1 588 082

PATENT SPECIFICATION (11) 1 588 082

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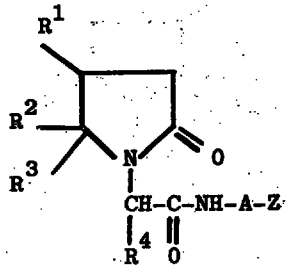
(19)

(54) PYRROLIDINEACETAMIDES AND METHODS FOR THEIR PRODUCTION

(71) We, PARKE, DAVIS & COMPANY, a corporation organised under the laws of the State of Michigan, one of the United States of America, of Joseph Campau at the River, Detroit, Michigan 48207, United States of America, 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:—

This inveention relates to N-(substituted-aminoalkyl)-2-oxo-1-pyrrolidineacetamides, and to their production.

According to the present invention, there is provided a compound having the following general formula:



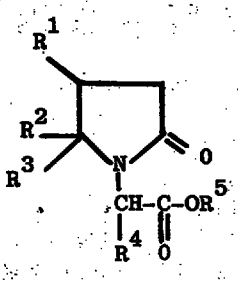
(I)

or an acid addition salt thereof, wherein R^1 is a hydrogen atom or a phenyl radical, each of R^2, R^3 and R^4, which are the same or different, is a hydrogen atom or a methyl radical, A is a divalent alkylene chain which has two, three or four carbon atoms and is optionally substituted with one or two methyl or ethyl radicals, the carbon atom of chain A adjacent the NH group being unsubstituted, and Z is a di(lower alkyl)amino), 4-morpholinyl, 4-(lower alkyl)-1-piperazinyl or (lower alkyl)$_n$-1-piperidinyl radical where n is zero or an integer having a value from 1 to 6, and a lower alkyl radical is an alkyl radical having up to 4 carbon atoms; with the proviso that when R^1 is a phenyl radical, both of R^2 and R^3 are hydrogen atoms.

The preferred compounds of the present invention are those wherein A is an ethylene or trimethylene chain, R^1 to R^4 are hydrogen atoms and Z is 2,6-dimethyl-1-piperidinyl.

The term "acid addition salts" are intended to mean salts formed by the addition of an acid. Typical examples of salts are as follows: pamoate, acetate, citrate, hydrochoride, sulphate, phosphate and benzoate. Pharmaceutically acceptable acid addition salts are preferred.

In accordance with the present invention, the foregoing compounds of formula I can be prepared by reacting a compound of the formula



II

with a compound of the formula

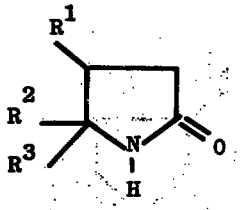
III

$$H_2N—A—Z$$

where R^1 to R^4, A and Z are as previously defined for formula I and R^5 is a lower alkyl radical containing up to 4 carbon atoms.

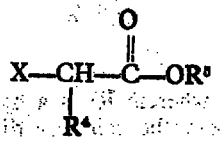
The foregoing reaction is preferably conducted in the absence of any solvent; however a solvent may be employed. A solvent such as a hydrocarbon (benzene, toluene or xylene) or an ether (dioxane, tetrahydrofuran or diethylene glycol dimethyl ether) may be used or a mixture thereof. While prefrably an excess of the amine of formula III is used (up to 50 per cent) approximately equimolar quantities of the two reactants II and II may be employed. The above reaction is generally conducted at a temperature of from 50° to 175°C. for a period of from 12 to 36 hours, preferably 90° to 150°C. for from 16 to 24 hours. The products may be isolated by conventional means such as distillation and/or crystallization. In addition, the product may be isolated either in free base form, or in the form of an acid addition salt by reaction with an appropriate acid. The compounds of this invention are bases or the corresponding acid addition salts of these bases. The bases and their acid addition salts may be conveniently converted from one form to the other by using an appropriate acid or base.

The starting materials of the formula II may be prepared by reacting a compound of the formula



IV

with a compound of the formula



V

in the presence of sodium hydride where R^1, R^2, R^3, R^4 and R^5 are as previously defined and X is a chlorine or bromine atom.

Compounds of the formulae IV and V are known compounds.

Compounds of the formula III may be prepared by reducing the cyano function of compounds of the formula

$$Z—(CR^6R^7)_{n^1}CN \qquad VI$$

using either $LiAlH_4$ or hydrogen in the presence of Raney cobalt, where Z is as previously defined, each of R^6 and R^7, which are the same or different, i.e. a hydrogen atom or a methyl or ethyl radical, and n^1 is an integer from one to three, with the proviso that in one molecule of the compound of formula VI no more than two of the radicals R^6 and R^7 are other than hydrogen atoms.

Compounds of the formula

$$Z—(CR^6R^7)_{n^1}CN \qquad VI$$

may be prepared by reacting a compound of the formula

ZH

with compounds of the formulae

$$H_2C{=}CHCN,\ HOCR^6R^7CN \text{ and } Br(Cr^6R^7)_{n^1}CN$$

where Z R^6 R^7 and n^1 are as previously defined.

The compounds of the present invention can exist in anhydrous form as well as in solvated, including hydrated, forms. In general, the hydrated forms and the solvated forms with pharmaceutically-acceptable solvents are equivalent to the anhydrous or unoslvated form for the purpose of the invention. In addition, they can exist in racemic form as well as in optically active d- and l-forms. Lastly, certain of the compounds of this invention can exist in *cis* or *trans* forms. This invention is intended to include all of these isomeric forms.

The compounds of the invention are new chemical compounds of value as pharmacological agents. More specifically, they are cognition activators which are potentially useful in treating patients suffering from senility. In addition, the alerting and attention focusing quality of these compounds would make them useful in treating patients having certain learning disabilities.

The compounds of this invention may be administered orally in the form of tablets, capsules and syrups, or parenterally by being dissolved in an appropriate isotonic solution.

The effectiveness of the aforementioned compounds is determined by the test given below which is designed to show the compounds' ability to reverse amnesia produced by an electroconvulsive shock.

One hundred male mice (Carworth, CF-1 strain, 19—21 g. at time of shipment) are divided into five groups of 20 mice each. Each mouse is placed, one at a time, on a small shelf attached to the outside wall of a test box. In this position the mouse is suspended in space. Therefore, the mouse is motivated to step from the shelf through a conveniently placed small hole into the interior of the box. As soon as the mouse has all four feet within the semidarkened interior of the box, the grid floor of the box is electrified (1.5 milliamps, 3 second duration) to produce a strong pain-fear reaction from the animal. About five second thereafter, the mouse is removed from the test box and placed in a group holding cage.

Two hours after the above training the mice are given a single electroconvusive shock produced by 20 milliamps delivered for 0.5 seconds through the ears. Immediately thereafter, the mice are returned to the holding cage.

Two hours after the convulsive treatment, the mice are injected intraperitoneally with the chemical being assessed. Usually three doses of the chemical will be tested at a time.

One hour after the drug treatment, the mice are tested for memory of the painful foot shock received within the shelf-box apparatus. This testing is accomplished by once again placing each mouse on the small shelf attached to the test box. Any mouse that stays on the shelf for 60 seconds without entering the box is counted as remembering the painful foot shock received within the box fixe hours earlier. Any mouse entering the box within the 60-second period is counted as having amnesia for the painful event.

Using this 60-second criterion, appropriate control experiments show (1.) 100 percent of mice will enter the box if no foot shock is delivered during the original training, (painful foot shock is necessary if the mice are to develop an aversion to entering the test box) (2.) 100 percent of mice will enter the box under the foregoing conditions even when treated with electroconvulsive shock at the three-hour point prior to testing (electroconvulsive shock treatment itself does not generate a fear of entering the test box).

The five groups of mice are treated as follows:

Group	Treatments
1) Ceiling Control Group:	Placebo
2) Base Line Control Group:	Electroconvulsive shock, Placebo
3) 1st Drug Dose Group:	Electroconvulsive shock, 2-oxo-4-phenyl-1-pyrrolidine-acetic acid, methyl ester
4) 2nd Drug Dose Group:	Electroconvulsive shock, 2-oxo-4-phenyl-1-pyrrolidine-acetic acid, methyl ester
5) 3rd Drug Dose Group:	Electroconvulsive shock, 2-oxo-4-phenyl-1-pyrrolidine-acetic acid, methyl ester

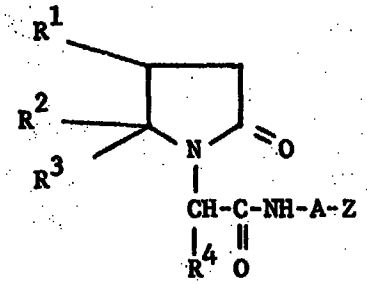
The percentage of amnesia reversal is determined as follows for each drug group:

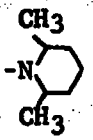
$$\text{percent amnesia reversal} = \frac{\text{Drug group} - \text{Base line control group}}{\text{Ceiling control group} - \text{Base line control group}}$$

The following criteria is used in interpreting the percent of amnesia reversal scores:

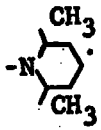
40 percent or more (active) 25 to 39 percent (boarderline) and 0 to 29 percent (inactive). The following table reports the results for certain compounds of the invention.

ACTIVITY TABLE

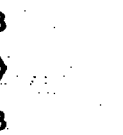
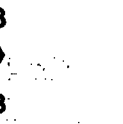
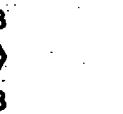
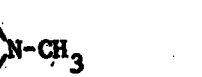
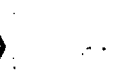


R^1	R^2	R^3	R^4	A	Z	% Amnesia Reversal at Indicated Dose, mg/kg in Mice 160	80	40	20	5.0	2.5	1.25	0.63
H	H	H	H	$-(CH_2)_2-$			10		70	70	50	20	10
H	H	H	H	$-(CH_2)_3-$	$-N(CH_3)_2$		46		46	31			
H	H	H	H	$-(CH_2)_2-$	$-N(C_2H_5)_2$		31		46	15			
H	H	H	H	$-(CH_2)_2-$			0		0	45	45	64	18

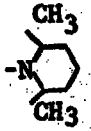
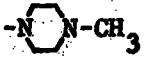
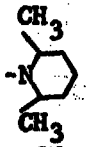
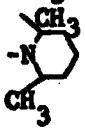
ACTIVITY TABLE
(cont.)

R^1	R^2	R^3	R^4	A	Z	% Amnesia Reversal at Indicated Dose, mg/kg in Mice							
						160	80	40	20	5.0	2.5	1.25	0.63
H	H	H	H	$-(CH_2)_2-$	$-N[CH(CH_3)_2]_2$		18		82	96	60	30	0
	H	H	H	$-(CH_2)_2-$	$-N(C_2H_5)_2$		8		0	42	27	0	0
	H	H	H	$-(CH_2)_3-$	$-N[CH(CH_3)_2]_2$		27		55	82	45	0	9
H	H	H	H	$-(CH_2)_2$	$-N[CH_2CH(CH_3)_2]_2$		15		23	54	33	25	
H	H	H	H	$-(CH_2)_3-$		60	100	70	55	50	33	25	
H	H	H	H	$-CH_2\overset{CH_3}{\underset{CH_3}{C}}-$		45	55	73	27	18			

ACTIVITY TABLE
(cont.)

R^1	R^2	R^3	R^4	A	Z	% Amnesia Reversal at Indicated Dose, mg/kg in Mice							
						160	80	40	20	5.0	2.5	1.25	0.63
H	CH_3	H	H	$-(CH_2)_2$			0		36	55	67	58	33
H	CH_3	CH_3	H	$-(CH_2)_3$		33	50	58	58	25			
	H	H	H	$-(CH_2)_2-$			33		44	67	40	10	0
H	H	H	H	$-CH_2\underset{\displaystyle CH_3}{\overset{}{C}}H-$			15		46	15			
H	CH_3	H	H	$-CH_2\underset{\displaystyle CH_3}{\overset{}{C}}H-$			45		36	18			
H	CH_3	H	H	$-(CH_2)_2-$	$-N[CH(CH_3)_2]_2$		56		0	0			

ACTIVITY TABLE
(cont.)

R^1	R^2	R^3	R^4	A	Z	% Amnesia Reversal at Indicated Dose, mg/kg in Mice							
						160	80	40	20	5.0	2.5	1.25	0.63
H	CH_3	CH_3	H	$-(CH_2)_2-$			80	44	40	22			
H	H	H	H	$-(CH_2)_3-$			54	58	31	17	0		
H	H	H	H	$-(CH_2)_3-$				45		18	9		
H	H	H	H	$-(CH_2)_3-$				38		69	69	27	9	0
H	H	H	CH_3	$-(CH_2)_2-$				61		42	17		
H	H	H	CH_3	$-(CH_2)_3-$				30	23	50	8		

The invention is further illustrated by the following examples:

Example 1.

A mixture of 17.1 g. of ethyl 2-oxo-1-pyrrolidineacetate (U.S. Patent No. 3,459,738) and 25.4 g. of *cis*-2-(2,6-dimethyl-1-piperidinyl)ethylamine (U.S. Patent No. 3,446,811) is heated at 95—100° C. for 16 hours. The excess *cis*-2-(2,6-dimethyl-1-piperidinyl)ethylamine is evaporated at reduced pressure and the residue is fractionated. The product, *cis*-N-[2-(2,6-dimethyl-1-piperidinyl)ethyl]-2-oxo-1-pyrrolidineacetamide, is obtained as an oil, b.p. 178—183°C./0.15 mm., which crystallizes on standing; m.p. 93—94.5° C. after two crystallizations from ethyl acetate-pentane.

A solution of 27.5 g. of the above base product in 150 ml. of acetonitrile is cooled to 0—5° C. and an excess of dry hydrogen chloride is bubbled in. The excess hydrogen chloride is destroyed by the addition of sufficient ethylene oxide. The resulting solution is diluted with ether, seeded, and allowed to crystallize. The hydrochloride salt is collected by filtration and recrystallized from 2-propanol-ether; m.p. 166—167° C.

Example 2.

From 12.8 g. of ethyl 2-oxo-1-pyrrolidineacetate and 15.3 g. of 3-(dimethylamino)propylamine (U.S. Patent No. 2,459,808), following the procedure of Example 1, there is obtained N-[3-(dimethylamino)propyl]-2-oxo-1-pyrrolidineacetamide; b.p. 157—159° C./0.15 mm.

Example 3.

From 12.8 g. of ethyl 2-oxo-1-pyrrolidineacetate and 17.4 g of 2-(diethylamino)ethylamine [J.A.C.S. *68*, 2006 (1946)], following the procedure of Exampe 1, there is obtained N-[2-diethylamino)ethyl]-2-oxo-1-pyrrolidineacetamide; b.p. 157° C./0.1 mm.

Example 4.

From 12.8 g. of ethyl 2-oxo-1-pyrrolidineacetate and 19.2 g. of 2-(1-piperidinyl)-ethylamine [Compt. rend. *233*, 1121 (1951)], following the procedure of Example 1, there is obtained 2-oxo-N-[2-(1-piperidinyl)ethyl]-1-pyrrolidineacetamide; b.p. 185—187° C./0.15 mm.

Example 5.

From 17.1 g. of ethyl 2-oxo-1-pyrrolidineacetate and 21 g. of 2-(diisopropylaminoamino)ethylamine [J.A.C.S. *78*, 486 (1956)], following the procedure of Example 1, there is obtained N-[2-[bis-(1-methylethyl)amino]ethyl]-2-oxo-1-pyrrolidineacetamide; b.p. 164° C./0.15 mm.

Example 6.

From 7.0 g. of methyl 2-oxo-4-phenyl-1-pyrrolidineacetate and 5.0 g. of 2-(diethylamino)ethylamine, following the procedure of Example 1, there is obtained N-[2-(diethylamino)ethyl]-2-oxo-4-phenyl-1-pyrrolidineacetamide in pure form as an oil, without need for distillation.

a) Methyl 2-oxo-4-phenylpyrrolidineacetate.

A total of 8.4 g. of 57% sodium hydride dispersion in mineral oil is washed successively with 200 ml. portions of toluene to remove the mineral oil. The residual sodium hydride is suspended in 600 ml. of tetrahydrofuran and the suspension is treated portionwise, with stirring, with 32.8 g. of 4-phenyl-2-pyrrolidinone (C.A. *53*:4253 g.). Upon completion of the addition, the stirred mixture is heated in the range of 35—65° C. from one to three hours (monitoring hydrogen evolution, followed by the dropwise addition of 21.8 g. of methy chloroacetate. After stirring for about 16 hours at 55—65°C. to insure completeness of reaction, the mixture is cooled and evaporated at reduced pressure. The residue is mixed with 200 ml. of water and extracted twice with 200 ml. portions of ether. The combined ether extract is dried, evaporated and fractionated at reduced pressure. Methyl 2-oxo-4-phenyl-1-pyrrolidineacetate is obtained as an oil, b.p. 158—159° C./0.15 mm.

Example 7.

From 6.2 g. of methyl 2-oxo-4-phenylpyrrolidineacetate and 8.0 g. of 3-(diisopropylamino)propylamine [J.A.C.S. *65*, 2012 (1943)], following the procedure of Example 1, there is obtained N-[3-[bis(1-methylethyl)amino]propyl]-2-oxo-4-phenyl-1-pyrrolidineacetamide in pure form as an oil, without need for distillation.

Example 8.

From 8.5 g. of thyl 2-oxo-1-pyrrolidineacetate and 12.9 g. of 2-(diisobutylamino)ethylene (British Patent No. 614,164), following the procedure of Exampe 1, there is obtained N-[2-[bis(2-methylpropyl)amino]ethyl]-2-oxo-1-pyrrolidineacetamide; b.p. 155—160° C. 0.1 mm.

Example 9.

A mixture of 8.5 g. of ethyl 2-oxo-1-pyrrolidineacetate and 9.4 g. of *cis*-3-(2,6-dimethyl-1-piperidinyl)propylamine (U.S. Patent No. 3,446,811) is heated at 95—100° C. under nitrogen and an air condenser plugged with cotton for 20 hours. The excess *cis*-3-(2,6-dimethyl-1-piperidinyl)propylamine is evaporated at reduced pressure and the residue is cooled to crystallize the product, *cis*-N-[3-(2,6-dimethyl-1-piperidinyl)propyl]-2-oxo-1-pyrrolidineacetamide; m.p. 69—70° C. after recrystallization from heptane and hexane. (The product can also be purified by distillation at reduced pressure; b.p. 185° C./0.1 mm.).

A solution of 27.5 g. of the above product in 150 ml. of acetonitrile is cooled to 0—5°C. and an excess of dry hydrogen chloride gas is introduced. The excess hydrogen chloride is destroyed by the addition of sufficient ethylene oxide. The resulting solution is diluted with ether, seeded, and allowed to crystallize. The hydrochloride salt is collected by filtration and recrystallized from 2-propanol-ether; m.p. 152—153° C.

Example 10.

From 8.56 g. of ethyl 2-oxo-1-pyrrolidineacetate and 12.5 g. of 2-methyl-2-(1-piperidinyl)propylamine [J.A.C.S. *68*, 13 (1946)], following the procedure of Example 9, there is obtained N-[2-methyl-2-(1-piperidinyl)propyl]-2-oxo-1-pyrrolidine acetamide; m.p. 69° C. after crystallization from heptane.

Example 11.

From 9.26 g. of ethyl 2-methyl-5-oxo-1-pyrrolidineacetate (British Patent No. 1,309,692) and 8.6 g. of *cis*-2-(2,6-dimethyl-1-piperidinyl)ethylamine, following the procedure of Example 9, there is obtained *cis*-N-[2-(2,6-dimethyl-1-piperidinyl)-ethyl]-2-methyl-5-oxo-1-pyrrolidineacetamide; m.p. 115—116° C. after crystallization from cyclohexane.

Example 12.

From 10 g. of ethyl 2,2-dimethyl-5-oxopyrrolidineacetate, (British Patent No. 1,309,692) and 10.5 g. of *cis*-3-(2,6-dimethyl-1-piperidinyl)propylamine, following the procedure of Example 9, there is obtained *cis*-N-[3-(2,6-dimethyl-1-piperidinyl)-prouyl]-,2,2-dimethyl-5-oxo-1-pyrrolidineacetamide; m.p. 86—87°C. after crystallization from isooctane.

Example 13.

From 7.0 g. of methyl 2-oxo-4-phenyl-1-pyrrolidineacetate and 5.0 g. of *cis*-2-(2,6-dimethyl-1-piperidinyl)-ethylamine, following the procedure of Example 9, there is obtained *cis*-N-[2-(2,6-dimethyl-1-piperidinyl)ethyl]-2-oxo-4-phenyl-1-pyrrolidineacetamide; m.p. 115—116° C. after recrystallization from cyclohexane.

Example 14.

From 7.0 g. of ethyl 2 - oxo- 1 - pyrrolidineacetate and 6.3 g. of 2 - (4-methyl-1-piperazinyl)propylamine, following the procedure of Example 9, there is obtained (±)-N-[2-(4-methyl-1-piperazinyl)propyl]-2-oxo-1-pyrrolideneacetamide; m.p. 84—85° C. after recrystallization from cyclohexane and from heptane.

a) 2-(4-Methyl-1-piperazinyl)propionitrile.

Lactonitrile (71.08 g.) is added in a dropwise manner to a stirred solution of 100.71 g. of 1-methyl-piperazine in 500 ml of benzene. The resulting warm solution is heated at reflux under a water separator until the theoretical amount of water is collected (about 4 hours). The solution is evaporated at reduced pressure and the residue is fractionated. The product, 2-(4-methyl-1-piperazinyl)propionitrile, is obtained as an oil, b.p. 128—130° C./23 mm.

b) 2-(4-Methyl-1-piperazinyl)propylamine.

2-(4-Methyl-1-piperazinyl)propionitrile (38.3 g.) in 50 ml of dry ether is added in a dropwise manner to a stirred solution of 19 g. of lithium aluminum hydride in 600 ml. of dry ether. The resulting mixture is heated at reflux for 1 hour, cooled and treated in sequence with 10 ml. of water, 7.5 ml. of 20% aqueous sodium hydroxide, and 35 ml. of water. The mixture is filtered and the filtrate is evaporated. The residue is fractionated at reduced pressure to give 2-(4-methyl-1-piperazinyl)-propylamine as an oil, b.p. 92—93° C./9 mm.

Example 15.

From 9.3 g. of ethyl 2-methyl-5-oxo-1-pyrrolidineacetate and 10.7 g. of 2-(1-piperidinyl)propylamine (J. Chem. Soc. *1947*, 1511), following the procedure of Example 9, there is obtained (±)-2-methyl-5-oxo-N-[2-(1-piperidinyl)propyl]-1-pyrrolidineacetamide; m.p. 111—112° C. after recrystallization from heptane.

Example 16.

From 9.2 g. of ethyl 2-methyl-5-oxo-1-pyrrolidineacetate and 8.7 g. of 2-(diisopropylamino)ethylamine, following the procedure of Example 9, there is obtained N-([2-[Bis(1-methylethyl)amino]ethyl]-2-methyl-5-oxo-1-pyrrolidineacetamide; m.p. 73—74° C. after recrystallization from hexane.

Example 17.

From 10 g. of ethyl 2,2-dimethyl-5-oxo-1-pyrrolidineacetate and 11 g. of *cis*-2-2,6-dimethyl-1-piperidinyl)ethylamine, following the procedure of Exampe 9, there is obtained cis-N-]2-(2,6-dimethyl-1-piperidinyl)ethyl]-5,5-dimethyl-2-oxo-1-pyrrolideneacetamide as the hemihydrate; m.p. 94—94.5° C. after recrystallization from isooctane.

Example 18.

From 8.5 g. of ethyl 2-oxo-1-pyrrolidineacetate and 8.2 g. of 3-(4-morpholinyl)propylamine [J.A.C.S. *63*, 156 (1941)], following the procedure of Example 9, there is obtained N[3-(4-morpholinyl)propyl]-2-oxo-1-pyrrolidineacetate, m.p. 101—102° C. after recrystallization from isooctane.

Example 19.

From 8.5 g. of ethyl 2-oxo-1-pyrrolidineacetate and 14 g. of 3-(2,2,4,6-tetramethyl-1-piperidinyl)propylamine (U.S. Patent No. 3,446,811), following the procedue of Exampe 9, there is obtained N-[3-(2,2,4,6-tetramethyl-1-piperidinyl)propyl]-2-oxo-1-pyrrolidineacetamide; m.p. 85—87° C. after recrystallization from ethyl ether.

Example 20.

From 8.5 g. of ethyl 2-oxo-1-pyrrolidineacetate and 10.2 g. of 3-(4-methyl-1-piperazinyl)propylamine [J.A.C.S. *82*, 2386 (1960)], following the procedure of Example 9, there is obtained N-[3-(methyl-1-piperazinyl)propyl]-2-oxo-1-pyrrolidineacetamide; m.p. 93° C. after recrystallization from cyclohexane.

Example 21.

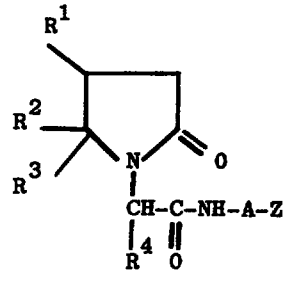
A mixture of 9.25 g. of ethyl α-methyl-2-oxo-1-pyrrolidineacetate (British Patent No. 1,309,692) and 11.2 g. of *cis*-2-(2,6-dimethyl-1-piperidinyl)ethylamine is heated under nitrogen and an air condenser plugged with cotton for 20 hours at 150° C. The excess *cis*-2-(2,6-dimethyl-1-piperidinyl)ethylamide is evaporated at reduced pressure and the residue is fractionated. The product, *cis*-(±)-N-[2-(2,6-dimethyl-1-piperidinyl)ethyl]-α-methyl-2-oxo-1-pyrrolidineacetamide, is obtained as an oil, b.p. 168—170° C./0.1 mm.

Example 22.

From 9.25 g. of ethyl α-methyl-2-oxo-1-pyrrolidineacetate and 10.5 g. of *cis*-3-(2,6-dimethyl-1-piperidinyl)propylamine, following the procedure of Example 21, there is obtined cis-(±)-N-[3-(2,6-dimethyl-1-piperidinnyl)propyl]α-methyl-2-oxo-1-pyrrolidineacetamide; b.p. 165—170° C./0.1 mm.

WHAT WE CLAIM IS:—

1. A compound having the following general formula:



(I)

Example 15.

From 9.3 g. of ethyl 2-methyl-5-oxo-1-pyrrolidineacetate and 10.7 g. of 2-(1-piperidinyl)propylamine (J. Chem. Soc. *1947*, 1511), following the procedure of Example 9, there is obtained (±)-2-methyl-5-oxo-N-[2-(1-piperidinyl)propyl]-1-pyrrolidineacetamide; m.p. 111—112° C. after recrystallization from heptane.

Example 16.

From 9.2 g. of ethyl 2-methyl-5-oxo-1-pyrrolidineacetate and 8.7 g. of 2-(diisopropylamino)ethylamine, following the procedure of Example 9, there is obtained N-([2-[Bis(1-methylethyl)amino]ethyl]-2-methyl-5-oxo-1-pyrrolidineacetamide; m.p. 73—74° C. after recrystallization from hexane.

Example 17.

From 10 g. of ethyl 2,2-dimethyl-5-oxo-1-pyrrolidineacetate and 11 g. of *cis*-2-2,6-dimethyl-1-piperidinyl)ethylamine, following the procedure of Exampe 9, there is obtained cis-N-]2-(2,6-dimethyl-1-piperidinyl)ethyl]-5,5-dimethyl-2-oxo-1-pyrrolideneacetamide as the hemihydrate; m.p. 94—94.5° C. after recrystallization from isooctane.

Example 18.

From 8.5 g. of ethyl 2-oxo-1-pyrrolidineacetate and 8.2 g. of 3-(4-morpholinyl)propylamine [J.A.C.S. *63*, 156 (1941)], following the procedure of Example 9, there is obtained N[3-(4-morpholinyl)propyl]-2-oxo-1-pyrrolidineacetate, m.p. 101—102° C. after recrystallization from isooctane.

Example 19.

From 8.5 g. of ethyl 2-oxo-1-pyrrolidineacetate and 14 g. of 3-(2,2,4,6-tetramethyl-1-piperidinyl)propylamine (U.S. Patent No. 3,446,811), following the procedue of Exampe 9, there is obtained N-[3-(2,2,4,6-tetramethyl-1-piperidinyl)propyl]-2-oxo-1-pyrrolidineacetamide; m.p. 85—87° C. after recrystallization from ethyl ether.

Example 20.

From 8.5 g. of ethyl 2-oxo-1-pyrrolidineacetate and 10.2 g. of 3-(4-methyl-1-piperazinyl)propylamine [J.A.C.S. *82*, 2386 (1960)], following the procedure of Example 9, there is obtained N-[3-(methyl-1-piperazinyl)propyl]-2-oxo-1-pyrrolidineacetamide; m.p. 93° C. after recrystallization from cyclohexane.

Example 21.

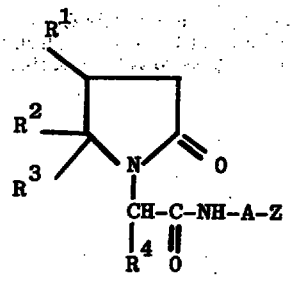
A mixture of 9.25 g. of ethyl α-methyl-2-oxo-1-pyrrolidineacetate (British Patent No. 1,309,692) and 11.2 g. of *cis*-2-(2,6-dimethyl-1-piperidinyl)ethylamine is heated under nitrogen and an air condenser plugged with cotton for 20 hours at 150° C. The excess *cis*-2-(2,6-dimethyl-1-piperidinyl)ethylamide is evaporated at reduced pressure and the residue is fractionated. The product, *cis*-(±)-N-[2-(2,6-dimethyl-1-piperidinyl)ethyl]-α-methyl-2-oxo-1-pyrrolidineacetamide, is obtained as an oil, b.p. 168—170° C./0.1 mm.

Example 22.

From 9.25 g. of ethyl α-methyl-2-oxo-1-pyrrolidineacetate and 10.5 g. of *cis*-3-(2,6-dimethyl-1-piperidinyl)propylamine, following the procedure of Example 21, there is obtined cis-(±)-N-[3-(2,6-dimethyl-1-piperidinnyl)propyl]α-methyl-2-oxo-1-pyrrolidineacetamide; b.p. 165—170° C./0.1 mm.

WHAT WE CLAIM IS:—

1. A compound having the following general formula:



(I)

or an acid addition salt thereoef, wherein R^1 is a hydrogen atom or a phenyl radical, each of R^2, R^3 and R^4, which are the same or different, is a hydrogen atom or a methyl radical, A is a divalent alkylene chain which has two, three or four carbon atoms and is optionally substituted with one or two methyl or ethyl radicals, the carbon atoms of chain A adjacent the NH group being unsubstituted, and Z is a di(lower alkyl)amine, 4-morpholinyl, 4-(lower alkyl)-1-piperazinyl or (lower alkyl)$_n$-1-piperidinyl radical where n is zero or an integer having a value from 1 to 6, and a lower alkyl radical is an alkyl radical having up to 4 carbon atoms; with the proviso that when R^1 is a phenyl radical, both of R^2 and R^3 are hydrogen atoms.

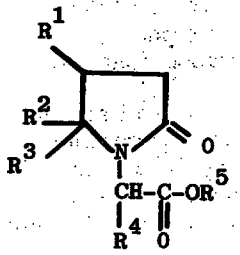
2. A compound having the formula I defined in claim 1, or an acid-addition salt thereof, wherein R^1, R^2, R^3 and R^4 are hydrogen atoms, A is an ethylene or trimethylene chain and Z is 2,6-dimethyl-1-piperidinyl.

3. The compound of *cis*-N-[2-(2,6-dimethyl-1-piperidinyl)ethyl]-2-oxo-1-pyrrolidine-acetamide or an acid addition salt thereof.

4 . The compound *cis*-N-[3-(2,6-dimethyl-1-piperidinyl)propyl]-2-oxo-1-pyrrolidineacetamide or an acid addition salt thereof.

5. The compound N-[2-[bis-(1-methylethyl)amino]-ethyl]-2-oxo-1-pyrrolidine-acetamide or an acid addition salt thereof.

6. A process for the preparation of a compound according to Claim 1, which comprises reacting a compound of the formula



(II)

with a compound of the formula

$$H_2N—A—Z$$

where R^1 to R^4, A and Z are as previously defined in Claim 1 and R^5 is a lower alkyl radical containing up to 4 carbon atoms, and isolating the product as the free base or as an acid addition salt thereof.

7. The process of Claim 6, where R^1 to R^4 are hydrogen atoms, A is an ethylene Chain, Z is 2,6-dimethyl-1-piperidinyl and R^5 is a lower alkyl radical.

8. The process of Claim 6, wherein R^1 to R^4 are hydrogen atoms, A is a trimethylene chain, Z is 2,6-dimethyl-1-piperidinyl and R^5 is a lower alkyl radical.

9. A process for producing a compound having formula I as defined in Claim 1 or an acid addition salt thereof, substantially as described in any one of the foregoing Examples.

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