The present invention relates to a new compound, (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide, as well as to processes for its preparation. It also relates to therapeutic compositions containing the said compound.

British Patent no. 1,309,692 filed by the Applicant Company describes alpha-ethyl-2-oxo-1-pyrrolidineacetamide (melting point 122°C), and states that substances of this type can be used in the therapeutic field, for example for the treatment of motion sickness, hyperkinesia, hypertension and epilepsy.

Moreover, it also mentions that these compounds can be used in the field of memory disorders in normal or pathological conditions.

It is furthermore also known that alpha-ethyl-2-oxo-1-pyrrolidineacetamide possesses a protective activity against aggressions of the central nervous system caused by hypoxia, cerebral ischaemia etc. (Pharmazie, 37/11, (1982), 753-765).

Continuing its research work in this field, the Applicant Company has prepared and isolated the laevorotatory enantiomer of alpha-ethyl-2-oxo-1-pyrrolidineacetamide, and has found that this compund is distinguished in a completely unpredictable manner from the known racemic form

(1) by a protective activity against hypoxia (anti-hypoxia) which is 10 times higher and

(2) by a protective activity against cerebral ischaemia (anti-ischaemia) which is 4 times greater.

As a result of this unexpected combination of properties, the laevorotatory enantiomer of alpha-ethyl-2-oxo-1-pyrrolidineacetamide is much more suitable for the treatment and prevention of aggressions of the hypoxic and ischaemic type of the central nervous system. The important contribution of the hypoxic phenomenon in certain pathologies of the central nervous system suggests that this product has a therapeutic effect in the treatment of the consequences of cerebral vascular accidents and of cranial traumas, of the sequelae of the ageing process or of circulatory insufficiencies of the central nervous system resulting from cerebroischaemic accidents or

hypoxia occurring e.g. during birth. In a broader sense, this product may also be used on conditions of the hypoxic type of other organs or tissues: heart and kidneys.

The present invention accordingly relates to the laevorotatory enantiomer of alpha-ethyl-2-oxo-1-pyrrolidineacetamide which has the absolute S configuration, the said compound being substantially free from the dextrorotatory enantiomer having the absolute R configuration.

(S)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide according to the present invention cannot be obtained directly from the racemic form by separation of the two enantiomers. It may be prepared by one or other of the following processes:

(a) (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetic acid is reacted successively with (1) an alkyl haloformate of the formula HalCOOZ in which Hal represents a halogen atom and Z an alkyl radical having 1 to 4 carbon atoms and with (2) ammonia. The alkyl haloformate is preferably ethyl chloroformate.

This reaction is generally carried out in methylene chloride at a temperature between -10 and -60°C.

The (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetic acid used in this reaction can be obtained from racemic (±)-alpha-ethyl-2-oxo-1-pyrrolidineacetic acid by chemical resolution in accordance with methods which are known per se, for example by forming a salt of this acid with an optically active base and isolating the salt formed with the (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetic acid by successive crystallizations in a suitable solvent (e.g. benzene).

By way of examples of optically active bases which can be used for this resolution there may be mentioned alkaloids, such as brucine, quinine, strychnine, quinidine and cinchonidine, and amines, such as alpha-methyl-benzylamine and dehydroabietylamine (c.f. S.H. WILEN et al., Tetrahedron, 33, (1977), 2725-2736). Particularly favourable results are obtained by using alpha-methyl-benzylamine and dehydroabietylamine.

The racemic (±)-alpha-ethyl-2-oxo-1-pyrrolidineacetic acid used as the starting material can be obtained by saponification of the

corresponding alkyl esters, the synthesis of which has been described in British Patent no. 1,309,692.

(b) An (S)-2-amino-butanamide of the formula

$$X\text{-}CH_2CH_2\text{-}Y\text{-}NHCH(C_2H_5)CONH_2 \qquad (A)$$

in which

X represents a ZOOC- or $HalCH_2$- radical, Z being an alkyl radical having 1 to 4 carbon atoms and Hal a halogen atom, preferably chlorine or bromine, and

Y represents a $-CH_2-$ or -CO- radical,

with the proviso that Y is a $-CH_2-$radical when X represents a ZOOC- radical and Y is a -CO- radical when X represents a $HalCH_2$-radical.

The cyclization of (S)-2-amino-butanamide of formula A is carried out in an inert solvent, such as toluene or methylene chloride, at a temperature between 0°C and the boiling point of the solvent. This cyclization is carried out in the presence of a basic substance as a catalyst. This catalyst is 2-hydroxypyridine when the compound of formula A is an ester (X = ZOOC-) and tetrabutylammonium bromide when the compound of formula A is a halide (X = $HalCH_2$-).

When X represents a ZOOC- radical and Y is a $-CH_2-$ radical, the compound of formula A is an alkyl (S)-4-[[1-aminocarbonyl)propyl]-amino]-butyrate of formula $ZOOCCH_2CH_2CH_2NHCH(C_2H_5)CONH_2$, in which Z has the meaning given above. The latter can be prepared by condensing (S)-2-amino-butanamide with an alkyl 4-halobutyrate of the formula $ZOOCCH_2CH_2CH_2\text{-}Hal$, in which Z has the meaning given above and Hal is a halogen atom.

When X represents a $HalCH_2$- radical and Y is therefore a -CO- radical, the compound of formula A is an (S)-N-[1-(aminocarbonyl)propyl]-4-halo-butanamide of the formula $HalCH_2CH_2CH_2CONHCH(C_2H_5)CONH_2$, in which Hal has the meaning given above. The latter can be prepared by condensing (S)-2-amino-butanamide with a 4-halobutyryl halide of the formula $HalCH_2CH_2CH_2COHal$, in which Hal is a halogen atom.

The reaction between (S)-2-amino-butanamide on the one hand and the alkyl 4-halobutyrate or 4-halobutyryl halide on the other hand is generally carried out in an inert solvent, such as benzene, toluene, methylene chloride or acetonitrile, at a temperature between -5 and

+100°C and in the presence of an acid acceptor, such as a tertiary organic base (e.g. triethylamine) or an inorganic base (e.g. potassium carbonate or hydroxide or sodium carbonate or hydroxide).

When X represents a $HalCH_2$- radical and Y a -CO- radical, it is not essential to isolate the compound of formula A obtained from the starting materials mentioned above. In fact, the compound of formula A, obtained in situ, can be cyclized directly to the (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide according to the present invention (see example 4 below).

The (S)-2-amino-butanamide used as the starting material can be obtained from (S)-2-aminobutyric acid by ammonolysis of the corresponding methyl ester in accordance with the method described by K. FOLKERS et al. in J.Med.Chem.14,(6),(1971);484-487.

The examples which follow illustrate the invention without limiting it. In these examples, the optical purity of the products obtained was verified by calorimetric determination of the differential enthalpies (C. FOUQUEY AND J. JACQUES, Tetrahedron,23,1967,4009-19).

Example 1. a) Preparation of the (R)-alpha-methyl-benzylamine salt of (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetic acid.

8.7 kg (50.8 mol) racemic (±)-alpha-ethyl-2-oxo-1-pyrrolidineacetic acid are suspended in 21.5 litres anhydrous benzene in a 50 litre reactor. A solution containing 3.08 kg (25.45 mol) (R)-(+)-alpha-methyl-benzylamine and 2.575 kg (25.49 mol) triethylamine in 2.4 litres anhydrous benzene is progressively added to this suspension. The mixture is then heated under reflux until complete dissolution is achieved. It is cooled and allowed to crystallize for a few hours. 5.73 kg (R)-alpha-methyl-benzylamine salt of (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetic acid are thus obtained.

m.p.: 148 - 151°C. Yield: 77.1%.

This salt may be purified by heating under reflux in 48.3 litres benzene for 4 hours. The mixture is cooled and filtered. 5.040 kg of the desired salt are thus obtained.

m.p.: 152 - 153.5°C. Yield: 67.85%.

b) Preparation of (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetic acid

5.04 kg salt obtained in a) above are dissolved in 9 litres water. 710 g of a 30% solution of sodium hydroxide are added slowly. The pH reaches 12.6 and the temperature does not exceed 25°C. The solution is stirred for a further 20 minutes and the alpha-methyl-benzylamine liberated is extracted several times with a total volume of 18 litres benzene.

The aqueous phase is then acidifed to a pH of 1.1 by addition of 3.2 litres 6 N hydrochloric acid. The precipitate formed is filtered off, washed with water and dried.

The filtrate is extracted several times with a total volume of 50 litres methylene chloride. The organic phase is dried over sodium sulphate, filtered and evaporated to dryness under reduced pressure.

The residue obtained after evaporation and the precipitate isolated previously are dissolved together in 14 litres hot methylene chloride. The methylene chloride is distilled and replaced at the distillation rate by 14 litres toluene, in which the product crystallizes. The mixture is cooled to ambient temperature and the crystals are filtered. 2.780 kg (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetic acid are thus obtained.

m.p.: 125.9°C. $[\alpha]_D^{20} = -26.4^\circ$ (c = 1, acetone).

Yield: 94.5%.

c) Preparation of (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide

34.2 g (0.2 mol) (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetic acid are suspended in 225 ml methylene chloride, cooled to -30°C. 24.3 g (0.24 mol) triethylamine are added dropwise in the course of 15 minutes. The reaction mixture is then cooled to -40°C and 24.3 g (0.224 mol) ethyl chloroformate are added in the course of 12 minutes. A stream of ammonia is then passed through for 4 and a half hours. The mixture is allowed to return to ambient temperature and the ammonium salts formed are removed by filtration and washed with methylene chloride. The solvent is distilled off under reduced pressure. The solid residue thus obtained is dispersed in 55 ml toluene, the dispersion is stirred for 30 minutes and then filtered and the product is recrystallized from 280 ml ethyl acetate in the presence of 9 g moleculare sieve 0.4 nm in powder form.

24.6 g (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide are obtained.

m.p.: 115 - 118°C. $[\alpha]_D^{25} = -89.7^\circ$C (c = 1, acetone). Yield: 72.3%.

Analysis for $C_8H_{14}N_2O_2$ in %

calculated:	C 56.45	H 8.29	N 16.46
found:	56.71	8.22	16.48

The racemic (±)-alpha-ethyl-2-oxo-1-pyrrolidineacetic acid used in this synthesis was prepared in the manner described below.

A solution containing 788 g (19.7 mol) sodium hydroxide in 4.35 litres water is added in the course of two hours to a 20 litre flask containing 3.65 kg (18.34 mol) ethyl (±)-alpha-ethyl-2-oxo-1-pyrrolidineacetate at a temperature not exceeding 60°C. When this addition has ended, the temperature of the mixture is raised to 80°C and the alcohol formed is distilled off until the temperature of the mixture reaches 100°C. The mixture is cooled to 0°C and 1.66 litres (19.80 mol) 12 N hydrochloric acid are added in the course of 2 and a half hours. The precipitate is filtered off, washed with two litres toluene and recrystallized from isopropyl alcohol. 2.447 kg racemic (±)-alpha-ethyl-2-oxo-1-pyrrolidineacetic acid of melting point 155 - 156°C are thus obtained. Yield: 78%.

Analysis for $C_8H_{13}NO_3$ in %

calculated:	C 56.12	H 7.65	N 8.18
found:	55.82	8.10	7.97

Example 2. a) Preparation of ethyl (S)-4-[[1-(aminocarbonyl)propyl]amino]-butyrate

143.6 ml (1.035 mol) triethylamine are added to a suspension of 47.75 g (0.345 mol) (S)-2-amino-butanamide hydrochloride ($[\alpha]_D^{25}$: +26.1°C; c = 1, methanol) in 400 ml toluene. The mixture is heated to a 80°C and 67.2 g (0.345 mol) ethyl 4-bromobutyrate are introduced dropwise.

The reaction mixture is kept at 80°C for 10 hours and then filtered hot to remove the triethylamine salts. The filtrate is evaporated under reduced pressure and 59 g of an oily residue consisting mainly of the monoalkylation product and containing a little dialkylated derivative are obtained.

The product obtained in the crude state was used as such, without additional purification, in the preparation of (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide by cyclization.

b) Preparation of (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide

54 g crude product obtained in a) above are dissolved in 125 ml toluene in the presence of 2 g 2-hydroxypyridine. The mixture is kept at 110°C for 12 hours.

The insoluble matter is filtered off hot and the filtrate is then evaporated under reduced pressure.

The residue is purified by chromatography on a column of 1.1 kg silica (column diameter: 5 cm; eluent: a mixture of ethyl acetate, methanol and concentrated ammonia in proportions by volume of 85:12:3).

The product isolated is recrystallized from 50 ml ethyl acetate. 17.5 g (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide are thus obtained.

m.p.: 117°C. $[\alpha]_D^{25}$: -90.0° (c = 1, acetone). Yield: 41%.

Example 3. a) Preparation of (S)-N-[1-(aminocarbonyl)propyl]-4-chloro-butanamide

345.6 g (2.5 mol) ground potassium carbonate and 138.5 g (1 mol) (S)-2-amino-butanamide hydrochloride are mixed in 2.5 litres acetonitrile. The reaction mixture is cooled to 0°C and a solution of 129.2 g (1.2 mol) 4-chlorobutyryl chloride in 500 ml acetonitrile is introduced dropwise. After the addition, the reaction mixture is allowed to return to ambient temperature; the insoluble matter is removed by filtration and the filtrate is evaporated under reduced pressure. The crude residue obtained is stirred in 1.2 litres anhydrous ether for 30 minutes at a temperature between 5 and 10°C. The precipitate is filtered off, washed with 2 portions of 225 ml ether and dried in vacuo. 162.7 g (S)-N-[1-(aminocarbonyl)propyl]-4-chlorobutanamide are thus obtained.

m.p.: 118 - 123°C. $[\alpha]_D^{25}$: -18° (c = 1, methanol). Yield: 78.7%.

The crude product thus obtained is particularly suitable for the cyclization stage which follows. However, it can be purified by stirring for one hour in anhydrous ethyl acetate.

m.p.: 120 - 122°C. $[\alpha]_D^{25}$: -22.2° (c = 1, methanol).

2) Preparation of (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide

6.2 g (0.03 mol) (S)-N-[1-(aminocarbonyl)propyl]-4-chlorobutanamide and 0.484 g (0.0015 mol) tetrabutylammonium bromide are mixed in 45 ml methylene chloride at 0°C under a nitrogen atmosphere. 2.02 g (0.036 mol)

pulverulent potassium hydroxide are added in the course of 30 minutes without exceeding +2°C in the reaction mixture. The mixture is subsequently stirred for one hour, a further 0.1 g (0.0018 mol) ground potassium hydroxide is then added and stirring is continued at 0°C for 30 minutes. The mixture is allowed to return to ambient temperature. The insoluble matter is removed by filtration and the filtrate is concentrated under reduced pressure. The residue obtained is recrystallized from 40 ml ethyl acetate in the presence of 1.9 g 0.4 nm molecular sieve, which is removed by hot filtration. 3.10 g (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide are thus obtained.

m.p.: 116.7°C. $[\alpha]_D^{25}$: -90.1° (c = 1, acetone). Yield: 60.7%.

Example 4. Preparation of (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide

This examples illustrates a variant of the process of example 3, in which the intermediate 4-chlorobutanamide obtained in situ is not isolated.

84 g anhydrous sodium sulphate are added to a suspension of 69.25 g (0.5 mol) (S)-2-amino-butanamide hydrochloride in 600 ml methylene chloride at ambient temperature. The mixture is cooled to 0°C and 115 g ground potassium hydroxide followed by 8.1 g (0.025 mol) tetrabutylammonium bromide, dissolved in 100 ml methylene chloride, are added. A solution of 77.5 g 4-chlorobutyl chloride in 100 ml methylene chloride is added dropwise at 0°C, with vigorous stirring. After 5 hours of reaction, a further 29 g ground potassium hydroxide are added. Two hours later, the reaction mixture is filtered over Hyflo-cell (Hyflo-cell is a brand name) and the filtrate is evaporated under reduced pressure. The residue (93.5 g) is dispersed in 130 ml hot toluene for 45 minutes. The mixture is filtered and the filtrate is evaporated under reduced pressure. The residue (71.3 g) is dissolved hot in 380 ml ethyl acetate, to which 23 g 0.4 nm molecular sieve in powder form are added. This mixture is heated under reflux and filtered hot. After cooling the filtrate, the desired product crystallizes. 63 g (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide are thus obtained.

m.p.: 117°C. $[\alpha]_D^{25}$: -91.3°C (c = 1, acetone). Yield: 74.1%.

Pharmacological tests

Racemic alpha-ethyl-2-oxo-1-pyrrolidineacetamide (product A) and (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide (product B) according to the present invention were subjected to pharmacological tests.

I. Protection against hypoxia (mouse).

a. Principle (C. GIURGEA and F. MOURAVIEFF-LESUISSE; Proc.Xth Intern. Congr. of the Coll.Intern.Neuro-psych. - Pergamon Press, Oxford and New York, 1978, p.1623-1631).

The principle of this test lies in measuring the possibilities of survival of the organism subjected to an atmosphere in which the oxygen level is progressively decreased. Due to the particular sensitivity of the nervous system to this type of aggression, the results obtained in this test can be interpreted as a measure of the resistance of the nervous system. The products which increase the resistance of the animals are consequently suitable for the treatment and prevention of aggressions of the hypoxic type of the central nervous system.

b. Method.

The apparatus consists of an airtight transparent cage measuring 37 cm high, 39 cm deep and 97 cm wide. This 140 litre cage is provided with 60 transparent compartments of 6 x 10 x 10 cm for separate accommodation of 60 mice.

A fan ensures mixing of the atmosphere which circulates between the compartments through a grid floor. The cage is equipped with a device for introducing nitrogen at a constant flow rate, and with an opening communicating with the ambient air.

The animals are male mice (NMRI strain) of 20 to 22 g. These are fasted from the day before the test. The experiment is carried out on the following day, simultaneously on three groups of 20 mice; a control group receives water (25 ml/kg) orally, and the other two groups each receive, perorally, a product to be tested.

Twenty-five minutes after the administration, the animals are distributed randomly amongst the compartments so that none of the

three groups of animals is located in a preferential area of the cage. Thirty minutes after the administration, the cage is closed and nitrogen is admitted at a constant flow rate (7.750 litres industrial nitrogen per minute) for about 37 minutes; the atmosphere thus contains 3.7% oxygen.

The cage remains closed until the critical moment when no more than three survivors are observed amongst the twenty control animals. At this moment, the cage is opened and ambient air is admitted. A few moments later, the survivors in each group of animals are counted.

For each dose of product to be tested, the experiments are repeated once or twice, and the results are pooled to give a minimum of 40 (or 60) animals treated per dose and 40 (or 60) corresponding control animals.

For each dose of product tested, the number of surviving animals amongst those treated with the product is compared with the number of surviving animals amongst the control animals. The difference between these numbers expresses the protective activity of the product against hypoxia caused by lack of oxygen. The statistical significance (P) of this difference is evaluated by the Fischer-Yates test.

c. Results.

Table I below gives the results obtained for increasing doses of products Z and B.

TABLE I

Product tested	Oral dose in mmol/kg	Number of surviving animals		P
		controls	treated	
A	0.032	12/60	16/60	NS
	0.1	8/60	7/60	NS
	0.16	12/60	12/60	NS
	0.32	10/60	30/60	<0.001
B	0.016	5/40	11/40	NS
	0.032	8/40	17/40	<0.6

TABLE I (contd.)

Product tested	Oral dose in mmol/kg	Number of surviving animals		P
		controls	treated	
	0.1	6/40	19/40	<0.005
	0.16	6/40	19/40	<0.005
	0.32	5/40	17/40	<0.01

NS = difference not significant.

d. Conclusions.

In this test, the laevorotatory enantiomer according to the invention (product B) increases the survival of the animals deprived of oxygen from a dose of 0.032 mol/kg. The racemate (product A) exerts a similar activity only from 0.32 mmol/kg (first effective dose), and is thus 10 times less active than the laevorotatory enantiomer.

II. Protection from cerebral ischaemia (rats).

a. Principle (C.GIURGEA and F. MOURAVIEFF-LESUISSE; loc.cit. under I.a.).

Electroencephalographic controls have shown that ligature of the two common carotids in the rat causes a true cerebral ischaemia: the electroencephalogram trace flattens and even becomes isoelectric (electric silence).

b. Method

Male Wistar rats weighing 250 and 350 g are anaesthetized with pentobarbital administered intraperitoneally in a dose of 50 mg/kg (0.5 ml/100 g).

Immediately after the anaesthesia, either the product to be tested, dissolved in a isotonic solution of sodium chloride (treated animals), or only an isotonic solution of sodium chloride or placebo (control animals) is administered intraperitoneally in an amount of 0.5 ml/100 g to the animals.

About 20 minutes later, the two common carotids are exposed and about ten minutes later they are ligatured simultaneously. This operation is effected simultaneously on the control animals and on the treated animals.

One hour after administration of the product to be tested or of the placebo, the same dose of either the product to be tested (to the treated animals) or the placebo (to the control animals) is administered again intraperitoneally.

Five hours after the first administration, a dose either of the product to be tested (to the surviving treated animals) or of placebo (to the surviving control animals) is injected a third time.

Twenty-four hours after the first administration, the efficacy of the ligature is verified in all the animals under pentobarbital anaesthesia by section of the carotids downstream of the ligature.

The number of surviving animals is recorded amongst both the treated animals and the control animals. For each dose of product tested, the number of surviving animals amongst those treated with the product is compared with the number of surviving animals amongst the control animals. The difference expresses the protective activity of the compound against the lethality induced by the simultaneous ligature of the two carotids. The statistical significance (P) of this difference is evaluated by the Brandt-Snedecor test.

c. Results.

Table II below gives the results obtained for increasing doses of products A and B:

TABLE II

Product tested	ip dose in mmol/kg	Number of surviving animals		P
		controls	treated	
A	0.32	6/29	8/29	NS
	0.64	11/30	21/30	0.01
B	0.1	9/29	14/29	NS
	0.16	6/29	14/30	0.05

TABLE II (contd.)

Product tested	ip dose in mmol/kg	Number of surviving animals		P
		controls	treated	
	0.32	8/30	19/29	0.01

NS = difference not significant.

d. Conclusions.

Table II shows that the racemate (product A) is only active from a dose of 0.64 mmol/kg. In contrast, the laevorotatory enantiomer according to the invention (product B) protects the animals from the lethality induced by simultaneous ligature of the two carotids from 0.16 mmol/kg and thus proves to be 4 times more active than the racemate.

III. Toxicity

Table III below gives, for the products A and B, the LD 50 in mg/kg intravenously determined on the male mouse and the male rat:

TABLE III

Product tested	LD 50 in mg/kg	
	mouse	rat
A	1790	1500
B	1081	1038

It can be seen from this table that the laevorotatory enantiomer according to the invention (product B) is, like the racemate (product A) of very low toxicity and that the toxic dose is well above the active dose.

The compound according to the present invention can be administered either orally in the form of solid or liquid compositions, for example in the form of tablets, capsules, coated tablets, gelatin capsules, solutions or syrups, or parenterally in the form of injectable solutions or suspensions.

The pharmaceutical forms such as solutions or tablets are prepared by the methods conventionally used by pharmacists. The compound according to the invention is mixed with a solid or liquid, non-toxic, pharmaceutically acceptable carrier and if appropriate with a dispersing agent, a stabilizer and, if necessary, with colouring agents, sweeteners etc.

Solid pharmaceutical excipients for preparation of tablets or capsules are, for example, starch, talc, calcium carbonate, lactose, sucrose, magnesium stearate etc.

The percentage of active product in the pharmaceutical compositions can vary within very wide limits, depending on the mode of administration and the condition of the patient, and the dosage for humans can vary between 250 mg and 3 g per day under these conditions.

As a non-limiting example of a composition containing the compound according to the invention, there is given below an example of a capsule of 100 mg which can be used orally.

Product B	100 mg
Avicel*	217 mg
Mg stearate	5 mg

*Avicel is a brand name for a microcrystalline cellulose.

CLAIMS for the Contracting States: BE, CH, DE, FR, GB, IT, LI, LU, NL, SE.

1. (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide.

2. Process for the preparation of (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide, characterized in that (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetic acid is reacted, at a temperature between -10°C and 60°C, successively with (1) an alkyl haloformate of the formula HalCOOZ, in which Hal represents a halogen atom and Z an alkyl radical having 1 to 4 carbon atoms and with (2) ammonia.

3. Process for the preparation of (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide, characterized in that an (S)-2-amino-butanamide of the formula

$$X\text{-}CH_2CH_2\text{-}Y\text{-}NHCH(C_2H_5)CONH_2 \quad (A)$$

in which X represents a ZOOC- or $HalCH_2$- radical, Z being an alkyl radical having 1 to 4 carbon atoms and Hal a halogen atom, and

Y represents a $-CH_2-$ or -CO- radical,

with the proviso that Y is a $-CH_2-$ radical when X represents a ZOOC- radical and Y is -CO- radical when X represents a $HalCH_2$- radical, is cyclized in an inert solvent and in the presence of a basic catalyst selected from 2-hydroxypyridine or tetrabutylammonia bromide in the presence of potassium hydroxide.

4. Process according to claim 3, characterized in that the compound of formula A is an alkyl (S)-4-[[1-(aminocarbonyl)propyl]amino]-butyrate of the formula $ZOOCCH_2CH_2CH_2NHCH(C_2H_5)CONH_2$, and in that it is prepared by condensing (S)-2-amino-butanamide with an alkyl 4-halobutyrate of the formula $ZOOCCH_2CH_2CH_2Hal$, Z having the meaning given in claim 3 and Hal being a halogen atom.

5. Process according to claim 3, characterized in that the compound of formula A is an (S)-N-[1-(aminocarbonyl)-propyl]-4-halobutanamide of the formula $HalCH_2CH_2CH_2CONHCH(C_2H_5)CONH_2$, and in that it is prepared by

* C L M S *

condensing (S)-2-amino-butanamide with a 4-halobutyryl halide of the formula $HalCH_2CH_2CH_2COHal$, Hal being a halogen atom.

6. Therapeutic compositions containing a therapeutically effective amount of (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide in association with solid or liquid pharmaceutical excipients.

* C L M S *

CLAIMS for the Contracting State: AT

1. Process for the preparation of (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide, characterized in that

a) (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetic acid is reacted, at a temperature between -10°C and 60°C, successively with (1) an alkyl haloformate of the formula HalCOOZ, in which Hal represents a halogen atom and Z an alkyl radical having 1 to 4 carbon atoms and with (2) ammonia; or

b) an (S)-2-amino-butanamide of the formula

$$X\text{-}CH_2CH_2\text{-}Y\text{-}NHCH(C_2H_5)CONH_2 \quad (A)$$

in which

X represents a ZOOC- or $HalCH_2$- radical, Z being an alkyl radical having 1 to 4 carbon atoms and Hal a halogen atom, and

Y represents a $-CH_2-$ or -CO- radical,

with the proviso that Y is a $-CH_2-$ radical when X represents a ZOOC- radical and Y is -CO- radical when X represents a $HalCH_2$- radical, is cyclized in an inert solvent and in the presence of a basic catalyst selected from 2-hydroxypyridine or tetrabutylammonia bromide in the presence of potassium hydroxide.

2. Process according to claim 1, characterized in that the compound of formula A is an alkyl (S)-4-[[1-(aminocarbonyl)propyl]amino]-butyrate of the formula $ZOOCCH_2CH_2CH_2NHCH(C_2H_5)CONH_2$, and in that it is prepared by condensing (S)-2-amino-butanamide with an alkyl 4-halobutyrate of the formula $ZOOCCH_2CH_2CH_2Hal$, Z being an alkyl radical having 1 to 4 carbon atoms and Hal a halogen atom.

3. Process according to claim 1, characterized in that the compound of formula A is an (S)-N-[1-(aminocarbonyl)-propyl]-4-halobutanamide of the formula $HalCH_2CH_2CH_2CONHCH(C_2H_5)CONH_2$, and in that it is prepared by condensing (S)-2-amino-butanamide with a 4-halobutyryl halide of the formula $HalCH_2CH_2CH_2COHal$, Hal being a halogen atom.

* C L M S *