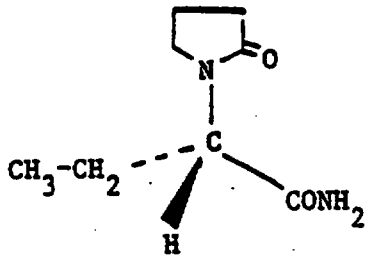
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# A process for the preparation of (S)-α-ethyl-2-oxo-1-pyrrolidineacetamide.

The present invention relates to a new process for the preparation of (S)-α-ethyl-2-oxo-1-pyrrolidineacetamide which has the formula




U.S. Patents No. 4,696,943 and No. 4,837,223 in the name of the Applicant describe this compound, which has the absolute S configuration and state that it has particular therapeutic properties which completely unexpectedly distinguish it from the racemic form. Thanks to its properties, the S enantiomer is more suitable than the racemic form for the treatment and prevention of hypoxic and ischemic type aggressions of the central nervous system.

The preparation of (S)-α-ethyl-2-oxo-1-pyrrolidineacetamide is described in the above mentioned U.S. Patents No. 4,696,943 and No. 4,837,223. According to these patents, the compound cannot be obtained directly from the racemic mixture by separation of the two enantiomers. It has to be prepared by other methods, and these U.S. patents specifically describe two processes for the preparation of the compound. In the first process, (S)-α-ethyl-2-oxo-1-pyrrolidineacetic acid is reacted successively with an alkyl haloformate, preferably ethyl chloroformate, and with ammonia. In the second process, an alkyl (S)-4-[[1-(aminocarbonyl)propyl]amino]butyrate or an (S)-N-[1-(aminocarbonyl)propyl]-4-halobutanamide is cyclized, the two compounds themselves being prepared from (S)-2-aminobutanamide.

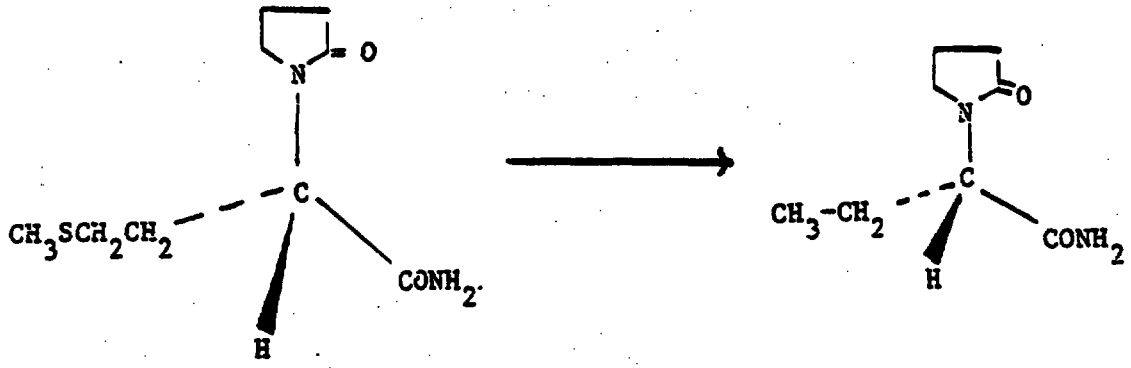
These two processes have in common the same disadvantage. Both require the preparation of a starting reactant which already has the correct stereochemical configuration. This starting reactant is obtained by resolution of the corresponding racemic compound, respectively racemic (±)-α-ethyl-2-oxo-1-pyrrolidineacetic acid in the case of the first

process and racemic (±)-2-amino-butanamide in the case of the second process. Prior separation of the enantiomer with the desired configuration from the corresponding racemic compound necessarily causes, from the beginning, a loss of 50% of the raw material employed. Moreover, if it is taken into account that recovery of an optical isomer is rarely carried out in a quantitative yield, the total loss of raw material incurred is much greater than 50% of the starting racemic compound.

A process which would not have this disadvantage, while remaining relatively easy to carry out, would be extremely desirable.

The present invention thus provides a new process for the preparation of (S)-α-ethyl-2-oxo-1-pyrrolidineacetamide which does not have the disadvantage of the previous processes and which, as a consequence, is more economical. Moreover, this new process also offers the advantage of using a naturally occurring amino acid, L-methionine, or its readily accessible amide as the starting material.

The process according to the present invention for the preparation of (S)-α-ethyl-2-oxo-1-pyrrolidineacetamide comprises hydrogenolysis of (S)-α-[2-(methylthio)ethyl]-2-oxo-1-pyrrolidineacetamide by means of a desulphurizing reagent, in accordance with the equation

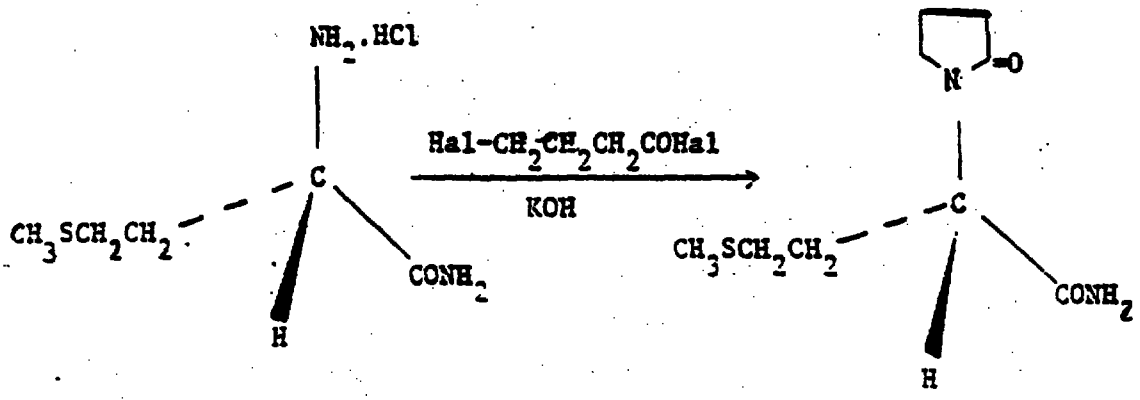



The desulphurization of (S)-α-[2-(methylthio)ethyl]-2-oxo-1-pyrrolidineacetamide is stereoselective. This reaction is generally carried out in water at a temperature between 50 en 100°C in the presence of a desulphurizing reagent such as $NaBH_4/NiCl_2.6H_2O$ (R.B. BOAR et al., J.Chem.Soc., Perkin Trans.I (1973),654), Raney nickel W-2 or, preferably, Raney nickel T-1 under normal or increased pressure (X. DOMINGUEZ et al., J.Org.Chem.26,(1961),1625).

The (S)-α-[2-(methylthio)ethyl]-2-oxo-1-pyrrolidineacetamide which is the starting compound in this process is a new compound. It can be

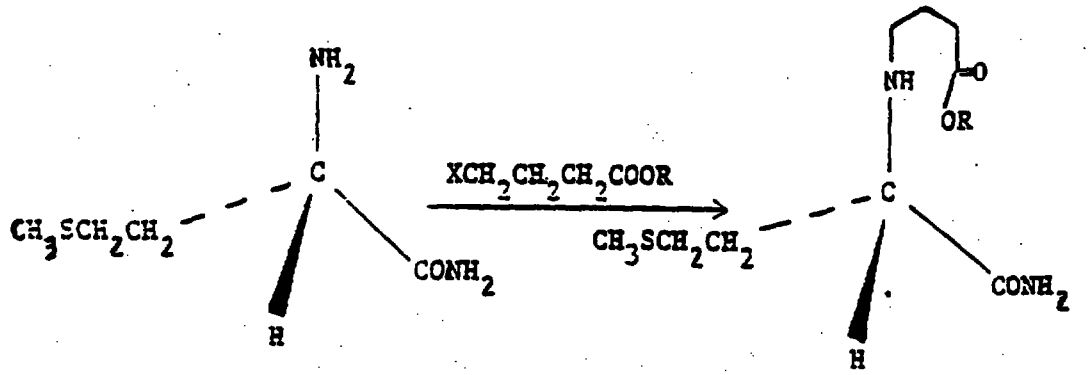
prepared by one or other of the following two methods:

1) reacting (S)-2-amino-4-(methylthio)butanamide hydrochloride with a 4-halobutyryl halide of the formula $HalCH_2CH_2CH_2COHal$ in which Hal is a halogen atom, preferably a chlorine atom, in accordance with the equation



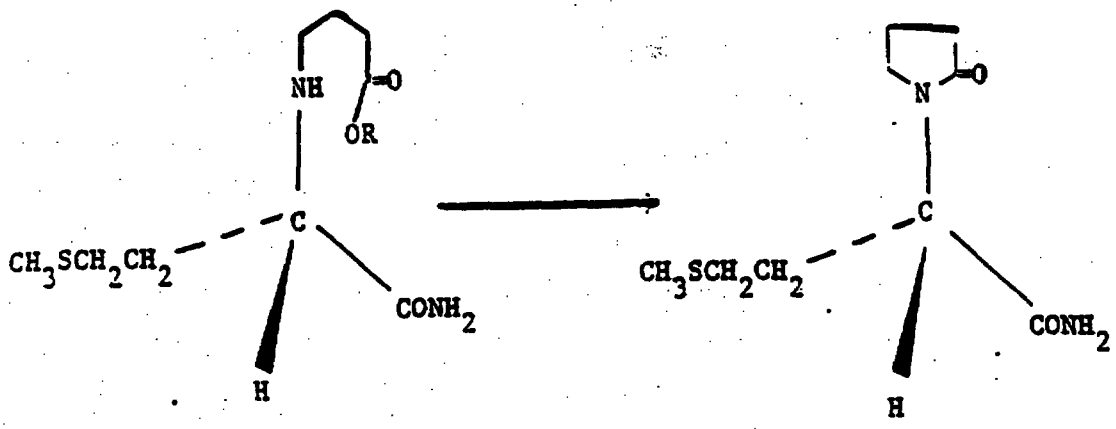

This reaction is generally carried out in an inert solvent, for example dichloromethane, at a temperature of about 0°C in the presence of a catalyst, such as tetrabutylammonium bromide in the presence of powdered potassium hydroxide.

2) a) reacting first (S)-2-amino-4-(methylthio)butanamide with an alkyl 4-halobutyrate of the formula $XCH_2CH_2CH_2COOR$, in wich X is a halogen atom and R is an alkyl radical having 1 to 4 carbon atoms, in accordance with the equation




This reaction is generally carried out by heating for several hours at a temperature between 80 and 100°C in an inert solvent, such as toluene, in the presence of an acid acceptor such as a tertiary organic base, such as, for example, triethylamine.

b) then cyclizing the alkyl (S)-4-[[1-(aminocarbonyl)-3-(methylthio)propyl]amino]-butyrate obtained in step a), in accordance with the equation



This cyclization is generally carried out in an inert solvent, such as for example toluene or xylene, by heating at a temperature between 100 and 130°C for several hours in the presence of a catalyst, such as 2-hydroxypyridine.

(S)-2-Amino-4-(methylthio)butanamide, as the free base, can be prepared from L-methionine according to the method of E. SANDRIN and R.A. BOISSONNAS, Helv.Chim.Acta,46,(1963),1637-1669.
M.P.: 50-51°C. $[\alpha]_D^{22}$ = -27.7° (c = 2, dimethylformamide).

(S)-2-Amino-4-(methylthio)butanamide hydrochloride, which is a known compound, can be prepared from the base according to the process described by A. EBERLE et al., Helv.Chim.Acta,61,(1978),2360-74.
M.P.: 212-215°C. $[\alpha]_D^{25}$ = +26.4° (c = 1, dimethylformamide).

The following example is given for the purpose of illustrating the invention.

In this example, the optical purity of the final product was verified by calorimetric determination of the differential enthalpies (C. FOUQUEY and J. JACQUES, Tetrahedron,23,(1967),4009-19).

Example.

I. Preparation of the starting (S)-α-[2-(methylthio)ethyl]-2-oxo-1-pyrrolidineacetamide.

1) From a 4-halobutyryl halide.

84 g of anhydrous sodium sulphate are added to a suspension of 92.25 g (0.5 mole) of (S)-2-amino-4-(methylthio)butanamide in 600 ml of dichloromethane at room temperature. The mixture is then cooled to 0°C and 115 g of ground potassium hydroxide and 8.1 g

(0.025 mole) of tetrabutylammonium bromide dissolved in 100 ml of dichloromethane are added in succession. A solution containing 77.5 g (0.55 mole) of 4-chlorobutyryl chloride in 100 ml of dichloromethane is added dropwise at the same temperature, and with vigorous stirring. During the addition, the reaction medium is diluted by simultaneous introduction of 550 ml of dichloromethane. After stirring at 0°C for two hours, 29 g of ground potassium hydroxide are added to the mixture. After four and a half hours' reaction, a further 29 g of ground potassium hydroxide are added and stirring is continued for one hour at 0°C. The reaction mixture is then filtered over Hyflocel and the filtrate is evaporated under reduced pressure. The residue is purified by chromatography over silica (eluent: mixture of dichloromethane-methanol-ammonia 95.5:4.5:0.2 v/v/v). 66 g of (S)-α-[2-(methylthio)ethyl]-2-oxo-1-pyrrolidineacetamide are obtained in the form of a white powder. $[\alpha]_D^{25}$ = - 39.1° (c = 1, methanol).

Yield: 61%.

Analysis for $C_9H_{16}N_2O_2S$ in %:

| | | | |
|---|---|---|---|
| calc. : | C 50.00 | H 7.41 | N 12.96 |
| found : | 50.15 | 7.80 | 12.94 |

2) From an alkyl 4-halobutyrate.

a) Ethyl (S)-4-[[1-(aminocarbonyl)-3-(methylthio)propyl]-amino]butyrate.

10.57 ml (76 mmoles) of triethylamine are added to a suspension of 10 g (68 mmoles) of (S)-2-amino-4-(methylthio)butanamide in 100 ml of toluene. The mixture is heated to 80-85°C, with vigorous stirring, and 13.26 g (68 mmoles) of ethyl 4-bromobutyrate are added dropwise. This temperature is maintained for 8 hours. The solvent is then evaporated off under reduced pressure and the residue is taken up in 100 ml of dichloromethane. The mixture is heated under reflux for 30 minutes and filtered hot. The filtrate is evaporated to dryness and the residue obtained is purified by chromatography over silica (eluent: mixture of ethyl acetate-methanol-ammonia 10:0.1:0.1 v/v/v). 6.2 g of ethyl (S)-4-[[1-(aminocarbonyl)-3-(methylthio)propyl]amino]butyrate are thus obtained. $[\alpha]_{436}^{25}$ = -14.1° (c = 1, methanol). Yield: 35%.

This intermediate compound is used as such without further purification for carrying out the final cyclization.

b) 0.6 g (2.29 mmoles) of the crude product obtained in a) and 21.3 mg (0.225 mmole) of 2-hydroxypyridine are mixed in 1.15 ml of p-xylene. The mixture is heated at 130°C under nitrogen for 4 and a half hours. It is then cooled and stirred for 30 minutes at room temperature. The precipitate which forms is filtered off and recrystallized from ethyl acetate. 0.18 g of (S)-α-[2-methylthio)-ethyl]-2-oxo-1-pyrrolidineacetamide are obtained. $[\alpha]_D^{25}$ = -36.5° (c = 1, methanol). Yield: 36%.

Analysis for $C_9H_{16}N_2O_2S$ in %:

| | | | |
|---|---|---|---|
| calc.: | C 50.00 | H 7.41 | N 12.96 |
| found: | 49.88 | 7.49 | 12.68 |

II. Preparation of (S)-α-ethyl-2-oxo-1-pyrrolidineacetamide.

50 g of Raney nickel T-1 (X.A. DOMINGUEZ et al., J.Org.Chem.26, (1961),1625), 386 ml of water and 7 g (0.0324 mole) of (S)-α-[2-(methylthio)ethyl]-2-oxo-1-pyrrolidineacetamide are introduced successively into a one litre three-necked round-bottomed flask. The mixture is heated to 75°C and stirred at this temperature for one hour. It is filtered and the water is evaporated off under reduced pressure. The residue (5.3 g) is recrystallized from 60 ml of ethyl acetate. 3.87 g of (S)-α-ethyl-2-oxo-1-pyrrolidineacetamide are obtained. M.P.: 112-115°C. $[\alpha]_D^{25}$ = -90° (c = 1, acetone).

Yield: 69%.

Analysis for $C_8H_{14}N_2O_2$ in %:

| | | | |
|---|---|---|---|
| calc.: | C 56.45 | H 8.29 | N 16.46 |
| found: | 56.30 | 8.42 | 16.18 |

* C L M S *

## CLAIMS

1. A process for the preparation of (S)-α-ethyl-2-oxo-1-pyrrolidineacetamide, characterized in that (S)-α-(2-(methylthio)ethyl)-2-oxo-1-pyrrolidine-acetamide is subjected to hydrogenolysis by means of a desulphurizing reagent.

2. A process according to claim 1, characterized in that the desulphurizing reagent is Raney nickel T-1.

3. A process according to claim 1, characterized in that the desulphurizing reagent is $NaBH_4/NiCl_2.6H_2O$.

4. A process according to claim 1, characterized in that the desulphurizing reagent is Raney nickel W-2.

5. A process according to any of claim 1 to 4, characterized in that the hydrogenolysis is carried out in water at a temperature between 50 and 100°C.

6. (S)-α-(2-(methylthio)ethyl)-2-oxo-1-pyrrolidineacetamide.

7. A process for preparing (S)-α-(2-(methylthio)-ethyl)-2-oxo-1-pyrrolidineacetamide comprising reacting (S)-2-amino-4-(methylthio)butanamide hydrochloride with a 4-halobutyryl halide.

8. A process as claimed in claim 7, wherein the 4-halobutyryl halide is 4-chlorobutyryl chloride.

9. A process as claimed in claim 7 or claim 8 wherein said reaction is carried out in an inert solvent.

10. A process as claimed in claim 9, wherein the inert solvent is dichloromethane.

11. A process as claimed in claim 9 or claim 10, wherein said reaction is carried out in the presence of a catalyst.

12. A process as claimed in claim 11, wherein the catalyst is tetrabutylammonium bromide and powdered potassium hydroxide.

13. A process for producing (S)-α-(2-(methylthio) ethyl)-2-oxo-1-pyrrolidineacetamide, comprising:-
(1) reacting (S)-2-amino-4-(methylthio)butanamide with

* C L M S *

an alkyl 4-halobutyrate of the formula $XCH_2CH_2CH_2COOR$, in which X represents a halogen atom and R represents an alkyl radical having 1 to 4 carbon atoms, to form an alkyl (S)-4-[[1-(aminocarbonyl)-3-(methylthio)-propyl]amino]-butyrate, and;

(2) cyclizing the alkyl (S)-4-[[1-(amino-carboxyl)-3-(methylthio)-propyl]amino]-butyrate obtained in Step (1) in an inert solvent by heating at a temperature between 100 and 130°C in the presence of a catalyst.

14. A process as claimed in claim 13, wherein the inert solvent is toluene or xylene.

15. A process as claimed in claim 13 or claim 14, wherein the catalyst is 2-hydroxypyridine.

16. A process as claimed in any of claims 13, 14 or 15, wherein said first reaction step is carried out at a temperature between 80 and 100°C in an inert solvent, in the presence of an acid acceptor.

17. A process as claimed in claim 16, wherein the inert solvent is toluene.

* C L M S *

18. A process as claimed in claim 16 or 17, wherein the acid acceptor is triethylamine.

19. A process as claimed in claim 1 substantially as hereinbefore described.

20. A process as claimed in claim 7, substantially as hereinbefore described.

21. A process as claimed in claim 13, substantially as hereinbefore described.