The present invention relates to a new compound, (R)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide, and 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.

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

(1) by a mnesic activity which is about 10 times higher and
(2) by a toxicity which is 3 times lower.

As a result of this unexpected combination of properties, the dextrorotatory enantiomer of alpha-ethyl-2-oxo-1-pyrrolidineacetamide is much more suitable for the treatment of cerebral insufficiencies, memory disorders and difficulties both in mental concentration and in learning and studying.

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

(R)-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) (R)-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 (R)-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 (R)-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 a 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 (R)-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 representa a ZOOC- radical and Y is a -CO- radical when X represents a $HalCH_2-$ radical, is cyclized.

The cyclization of (R)-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 (R)-4-[[1-(aminocarbonyl)propyl]-amino]butyrate of the 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 (R)-2-amino-butanamide with an alkyl 4-halobutyrate of the formula $ZOOCCH_2CH_2CH_2-Hal$, 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 (R)-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. This latter can be prepared by condensing (R)-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 (R)-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 acetone, 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 (R)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide according to the present invention (see example 4 below).

The (R)-2-amino-butanamide used as the starting material can be obtained from (R)-2-amino-butyric 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),484-7.

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

513 g (3 mol) racemic (±)-alpha-ethyl-2-oxo-1-pyrrolidineacetic acid are suspended in 1.26 litres anhydrous benzene in a 4 litre flask. A solution containing 181.5 g (1.5 mol) (S)-(-)-alpha-methyl-benzylamine and 151.8 g (1.5 mol) triethylamine in 2 litres anhydrous benzene is added to this suspension. The mixture in then heated under reflux until complete dissolution is achieved. It is cooled and allowed to crystallize for a few hours. The crystals are filtered off and washed twice with 400 ml benzene. 337 g (S)-alpha-methyl-benzylamine salt of (R)-alpha-ethyl-2-oxo-1-pyrrolidineacetic acid are thus obtained.
m.p.: 145-149°C. Yield: 76.9%.

This salt may be purified by heating under reflux in 3 litres benzene for 4

hours. It is cooled and filtered. 297.7 g of the desired salt are thus obtained.

m.p.: 149 - 152°C. Yield: 68%

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

297.7 g salt obtained in a) above are dissolved in 0.6 litre water. 147.3 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 with 7 portions of 150 ml benzene.

The aqueous phase in then acidified to a pH of 1.1 by addition of 188 ml 6 N hydrochloric acid.

The mixture is stirred for 45 minutes and the acid liberated is extracted with 5 portions of 200 ml methylene chloride. The organic phases are combined and dried over magnesium sulphate and the solvent is evaporated. 170.5 g (R)-alpha-ethyl-2-oxo-1-pyrrolidineacetic acid are obtained.

m.p.: 126°C. $[\alpha]_D^{20}$: +27.3° (c = 1, acetone). Yield: 98%.

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

17.1 g (0.1 mol) (R)-alpha-ethyl-2-oxo-1-pyrrolidineacetic acid are suspended in 100 ml methylene chloride, cooled to -13°C. 13.9 ml triethylamine are added dropwise. 9.56 ml ethyl chloroformate are added to the solution obtained without exceeding -13°C. The mixture is stirred for half and hour and a stream of ammonia is then passed through for about two 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 and the residue is recrystallized from ethyl acetate in the presence of 10 g molecular sieve (0.3 to 0.4 nm) in powder form.

11.2 g (R)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide are obtained.

m.p.: 115-117°C. $[\alpha]_D^{25}$: +90.7° (c = 1, acetone). Yield: 66%.

Analysis for $C_8H_{14}N_2O_2$ in %

calculated:	C 56.45	H 8.29	N 16.46
found:	56.38	8.36	16.43

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 (R)-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) (R)-2-amino-butanamide hydrochloride ($[\alpha]_D^{25}$: -26.1°; c = 1, methanol) in 400 ml toluene. The mixture is heated to 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 (R)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide by cyclization.

b) Preparation of (R)-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.

A small amount of 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 (R)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide are thus obtained.
m.p.: 117°C. $[\alpha]_D^{25}$: +90.0° (c = 1, acetone). Yield: 41.2%.

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

31.1 g (0.225 mol) ground potassium carbonate and 12.47 g (0.09 mol) (R)-2-amino-butanamide hydrochloride are mixed in 160 ml acetone. The reaction mixture is cooled to 0°C and a solution of 15.23 g (0.108 mol) 4-chlorobutyryl chloride in 25 ml acetone 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 100 ml anhydrous ether for 15 minutes at a temperature between 5 and 10°C. The precipitate is filtered off, washed with 2 portions of 30 ml ether and dried in vacuo. 16 g (R)-N-[1-(aminocarbonyl)propyl]-4-chlorobutanamide are thus obtained.

m.p.: 127 - 129°C. $[\alpha]_D^{25}$: +22.2° (c = 1, methanol). Yield: 86%.

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

6.2 g (0.03 mol) (R)-N-[1-(aminocarbonyl)propyl]-4-chlorobutanamide and 0.484 g (0.0015 mol) tetrabutylammonium bromide are mixed in 42 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 15 minutes and then allowed to return to ambient temperature. The insoluble matter is removed by filtration and the filtrated is concentrated under reduced pressure. The residue obtained is stirred in 25 ml carbon tetrachloride for 30 minutes and then filtered off and dried. The product is recrystallized from 45 ml ethyl acetate in the presence of 1.7 g 0.4 nm molecular sieve, which is removed by hot filtration. 3.85 g (R)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide are thus obtained.

m.p.: 116 - 118°C. $[\alpha]_D^{25}$: +89.8° (c = 1, acetone). Yield: 75.4%.

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

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

23 g pulverulent potassium hydroxide and 9 g Hyflo-cel (Hyflo-cel is a tradename) are added to a suspension of 13.86 g (0.1 mol) (R)-2-amino-butanamide hydrochloride in 60 ml methylene chloride at ambient temperature under a nitrogen atmosphere and with vigorous stirring.

The mixture is stirred for 1 hour and the temperature is then lowered to about 5°C. 6.52 g (0.02 mol) tetrabutylammonium bromide are then added, followed by a solution of 12.46 ml 4-chlorobutyryl chloride in 25 ml methylene chloride in the course of three hours. The mixture is then stirred at 5°C for one hour and subsequently allowed to return to ambient temperature, and stirring is continued for 23 hours.

The reaction mixture is filtered and the organic phase is evaporated under reduced pressure.

The residue is taken up in hot toluene (400% by volume/weight) and the mixture is filtered. The solid is dissolved hot in ethyl acetate (400% by volume/weight), to which is added a 0.4 nm molecular sieve in powder form (32% weight/weight). This mixture is heated under reflux and filtered hot. After the filtrate has been cooled, the desired product crystallizes. 9.18 g (R)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide are thus obtained. M.p.: 117°C. $[\alpha]_D^{25}$: +89.7° (c = 1, acetone). Yield: 54%.

Pharmacological tests.

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

I. Mnesic activity.

The activity on the memory is demonstrated by the test of antagonism of the amnesia-inducing effect of an electric shock (S.J. SARA and M. DAVID, Psychopharmacologia, 36, (1974), 59-66).

The principle of the test is as follows:

The reaction of withdrawal of a rat's paw when subjected to an increasing pressure is observed. The pressure at which the reaction takes place is referred to as the "reaction threshold". This threshold is expressed by the number of graduations read directly from the scale of the apparatus (analgesia-meter UGO BASILE Milan) and thus corresponds to the miniumum pressure which, applied to the paw of the animals, causes the withdrawal (learning session). Three measurements are performed at intervals of 30 minutes.

When tested 24 hours after the end of the learning, non-treated animals show a natural retention of the previous trial, which corresponds to a threshold of the order of 8 to 11 graduations. The amnesia-inducing effect is obtained by applying a transtemporal supramaximal electric shock (100 mA, 120 volts, 0.2 sec.) to rats 15 minutes after the end of the learning. This amnesia-inducing effect due to the electric shock manifests itself, when measuring the retention after 24 hours, in an increase in the avoidance threshold which thus corresponds to that of naive animals

(without a learning session), that is to say a threshold of between 14 and 19 graduations.

For each product to be tested, the minimum effective dose (in kg/kg) which re-establishes a normal threshold of between 8 and 11 graduations 24 hours after learning in animals subjected to electric shock is determined.

The products to be tested are administered subcutaneously, as a 10% solution or suspension, to groups of 10 rats (female Wistar rats weighing 150 g) 5 minutes after the end of the learning. At the same time, a control groups of 10 rats receives only a 0.9% aqueous sodium chloride solution.

In this test, the dextrorotatory enantiomer according to the invention (product B) proves to be 10 times more active than the racemate (product A) in protecting the animals from the amnesia-inducing effect of the electric shock.

Product tested	Effective dose (mg/kg)
A	1.70
B	0.17

II. Toxicity.

The following table gives, for products A and B, the LD 50 in mg/kg, determined on the male mouse and the male rat after intravenous administration:

Product tested	LD 50 in mg/kg	
	mouse	rat
A	1790	1500
B	5603	5000

It can be seen from this table that the dextrorotatory enantiomer according to the invention (product B) is three times less toxic than the racemate (product A).

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 coloring 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.

The dosage for humans may vary between 250 mg and 4 g per day.

As non-limiting examples of a composition containing the compound according to the invention there are given below an examples of a solution for oral use and of a no. 0 capsule which can be administered orally.

Ampoule of solution for oral use	
product B	2.5 g
sorbitol (70% in water)	3.0 g
glycerol	2.5 g
glycamil	0.025 g
methylparaben	0.0135 g
propylparabena	0.0015 g
sodium saccharinate	0.06 g
liquorice essence	0.05 g
purified water to make up to	10 ml

Capsule no. 0 of 500 mg	
product B	500 mg
Avicel(*)	50 mg
magnesium stearate	5 mg

(*) Avicel is a tradename for a microcrystalline cellulose

The use of a combination of therapies consisting of administration of a medicament which stimulates metabolism of the brain, for example piracetam (2-oxo-1-pyrrolidineacetamide) and a choline percursor, such as lecithin or a salt of choline, has recently been proposed for the treatment of memory deficiencies associated with ageing in humans.

According to United States Patent no. 4,385,053, these two substances (piracetam and a choline precursor) co-act synergistically by providing a significant improvement in memory capabilities in elderly persons suffering from memory deficiencies, and in particular senile dementia of the Alzheimer type.

The Applicant Company has now found a similar synergistic effect between the dextrorotatory enantiomer according to the invention and a choline precursor. The dextrorotatory enantiomer according to the invention can thus advantageously be used in association with a cholinergic precursor for the central nervous system for the treatment of memory deficiencies associated with ageing, senile dementia of the Alzheimer type etc. in order to obtain a beneficial clinical effect on the learning and memory retention faculties and on mental faculties in general.

Cholinergic precursor is to be understood as meaning not only choline or one of its salts but also any substance which releases choline in the organism, such as, for example, lecithin or phosphatidylcholine. In order to obtain the desired effect, it is essential for the said precursor to be capable of increasing both the level of choline in the blood and the availability of the said choline for acetylcholine synthesis in the brain.

When the dextrorotatory enantiomer according to the invention is used together with a cholinergic precursor, it may be administered before or after the administration of the said precursor. The two products can thus be administered simultaneously, separately or over a period of time, preferably simultaneously. In addition, the dextrorotatory enantiomer according to the invention may be administered by a route identical to or different from that used for administration of the cholinergic precursor. Oral administration of the two compounds in the pharmaceutical forms conventionally used (tablets, capsules, solutions) has proved to be particularly effective. It is also possible to administer the dextrorotatory enantiomer according to the invention and the cholinergic precursor in the form of a single dosage unit.

In this particular application, the dextrorotatory enantiomer according to the invention is preferably administered orally in a dose of 100 mg to 4 g per day, whereas the cholinergic precursor is preferably administered orally in a manner such patients are provided with a daily dose of choline of between 1 and 10 g. For example, 2 to 25 g per day phosphatidylcholine or 1 to 30 g per day choline salt are administered. In healthy volunteers, a synergism effects was found by quantitative analysis of the electroencephalogram after a single simultaneous oral administration of 1.5 g dextrorotatory enantiomer according to the invention and 25 g lecithin (18 g phosphatidylcholine).



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

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

2. Process for the preparation of (R)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide, characterized in that (R)-alpha-ethyl-2-oxo-1-pyrrolidineacetic acid is reacted, at a temperature between -10°C and -60°C, 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 (R)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide, characterized in that an (R)-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, 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, is cyclized in an inert solvent and in the presence of a basic catalyst selected from 2-hydroxypyridine or tetrabutylammonium bromide in the presence of potassium hydroxide.

4. Process according to claim 3, characterized in that the compound of formula A is an alkyl (R)-4-[[1-(aminocarbonyl)propyl]amino]-butyrate of the formula $ZOOCCH_2CH_2CH_2NHCH(C_2H_5)CONH_2$ and that it is prepared by condensing (R)-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 (R)-N-[1-(aminocarbonyl)propyl]-4-halobutanamide of the formula $HalCH_2CH_2CH_2NHCH(C_2H_5)CONH_2$ and that it is prepared by condensing

(R)-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 (R)-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 (R)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide, characterized in that:

a) (R)-alpha-ethyl-2-oxo-1-pyrrolidineacetic acid is reacted, at a temperature between -10°C and -60°C, 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 (R)-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, 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, is cyclized in an inert solvent and in the presence of a basic catalyst selected from 2-hydroxypyridine or tetrabutylammonium bromide in the presence of potassium hydroxide.

2. Process according to claim 1, characterized in that the compound of formula A is an alkyl (R)-4-[[1-(aminocarbonyl)propyl]amino]-butyrate of the formula $ZOOCCH_2CH_2CH_2NHCH(C_2H_5)CONH_2$ and that it is prepared by condensing (R)-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 (R)-N-[1-(aminocarbonyl)propyl]-4-halobutanamide of the formula $HalCH_2CH_2CH_2NHCH(C_2H_5)CONH_2$ and that it is prepared by condensing (R)-2-amino-butanamide with a 4-halobutyryl halide of the formula $HalCH_2CH_2CH_2COHal$, Hal being a halogen atom.