino-beta-hydroxybutyric acid, and involve several steps such as protection with a silylating agent, alkylation, cyclisation and final aminolysis to give the carbamoylmethyl group attached to the heterocyclic nitrogen atom. These kinds of known processes involves the use of particular anhydrous solvents and of bases or of acid-accepting compounds, which require special equipment and precautions in order to maintain an anhydrous environment.

In addition, CH-A-599 151 describes a process for the preparation of a single related compound, piracetam which is unsubstituted at the 4-position of the pyrrolidine ring. The process includes a cyclisation step carried out under vigorous conditions i.e. high temperatures, for unspecified periods of time.

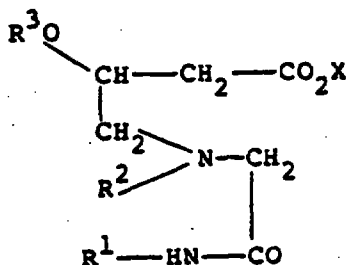
The main aim of the present invention is to overcome the problems of the known processes and, in particular, to provide a process for the preparation of 2-oxo-1-pyrrolidineacetamides which does not require the use of anhydrous conditions, nor, therefore, the equipment and precautions that would otherwise be necessary. A further aim of the present invention is to provide a process that makes use of cheap and readily available starting materials. Another aim of the present invention is to provide a process that permits the desired 2-oxo-1-pyrrolidineacetamide derivatives to be obtained with good selectivity.

According to the present invention there is provided a process for preparing a pyrrolidinone derivative of structure (1)



(1)

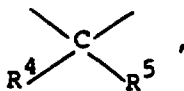
in which R is hydrogen, straight or branched alkyl of 1 to 4 carbon atoms, or acyl containing 1 to 10 carbon atoms, characterised in that a compound of structure (2)



(2)

wherein

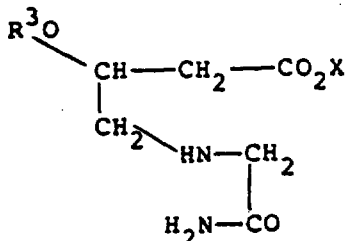
R¹ is hydrogen and R² is benzyl, α-methylbenzyl or p-methoxybenzyl or R¹ and R² can together form a group



where R⁴ and R⁵ are independently hydrogen, alkyl containing 1 to 4 carbon atoms, phenyl or together are 1,4-butylene or 1,5-pentylene (-(CH₂)₅)-;

R³ is hydrogen or straight or branched alkyl of 1 to 4 carbon atoms; and

X is straight or branched alkyl containing 1 to 10 carbon atoms; is subjected to N-deprotection to give a compound of structure (3)



(3)

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which is cyclized intramolecularly; and optionally when R³ is hydrogen the product is acylated or alkylated into a compound in which R is acyl or alkyl.

In compound (1), "acyl" in the definition of R is, suitably, alkanoyl.

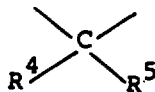
In compound (2) preferably R¹ and R² together form a 2-methyl-propan-1,1-diyl group



In compound (2) preferably R³ is hydrogen.

When R² is benzyl, α -methylbenzyl or p-methoxybenzyl the compound of structure (2) can be deprotected via catalytic hydrogenation using for instance a 5% Pd/C catalyst at temperatures between 0° and 40°C and at pressures between ambient and 10 Torr. The reaction is performed in a suitable solvent, e.g. alcohol, an aliphatic or aromatic hydrocarbon, water, or mixture of these. Alternatively debenzylation can be achieved by treatment with a mixture of formic acid and methanol and a palladium catalyst. The subsequent cyclisation takes place at 0° to 120°C, preferably 60° to 80°C, with or without solvent. The solvent, if used, is selected from those mentioned above for the debenzylation, or is acetonitrile.

When R¹ and R² together form a group



deprotection and intramolecular cyclisation can be effected by heating with water at temperatures between 90° and 160°C, preferably between 100° and 130°C. It is convenient to use water or mixtures of solvents and water. Preferably the solvent is a 95% mixture of an organic solvent with water (5%). As organic co-solvents may be used dimethylformamide (DMF), dimethylsulphoxide (DMSO), dimethylacetamide (DMA), acetonitrile and alcohols such as ethanol, etc. Preferably the reaction is carried out in the presence of a carboxylic acid, e.g. acetic acid or benzoic acid. Although catalytic quantities of carboxylic acids are effective preferably about one molar equivalent of a carboxylic acid is used.

The compound of structure (1) in which R is hydrogen is oxiracetam and is a particularly useful product of this invention.

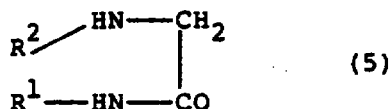
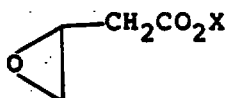
The compounds of structure (1) in which R is hydrogen can be converted into a compound in which R is acyl or alkyl by reaction with an acyl halide (preferably a chloride) or acid anhydride using conventional procedures, or by using an alkyl halide (preferably a bromide or iodide) or sulphate using conventional procedures.

The compounds prepared by the process of the present invention have a centre of asymmetry at the carbon atom in the 4-position, where the -OR substituent is attached, hence it is possible to obtain them as separate enantiomers or as a racemic mixture thereof.

If desired the deprotected intermediates of structure (3) may be isolated, preferably in the form of a salt with an acid selected from organic or inorganic acids such as hydrochloric, hydrobromic, sulphuric, p-toluenesulphonic, acetic, oxalic, maleic, malic acids etc. A preferred intermediate of structure (2) is that wherein R³ is hydrogen and R¹ and R² together form a 2-methyl-propan-1,1-diyl group.

The intermediates of structure (2) and (3) are novel and form an important aspect of this invention.

The intermediates of structure (2) can be prepared by reacting



an alkyl 3,4-epoxybutanoate of the structure (4) where X is alkyl of 1-10 carbon atoms, with a glycineamide derivative of structure (5) (in which R¹ and R² are as defined in structure (2)) to form a compound of structure (2) in which R³ is hydrogen; and optionally reacting the product with an alkyl halide (preferably a bromide or iodide), dialkyl sulphate, acyl halide (preferably a chloride) or acid anhydride to form a compound of structure (2) in which R³ is other than hydrogen.

The condensation reaction between (4) and (5) may take place without the use of solvents or in the presence of organic solvents, water or mixtures of these in proportions of from 1:5 to 20:1, preferable from 1:1 to 1:3 or organic solvent and water. As organic solvent may be used a wide variety of inert solvents e.g. acetonitrile, alcohols such as isopropanol, acetone etc.

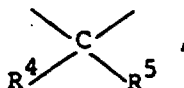
The condensation is performed at a temperature of 20° to 120°C, preferably 70-100°C. In the condensation phase the two reagents may be used in stoichiometric proportions, or an excess of one of them may be used, preferably a ratio of from 1:1 to 1:1.1 of the amine derivative (5) and the epoxyster (4).

The intermediate of structure (2) in which R³ is hydrogen that results from the condensation may be isolated and purified, or may be converted at once into compound I, by deprotection and cyclisation. These

reactions may be carried out in the same mixture as the condensation reaction, in the absence of solvent, with the same solvent, or by replacing the initial solvent with one or more high-boiling solvents.

The alkyl 3,4-epoxybutanoates (4) can be prepared by known methods described in the literature, for instance from alkyl 3,4-butenates by epoxidation with peroxide compounds such as organic and inorganic peracids, hydrogen peroxide etc, (e.g. by the general procedure of C. Venturello et al. *J. Org. Chem.* 48 3831 (1983) or by dehydrohalogenation of 3-halo-4-hydroxybutyrates (cf R Rambaud and S Ducher, *Bull. Soc. Chim. Fr.*, 466 (1966)).

The imidazolidinones of structure (5) in which R¹ and R² together form a group



may be prepared from glycineamide and suitable carbonyl compounds, or from alkyl alkylidenaminoacetates and ammonia, by methods described in the literature, e.g. A. C. Davis and A. L. Levy, *J. Chem. Soc.*, 3479 (1951); P. G. Wiering and H. Steinberg, *Rec. Trav. Chim. Pays-Bas* 111, 284 (1971).

The invention is illustrated by the following Preparations and Examples:

Preparation 1

2-Methylpropyl-3,4-epoxybutanoate

Sodium tungstate dihydrate (0.852 g, 2.5 mmol), 85% phosphoric acid (0.850 ml, 5 mmol) 36.3% hydrogen peroxide (5.6 ml, 60 mmol) were dissolved in 20 ml of water and the pH was adjusted to 1.6 by 10% sulphuric acid. The solution was heated to 70°C, and under vigorous stirring a solution of 2-methylpropyl 3-butenate (7.1 g, 50 mmol), trimethylcaprylammonium chloride (0.41 g) in 1,2-dichloroethane (15 ml) was added. After 6 hours the mixture was cooled, then the layers were separated. The aqueous phase was washed with 30 ml of dichloroethane. Organic layers were collected, washed with 2 x 40 ml of saturated solution of sodium sulphate, dried and distilled. The title compound was obtained as a colourless oil, b.p. 104—108° 30 mmHg.

Preparation 2

(a) A stream of hydrogen was bubbled into a solution of 2-methylpropyl-4-[N-(carbamoylmethyl)benzylamino]-3-hydroxybutanoate (1 g) in ethanol (30 ml) containing Pd/C 5% (100 mg) for 1 hr. The catalyst was filtered and oxalic acid (0.28 g) was added. The resulting solution was chilled overnight and the precipitate was collected to give 200 mg of 2-methylpropyl 4-(carbamoylmethylamino)-3-hydroxybutanoate oxalate, m.p. 145°C dec.

(b) In the same way, from 3 g of 2-methylpropyl 4-[N-(carbamoylmethyl)benzylamino]-3-hydroxybutanoate (3 g) and maleic acid (2.16 g) 210 mg of 2-methylpropyl-4-(carbamoylmethylamino)-3-hydroxybutanoate maleate (m.p. 109°C dec.) were obtained.

Example 1

1.3 g of 1,4-diazaspiro[4,5]decan-2-one ((5); R₄ + R₅ = —(CH₂)₅—) (8.4 mmoles) are heated and stirred with magnetic stirring, with 1.5 g 2-methylpropyl 3,4-epoxybutanoate ((4), X = isobutyl) (9.5 mmoles) up to 110° (external temperature) for 24h. The mixture is cooled, and the dark mass obtained is washed with 10 ml boiling ethyl acetate. This is decanted, and the solid obtained is crystallised from methanol to give oxiracetam as a crystalline white powder, m.p. 167—70°C.

Example 2

1 g of 2,2-dimethyl-4-imidazolidinone ((5); R₄ = R₅ = CH₃) (8.76 mmoles) is dissolved in 5 ml acetonitrile. 1 g 2-methylpropyl 3,4-epoxybutanoate ((4); X = isobutyl) (6.32 mmoles) is added and the mixture is boiled for 30 h with stirring. The mixture is cooled, the solvent is decanted off, the resulting dark solid mass is taken up in ethanol, and the solid oxiracetam obtained is filtered off, m.p. 167—70°C.

Example 3

0.650 g 2,2-dimethyl-4-imidazolidinone ((5); R₄ = R₅ = CH₃) (5.7 mmoles) is dissolved in 5 ml isopropanol. 1 g 2-methylpropyl 3,4-epoxybutanoate ((4); X = isobutyl) (6.32 mmoles) is added. The mixture is boiled for 9 h. A further 1 g of epoxyster is added and boiling is continued for a further 9h. After cooling, the solvent is decanted and the dark mass obtained is taken up in ethanol. The solid obtained is filtered, to give oxiracetam, m.p. 167—70°C.

Example 4

1 g of 2,2-dimethyl-4-imidazolidinone ((5); R₄ = R₅ = CH₃) (8.76 mmoles) are heated at 165°C (external temperature) for 1h 30 min with 2 g 2-methylpropyl 3,4-epoxybutanoate ((4); X = isobutyl) (12.64 mmoles). 0.17 ml of water and 5 ml ethanol are added, and boiling is continued for a further 2h. The mixture is cooled and filtered. Oxiracetam is obtained as a white crystalline powder, m.p. 167—70°C.

Example 5

1 g of 2,2-dimethyl-4-imidazolidinone ((5); $R_4 = R_5 = \text{CH}_3$) (8.70 mmoles) is dissolved in 1 ml water. 1.5 g 2-methylpropyl 3,4-epoxybutanoate ((4); $X = \text{isobutyl}$) (9.48 mmoles) are added and the mixture is heated at 50° for 11h with stirring by a magnetic stirrer. Heating is then continued at the boiling point for a further 11h. The mixture is cooled, 10 ml acetone is added, stirring is performed for 30 min and the mixture is filtered. The product obtained is crystallised from methanol to give oxiracetam of m.p. 167—70°C as a white crystalline powder.

Example 6

0.5 g 2,2-dimethyl-4-imidazolidinone ((5); $R_4 = R_5 = \text{CH}_3$) (4.38 mmoles) are heated at 115°C (external temperature) for 12h with stirring by a magnetic stirrer, with 0.57 g ethyl 3,4-epoxybutanoate ((4); $X = \text{C}_2\text{H}_5$) (4.38 mmoles). The mixture is cooled, taken up with methanol and filtered. Oxiracetam is obtained, m.p. 167—70°C.

Example 7

1 g 2,2-dimethyl-4-imidazolidinone ((5); $R_4 = R_5 = \text{CH}_3$) (8.76 mmoles) is dissolved in 1 ml water. 2 g 2-methylpropyl 3,4-epoxybutanoate is added and stirring is continued at ambient temperature for 10 days. The oil obtained is chromatographed on silica, eluting with 1:1 acetone/methanol. The main fraction is collected, dehydrated using MgSO_4 , and evaporated. An oil is obtained, which solidifies on rubbing, is taken up in hexane and filtered. 1.8 g 2-methylpropyl 2,2-dimethyl-4-oxo-1-imidazolidine- β -hydroxybutyrate is obtained ((2); $R_3 = \text{H}$, $R_4 = R_5 = \text{CH}_3$, $X = \text{isobutyl}$), m.p. 76—8°C, a white solid (75.5%). This compound is dissolved in 3 ml acetonitrile and 1 ml water, and boiled for 72h. After evaporating, the product is taken up with ethanol and filtered, oxiracetam is obtained as a white crystalline powder, m.p. 167—70°C.

Example 8

6.52 g 2-(1-methylethyl)-4-imidazolidinone hydrochloride ((5); $R_4 = \text{H}$, $R_5 = \text{isopropyl}$) (0.04 moles) are dissolved in 40 ml water and treated with 2.8 g potassium carbonate (0.02 mole). 7 g 2-methylpropyl 3,4-epoxybutanoate are added ((4); $X = \text{isobutyl}$) (0.044 mole) and 25 ml acetone. The mixture is heated at 60°C for 48h with stirring. The mixture is reduced to a small volume, the solid is filtered and washed with ether. 3.5 g of a white solid, m.p. 135—40°C is obtained. The liquor from which this solid was separated is evaporated to dryness and chromatographed on silica, eluting with 8:2 ethylacetate/methanol. The main fractions are collected and evaporated to give a further 2.9 g compound of m.p. 135—40°C, giving a total of 6.4 g 2-methylpropyl 2-(1-methylethyl)-4-oxo-1-imidazolidine- β -hydroxybutanoate ((2); $R_3 = R_4 = \text{H}$, $R_5 = \text{isopropyl}$, $X = \text{isobutyl}$). 1 g of this compound (3.5 mmoles) is heated to boiling for 8h in 6 ml dimethyl sulfoxide + 2 ml water. After evaporation, the residue is taken up with acetone, filtered, dried in vacuo and crystallised from methanol. 0.32 g Oxiracetam is obtained as a white crystalline powder, m.p. 167—70°C (yield 57.8%).

Example 9

5.8 g of 2-(1-methylethyl)-4-imidazolidinone hydrochloride ((5); $R_4 = \text{H}$, $R_5 = \text{isopropyl}$) (0.035 moles) are shaken in 10 ml water and treated with 2.4 g potassium carbonate (0.0174 moles). 4.5 g ethyl 3,4-epoxybutanoate and 6 ml acetone are added, and stirring is maintained for 45h at 70°C. After evaporation, the residue is chromatographed on silica, eluting with 8:2 ethyl acetate/methanol. The main fractions are collected and evaporated. The oil that remains is taken up with ethyl acetate. After being left to stand overnight the white compound obtained is filtered: 1.3 g ethyl 2-(1-methylethyl)-4-oxo-1-imidazolidine- β -hydroxybutanoate m.p. 118—122°C. 0.95 g of this compound (3.7 mmoles) are heated to boiling for 15h in 4 ml DMF and 1 ml water. After evaporation in vacuo, the residue is taken up with methanol, and the solution is filtered. 0.37 g oxiracetam is obtained as a white crystalline powder, m.p. 167—70°C (63.2%).

Example 10

19 g 2-(1-Methylethyl)imidazolidinone ((5); $R_4 = \text{H}$, $R_5 = \text{isopropyl}$) (0.15 moles) are dissolved in 100 ml water and 150 ml acetone. 2-Methylpropyl-3,4-epoxybutanoate (0.15 moles) are added and the mixture is heated and stirred for 48h at 70°C. The acetone is evaporated in vacuo and 100 ml DMF are added, followed by boiling for 21h. The mixture is reduced to a small volume in vacuo, the residue is taken up with 40 ml water and washed with 2 $\times$ 40 ml methylene chloride. The aqueous phase is evaporated to dryness and redissolved in 15 ml methanol. This is left to stand for 3h at 0°C, filtered and dried to give oxiracetam as a white crystalline powder, m.p. 167—70°C.

Example 11

12 g 2-(1-methylethyl)-4-imidazolidinone hydrochloride ((5); $R_4 = \text{H}$, $R_5 = \text{isopropyl}$) (0.073 moles) are shaken with 20 ml water and treated with 5 g potassium carbonate (0.036 moles). 8.5 g methyl 3,4-epoxybutanoate (0.073 moles) and 12 ml acetone are added. The mixture is stirred for 45h at 70°C. After evaporating, the residue is chromatographed on silica, eluting with 8:2 ethyl acetate/methanol. The main fractions are combined and evaporated. 2.5 g of methyl 2-(1-methylethyl)-4-oxoimidazolidine- β -hydroxybutanoate, m.p. 109—122°C, are obtained as a white powder (14.4%). 2.0 g of this compound (0.0082 mole)

are heated to boiling for 15h with 8.8 ml DMF and 2.2 ml water. After evaporation in vacuo, the residue is taken up with methanol, and filtered. 0.74 g oxiracetam is obtained as a white crystalline powder, m.p. 167—70°C (57.4%).

Example 12

A mixture of 0.7 g 2-phenylimidazolidine-4-one and 1 g 2-methylpropyl 3,4-epoxybutanoate are heated for 12h at 70° (external temperature) in 2 ml water and 2 ml acetone. After evaporating, the residue is taken up with ether and the white solid obtained is filtered, and recrystallised from ethyl/acetate. 2-Methylpropyl-2-phenyl-4-oxoimidazolidine-β-hydroxybutanoate is obtained as a white powder, m.p. 126—128°C.

Example 13

A solution of 0.65 g 2-methylpropyl 2-phenyl-4-oxoimidazolidine-β-hydroxybutanoate in 1.5 ml dimethyl sulfoxide and 0.5 ml water is heated at reflux for 16h. After evaporating, the residue is chromatographed on silica, eluting with 7:3 ethyl acetate/methanol. Oxiracetam is obtained as a white powder, m.p. 167—70°C.

Example 14

A. 2-Methylpropyl 4-[N-(carbamoylmethyl)benzylamino]-β-hydroxybutanoate ((2); $R_2 = CH_2C_6H_5$, $R_3 = H$, X = isopropyl).

A mixture of benzylaminoacetamido ((5) $R_1 = H$, $R_2 = CH_2C_6H_5$) (1.64 g) and 2-methylpropyl 3,4-epoxybutanoate (1.58 g) are heated for many hours at 30°C with magnetic stirring. The reaction mixture is taken up with ligroin and the resulting solid is filtered. Recrystallisation is from ether/ligroin. 2.7 g of title compound m.p. 99—100°C are obtained.

B. 4-Hydroxy-2-oxo-1-pyrrolidineacetamide (oxiracetam).

A solution of compound A (1 g) in 25 ml ethanol is hydrogenated at ambient temperature and pressure in the presence of 100 mg 5% Pd/C. The catalyst is filtered off and the solvent evaporated to give 0.72 g 2-methylpropyl 4-(carbamoylmethylamino)-3-hydroxybutanoate. This compound is dissolved in situ in 10 ml acetonitrile and heated at reflux for 8h. After evaporation of the solvent, the residue is crystallised from ethanol. Oxiracetam is obtained as a white crystalline powder of m.p. 167—70°C.

Example 15

1-Carbamoylmethyl-4-acetoxy-2-pyrrolidone.

A mixture of 5.53 g oxiracetam and 44.3 ml acetyl chloride is heated at reflux for 15 min. After cooling, the solvent is evaporated in vacuo and the oil remaining is taken up in a little aqueous sodium bicarbonate, and solid sodium bicarbonate is added with stirring until neutrality is achieved. Most of the water present is removed by treating with methyl isobutyl ketone in vacuo, the residue is taken up with methylene chloride, dried with sodium sulphate and evaporated in vacuo. The oil remaining is triturated in isopropyl alcohol/diethyl ether and recrystallised from 20:80 isopropyl alcohol/isopropyl ether to give 1-carbamoylmethyl-4-acetoxy-2-pyrrolidone which when purified by chromatography melts at 84—86°C.

Example 16

4-Hydroxy-2-oxo-1-pyrrolidineacetamide (oxiracetam).

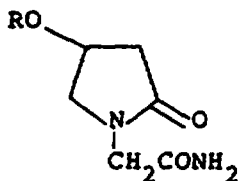
A solution of 2-methylpropyl 2-(1-methylethyl)-4-oxoimidazolidine-β-hydroxybutanoate (15 g, 52.4 mmol), benzoic acid (6.4 g, 52.4 mmol) and water (3.75 ml, 208 mmol) in n-pentanol (90 ml) was refluxed under nitrogen for 6 hr. After cooling the mixture was extracted twice with water (35 ml). The aqueous extracts were evaporated to dryness and the residue was crystallized from methanol to give 5.15 g (62.1%) of the title compound, m.p. 167—70°C.

The description above illustrates how the process of the invention achieves the stated aims, permitting the use as starting material an easily and cheaply available glycinamide derivative, and allowing the use of aqueous solvents without the need to ensure anhydrous conditions.

The process can be worked with good selectivity for the desired compound and little formation of by-products, thanks to the use of the starting amine in the form of a secondary amine.

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

1. A process for preparing a pyrrolidinone derivative of structure (1)



(1)



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are heated to boiling for 15h with 8.8 ml DMF and 2.2 ml water. After evaporation in vacuo, the residue is taken up with methanol, and filtered. 0.74 g oxiracetam is obtained as a white crystalline powder, m.p. 167—70°C (57.4%).

Example 12

A mixture of 0.7 g 2-phenylimidazolidine-4-one and 1 g 2-methylpropyl 3,4-epoxybutanoate are heated for 12h at 70° (external temperature) in 2 ml water and 2 ml acetone. After evaporating, the residue is taken up with ether and the white solid obtained is filtered, and recrystallised from ethyl/acetate. 2-Methylpropyl-2-phenyl-4-oxoimidazolidine-β-hydroxybutanoate is obtained as a white powder, m.p. 126—128°C.

Example 13

A solution of 0.65 g 2-methylpropyl 2-phenyl-4-oxoimidazolidine-β-hydroxybutanoate in 1.5 ml dimethyl sulfoxide and 0.5 ml water is heated at reflux for 16h. After evaporating, the residue is chromatographed on silica, eluting with 7:3 ethyl acetate/methanol. Oxiracetam is obtained as a white powder, m.p. 167—70°C.

Example 14

A. 2-Methylpropyl 4-[N-(carbamoylmethyl)benzylamino]-β-hydroxybutanoate ((2); $R_2 = CH_2C_6H_5$, $R_3 = H$, $X = isopropyl$).

A mixture of benzylaminoacetamido ((5) $R_1 = H$, $R_2 = CH_2C_6H_5$) (1.64 g) and 2-methylpropyl 3,4-epoxybutanoate (1.58 g) are heated for many hours at 30°C with magnetic stirring. The reaction mixture is taken up with ligroin and the resulting solid is filtered. Recrystallisation is from ether/ligroin. 2.7 g of title compound m.p. 99—100°C are obtained.

B. 4-Hydroxy-2-oxo-1-pyrrolidineacetamide (oxiracetam).

A solution of compound A (1 g) in 25 ml ethanol is hydrogenated at ambient temperature and pressure in the presence of 100 mg 5% Pd/C. The catalyst is filtered off and the solvent evaporated to give 0.72 g 2-methylpropyl 4-(carbamoylmethylamino)-3-hydroxybutanoate. This compound is dissolved in situ in 10 ml acetonitrile and heated at reflux for 8h. After evaporation of the solvent, the residue is crystallised from ethanol. Oxiracetam is obtained as a white crystalline powder of m.p. 167—70°C.

Example 15

1-Carbamoylmethyl-4-acetoxy-2-pyrrolidone.

A mixture of 5.53 g oxiracetam and 44.3 ml acetyl chloride is heated at reflux for 15 min. After cooling, the solvent is evaporated in vacuo and the oil remaining is taken up in a little aqueous sodium bicarbonate, and solid sodium bicarbonate is added with stirring until neutrality is achieved. Most of the water present is removed by treating with methyl isobutyl ketone in vacuo, the residue is taken up with methylene chloride, dried with sodium sulphate and evaporated in vacuo. The oil remaining is triturated in isopropyl alcohol/diethyl ether and recrystallised from 20:80 isopropyl alcohol/isopropyl ether to give 1-carbamoylmethyl-4-acetoxy-2-pyrrolidone which when purified by chromatography melts at 84—86°C.

Example 16

4-Hydroxy-2-oxo-1-pyrrolidineacetamide (oxiracetam).

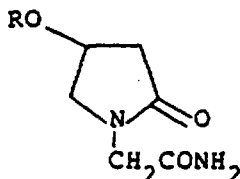
A solution of 2-methylpropyl 2-(1-methylethyl)-4-oxoimidazolidine-β-hydroxybutanoate (15 g, 52.4 mmol), benzoic acid (6.4 g, 52.4 mmol) and water (3.75 ml, 208 mmol) in n-pentanol (90 ml) was refluxed under nitrogen for 6 hr. After cooling the mixture was extracted twice with water (35 ml). The aqueous extracts were evaporated to dryness and the residue was crystallized from methanol to give 5.15 g (62.1%) of the title compound, m.p. 167—70°C.

The description above illustrates how the process of the invention achieves the stated aims, permitting the use as starting material an easily and cheaply available glycine derivative, and allowing the use of aqueous solvents without the need to ensure anhydrous conditions.

The process can be worked with good selectivity for the desired compound and little formation of by-products, thanks to the use of the starting amine in the form of a secondary amine.

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

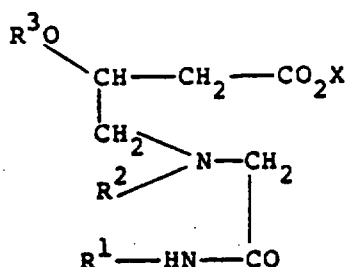
1. A process for preparing a pyrrolidinone derivative of structure (1)



(1)



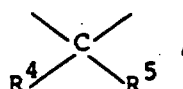
in which R is hydrogen, straight or branched alkyl of 1 to 4 carbon atoms, or acyl containing 1 to 10 carbon atoms, characterised in that a compound of structure (2)



(2)

wherein

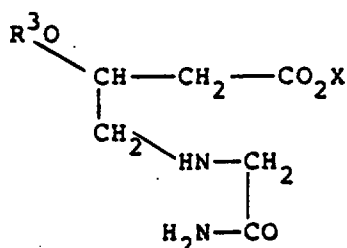
R¹ is hydrogen and R² is benzyl, α-methylbenzyl or p-methoxybenzyl or R¹ and R² together form a group



wherein R⁴ and R⁵ are independently hydrogen, alkyl containing 1 to 4 carbon atoms, or phenyl or together are 1,4-butylene or 1,5-pentylene (—(CH₂)₅—);

R³ is hydrogen or straight or branched alkyl of 1 to 4 carbon atoms; and

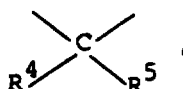
X is straight or branched alkyl containing 1 to 10 carbon atoms; is subjected to N-deprotection to give a compound of structure (3)



(3)

which is cyclised intramolecularly; and optionally when R³ is hydrogen the product is converted into a compound in which R is acyl or alkyl.

2. A process according to Claim 1 or in which R¹ and R² together form a group



in which R⁴ and R⁵ are as described in claim 1 and deprotection and intramolecular cyclisation are effected by heating at a temperature between 90° and 160°C, in the presence of a carboxylic acid.

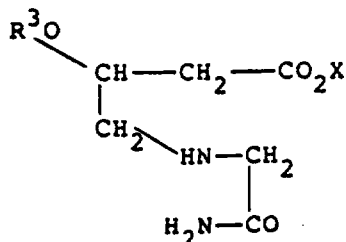
3. A process according to Claim 1 or Claim 2 in which R¹ and R² together form a 2-methyl-propan-1,1-diyl group



and R³ is hydrogen.

4. A process according to Claim 1 in which R² is benzyl, α-methylbenzyl or p-methoxybenzyl and the compound of structure (2) is deprotected using catalytic hydrogenation with a palladium-on-charcoal catalyst.

5. A compound of structure (3)



(3)

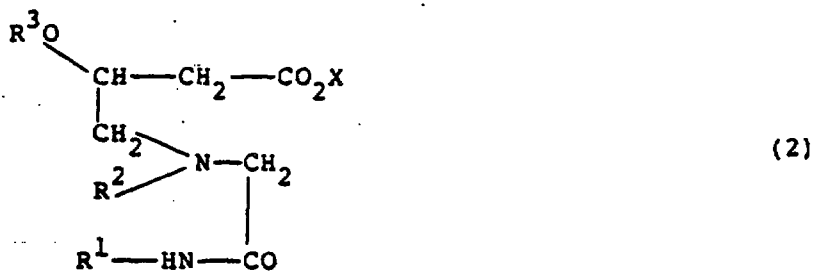


0 154 490

and acid addition salts thereof, in which R³ is hydrogen or straight or branched alkyl of 1 to 4 carbon atoms and X is straight or branched alkyl containing 1 to 10 carbon atoms.

6. A compound of Claim 5 in which R³ is hydrogen in the form of an acid addition salt.

7. A compound of structure (2)



where R⁴ and R⁵ are independently hydrogen, alkyl containing 1 to 4 carbon atoms, or phenyl or together are 1,4-butylene or 1,5-pentylene (—(CH₂)₅—);

R³ is hydrogen or straight or branched alkyl of 1 to 4 carbon atoms; and

X is straight or branched alkyl containing 1 to 10 carbon atoms.

8. A process for preparing a pyrrolidinone derivative of structure (1)



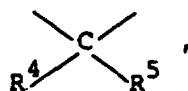
in which R is hydrogen, straight or branched alkyl of 1 to 4 carbon atoms, or acyl containing 1 to 10 carbon atoms, characterised in that an alkyl 3,4-epoxybutanoate of structure (4)



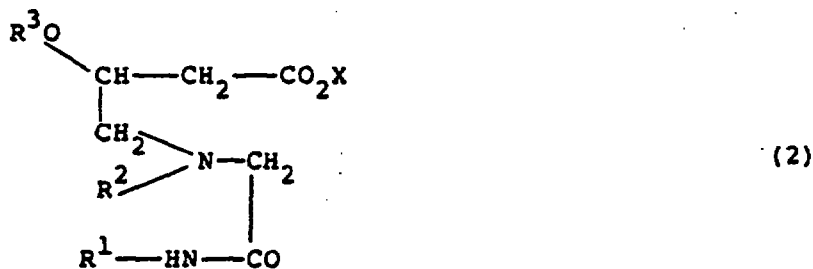
where X is alkyl of 1—10 carbon atoms is reacted with a glycineamide derivative of structure (5)



where R¹ is hydrogen and R² is benzyl or substituted benzyl, or R¹ and R² can together form a group

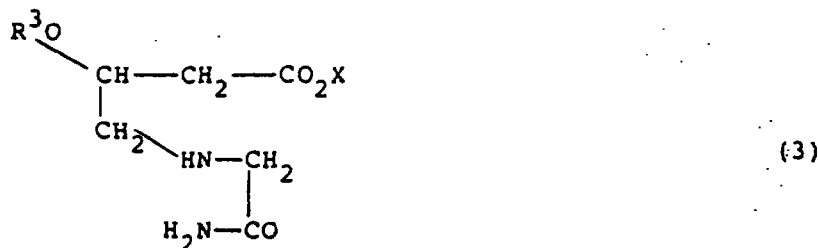


where R⁴ and R⁵ are independently hydrogen, alkyl containing 1 to 4 carbon atoms, optionally substituted aryl or together are 1,4-butylene or 1,5-pentylene (—(CH₂)₅—) at a temperature of 20° to 120°C to give a compound of structure (2)





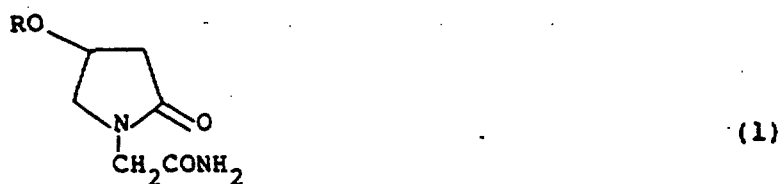
in which R^3 is hydrogen, and optionally the product is alkylated into a compound of structure (2) in which R^3 is straight or branched alkyl of 1 to 4 carbon atoms and the compound of structure (2) is subjected to N-deprotection to give a compound of structure (3)



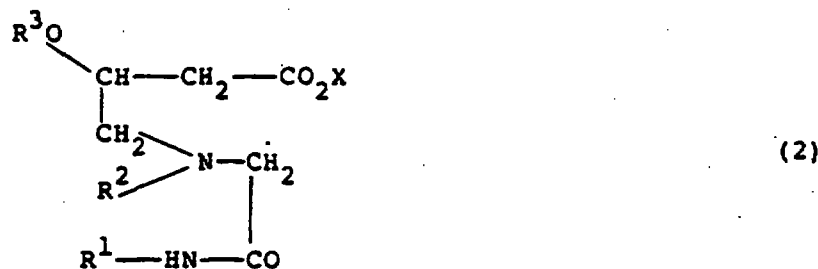
which is cyclised intramolecularly; and optionally when R^3 is hydrogen the product is alkylated or acylated into a compound in which R is acyl or alkyl.

Claims for the Contracting State: AT

1. A process for preparing a pyrrolidinone derivative of structure (1)

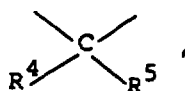


in which R is hydrogen, straight or branched alkyl of 1 to 4 carbon atoms, or acyl containing 1 to 10 carbon atoms, characterised in that a compound of structure (2)



wherein

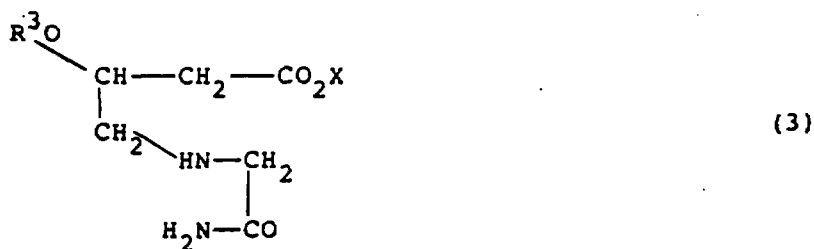
R^1 is hydrogen and R^2 is benzyl, α -methylbenzyl or p-methoxybenzyl or R^1 and R^2 together form a group



where R^4 and R^5 are independently hydrogen, alkyl containing 1 to 4 carbon atoms or phenyl or together are 1,4-butylene or 1,5-pentylene ($-(CH_2)_5-$);

R^3 is hydrogen or straight or branched alkyl of 1 to 4 carbon atoms; and

X is straight or branched alkyl containing 1 to 10 carbon atoms; is subjected to N-deprotection to give a compound of structure (3)

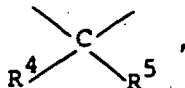


which is cyclised intramolecularly; and optionally when R^3 is hydrogen the product is converted into a compound in which R is acyl or alkyl.



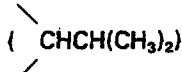
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2. A process according to Claim 1 or in which R¹ and R² together form a group



in which R⁴ and R⁵ are as described in claim 1 and deprotection and intramolecular cyclisation are effected by heating at a temperature between 90° and 160°C, in the presence of a carboxylic acid.

3. A process according to Claim 1 or Claim 2 in which R¹ and R² together form a 2-methyl-propan-1,1-diyl group

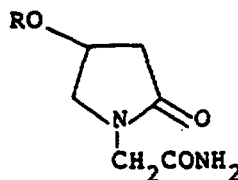


and R³ is hydrogen.

4. A process according to Claim 1 in which R² is benzyl, α-methylbenzyl or p-methoxybenzyl and the compound of structure (2) is deprotected using catalytic hydrogenation with a palladium-on-charcoal catalyst.

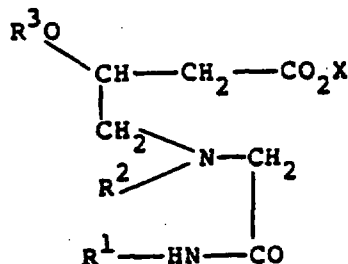
Patentansprüche für die Vertragsstaaten: BE CH DE FR GB IT LI LU NL SE

1. Verfahren zur Herstellung eines Pyrrolidinon-Derivats der Formel (I)



(1)

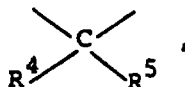
wobei R ein Wasserstoffatom, ein unverzweigter oder verzweigter Alkylrest mit 1 bis 4 Kohlenstoffatomen oder ein Acylrest mit 1 bis 10 Kohlenstoffatomen ist, dadurch gekennzeichnet, daß man aus einer Verbindung der Formel (2)



(2)

in der

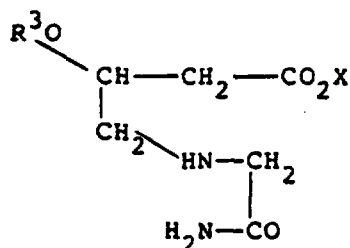
R¹ ein Wasserstoffatom und R² eine Benzyl-, α-Methylbenzyl- oder p-Methoxybenzylgruppe ist oder R¹ und R² zusammen den Rest



darstellen und R⁴ und R⁵ unabhängig voneinander ein Wasserstoffatom, ein Alkylrest mit C₁₋₄-Kohlenstoffatomen oder eine Phenylgruppe oder zusammen eine 1,4-Butylen- oder 1,5-Pentylengruppe (—CH₂)₅— sind,

R³ ein Wasserstoffatom oder ein unverzweigter oder verzweigter Alkylrest mit 1 bis 4 Kohlenstoffatomen und

X ein unverzweigter oder verzweigter Alkylrest mit 1 bis 10 Kohlenstoffatomen ist, die N-Schutzgruppe abspaltet, die erhaltene Verbindung der Formel (3)

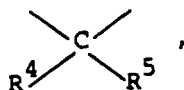


(3)



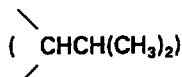
intramolekular cyclisiert und gegebenenfalls, wenn R^3 ein Wasserstoffatom ist, das Produkt zu einer Verbindung umsetzt, in der R ein Acyl- oder Alkylrest ist.

2. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß R^1 und R^2 zusammen den Rest



darstellen, und R^4 und R^5 die in Anspruch 1 angegebene Bedeutung haben und man die Abspaltung der N-Schutzgruppe und die intramolekulare Cyclisation durch Erhitzen auf eine Temperatur zwischen 90 und 160°C in Anwesenheit einer Carbonsäure bewirkt.

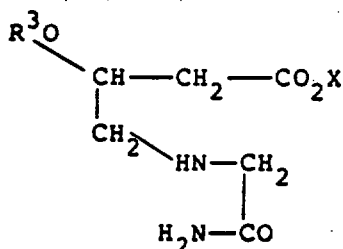
3. Verfahren nach Anspruch 1 oder 2, dadurch gekennzeichnet, daß R^1 und R^2 zusammen eine 2-Methyl-propan-1,1-diylgruppe



bilden und R^3 ein Wasserstoffatom ist.

4. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß R^2 eine Benzyl-, α -Methylbenzyl- oder p-Methoxybenzylgruppe ist und man die N-Schutzgruppe der Verbindung (2) durch katalytische Hydrierung mit einem Palladium-auf-Kohle-Katalysator abspaltet.

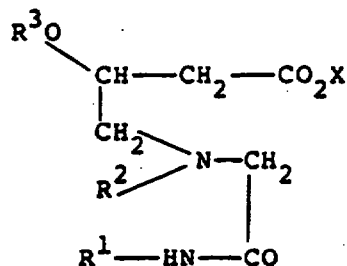
5. Eine Verbindung der Formel (3)



und ihre Säureadditionssalze, in der R^3 ein Wasserstoffatom oder ein unverzweigter oder verzweigter Alkylrest mit 1 bis 4 Kohlenstoffatomen und X ein unverzweigter oder verzweigter Alkylrest mit 1 bis 10 Kohlenstoffatomen ist.

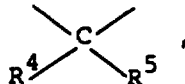
6. Eine Verbindung nach Anspruch 5, in der R^3 ein Wasserstoffatom in der Form eines Säureadditionssalzes ist.

7. Eine Verbindung der Formel (2)



in der

R^1 ein Wasserstoffatom und R^2 eine Benzyl- oder substituierte Benzylgruppe ist, oder R^1 und R^2 zusammen den Rest

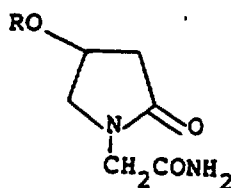


darstellen und R^4 und R^5 unabhängig voneinander ein Wasserstoffatom, ein Alkylrest mit C_{1-4} -Kohlenstoffatomen, eine Phenylgruppe oder zusammen eine 1,4-Butylen- oder 1,5-Pentylengruppe $-(\text{CH}_2)_5-$ sind,

R^3 ein Wasserstoffatom oder ein unverzweigter oder verzweigter Alkylrest mit 1 bis 4 Kohlenstoffatomen, und

X ein unverzweigter oder verzweigter Alkylrest mit 1 bis 10 Kohlenstoffatomen ist.

8. Verfahren zur Herstellung eines Pyrrolidinon-Derivats der Formel (1)

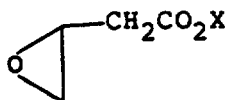




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in der R ein Wasserstoffatom, ein unverzweigter oder verzweigter Alkylrest mit 1 bis 4 Kohlenstoffatomen oder ein Acylrest mit 1 bis 10 Kohlenstoffatomen ist, dadurch gekennzeichnet, daß man einen 3,4-Epoxybutansäurealkylester der Formel (4)

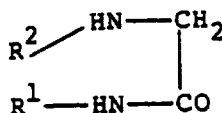
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(4)

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in der X ein Alkylrest mit 1 bis 10 Kohlenstoffatomen ist, mit einem Glycinamid-Derivat der Formel (5)

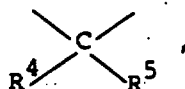


(5)

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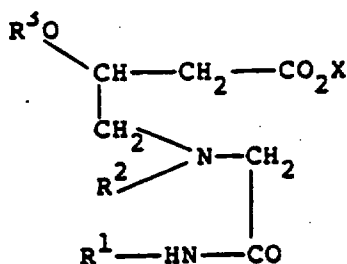
in der R¹ ein Wasserstoffatom und R² eine Benzyl- oder substituierte Benzylgruppe ist oder R¹ und R² zusammen den Rest

20



darstellen, und R⁴ und R⁵ unabhängig voneinander ein Wasserstoffatom, ein Alkylrest mit 1 bis 4 Kohlenstoffatomen, gegebenenfalls substituierter Arylrest oder zusammen eine 1,4-Butylen- oder 1,5-Pentylengruppe $-(CH_2)_5-$ sind, bei einer Temperatur von 20 bis 120°C umgesetzt, die erhaltene Verbindung der Formel (2)

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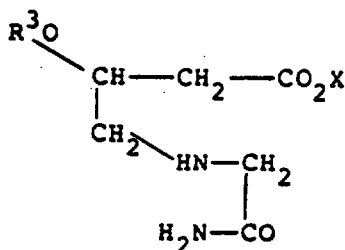
(2)

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in der R³ ein Wasserstoffatom ist, gegebenenfalls zu einer Verbindung der Formel (2) alkyliert, in der R³ ein unverzweigter oder verzweigter Alkylrest mit 1 bis 4 Kohlenstoffatomen ist, aus der Verbindung der Formel (2) die N-Schutzgruppe abspaltet, die erhaltene Verbindung der Formel (3)

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(3)

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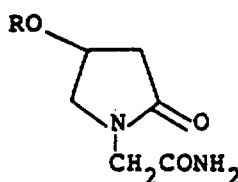
intramolekular cyclisiert, und gegebenenfalls, wenn R³ ein Wasserstoffatom ist, das Produkt acyliert oder alkyliert und dadurch in eine Verbindung überführt, in der R ein Acyl- oder Alkylrest ist.

Patentansprüche für den Vertragsstaat: AT

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1. Verfahren zur Herstellung eines Pyrrolidinon-Derivats der Formel (I)

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(1)

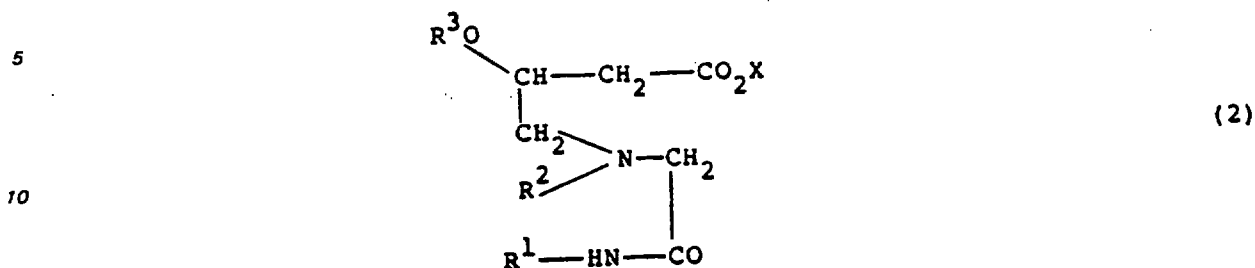
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wobei R ein Wasserstoffatom, ein unverzweigter oder verzweigter Alkylrest mit 1 bis 4 Kohlenstoffatomen



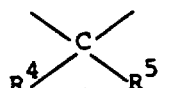
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oder ein Acylrest mit 1 bis 10 Kohlenstoffatomen ist, dadurch gekennzeichnet, daß man aus einer Verbindung der Formel (2)



in der

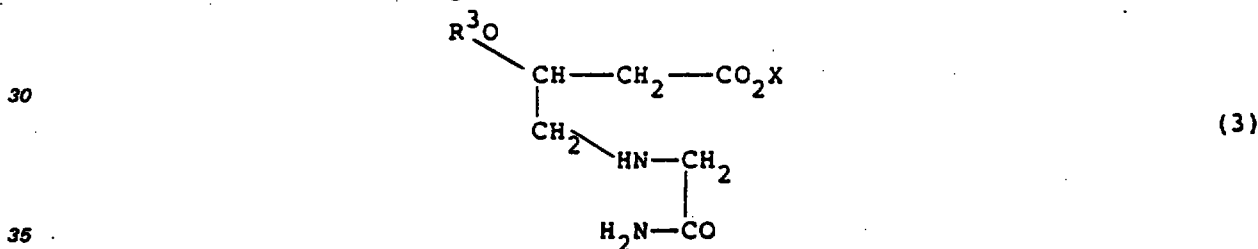
15 R^1 ein Wasserstoffatom und R^2 eine Benzyl-, α -Methylbenzyl- oder p-Methoxybenzylgruppe ist oder R^1 und R^2 zusammen den Rest



20 darstellen und R^4 und R^5 unabhängig voneinander ein Wasserstoffatom, ein Alkylrest mit C_{1-4} -Kohlenstoffatomen oder eine Phenylgruppe oder zusammen eine 1,4-Butylen- oder 1,5-Pentylengruppe ($-(CH_2)_5-$) sind,

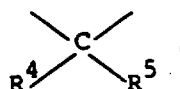
R^3 ein Wasserstoffatom oder ein unverzweigter oder verzweigter Alkylrest mit 1 bis 4 Kohlenstoffatomen und

25 X ein unverzweigter oder verzweigter Alkylrest mit 1 bis 10 Kohlenstoffatomen ist, die N-Schutzgruppe abspaltet, die erhaltene Verbindung der Formel (3)



intramolekular cyclisiert und gegebenenfalls, wenn R^3 ein Wasserstoffatom ist, das Produkt zu einer Verbindung umsetzt, in der R ein Acyl- oder Alkylrest ist.

40 2. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß R^1 und R^2 zusammen den Rest



45 darstellen, und R^4 und R^5 die in Anspruch 1 angegebene Bedeutung haben und man die Abspaltung der N-Schutzgruppe und die intramolekulare Cyclisation durch Erhitzen auf eine Temperatur zwischen 90 und 160°C in Anwesenheit einer Carbonsäure bewirkt.

3. Verfahren nach Anspruch 1 oder 2, dadurch gekennzeichnet, daß R^1 und R^2 zusammen eine 2-Methyl-propan-1,1-diylgruppe



bilden und R^3 ein Wasserstoffatom ist.

55 4. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß R^2 eine Benzyl-, α -Methylbenzyl- oder p-Methoxybenzylgruppe ist und man die N-Schutzgruppe der Verbindung (2) durch katalytische Hydrierung mit einem Palladium-auf-Kohle-Katalysator abspaltet.

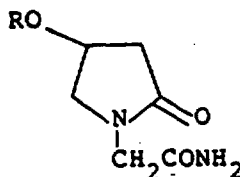
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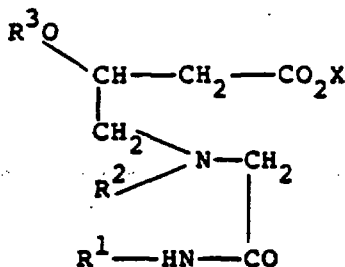
Revendications pour les Etats contractants: BE CH DE FR GB IT LI LU NL SE

1. Un procédé pour la préparation d'un dérivé de pyrrolidinone de la structure (1)



(1)

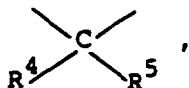
dans laquelle R est de l'hydrogène, de l'alcyle droit ou ramifié de 1 à 4 atomes de carbone, ou de l'acyle contenant de 1 à 10 atomes de carbone, caractérisé par le fait qu'un composé de la structure (2)



(2)

dans laquelle

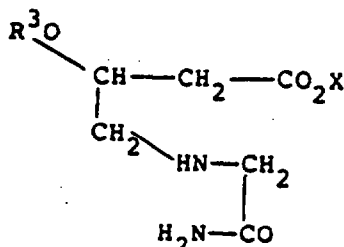
R¹ est de l'hydrogène et R² est du benzyle, alpha-méthyle benzyle ou p-méthoxybenzyle ou R¹ et R² ensemble forment un groupe



dans lequel R⁴ et R⁵ sont indépendamment de l'hydrogène, de l'alcyle contenant de 1 à 4 atomes de carbone ou du phényle, ou bien ensemble, ils sont 1,4 butylène ou 1,5-pentylène (—(CH₂)₅);

R³ est de l'hydrogène ou de l'alcyle droit ou ramifié de 1 à 4 atomes de carbone; et

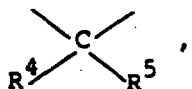
X est de l'alcyle droit ou ramifié contenant de 1 à 10 atomes de carbone; est soumis à la déprotection-N afin de donner un composé de la structure (3)



(3)

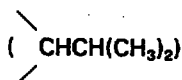
qui est cyclisé intramoléculairement; et facultativement lorsque R³ est de l'hydrogène, le produit est converti en un composé dans lequel R est acyle ou alcyle.

2. Un procédé selon la revendication 1 ou, dans lequel R¹ et R² ensemble forment un groupe



et dans lequel R⁴ et R⁵ sont comme décrits dans la revendication 1 et la déprotection et la cyclisation intramoléculaire sont réalisées par chauffage à une température d'entre 90° et 160°C, en présence d'un acide carboxylique.

3. Un procédé selon la Revendication 1 ou 2 dans laquelle R¹ et R² ensemble forment un groupe 2-méthyl-propane-1,1-diyl

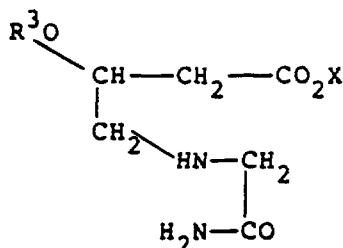


et R³ est hydrogène.

4. Un procédé selon la revendication 1 dans lequel R² est du benzyle, alpha-méthylbenzyle ou p-méthoxybenzyle et le composé de la structure (2) est déprotégé au moyen de l'hydrogénation catalytique avec un catalyseur au palladium sur charbon de bois.



5. Un composé de la structure (3)

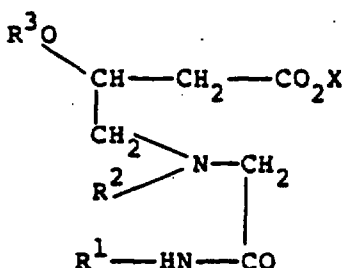


(3)

et les sels d'addition d'acide des mêmes, dans lesquels R^3 est de l'hydrogène ou de l'alcyle droit ou ramifié de 1 à 4 atomes de carbone et X est de l'alcyle droit ou ramifié contenant de 1 à 10 atomes de carbone.

6. Un composé de la revendication 5 dans lequel R^3 est de l'hydrogène sous forme d'un sel d'addition d'acide.

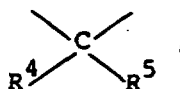
7. Un composé de la structure (2)



(2)

dans laquelle

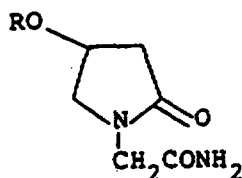
R^1 est de l'hydrogène et R^2 est benzyle ou benzyle substitué, ou bien R^1 et R^2 peuvent former ensemble un groupe



dans lequel R^4 et R^5 sont indépendamment de l'hydrogène, de l'alcyle contenant de 1 à 4 atomes de carbone, ou du phényle, ou bien ensemble, ils sont 1,4-butylène ou 1,5-pentylène $(-(\text{CH}_2)_2)_2$;

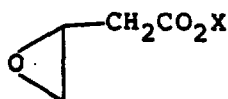
R^3 est de l'hydrogène ou de l'alcyle droit ou ramifié de 1 à 4 atomes de carbone; et X est de l'alcyle droit ou ramifié contenant de 1 à 10 atomes de carbone.

8. Un procédé pour la préparation d'un dérivé de la pyrrolidinone de la structure (1)



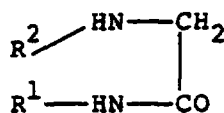
(1)

dans laquelle R est de l'hydrogène, de l'alcyle droit ou ramifié de 1 à 4 atomes de carbone, caractérisé par le fait qu'un alcyle, 3,4-époxybutanoate de la structure (4)



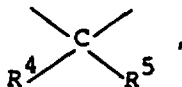
(4)

dans laquelle X est de l'alcyle de 1-10 atomes de carbone et est mis en réaction avec un dérivé glycinéamide de la structure (5)



(5)

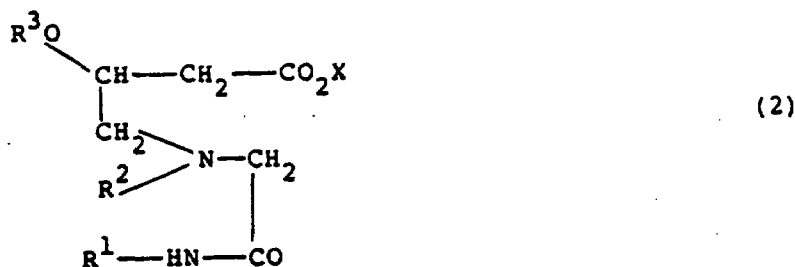
dans laquelle R^1 est de l'hydrogène et R^2 est du benzyle ou benzyle substitué, ou bien R^1 et R^2 peuvent former ensemble un groupe



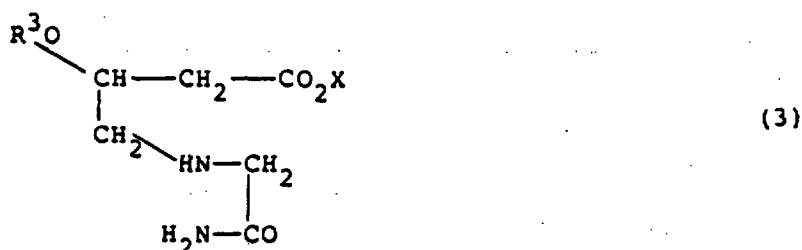


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dans lequel R^4 et R^5 sont indépendamment de l'hydrogène, de l'alcoyle contenant de 1 à 4 atomes de carbone, de l'aryle facultativement substitué ou bien, ensemble, ils sont 1,4-butylène ou 1,5-pentylène $-(CH_2)_5-$ à une température de 20° à 120°C, pour donner un composé de la structure (2)



dans laquelle R^3 est de l'hydrogène, et le produit est facultativement alcoylé en un composé de la structure (2) dans laquelle R^3 est de l'alcoyle droit ou ramifié de 1 à 4 atomes de carbone et le composé de la structure (2) est soumis à la déprotection-N pour donner un composé de la structure (3)



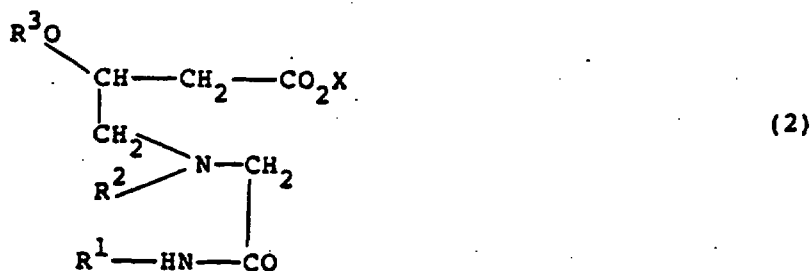
qui est cyclisé intramoléculairement, et facultativement, lorsque R^3 est de l'hydrogène, le produit est alcoylé ou acylé en un composé dans lequel R est acyle ou alcoyle.

Revendications pour l'Etat contractant: AT

1. Un procédé pour la préparation d'un dérivé de pyrrolidinone de la structure (1)

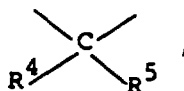


dans laquelle R est de l'hydrogène, de l'alcoyle droit ou ramifié de 1 à 4 atomes de carbones, ou de l'acyle contenant de 1 à 10 atomes de carbone, caractérisé par le fait qu'un composé de la structure (2)



dans laquelle

R^1 est de l'hydrogène et R^2 est du benzyle, alpha-méthyle benzyle ou p-méthoxybenzyle ou R^1 et R^2 ensemble forment un groupe



dans lequel R^4 et R^5 sont indépendamment de l'hydrogène, de l'alcoyle contenant de 1 à 4 atomes de carbone ou du phényle, ou bien ensemble, ils sont 1,4 butylène ou 1,5-pentylène $-(CH_2)_5-$

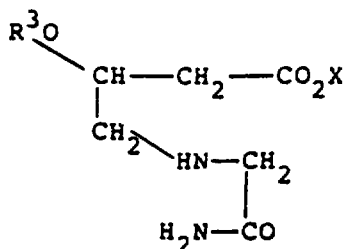


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R³ est de l'hydrogène ou de l'alcyle droit ou ramifié de 1 à 4 atomes de carbone; et
X est de l'alcyle droit ou ramifié contenant de 1 à 10 atomes de carbone;
est soumis à la déprotection-N afin de donner un composé de la structure (3)

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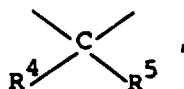
(3)

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qui est cyclisé intramoléculairement; et facultativement lorsque R³ est de l'hydrogène, le produit est converti en un composé dans lequel R est acyle ou alcyle.

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2. Un procédé selon la revendication 1 ou, dans lequel R¹ et R² ensemble forment un groupe



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et dans lequel R⁴ et R⁵ sont comme décrits dans la revendication 1 et la déprotection et la cyclisation intramoléculaire sont réalisées par chauffage à une température d'entre 90° et 160°C, en présence d'un acide carboxylique.

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3. Un procédé selon la Revendication 1 ou 2 dans laquelle R¹ et R² ensemble forment un groupe 2-méthyl-propane-1,1-diyl



et R³ est hydrogène.

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4. Un procédé selon la revendication 1 dans lequel R² est du benzyle, alpha-méthylbenzyle ou p-méthoxybenzyle et le composé de la structure (2) est déprotégé au moyen de l'hydrogénation catalytique avec un catalyseur au palladium sur charbon de bois.

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