

PATENT SPECIFICATION

(11) 1 539 817

1 539 817

- (21) Application No. 43934/76 (22) Filed 22 Oct. 1976
 (23) Complete Specification filed 20 Oct. 1977
 (44) Complete Specification published 7 Feb. 1979
 (51) INT CL² C07D 207/26; A61K 31/40, 31/55; C07D 223/10
 (52) Index at acceptance

C2C 1173 1341 1731 215 220 225 226 22Y 247 250 251
 25Y 281 282 30Y 342 34Y 351 352 366 368 575
 584 594 625 628 62X 63X 658 65X 802 80Y KM KZ

(72) Inventors LUDOVIC RODRIGUEZ and LUCIEN MARCHAL

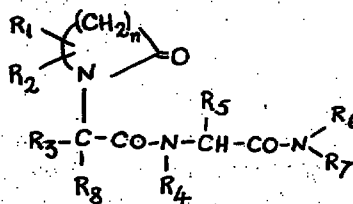


(54) N-SUBSTITUTED LACTAMS

(71) We, UCB, of 4, Chaussée de Charleroi, Saint-Gilles-lez-Bruxelles, Belgium, a Body Corporate organised under the laws of Belgium, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention is concerned with new N-substituted lactams, with the preparation thereof, with pharmaceutical compositions containing them and also with the therapeutic use thereof.

These new compounds according to the present invention have the following general formula:—



wherein R₁, R₂, R₃, R₄, R₅, R₆ and R₇, which may be the same or different, are hydrogen atoms, alkyl radicals containing up to 4 carbon atoms or phenyl radicals; R₈ is a hydrogen atom or R₈ and R₃ together form an ethylene or trimethylene radical, and n is 3, 4 or 5.

Since n is 3, 4 or 5, the compounds of general formula (I) are, respectively, derivatives of 2-pyrrolidinone, 2-piperidinone or hexahydro-2H-azepine-2-one.

Preferred compounds are those of general formula (I), wherein at least one of the symbols R₁, R₂, R₃, R₄, R₅ and R₇ represents an alkyl radical containing up to 4 carbon atoms.

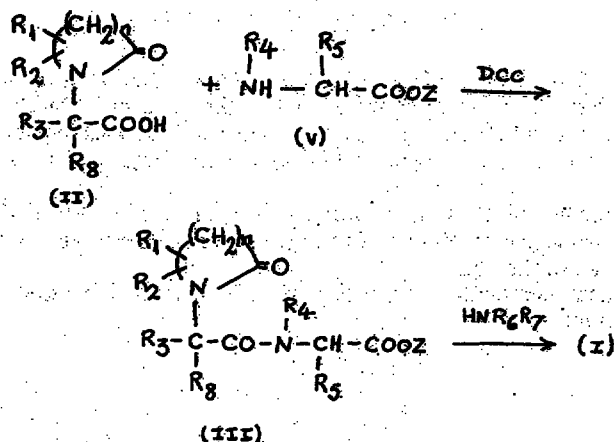
The compounds of general formula (I) have valuable pharmaceutical properties. In particular, they have a beneficial activity on mnemonic processes and a protective activity against aggressions of the hypoxic type. Therefore, their first use is in the field of geropsychiatry, in which disorders of the memory occur due not only to senile cellular alterations but also to a decrease in the supply of oxygen to the brain as the result of isolated or repeated vascular accidents (see, for example, V. C. Hachinski, *Lancet* II, 207/1974). Furthermore, the compounds of general formula (I) are useful in numerous other clinical fields, such as the prevention and treatment of cerebrovascular or cardiovascular injuries, post-traumatic or toxic comas, memory disorders and difficulties in connection with mental concentration. Compounds are already known which possess these properties, particularly, piracetam (2-oxo-1-pyrrolidineacetamide). However, this compound has the disadvantage of being effective only in large doses. Therefore, one object of the present invention is to provide compounds having the same properties as piracetam but which are effective in smaller doses.

In addition, the compounds (I) have an interesting activity as platelet anti-aggregants and can, therefore, also be used in the treatment of myocardial infarcts resulting from platelet hyperaggregability or hyperadhesivity, in extracorporeal circulations, in the case of vascular prostheses or in the treatment of thromboembolic diseases and hyperaggregability in coronary patients.

Consequently, the present invention also provides pharmaceutical compositions

comprising at least one compound of general formula (I), in admixture with a solid or liquid pharmaceutical diluent or carrier.

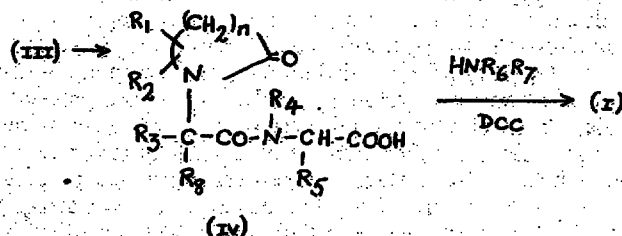
The compounds of general formula (I) can be prepared in accordance with the equation given hereinafter, which only entails known reactions. As a general rule, a lactam-N-acetic acid of general formula (II) is condensed in an inert medium, such as chloroform or methylene chloride, with an amino-acid ester of general formula (V) in the presence of a coupling agent, for example, dicyclohexylcarbodiimide (DCC), the ester of general formula (III) thus obtained then being reacted with a nitrogen compound of the general formula HNR_6R_7 , for several hours at a temperature which is generally between ambient temperature and the reflux temperature of the reaction mixture, optionally in the presence of a catalyst, such as sodium methoxide, thus finally giving compounds of general formula (I):



In the above equation, R_1 to R_5 and n have the same meanings as above and Z is an alkyl radical containing up to 4 carbon atoms or a benzyl radical.

Certain modifications of the reaction conditions may be found necessary in certain cases, for the sake of greater ease of carrying out. Thus, when the amine HNR_6R_7 is methylamine, the reaction is carried out at a low temperature ($-20^\circ\text{C}.$) because of the volatility thereof, thus making it unnecessary to work in an autoclave. Such modifications are within the scope of the expert.

As an alternative, an ester of general formula (III) may be converted into the corresponding acid of general formula (IV) by cautious hydrolysis with a dilute aqueous alcoholic solution of sodium hydroxide. In the particular case in which Z is a benzyl radical, the ester of general formula (III) can be converted into the acid of general formula (IV) by catalytic hydrogenation in the presence of palladium supported on carbon (Pd/C). The acid of general formula (IV) is then condensed with a nitrogen compound of the general formula HNR_6R_7 , in the presence of a coupling agent, for example DCC, in order to obtain compounds of general formula (I), in accordance with the following equation:

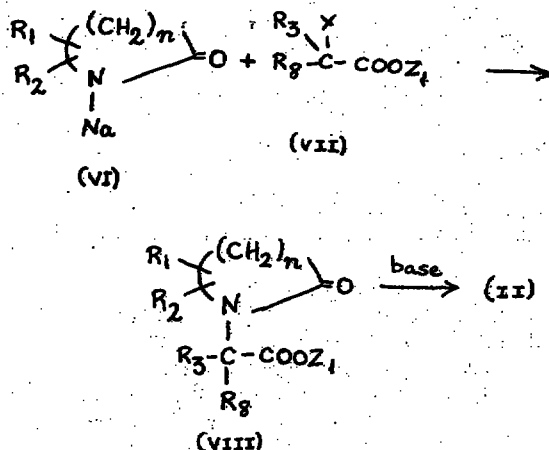


in which R_1 and R_5 and n have the same meanings as above.

In the reactions above, the coupling agents are those conventionally used in the formation of peptide bonds. Among these, use may be made of those mentioned in the article by Y. S. Klausner and M. Bodansky in *Synthesis*, 1972, 453—463, more particularly of dicyclohexylcarbodiimide and 1-ethoxy-carbonyl-2-ethoxy-1,2-dihydroquinoline.

The lactam-N-acetic acids of general formula (II), which are starting materials, can be obtained, for example, by condensing a sodium salt of an R_1 , R_2 -substituted

lactam of general formula (VI) with a lower alkyl ester of an R_3 , R_8 -substituted chloro- or bromoacetic acid of general formula (VII), the ester thus obtained of general formula (VIII) then being hydrolysed with a base, such as sodium hydroxide, to give a lactam-N-acetic acid of general formula (II), in accordance with the following equation:



in which R_1 , R_2 , R_3 , R_8 and n have the same meanings as above, Z_1 is an alkyl radical containing up to 4 carbon atoms or a benzyl radical and X is a chlorine or bromine atom.

The last-mentioned process has already been described in literature (see, for example, L. Fontanella *et al.*, Pharm. Ed. Sci. 28, (6), 448/1973).

The following Examples are given for the purpose of illustrating the present invention:—

1. Synthesis of esters of general formula (III).

a) Ethyl N-(2-oxo-1-pyrrolidineacetyl)-glycinate.

167.4 g. (1.2 mole) ethyl glycinate hydrochloride are suspended in 4 litres of methylene chloride, the hydrochloric acid being neutralised by adding 168 ml. (1.2 mole) triethylamine. The reaction mixture is cooled to about 0°C. and a suspension of 171.6 g. (1.2 mole) 2-oxo-1-pyrrolidineacetic acid in 1500 ml. methylene chloride is added. Without allowing the temperature to rise above 5°C., a solution of 272 g. (1.4 mole) DCC in 300 ml. methylene chloride is added dropwise to this mixture. Stirring is maintained for 2 hours at the same temperature and the reaction mixture is then allowed to return to ambient temperature, while stirring for 16 hours. 80 ml. acetic acid are then added, the reaction mixture is cooled to 0°C. and the precipitate is filtered off. The filtrate is evaporated to dryness and the residue redissolved in ethyl acetate, followed by filtering to remove insoluble matter. The filtrate is treated with highly-absorbing active charcoal (Norite), again filtered and the filtrate is distilled at 190°C. at a pressure of 0.01 mm.Hg. There are thus obtained 256 g. of a syrup which is stirred with 1500 ml. anhydrous diethyl ether and which is crystallised by cooling in an ice bath. 177.5 g. ethyl N-(2-oxo-1-pyrrolidineacetyl)-glycinate are thus obtained (yield: 64% of theory); m.p. 63–64°C. The melting point of a sample recrystallised from a 1:2 v/v mixture of ethyl acetate and anhydrous diethyl ether is 64–65°C.

Analysis

$C_{10}H_{16}N_2O_4$ (M.W. 228)

calculated: C 52.63%; H 7.01%; N 12.28%

found : 52.70%; 6.98%; 12.20%

IR spectrum (in KBr) in cm^{-1} : 3250 (NH amide); 1746 (CO ester); 1675 (CO lactam); 1655 (CO amide); 1540 (NH amide); 1191 (ester).

The following compounds of general formula (III) are also prepared in the same manner. For these intermediate compounds, the IR spectrum is close to that indicated above. The melting point or boiling point, as the case may be, and the yield are indicated for each compound:

b) Benzyl N-(2-oxo-1-pyrrolidineacetyl)-glycinate.

m.p. 92°C.; yield: 58% of theory. (Formula III: $n=3$; Z =benzyl).

- c) *Ethyl N-(α -ethyl-5,5-dimethyl-2-oxo-1-pyrrolidineacetyl)-glycinate.*
m.p. 61°C.; yield: 68% of theory. (Formula III: $n=3$; $R_1=R_2=5$ -methyl;
 $R_3=Z$ =ethyl).
- d) *Ethyl N-(α ,5,5-trimethyl-2-oxo-pyrrolidineacetyl)-glycinate.*
m.p. 88°C.; yield: 55% of theory. (Formula III: $n=3$; $R_1=R_2=5$ -methyl;
 R_3 =methyl; Z =ethyl).
- e) *Ethyl N-(α -ethyl-2-oxo-1-pyrrolidineacetyl)-glycinate.*
m.p. 70°C.; yield: 63% of theory. (Formula III: $n=3$; $R_3=Z$ =ethyl).
- f) *Ethyl N-(α -methyl-2-oxo-1-pyrrolidineacetyl)-glycinate.*
m.p. 48°C.; yield: 66% of theory. (Formula III: $n=3$; R_3 =methyl; Z =ethyl).
- g) *Ethyl 2-[1-(2-oxo-pyrrolidino)-cyclopropanecarboxamido]-acetate.*
m.p. 171°C.; yield: 51% of theory. (Formula III: $n=3$; R_3+R_8 =ethylene;
 Z =ethyl).
- h) *Ethyl N-(2-oxo-1-pyrrolidineacetyl)-sarcosinate.*
b.p. 160°C./0.01 mm. Hg; yield: 67% of theory. (Formula III: $n=3$; R_4 =methyl;
 Z =ethyl).
- i) *Benzyl N-(2-oxo-1-pyrrolidineacetyl)-sarcosinate.*
syrup; yield: 87% of theory; IR spectrum (film) in cm^{-1} : 1745, 1690, 1660, 1190,
742, 698. (Formula III: $n=3$; R_4 =methyl; Z =benzyl).
- j) *N-(2-Oxo-1-pyrrolidineacetyl)-alanine methyl ester.*
syrup; yield: 79% of theory; IR spectrum (film) in cm^{-1} : 3280, 1745, 1690,
1665, 1540 (NH), 1215. (Formula III: $n=3$; $R_3=Z$ =methyl).
- k) *Ethyl N-(2-oxo-1-pyrrolidineacetyl)-2-phenylglycinate.*
m.p. 89°C.; yield: 80% of theory. (Formula III: $n=3$; R_3 =phenyl; Z =ethyl).
- l) *Ethyl N-(2-oxo-4-phenyl-1-pyrrolidineacetyl)-glycinate.*
m.p. 79°C.; yield: 77% of theory. (Formula III: $n=3$; $R_1=4$ -phenyl; Z =ethyl).
- m) *Ethyl N-(2-oxo- α -phenyl-1-pyrrolidineacetyl)-glycinate.*
m.p. 115°C.; yield: 66% of theory. (Formula III: $n=3$; R_3 =phenyl; Z =ethyl).
- n) *Ethyl N-(5-methyl-2-oxo-1-pyrrolidineacetyl)-glycinate.*
syrup; yield: 100% of theory. IR spectrum (in KBr) in cm^{-1} : 3300, 1740,
1680—1660, 1530, 1200. (Formula III: $n=3$; $R_1=5$ -methyl; Z =ethyl).
- o) *Ethyl N-(hexahydro-2-oxo-1H-azepine-1-acetyl)-glycinate.*
m.p. 104°C.; yield: 61% of theory. (Formula III: $n=5$; Z =ethyl).
- p) *Ethyl N-(α -n-butyl-2-oxo-1-pyrrolidineacetyl)-glycinate.*
m.p. 79°C.; yield: 75% of theory. (Formula III: $n=3$; $R_3=n$ -butyl; Z =ethyl).
- q) *Ethyl N-(3-n-butyl-2-oxo-1-pyrrolidineacetyl)-glycinate.*
syrup; yield: 100% of theory; IR spectrum (film) in cm^{-1} : 3300, 2935 (CH_2),
1750, 1670, 1535, 1200. (Formula III: $n=3$; $R_1=3$ -n-butyl; Z =ethyl).

2. Synthesis of acids of general formula (IV).

a) *N-(2-Oxo-1-pyrrolidineacetyl)-glycine.*

2.9 g. (0.01 mole) benzyl N-(2-oxo-1-pyrrolidineacetyl)-glycinate (compound 1.b) above) are dissolved in 50 ml. acetic acid and hydrogenated in the presence of palladium/carbon (Pd/C) at ambient temperature, under a hydrogen pressure of 4 kg. The catalyst is filtered off, the filtrate is evaporated to dryness and the syrup obtained is triturated with anhydrous diethyl ether, a white powder being obtained; 2 g. N-(2-oxo-1-pyrrolidineacetyl)-glycine are thus isolated; m.p. 149—150°C. Yield: 100% of theory.

Analysis:

$\text{C}_8\text{H}_{12}\text{N}_2\text{O}_4$ (M.W. 200)

calculated: C 48.0%; H 6.0%; N 14.0%

found: 47.6%; 6.21%; 13.88%

IR spectrum (in KBr) in cm^{-1} : 3345 (NH), 1710 (CO), 1675 (CO), 1620 (CO), 1512 (NH), 1220 (C—OH).

N-(2-oxo-1-pyrrolidineacetyl)-sarcosine is prepared in the same manner; m.p. 178°C.; yield: 67% of theory. (Formula IV: $n=3$; R_4 =methyl).

b) 2-[1-(2-Oxo-pyrrolidino)-cyclopropanecarboxamido]-acetic acid.

(Formula IV: $n=3$; R_3+R_8 =ethylene).

A solution of 3.5 g. sodium hydroxide in 80 ml. water is added to a solution of 20.4 g. (0.08 mole) ethyl 2-[1-(2-oxo-pyrrolidino)-cyclopropanecarboxamido]-acetate in 80 ml. methanol. The resulting solution is heated at 40°C. for 5 hours. The methanol is evaporated and the residue is taken up in water and acidified with con-

centrated hydrochloric acid to a pH of 1. The mixture is evaporated to dryness and the residue is recrystallised from water, 13 g. 2-[1-(2-oxo-pyrrolidino)-cyclopropane-carboxamido]-acetic acid being obtained (yield: 69% of theory); m.p. 211°C.

Analysis:

$C_{10}H_{14}N_2O_4$
calculated: C 53.14%; H 6.24%; N 12.39%
found : 53.20%; 6.03%; 12.36%

IR spectrum (in KBr) in cm^{-1} : 3460, 3300, 2700—2500, 1735 (CO), 1670 (CO), 1645 (CO), 1530 (NH), 1202.

3. Synthesis of lactams of general formula (I).

a) 2-(2-Oxo-1-pyrrolidineacetamido)-acetamide (compound A).

(Formula I: $n=3$; all R symbols are hydrogen).

17.1 g. (0.075 mole) ethyl N-(2-oxo-1-pyrrolidineacetyl)-glycinate are dissolved in 350 ml. methanol. The solution is saturated with a current of ammonia (about 2 hours), stirring being maintained for 3 hours at ambient temperature. After the reaction mixture has been evaporated to dryness *in vacuo*, the residue crystallises quickly, 14.9 g. 2-(2-oxo-1-pyrrolidineacetamido)-acetamide being obtained (yield: 100% of theory); m.p. 147—148°C.

Analysis:

$C_8H_{13}N_3O_5$ (M.W. 199)
calculated: C 48.24%; H 6.53%; N 21.10%
found : 48.11%; 6.49%; 21.24%

IR spectrum (in KBr) in cm^{-1} : 3360 and 3220 (NH₂, NH), 1703 (CO-pyrrolidone), 1668 and 1652 (CO amide), 1565 (NH).

b) N-n-Butyl-2-(2-oxo-1-pyrrolidineacetamido)-acetamide. (Compound B).

(Formula I): $n=3$; $R_6=n$ -butyl).

9.12 g. (0.04 mole) ethyl N-(2-oxo-1-pyrrolidineacetyl)-glycinate are heated for 12 hours under reflux with 7.7 g. (0.1 mole) *n*-butylamine. The reaction mixture is evaporated to dryness and the crystallised residue is washed with diethyl ether. The residual product is dried, after filtration and washing with diethyl ether. 9.9 g. N-n-Butyl-2-(2-oxo-1-pyrrolidineacetamido)-acetamide are thus obtained (yield: 97% of theory); m.p. 105—106°C.

Analysis:

$C_{12}H_{21}N_3O_5$ (M.W. 255)
calculated: C 56.51%; H 8.23%; N 16.47%
found : 56.66%; 8.34%; 16.36%

IR spectrum (in KBr) in cm^{-1} : 3285 (NH), 1680 (CO lactam), 1670 and 1650 (CO amide), 1550 (NH).

c) N-Methyl-2-(2-oxo-1-pyrrolidineacetamido)-acetamide. (Compound C).

(Formula I): $n=3$, $R_6=methyl$.

31 g. (1 mole) methylamine are added to 18.24 g. (0.08 mole) ethyl N-(2-oxo-1-pyrrolidineacetyl)-glycinate and the reaction mixture is kept at -20°C. for 8 hours, while stirring. It is then evaporated and the residue is recrystallised from absolute ethanol, 15.7 g. N-methyl-2-(2-oxo-1-pyrrolidineacetamido)-acetamide being obtained (yield: 92% of theory); m.p. 139—140°C.

Analysis:

$C_9H_{15}N_3O_5$ (M.W. 213)
calculated: C 50.74%; H 7.04%; N 19.72%
found : 50.80%; 7.10%; 19.60%

IR spectrum (in KBr) in cm^{-1} : 3250 (NH), 1680 and 1660 (CO), 1550 (NH).

d) 2-(2-Oxo-1-pyrrolidineacetamido)-N-phenylacetamide (Compound D).

(Formula I): $n=3$, $R_6=phenyl$.

23.3 g. (0.102 mole) ethyl N-(2-oxo-1-pyrrolidineacetyl)-glycinate are mixed in a round bottomed flask with 51 ml. (0.51 mole) aniline and 10.5 ml. methanol. 0.39 g. (0.017 mole) Sodium is added portionwise to this solution. The temperature of the

reaction mixture is brought to about 50°C. in order to dissolve the sodium completely and reflux heating is then maintained for about 17 hours. The methanol is then removed and 150 ml. anhydrous toluene are added. The precipitate formed is filtered off, washed with diethyl ether and recrystallised from absolute ethanol, 7.4 g. 2-(2-oxo-1-pyrrolidineacetamido)-N-phenylacetamide being obtained (yield: 26.5% of theory); m.p. 200—201°C.

Analysis:



calculated: C 61.14%; H 6.18%; N 15.28%

found : 61.12%; 6.22%; 15.30%

IR spectrum (in KBr) in cm^{-1} : 3320 (NH), 1690, 1670 and 1653 (CO), 1555 (NH), 750 and 692 (phenyl).

e) 2-(N-Methyl-2-oxo-1-pyrrolidineacetamido)-N-phenylacetamide. (Compound E).

(Formula (I): $n=3$; R_2 =methyl; R_3 =phenyl).

A solution of 3.8 g. (0.04 mole) aniline in 40 ml. methylene chloride is added to a suspension of 8.6 g. (0.04 mole) N-(2-oxo-1-pyrrolidineacetyl)-sarcosine in 60 ml. methylene chloride. The reaction mixture is cooled to 0°C. and 9.2 g. (0.044 mole) DCC, dissolved in 20 ml. methylene chloride, are added dropwise. Stirring is maintained for 2 hours at a temperature between 0 and 5°C. and then for 18 hours at ambient temperature. The dicyclohexylurea formed is then filtered off and 6 ml. acetic acid are added to the filtrate, which is evaporated to dryness *in vacuo*. The residue is taken up in ethyl acetate, insoluble matter (dicyclohexylurea) is filtered off and the filtrate is evaporated to dryness. A syrup is obtained which is stirred with toluene in order to crystallise it. Silica column chromatography can also be used (eluent: methanol/chloroform (1:9 v/v)). The product is filtered off, washed with diethyl ether and dried, 9.5 g. 2-(N-methyl-2-oxo-1-pyrrolidineacetamido)-N-phenylacetamide thus being obtained (yield: 82% of theory); m.p. 145—146°C.

Analysis:



calculated: C 62.33%; H 6.57%; N 14.54%

found : 62.30%; 6.50%; 14.48%

IR spectrum (in KBr) in cm^{-1} : 3320 and 3300 (NH), 1680, 1655 and 1610 (CO), 1550 (NH), 757 and 692 (phenyl).

The following compounds of general formula (I) are also prepared in the manner described above:

Compound F

N-isopropyl-2-(2-oxo-1-pyrrolidineacetamido)-acetamide.

m.p. 140°C.; yield: 80% of theory. (Formula I: $n=3$; R_2 =isopropyl).

Compound G

2-(α -ethyl-5,5-dimethyl-2-oxo-1-pyrrolidineacetamido)-acetamide.

m.p. 151°C.; yield: 95% of theory. (Formula I: $n=3$; $R_1=R_2=5$ -methyl; R_3 =ethyl).

Compound H

2-(α ,5,5-trimethyl-2-oxo-1-pyrrolidineacetamido)-acetamide.

m.p. 202°C.; yield: 80% of theory. (Formula I: $n=3$; $R_1=R_2=5$ -methyl; R_3 =methyl).

Compound I

2-(α -ethyl-5,5-dimethyl-2-oxo-1-pyrrolidineacetamido)-N-propylacetamide.

m.p. 177°C.; yield: 90% of theory. (Formula I: $n=3$; $R_1=R_2=5$ -methyl; R_3 =ethyl; R_4 =propyl).

Compound J

2-(α -methyl-2-oxo-1-pyrrolidineacetamido)-acetamide.

m.p. 119°C.; yield: 85% of theory. (Formula I: $n=3$; R_2 =methyl).

Compound K

2-(α -ethyl-2-oxo-1-pyrrolidineacetamido)-acetamide.

m.p. 122°C.; yield: 70% of theory. (Formula I: $n=3$; R_3 =ethyl).

Compound L

2-[1-(2-oxo-pyrrolidino)-cyclopropanecarboxamido]-acetamide.

m.p. 180°C.; yield: 78% of theory. (Formula I: $n=3$; R_3+R_4 =ethylene).

Compound M

N,N-dimethyl-2-(2-oxo-1-pyrrolidineacetamido)-acetamide.

m.p. 121°C.; yield: 40% of theory. (Formula I: $n = 3$; $R_6 = R_7 = \text{methyl}$).

Compound N

2-(N-methyl-2-oxo-1-pyrrolidineacetamido)-acetamide.

m.p. 159°C.; yield: 40% of theory. (Formula I: $n = 3$; $R_4 = \text{methyl}$).

5

Compound O

N-methyl-2-(N-methyl-2-oxo-1-pyrrolidineacetamido)-acetamide.

m.p. 111°C.; yield: 61% of theory. (Formula I: $n = 3$; $R_4 = R_6 = \text{methyl}$).

Compound P

N,N-dimethyl-2-(N-methyl-2-oxo-1-pyrrolidineacetamido)-acetamide.

10

m.p. 78°C.; yield: 10% of theory. (Formula I: $n = 3$; $R_4 = R_6 = R_7 = \text{methyl}$).

Compound Q

2-methyl-2-(2-oxo-1-pyrrolidineacetamido)-acetamide.

m.p. 173°C.; yield: 50% of theory. (Formula I: $n = 3$; $R_5 = \text{methyl}$).

Compound R

15

2-(2-oxo-1-pyrrolidineacetamido)-2-phenylacetamide.

m.p. 195°C.; yield: 53% of theory. (Formula I: $n = 3$; $R_5 = \text{phenyl}$).

Compound S

2-(2-oxo-4-phenyl-1-pyrrolidineacetamido)-acetamide.

20

m.p. 160°C.; yield: 90% of theory. (Formula I: $n = 3$; $R_1 = 4\text{-phenyl}$).

Compound T

2-(5-methyl-2-oxo-1-pyrrolidineacetamido)-acetamide.

m.p. 131°C.; yield: 33% of theory. (Formula I: $n = 3$; $R_1 = 5\text{-methyl}$).

Compound U

2-(2-oxo- α -phenyl-1-pyrrolidineacetamido)-acetamide.

25

m.p. 174°C.; yield: 85% of theory. (Formula I: $n = 3$; $R_8 = \text{phenyl}$).

Compound V

2-(hexahydro-2-oxo-1H-azepine-1-acetamido)-acetamide.

m.p. 128°C.; yield: 80% of theory. (Formula I: $n = 5$).

Compound W

30

2-(α -*n*-butyl-2-oxo-1-pyrrolidineacetamido)-acetamide.

m.p. 93°C.; yield: 70% of theory. (Formula I: $n = 3$; $R_8 = n\text{-butyl}$).

Compound X

2-(3-*n*-butyl-2-oxo-1-pyrrolidineacetamido)-acetamide.

m.p. 152°C.; yield: 75% of theory. (Formula I: $n = 3$; $R_1 = 3\text{-}n\text{-butyl}$).

35

Compound Y

N-*tert*-butyl-2-(2-oxo-1-pyrrolidineacetamido)-acetamide.

m.p. 149–150°C.; yield: 25% of theory. (Formula I: $n = 3$; $R_8 = \text{tert-butyl}$).

Pharmacological results.

40

Certain of the compounds prepared above have been tested pharmacologically, the results obtained being given below:

I. Action on mnemonic processes:

45

A) The action on mnemonic processes is first shown by the ability of the compounds to improve a type of memory retention in rats. The principle of the active avoidance test (see M. Greindl and S. Preat, Arch. Int. Pharmacodyn. Therap., 223, (1), 168–171/1976) developed in our laboratories and used for this purpose may be described as follows: the reaction of withdrawal of a rat's paw when subjected to an increasing and measured pressure is observed. The pressure at which the withdrawal reaction takes place is called the reaction threshold. This threshold is expressed by the number of graduations of the scale of the apparatus used (Analgesy meter Ugo Basile, Milan) and thus corresponds to the minimum pressure which brings about withdrawal when applied to the animal's paw. It is read directly from the scale of the apparatus used.

50

When tested 24 hours later, the control animals show no apparent retention of the previous test; avoidance takes place at a stimulation intensity comparable to that applied the day before. Inversely, animals treated with a substance having a positive effect on the mnemonic processes (for example, piracetam) show a significant degree of retention: the stimulus at which the rats react by a reflex of avoidance is statistically lower than that of the control animals. A minimum of 20 rats are used per test (10 treated rats and 10 control rats) and the active dose is defined as the minimum dose which reduces the stimulus to below 11 graduations.

60

Subcutaneous administration of compounds of general formula (I), namely, compounds A, G, H, I, J, K, L, N, O, P, Q, R, V, W, give, under these conditions, the effects indicated in Table I below, this Table I showing that, in this test, these

60

(18)

8

1,539,817

8

compounds all exhibit an activity which is superior to that of piracetam, the action of which on mnemonic processes is well known:

TABLE I

compound	Active dose mg/kg	Active dose mM/kg
A	0.40	0.002
G	0.51	0.002
H	0.0024	0.00001
I	5.94	0.02
J	0.21	0.001
K	4.54	0.02
L	0.23	0.001
N	2.13	0.01
O	2.27	0.01
P	2.41	0.01
Q	2.13	0.01
R	2.75	0.01
V	2.27	0.01
W	2.55	0.01
Piracetam	3.50	0.025

B) The action on mnemonic processes is also shown by the reduction of the spinal fixation time, a test which has been described in literature (see C. Giurgea and F. Mouravieff-LeSuisse, Arch. Int. Pharmacodyn. 191, 2, 279/1971) as an elementary model and which provides pharmacological reactivity in good correlation with clinical physiopathology. In the rat, after unilateral section of the cerebellum, there is a postural asymmetry of the hind paws. This asymmetry may persist, even after spinal section, if the animal has passed a sufficient period of time in this position. This time, which is called the spinal fixation time, is 45 minutes under the experimental conditions applied here.

On the other hand, if spinal section is performed before the expiry of this period of time, for example 35 minutes after the onset of the asymmetry, the latter disappears.

No animal treated with placebos retains the asymmetry under these conditions.

Inversely, any product which allows the rats to retain the asymmetry (thus effecting spinal fixation) when the spinal section is performed after 35 minutes, is considered to be active.

Intraperitoneal administration of compound A gives rise to the effects described in Table II. By "number of animals" is to be understood the number of animals which responded positively to the test, in relation to the number of animals tested at the indicated dose:

TABLE II

Compound	Active dose mg/kg	Active dose mM/kg	Number of animals
A	6.4	0.032	3/7
	20.0	0.1	4/5
Piracetam	30	0.2	4/9 *

* Giurgea *et al.*, *loc. cit.*

II. Protection against aggressions of the hypoxic type.

Protection against aggressions of the hypoxic type is shown by a reduction of the lethality induced by a curariser, the duration of action of which is short, namely oxydipentonium chloride (Brevatonal). At the doses used, this curariser brings about a respiratory depression which, in turn, brings about a hypoxihypercapnic syndrome. A compound capable of protecting the brain during this brief period of hypoxia ensures survival. The compounds are administered to groups of 10 mice one hour before the injection of the curariser; in a parallel test, a control group of 10 mice are given physiological salt solution before the curariser. This test has also been developed in our laboratories (see, for the principle of this test, S. Levis *et al.*, Arch. Int. Pharmacodyn. Therap., 93, 1, 46—54/1953).

Intraperitoneal administration of compounds of general formula (I), namely, products A, B, F, G, H, I, J, K, L, give the results shown in Table III:

TABLE III

Product	Dose mg/kg	Dose mM/kg	Proportion of survivors	
			Animals treated	Control Animals
A	64	(0.32)	7/10	1/10
B	2.6	(0.01)	6/10	1/10
	8.2	(0.032)	8/10	1/10
F	24	(0.1)	4/10	0/10
G	2.6	(0.01)	4/10	1/10
	25.5	(0.1)	6/10	1/10
H	2.4	(0.01)	6/10	2/10
	24	(0.1)	10/10	1/10
I	30	(0.1)	5/10	1/10
	95	(0.32)	8/10	1/10
J	21	(0.1)	6/10	1/10
	68	(0.32)	10/10	1/10
K	23	(0.1)	7/10	1/10
L	23	(0.1)	8/10	1/10
Piracetam	45	(0.32)	1/10	0/10
	142	(1.0)	4/10	2/10
	454	(3.2)	8/10	1/10

Therefore, the compounds tested possess, for an equal dose, a far greater activity than piracetam.

III. Cardiac activity.

We have also observed that the compounds of general formula (I) possess a significant cardiac activity. This has been shown by the method employing the papillary muscle isolated from the rabbit heart, according to the method of H. G. Schoepke and F. E. Shideman, *J. Pharmacol. Exptl. Therap.* 133, 171/1961.

The reactivity of various compounds of general formula (I) after each experiment is checked against theophylline. Table IV gives some of the results observed, expressed as a percentage increase of the tension measured:

TABLE IV

Compound	Dose (μ g/ml)	Results (%)
E	100	22
H	10	10
K	100	44
M	10	10
X	100	24
Theophylline	100	38

In addition, product H showed, in the same test, a protective action against anoxia.

IV. Toxicity.

The tested compound have a remarkably low toxicity. Table V gives the toxicities, after intravenous administration, of some of the compounds of the present invention:

TABLE V

Product	LD ₅₀ , mM/kg rat	mg/kg
A	> 5	> 1000
B	> 4	> 1020
F	> 3	> 723
J	> 2.6	> 554
K	> 2.5	> 568
H	> 3.1	> 747
G	> 2.8	> 714
I	> 2.5 *	> 743

* intraperitoneal administration.

V. Posology and administration.

The compounds of general formula (I) can be administered *per os* in the form of solid or liquid compositions containing conventional excipients, for example, in the form of tablets, pills, sugar-coated pills, gelatine capsules, solutions or syrups, or in the form of suppositories for rectal administration or in the form of injectable solutions or suspensions. Compositions for parenteral administration include the known forms of this type of administration, for example, aqueous or oily solutions, suspensions or emulsions.

The posology is between 20 and 2000 mg. of active compound per day, obviously with variations depending upon the weight and conditions of the subject to be treated and also depending upon the mode of administration.

By way of example, a tablet composition containing a compound of general formula (I) is as follows:

Compound A	400 mg.
starch	61 mg.
polyvinyl-pyrrolidone	8 mg.
talc	26 mg.
magnesium stearate	5 mg.

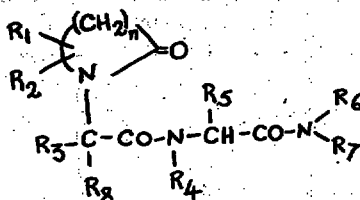


* C L M S *

12

1,539,817

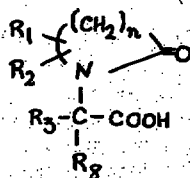
12

WHAT WE CLAIM IS:—**1. N-substituted lactams of the general formula:—**

wherein R_1 , R_2 , R_3 , R_4 , R_5 , R_6 and R_7 , which may be the same or different, are hydrogen atoms, alkyl radicals containing up to 4 carbon atoms or phenyl radicals; R_8 is a hydrogen atom or R_4 and R_3 together form an ethylene or trimethylene radical, and n is 3, 4 or 5.

2. 2-(2-Oxo-1-pyrrolidineacetamido)-acetamide.
3. N-*n*-Butyl-2-(2-oxo-1-pyrrolidineacetamido)-acetamide.
4. N-Isopropyl-2-(2-oxo-1-pyrrolidineacetamido)-acetamide.
5. 2-(α -Ethyl-5,5-dimethyl-2-oxo-1-pyrrolidineacetamido)-acetamide.
6. 2-(α ,5,5-Trimethyl-2-oxo-1-pyrrolidineacetamido)-acetamide.
7. 2-(α -Ethyl-5,5-dimethyl-2-oxo-1-pyrrolidineacetamido)-N-*n*-propylacetamide.
8. 2-(α -Methyl-2-oxo-1-pyrrolidineacetamido)-acetamide.
9. 2-(α -Ethyl-2-oxo-1-pyrrolidineacetamido)-acetamide.
10. 2-[1-(2-Oxo-pyrrolidino)-cyclopropane-carboxamido]-acetamide.
11. 2-(N-Methyl-2-oxo-1-pyrrolidineacetamido)-acetamide.
12. 2-(2-Oxo-1-pyrrolidineacetamido)-N-phenylacetamide.
13. 2-(N-Methyl-2-oxo-1-pyrrolidineacetamido)-N-phenylacetamide.
14. N,N-Dimethyl-2-(2-oxo-1-pyrrolidineacetamido)-acetamide.
15. N-Methyl-2-(2-oxo-1-pyrrolidineacetamido)-acetamide.
16. N-Methyl-2-(N-methyl-2-oxo-1-pyrrolidineacetamido)-acetamide.
17. N,N-Dimethyl-2-(N-methyl-2-oxo-1-pyrrolidineacetamido)-acetamide.
18. 2-Methyl-2-(2-oxo-1-pyrrolidineacetamido)-acetamide.
19. 2-(2-Oxo-1-pyrrolidineacetamido)-2-phenylacetamide.
20. 2-(2-Oxo-4-phenyl-1-pyrrolidineacetamido)-acetamide.
21. 2-(5-Methyl-2-oxo-1-pyrrolidineacetamido)-acetamide.
22. 2-(2-Oxo- α -phenyl-1-pyrrolidineacetamido)-acetamide.
23. 2-(Hexahydro-2-oxo-1H-azepine-1-acetamido)-acetamide.
24. 2-(α -*n*-Butyl-2-oxo-1-pyrrolidineacetamido)-acetamide.
25. 2-(3-*n*-Butyl-2-oxo-1-pyrrolidineacetamido)-acetamide.
26. N-*tert*-Butyl-2-(2-oxo-1-pyrrolidineacetamido)-acetamide.

27. A process for the preparation of N-substituted lactams according to claim 1, which comprises condensing, in an inert medium in the presence of a coupling agent, a lactam-N-acetic acid of the general formula:—



wherein R_1 , R_2 , R_3 and R_8 have the same meanings as in claim 1, with an ester of an amino acid of the general formula:—



wherein R_4 and R_5 have the same meanings as in claim 1 and Z is an alkyl radical containing up to 4 carbon atoms or a benzyl radical, and reacting the resulting ester of the general formula:—

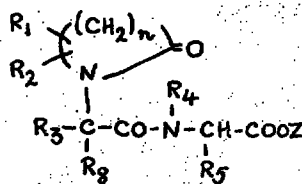


23

13

1,539,817

13

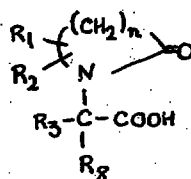


wherein R_1 , R_2 , R_3 , R_4 , R_5 , R_8 and Z have the same meanings as above, with a nitrogen compound of the general formula HNR_6R_7 , wherein R_6 and R_7 have the same meanings as in claim 1.

5

28. A process for the preparation of N-substituted lactams according to claim 1, which comprises condensing, in an inert medium in the presence of a coupling agent, a lactam-N-acetic acid of the general formula:—

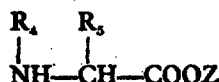
5



wherein R_1 , R_2 , R_3 and R_8 have the same meanings as in claim 1, with an ester of an aminoacid of the general formula:—

10

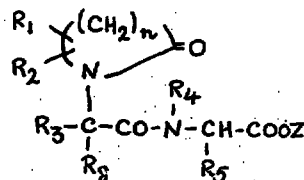
10



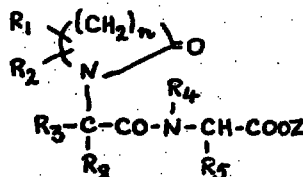
wherein R_4 and R_5 have the same meanings as in claim 1 and Z is an alkyl radical containing up to 4 carbon atoms or a benzyl radical, and converting the resulting ester of the general formula:—

15

15



wherein R_1 , R_2 , R_3 , R_4 , R_5 , R_8 and Z have the same meanings as above, into the corresponding acid of the general formula:—



20

20

wherein R_1 , R_2 , R_3 , R_4 , R_5 and R_8 have the same meanings as above, and condensing, in the presence of a coupling agent, the resulting acid with a nitrogen compound of the general formula HNR_6R_7 , wherein R_6 and R_7 have the same meanings as in claim 1.

25

25

29. A process according to claim 28, wherein the conversion of the ester into the acid is carried out by hydrolysis with a dilute aqueous alcoholic solution of sodium hydroxide.

30. A process according to claim 28, wherein the conversion of a benzyl ester into the acid is carried out by catalytic hydrogenation by means of palladium/carbon.

31. A process for the preparation of N-substituted lactams according to claim 1, substantially as hereinbefore described and exemplified.

30

30

32. N-Substituted lactams according to claim 1, whenever prepared by the process according to any of claims 27 to 31.



14

1,539,817

14

33. Pharmaceutical compositions, comprising at least one compound according to claim 1, in admixture with a solid or liquid pharmaceutical diluent or carrier.

VENNER, SHIPLEY & CO.,
Chartered Patent Agents,
Rugby Chambers,
2, Rugby Street,
London, WC1N 3QU.
Agents for the Applicants.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1979.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from
which copies may be obtained.