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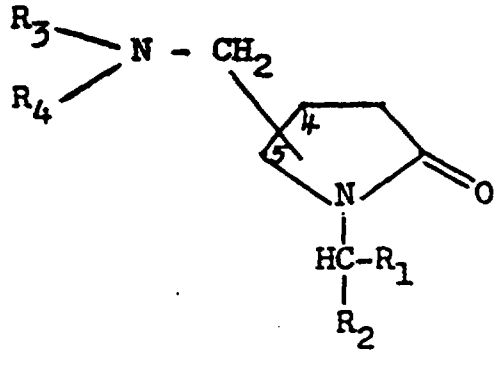
The invention relates to new 1-benzyl-aminoalkyl-pyrrolidinones and the acid addition salts thereof, processes for preparing them and pharmaceutical compositions which contain these compounds as active ingredient.

The new compounds are capable of counteracting the restriction in short-term memory after the administration of muscarinic cholinergic antagonists and also have a marked antihypoxia activity.

Nootropics of similar structure which are already described in the literature are 1-carbamoyl-methyl-pyrrolidin-2-one (Piracetam), 1-(p-methoxy-benzoyl)-pyrrolidin-2-one (Aniracetam) and 1-carbamoyl-methyl-4-hydroxy-pyrrolidin-2-one (Oxiracetam), see B.J.R. Nicolaus, Drug Development Res. 2, 464 (1982), P.L. Paytasch, J. Amer. Chem. Soc. 72, 1415 (1950).

It has now been found that the introduction of an aminomethyl group into the pyrrolidinone molecule improves the activity substantially compared with the known substances.

The invention relates to new 1-benzyl-aminoalkyl-pyrrolidinones of general formula



(I)

wherein

R_1 represents hydrogen or methyl,

R_2 represents a phenyl group which may be mono-

or disubstituted by alkoxy, fluorine, chlorine, bromine, trifluoromethyl, alkyl, hydroxy or nitro, or a pyridyl group, and

R_3 and R_4, which may be identical or different, represent hydrogen or an alkyl group with 1 to 2 carbon atoms or both groups R_3 and R_4 together with the nitrogen atom represent a saturated 5- or 6-membered ring which may contain an oxygen or nitrogen atom as a further heteroatom and may optionally be substituted by methyl, or they form an imidazole ring, and the aminoalkyl group is in the 4 or 5 position, and the acid addition salts thereof.

5-(Aminomethyl)-1-(α-methylbenzyl)-pyrrolidin-2-one is known from Japanese patent application JP-A-46 966 as an intermediate compound in the preparation of pharmaceutically active compounds, although the pharmacological activity of this compound was not disclosed.

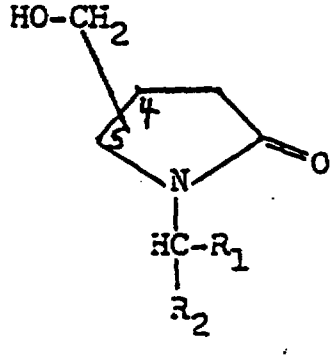
In general formula I the term "alkyl" indicates a straight-chained or branched alkyl group with 1 - 4 carbon atoms and the term "alkoxy" represents a group with 1 - 2 carbon atoms; the pyridyl ring mentioned as a definition of R_2 may be linked to the methylene bridge in the 2, 3 or 4 position.

If desired, the end products of general formula I may be converted by conventional methods into their physiologically harmless acid addition salts.

Suitable acids for this include both inorganic acids such as hydrohalic acids, sulphuric, phosphoric and aminosulphonic acid, and also organic acids such as formic, acetic, propionic, lactic, glycolic, gluconic, maleic, fumaric, succinic, tartaric, benzoic, salicylic, citric, ascorbic or p-toluene-sulphonic acid or oxyethane sulphonic acid.

The preferred compounds of general formula I are those wherein R_1 represents hydrogen, R_2 represents a phenyl group optionally substituted in the o- or p-position by fluorine, chlorine, methyl or methoxy, and R_3 and R_4 represent hydrogen or methyl.

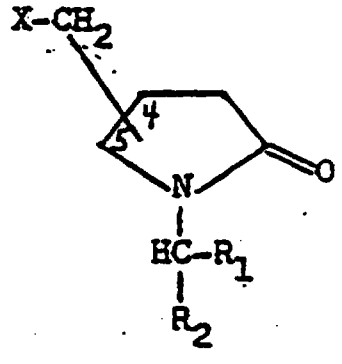
The invention further relates to processes for preparing the compounds of general formula I. Compounds in which the groups R_3 and/or R_4 are different from hydrogen are obtained, for example, starting from hydroxymethyl-pyrrolidinones of general formula



(II)

wherein

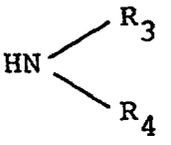
R_1 and R_2 are as hereinbefore defined, by reacting with a thionyl or a phosphorus halide or a tosyl or mesyl halide to form a compound of general formula III



(III)

wherein

R_1 and R_2 are as hereinbefore defined and X represents a halogen atom or a tosyloxy or mesyloxy group and subsequently reacting with a primary or secondary amine of general formula



(IV)

wherein

R_3 and R_4 are as hereinbefore defined.

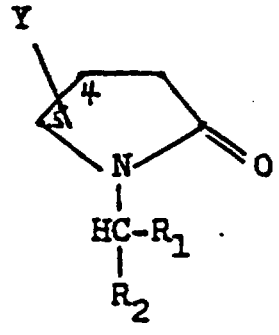
A compound of general formula II is converted either with a thionyl or phosphorus halide into the corresponding 4-halomethyl compound or with a tosyl or mesyl halide into the corresponding 4-tosyl or 4-mesyl ester. The reaction is preferably carried out using an inert organic solvent such as chloroform, methylene chloride, tetrahydrofuran or dimethylformamide at temperatures of between ambient temperature and the boiling point of the solvent used. In the case of esterification, a tertiary organic base such as triethylamine or pyridine is preferably added. The 4-halomethyl compounds produced as intermediates or the 4-tosyl or 4-mesyl esters may be isolated or may be reacted further in situ. When they are treated with primary or secondary amines the corresponding end products of general formula I are obtained. The reaction may be carried out in tetrahydrofuran, dioxan, acetonitrile or, preferably, in dimethylformamide; the temperatures are between about 50 and 150°C, and the individual reaction conditions depend on the basicity and the boiling point of the amine; the reaction may also be carried out without the use of a solvent in an excess of the amine. In the case of low-boiling amines, the reaction must be carried out in an autoclave, under certain circum-

stances.

The end products of general formula I with a free amino group are preferably synthesised by reacting a compound of general formula III with phthalimide or an alkali metal salt of phthalimide and cleaving the 4-phthalimidomethyl compound thus obtained with hydrazine.

The reaction with phthalimide is carried out in an inert organic solvent such as acetonitrile or an alcohol or preferably in dimethylformamide at elevated temperature (up to the boiling point of the reaction mixture). The 4-phthalimidomethyl compound may be isolated or reacted further <u>in situ</u>; the phthalimide group may be cleaved with hydrazine. For this cleaving, alcohols, tetrahydrofuran, dioxan or dimethylformamide or mixtures of alcohols and dimethylformamide may be used as solvents. Frequently the reaction starts even at ambient temperature; if desired, a higher temperature may be used in order to speed up the reaction.

Another possible method of preparing the nor compound consists in hydrogenation of a compound of general formula V



(V)

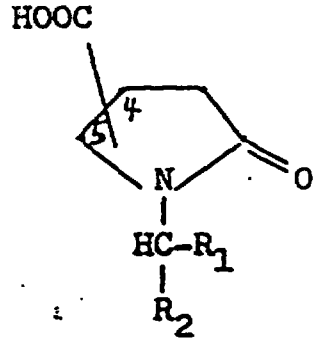
wherein

R_1 and R_2 are as hereinbefore defined and Y represents one of the groups $-CH_2N_3$ or -CN. The hydrogenation is preferably carried out using Raney nickel in methanol or with palladium in methanol/water, and possibly with the addition of ammonia,

in the case of the hydrogenation of the nitrile.

An azide of general formula V (Y = $-CH_2N_3$) is obtained by reacting a compound of general formula III wherein X represents a halogen atom or a tosyl or mesyl group with sodium azide in an inert organic solvent e.g. an alcohol or an ether such as tetrahydrofuran or dioxan.

A nitrile of general formula V (Y = -CN) may be prepared, for example, by reacting an acid of general formula VI



(VI)

dissolved in acetonitrile, R_1 and R_2 being as hereinbefore defined,
with chlorosulphonylisocyanate and subsequently with triethylamine or by dehydration of the corresponding carboxylic acid amide with $POCl_3$, for example (cf. H. Vorbrüggen, Tetrahedron Letters 1968, pages 1631 - 1634).

The new compounds of general formula I have a centre of asymmetry and therefore occur as racemates. These racemates may be converted in the usual way, e.g. by salt formation with optically active acids, into the corresponding diastereomers, which can then be converted into the optically active end products.

If desired, the alcohols of general formula II may be converted by ester formation with optically active acids into the corresponding mixtures of diastereomers which can then be resolved into the

corresponding diastereomers by conventional methods, e.g. by column chromatography or fractional crystallisation. After saponification of these esters, the enantiomeric alcohols are obtained from which the corresponding amines are prepared by method a) or b).

Starting from the pure enantiomeric nor compounds, the corresponding optically pure diethyl compounds may be obtained by reductive alkylation, e.g. with acetaldehyde/H_2/catalyst or the corresponding optically pure dimethyl compounds may be obtained with formaldehyde/formic acid.

The starting materials for the processes described above are already known or may be obtained by known methods. Thus, the pyrrolidinone carboxylic acid of general formula VI is prepared by reacting equimolar quantities of itaconic acid and a corresponding amine. The starting compound II can be obtained from the acid via the ester by selective reduction with a complex alkali metal borohydride (cf. German Patent Application P 33 26 724.3).

In the case of the 5-aminoalkyl compounds, the commercially available 5-pyrrolidinocarboxylic acids may be used as starting materials; these are esterified, alkylated at the nitrogen with optionally substituted benzyl halide and reacted further as described above.

The following end products may be obtained, for example, using the methods described, possibly in the form of their acid addition salts and possibly in the form of the pure enantiomers:

1-Benzyl-4-aminomethyl-pyrrolidin-2-one

1-(4-Methoxybenzyl)-4-aminomethyl-pyrrolidin-2-one

1-(3,4-Dimethoxybenzyl)-4-aminomethyl-pyrrolidin-2-one

1-(4-Methylbenzyl)-4-aminomethyl-pyrrolidin-2-one

1-(4-Fluorobenzyl)-4-aminomethyl-pyrrolidin-2-one

1-(4-Chlorobenzyl)-4-aminomethyl-pyrrolidin-2-one

1-(3-Trifluoromethylbenzyl)-4-aminomethyl-pyrrolidin-2-one

1-(4-Pyridylmethyl)-4-aminomethyl-pyrrolidin-2-one

1-(α-Methylbenzyl)-4-aminomethyl-pyrrolidin-2-one

1-Benzyl-4-piperidinomethyl-pyrrolidin-2-one

1-(4-Fluorobenzyl)-4-morpholino-pyrrolidin-2-one

1-Benzyl-4-(N-methylpiperazino)-pyrrolidin-2-one

1-Benzyl-4-imidazol-1-yl-pyrrolidin-2-one

1-Benzyl-4-methylaminomethyl-pyrrolidin-2-one

1-(p-Fluorobenzyl)-4-dimethylaminomethyl-pyrrolidin-2-one

1-Benzyl-4-diethylaminomethyl-pyrrolidin-2-one

1-(4-Nitrobenzyl)-4-aminomethyl-pyrrolidin-2-one

1-(4-Hydroxybenzyl)-4-aminomethyl-pyrrolidin-2-one

1-(o-Chlorobenzyl)-4-aminomethyl-pyrrolidin-2-one

1-(o-Chlorobenzyl)-4-diethylaminomethyl-pyrrolidin-2-one

1-(p-Methylbenzyl)-4-diethylaminomethyl-pyrrolidin-2-one

1-Benzyl-5-dimethylaminomethyl-pyrrolidin-2-one

1-Benzyl-5-diethylaminomethyl-pyrrolidin-2-one

1-Benzyl-5-morpholinomethyl-pyrrolidin-2-one

1-Benzyl-5-(4-methylpiperazino)-methyl-pyrrolidin-2-one

1-Benzyl-5-pyrrolidinomethyl-pyrrolidin-2-one

1-(4-Methylbenzyl)-5-dimethylaminomethyl-pyrrolidin-2-one

1-(4-Methylbenzyl)-5-diethylaminomethyl-pyrrolidin-2-one

1-(p-Chlorobenzyl)-5-dimethylaminomethyl-pyrrolidin-2-one

1-(p-Chlorobenzyl)-5-diethylaminomethyl-pyrrolidin-2-one

1-(3,4-Dichlorobenzyl)-5-dimethylaminomethyl-pyrrolidin-2-one

1-(3,4-Dichlorobenzyl)-5-diethylaminomethyl-pyrrolidin-2-one

1-(p-Methoxybenzyl)-5-dimethylaminomethyl-pyrrolidin-2-one

1-(p-Methoxybenzyl)-5-diethylaminomethyl-pyrrolidin-2-one

1-Benzyl-5-aminomethyl-pyrrolidin-2-one

The new pyrrolidinone derivatives have been investigated in animal experiments to determine their effectiveness in curing or alleviating conditions of restricted cerebral performance.

When administered to mice in dosages of up to 2 g/kg (a single oral application) to test their tolerance, the compounds showed no acute toxicity (observation period 14 days). In animal experiments, they show excellent effects on spontaneous cognitive performance such as experimentally restricted learning and memory processes. In tests with restriction of the short-term memory or where the transfer of the contents of the short term memory into the long term memory is prevented by the administration of a muscarinic cholinergic antagonist (scopolamine 0.6 mg/kg i.p.; see also Psychopharmacology 78, 104 - 111 (1982)), the compounds are capable of counteracting or even remedying this pharmacologically induced cerebral insufficiency.

The learning capabilities of rats in an active avoidance training (J. pharmacol. Methods, 8, 255 - 263 (1983)) are improved, as are their spontaneous habituation and exploratory orientation activity in a new environment.

In tests to determine the survival of animals in a closed chamber (hypoxia tolerance test) through which a gas mixture consisting of 96.5% N_2 and 3.5% O_2 was passed, the animals pre-treated with the new substances had a statistically highly significantly greater survival rate than control animals or animals pre-treated with piracetam. Moreover, the brain-protecting activity of the substances tested by this method was very marked even at a dosage of 50 mg/kg p.o.

The new pyrrolidinone derivatives were compared for their effectiveness with pyrrolidinones of different structure which are already used as drugs in human medicine (piracetam) in the field of cerebral insufficiency or organic brain psychodrome, post-traumatic and alcoholic brain damage, etc, or are currently being subjected to clinical trials (aniracetam).

The new compounds are clearly superior to the above-mentioned substances both in terms of the effective dose and also in the improvement in performance achieved in the animal experiments.

The new compounds may be used either on their own or in conjunction with other active substances according to the invention, possibly together with other pharmacologically active substances, e.g. other cerebro-activators. Suitable forms for administration include, for example, tablets, capsules, suppositories, solution, syrups, emulsions or dispersible powders. Suitable tablets may be prepared, for example, by mixing the or each active substance with known excipients, e.g. inert diluents such as calcium carbonate, calcium phosphate or lactose, disintegrants such as corn starch or alginic acid, binders such as starch or gelatine, lubricants such as magnesium stearate or talc, and/or agents for obtaining delayed release such as carboxypolymethylene, carboxymethylcellulose, cellulose acetate

phthalate or polyvinylacetate. The tablets may also consist of several layers.

Coated tablets may be produced similarly by coating cores produced analogously to the tablets with agents conventionally used in tablet coatings, e.g. collidone or shellac, gum arabic, talc, titanium dioxide or sugar. In order to achieve delayed release or avoid incompatibilities, the core may also consist of several layers. Similarly, the tablet coating may be made up of a number of layers in order to obtain delayed release, and the excipients mentioned for the tablets may be used.

Syrups of the active substances or combinations of active substances according to the invention may additionally contain a sweetener such as saccharin, cyclamate, glycerol or sugar and a flavour improving agent, e.g. a flavouring such as vanillin or orange extract. They may also contain suspension adjuvants or thickeners such as sodium carboxymethylcellulose, wetting agents, e.g. condensation products of fatty alcohols with ethylene oxide or preservatives such as p-hydroxybenzoates.

Injection solutions are prepared in the conventional way, e.g. by adding preservatives such as p-hydroxybenzoates or stabilisers such as alkali metal salts of ethylene diamine tetraacetic acid and these solutions are then transferred into injection vials or ampoules.

The capsules containing one or more active substances or combinations of active substances may be prepared, for example, by mixing the active substances with inert carriers such as lactose or sorbitol and packing them into gelatine capsules.

Suitable suppositories may be produced, for example, by mixing with carriers provided for this purpose such as neutral fats or polyethylene glycol or derivatives thereof.

The Examples which follow illustrate the invention without restricting its scope:

Example 1

1-Benzyl-4-aminomethyl-pyrrolidin-2-one

54 g (0.16 mol) of 4-phthalimidomethyl-1-benzyl-pyrrolidin-2-one are stirred into 1.3 litres of ethyl alcohol after the addition of 32 g of hydrazine hydrate for 4 hours at ambient temperature. The precipitate (phthalic acid hydrazide) is suction filtered and the filtrate is concentrated by evaporation. 500 ml of methylene chloride are added to the residue and it is extracted three times with 100 ml of water. The organic phase is dried and evaporated. The residue remaining is dissolved in 500 ml of methanol and 20 g (0.17 mol) of solid fumaric acid are added in batches at boiling temperature with stirring. When the mixture cools, colourless crystals are precipitated which are suction filtered and then washed with methanol and ether. Yield: 20 - 25 g (48 - 60% of theory), m.p. 209 - 211°C.
The compound contains ½ mol of fumaric acid.

The starting material is obtained as follows:

a) 94 g (0.46 mol) of 1-benzyl-4-hydroxymethyl-pyrrolidin-2-one are stirred with 700 ml of methylene chloride and 40 ml (0.54 mol) of thionyl-chloride for 25 hours while refluxing and the reaction mixture is then neutralised with dilute ammonia whilst being cooled. After separation, drying and evaporation, 85 - 90 g of a dark oil are left behind, which is used directly for further reaction.

b) 43.5 g (0.195 mol) of crude 1-benzyl-4-chloromethyl-pyrrolidin-2-one, 36 g (0.195 mol) of potassium

phthalimide and 700 ml of dimethylformamide are refluxed for 2 hours. The reaction mixture is then evaporated in vacuo and the residue is taken up in methylene chloride. It is extracted several times with water, the organic phase is dried and after chromatography on SiO_2 45 g (70% of theory) of the phthalimido compound are obtained, m.p. 108 - 109°C.

Example 2

1-Benzyl-4-aminomethyl-pyrrolidin-2-one

a) 58 g (0.29 mol) of 1-benzyl-4-nitrilo-pyrrolidin-2-one are dissolved in methanol and catalytically hydrogenated with the addition of liquid ammonia over Raney nickel. After the reaction solution has been concentrated by evaporation, it is dissolved in methanol, the residual catalyst is filtered off and after the filtrate has been heated to about 50°C it is mixed with 17 g of fumaric acid. The fumaric acid briefly goes into solution when stirred, then the crystallisation of the 1-benzyl-4-aminomethyl-pyrrolidin-2-one fumarate begins.
Yield: 68 g (= 91% of theory); m.p. 192 - 194°C.

b) The nitrilo compound is obtained in a 96% yield in the form of an oil from the corresponding amide, m.p. 162 - 166°C, by dehydration using $POCl_3$ in dimethylformamide at about 60°C.

Example 3

Resolution of 1-benzyl-4-aminomethyl-pyrrolidin-2-one

a) 24.0 g (0.117 mol) of 1-benzyl-4-aminomethyl-pyrrolidin-2-one are dissolved in 200 ml of

hot methanol and 17.6 g (0.117 mol) of L(+)-tartaric acid are also dissolved in 200 ml of hot methanol. The two solutions are combined and cooled to ambient temperature with stirring, whereupon the salt crystallises out. The crystals are suction filtered while cold, washed with cold methanol and dried.
Yield: 18.0 g of 4-aminomethyl-1-benzyl-pyrrolidin-2-one tartrate, m.p. 204 - 206°C (from methanol), α_D = +6.3° (c = 1.0; water).

b) In order to convert the tartrate into the base the tartrate is dissolved cold in 20 ml of water and 10 ml of concentrated sodium hydroxide solution and extracted three times with methylene chloride, then the combined methylene chloride phases are dried over $MgSO_4$ and the solvent is eliminated in vacuo. The (-)-4-aminomethyl-1-benzyl-pyrrolidin-2-one is obtained, α_D = -8.4° (c = 1.0; water).

c) The mother liquors obtained in the processing described in a) are concentrated by evaporation in vacuo. 38.0 g of the tartrate is obtained, which is taken up cold in 140 ml of water and 50 ml of concentrated sodium hydroxide solution and extracted three times with methylene chloride. The combined methylene chloride phases are dried over $MgSO_4$ and the solvent is eliminated in vacuo. 19.3 g of base are obtained, which is converted into the corresponding tartrate with D-(-)-tartaric acid as described in a). Yield: 19.0 g, m.p. 204 - 205°C.

d) The conversion of the tartrate into the base is carried out as described in b). 5.7 g of (+)-4-aminomethyl-1-benzyl-pyrrolidin-2-one are obtained with a rotation α_D = +8.4° (c = 1.0; water).

Example 4

(-)-1-Benzyl-4-dimethylaminomethyl-pyrrolidin-2-one

4.0 g (0.02 mol) of (-)-1-benzyl-4-aminomethyl-pyrrolidin-2-one and 5.4 g of 85% formic acid are mixed with 4.8 ml of formalin solution and stirred overnight at 100°C (oil bath). Then the excess acid is distilled off in vacuo and the residue is taken up in water, made alkaline with concentrated sodium hydroxide solution and extracted three times with methylene chloride. The combined methylene chloride phases are washed with water, dried over sodium sulphate, the solvent is concentrated in vacuo and the residue is filtered over an SiO_2 column (eluant: methylene chloride:methanol = 97:3). The uniform fraction is concentrated by evaporation in vacuo. The title compound is obtained in a yield of 3.5 g (in the form of an oil).

α_D = -7.6° (c = 1.0; methanol)

α_D = -16.8° (c = 1.0; water).

Analogously to Example 4, 6.1 g of (+)-1-benzyl-4-dimethylaminomethyl-pyrrolidin-2-one are obtained, α_D = +7.9° (c = 1.0; methanol), from 5.8 g (0.028 mol) of (+)-1-benzyl-4-aminomethyl-pyrrolidin-2-one, 7.9 g of 85% formic acid and 7 ml of formalin solution.

Example 5

1-Benzyl-4-di-ethylaminomethyl-pyrrolidin-2-one

14 g (0.06 mol) of crude 1-benzyl-4-chloromethyl-pyrrolidin-2-one, prepared as in Example 1a), 10 g of diethylamine and 50 ml of dimethylformamide are stirred or shaken for 2 hours at 150°C in the autoclave. The mixture is evaporated to dryness in vacuo and the residue is taken up in methylene chloride then washed first with water and finally the title compound is extracted twice with 25 ml

of 2 N HCl. The aqueous phase is removed, made alkaline with sodium hydroxide solution and the organic base is extracted with methylene chloride. The methylene chloride phase is concentrated by evaporation and the residue is distilled in vacuo. Yield: 10 g (61% of theory), $bp_{0.05}$ = 155 - 158°C.

Example 6

(-)-1-Benzyl-4-diethylaminomethyl-pyrrolidin-2-one

11.5 g (0.056 mol) of (-)-1-benzyl-4-aminomethyl-pyrrolidin-2-one, 130 ml of water, 13 g of acetaldehyde, 5.8 ml of concentrated hydrochloric acid and 6.5 g of Pd/C 20% are hydrogenated for 5 1/4 hours at 5 bar and at 25°C. The residue is evaporated, taken in 30 ml of water and extracted with methylene chloride. The aqueous hydrochloric acid solution is made alkaline and also extracted with methylene chloride. By distillation in a bulbed tube, 11.2 g (76.4% of theory) of the title compound are obtained, α_D = -9.4 (c = 1.0; methanol).

Analogously to Example 6, by hydrogenating 8.4 g (0.041 mol) of (+)-1-benzyl-4-aminomethyl-pyrrolidin-2-one, 95 ml of water, 9.5 acetaldehyde, 4.2 ml of concentrated hydrochloric acid and 4.7 g of Pd/C 20%, (+)-1-benzyl-4-diethylaminomethyl-pyrrolidin-2-one is obtained, α_D = +9.4 (c = 1.0; methanol).

Example 7

1-(4-Fluoro-benzyl)-4-N-methylpiperazinylmethyl-pyrrolidin-2-one

a) 24 g (0.11 mol) of 1-(4-fluorobenzyl)-4-hydroxymethyl-pyrrolidin-2-one are refluxed with 10 ml (0.14 mol) of thionyl chloride in 200 ml of methylene chloride first of all for 10 hours and then, after the

addition of another 10 ml of thionyl chloride, for a further 6 hours. Whilst cooling with ice, the product is neutralised with ammonia and after the organic phase has been separated off it is dried and concentrated by evaporation. 23 g (92% of theory) of a reddish-brown oil remain, which is used without any further purification.

b) 5 g (0.002 mol) of the above oil are refluxed for 1 - 2 hours with 4.4 g (0.04 mol) of 1-methyl-piperazine in 30 ml of dimethylformamide. The dimethylformamide is then substantially distilled off in vacuo, the residue is taken up in methylene chloride and washed with water and then the organic phase is dried and evaporated again. The residue is chromatographed on SiO_2 with methylene chloride/methanol 95:5 as eluant. The main fraction is concentrated by evaporation and the residue (5 g) is dissolved in 30 ml of methanol. 2.8 g of fumaric acid are added to this solution. 5.2 g (48% of theory) of the title compound are precipitated in crystalline form as the fumarate.
M.p. 179 - 180°C.

Example 8
1-(4-Fluorobenzyl)-4-morpholinomethyl-pyrrolidin-2-one

a) 8.9 g (0.04 mol) of 1-(4-fluorobenzyl)-4-hydroxy-methyl-pyrrolidin-2-one in 100 ml of absolute methylene chloride and 4.8 g of pyridine are mixed with 6.9 g (0.06 mol) of methanesulphonic acid chloride. The mixture is refluxed for 2.5 hours then cooled and extracted with dilute ammonia and water. The organic phase is dried and concentrated by evaporation. 11 g (93%

of theory) of crude ester are obtained, m.p. 84 - 86°C.

b) 6.7 g (0.023 mol) of ester and 2.6 g (0.03 mol) of morpholine are refluxed for 2 hours in 20 ml of dioxan. The solvent is evaporated off in vacuo and the residue is taken up in methylene chloride and extracted with 50 ml of 2 N hydrochloric acid. The aqueous extracts are made alkaline with ammonia and the oily base is extracted with methylene chloride. The methylene chloride phase is dried and concentrated by evaporation. The residue (4.2 g) is taken up in 30 ml of methanol and 1.2 g of fumaric acid are added in the warm. After cooling, the fumarate of the title compound is precipitated in crystalline form.
Yield: 7 g = 57% of theory of colourless crystals, m.p. 175 - 176°C.

Example 9
1-(4-Fluorobenzyl)-4-aminomethyl-pyrrolidin-2-one

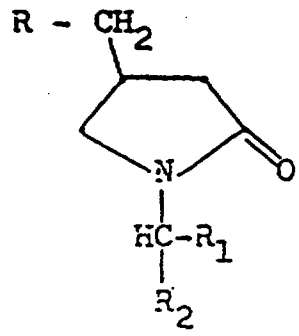
a) 4.0 g (0.013 mol) of mesyl ester, prepared according to Example 7, are refluxed for 30 minutes with 2.8 g (0.015 mol) of potassium phthalimide in 50 ml of dimethylformamide. The mixture is concentrated by evaporation in vacuo and the residue is taken up in methylene chloride, washed with water, the organic phase is dried and again concentrated by evaporation. The residue is triturated with ether and yields 3.6 g (78% of theory) of light grey crystals, m.p. 124 - 125°C.

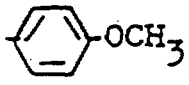
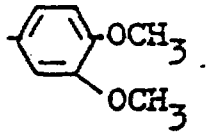
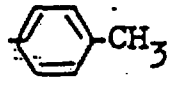
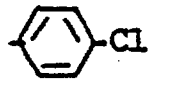
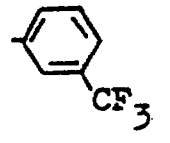
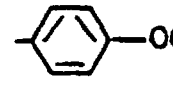
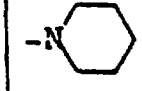
b) 3.5 g (0.1 mol) of the above phthalimide compound are stirred with 5.5 g of hydrazine hydrate in 200 ml of alcohol for 4 hours at ambient

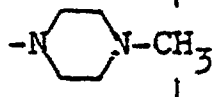
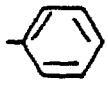
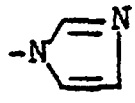
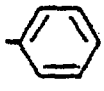
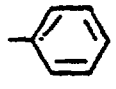
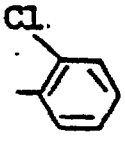
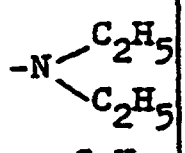
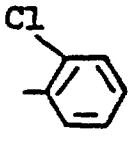
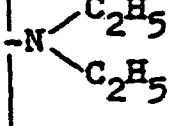
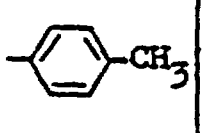
temperature. The mixture is worked up as described in Example 1. 2.5 g (89% of theory) of the fumarate of the title compound are obtained, m.p. 214 - 215°C.

The title compound may also be obtained by dissolving 5 g (16 mmol) of mesyl ester (see Example 7) in 100 ml of dimethylformamide and, after the addition of 1.3 g of sodium azide, heating the mixture to 100°C for 2 hours, hydrogenating the oil which is obtained in due course with Raney nickel in methanol and converting the base into the fumarate as described above.
Yield: 4.2 g (90% of theory).

The following end products were also obtained analogously to the procedure described in the above Examples:



Example No.	R	R_1	R_2	Mp.°C / Bp.°C
10	$-NH_2$	H		Mp. 215 - 216 (Fumarate)
11	$-NH_2$	H		Mp. 187 - 189 (Fumarate)
12	$-NH_2$	H		Mp. 225 - 226 (Fumarate)
13	$-NH_2$	H		Mp. 189 - 191 (Fumarate)
14	$-NH_2$	H		Mp. 168 - 169 (Fumarate)
15	$-NH_2$	H		Mp. 179 - 181 (Fumarate)
16	$-NH_2$	$-CH_3$		Mp. 167 - 168 (Fumarate)
17		H		Mp. 58 - 60 $Bp_{0.05}$ 180 (Base)

Example No.	R	R_1	R_2	Mp.°C / Bp.°C
18		H		Mp. 190 - 192 (Fumarate)
19		H		$Mp._{0.05}$ 230 (Base)
20	$-HN-CH_3$	H		$Bp._{0.05}$ 180 (Base)
21	$-NH_2$	H		Mp. 179 - 180 (Fumarate)
22		H		$Mp._{0.05}$ 156 (Base)
23		H		$Bp._{0.05}$ 175 (Base)

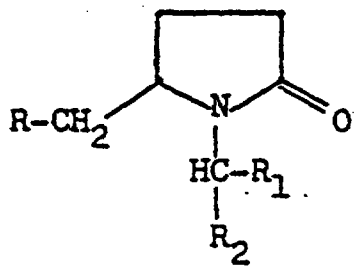
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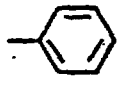
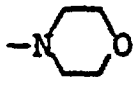
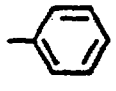
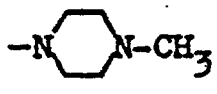
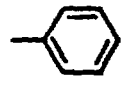
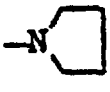
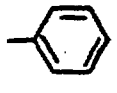
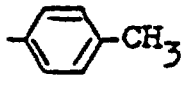
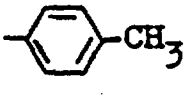
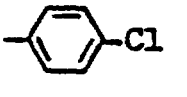
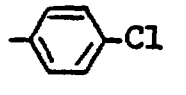
1-Benzyl-5-dimethylaminomethyl-pyrrolidin-2-one

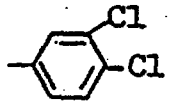
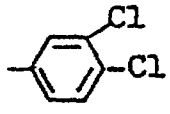
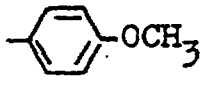
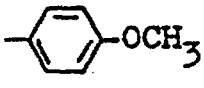
a) A solution of 10.26 g (0.05 mol) of 1-benzyl-5-hydroxymethyl-pyrrolidin-2-one (m.p. 76 - 77°C) and 5.6 g (0.055 mol) of triethylamine in 80 ml of methylene chloride is mixed with 6.3 g (0.055 mol) of methanesulphonic acid chloride in 20 ml of methylene chloride. The reaction mixture is then refluxed for 1 hour and, after being cooled, extracted with water. The organic phase is dried over anhydrous sodium sulphate and then concentrated by evaporation in a rotary evaporator. 14.1 g (yellow oil) of crude 1-benzyl-5-hydroxymethyl-pyrrolidin-2-one methanesulphonic acid ester is obtained, which is used in the next reaction step without any further purification.

b) 8.5 g (0.03 mol) of the mesylate obtained in a) are heated to 150°C for 3 hours with a solution of 10 g of dimethylamine in 60 ml of dioxan in an autoclave. After cooling the reaction mixture is concentrated to dryness in vacuo. The residue is dissolved in 2 N hydrochloric acid and extracted with ether. The acidic aqueous phase is made alkaline with concentrated ammonia and extracted with methylene chloride. The methylene chloride solution is dried and concentrated by evaporation. The residue (6.5 g) is converted into the acid fumarate of the title compound with an equivalent amount of fumaric acid. Yield: 6.4 g (61% of theory); m.p. 137 - 138°C.

The following were also prepared analogously to Example 25:



Example No.	R	R_1	R_2	Mp. °C / B p. °C
25	$-N(C_2H_5)_2$	H		Mp. 163 - 164 (Hydrochloride)
26		H		Mp. 167 - 169 (Oxalate)
27		H		Mp. 258 (Dihydrochloride)
28		H		Mp. 188 - 190 (Hydrochloride)
29	$-N(CH_3)_2$	H		Mp. 163 - 164 (Fumarate)
30	$-N(C_2H_5)_2$	H		Mp. 152 - 153 (Hydrochloride)
31	$-N(CH_3)_2$	H		Mp. 157 - 158 (Fumarate)
32	$-N(C_2H_5)_2$	H		Mp. 149 - 151 (Hydrochloride)

Example No.	R	R_1	R_2	Mp.°C / B.p.°C
33	$-N(CH_3)_2$	H		Mp. 167 - 168 (Fumarate)
34	$-N(C_2H_5)_2$	H		Mp. 159 - 161 (Hydrochloride)
35	$-N(CH_3)_2$	H		Oil (Base)
36	$-N(C_2H_5)_2$	H		Oil (Base)

Example 37

1-Benzyl-5-aminomethyl-pyrrolidin-2-one

16.4 g (0.07 mol) of 1-benzyl-5-hydroxymethyl-pyrrolidin-2-one methanesulphonic acid ester (see Example 25 a)) are dissolved in 200 ml of dimethylformamide and stirred for 90 minutes at 100°C after the addition of 4.6 g (0.07 mol) of sodium azide. After evaporation, partition between water and methylene chloride and working up of the organic phase, 13.8 g (92% of theory) of oil are obtained, which can be reacted further in its crude form. It is dissolved in 200 ml of methanol and, after the addition of Raney nickel, hydrogenated at 20°C and 5 bar. After the catalyst has been removed by suction filtering and the filtrate has been evaporated, 11 g (85% of theory) of oil are obtained which when dissolved in methanol and after the addition of fumaric acid yields the desired hemifumarate of the title compound (m.p. 187 - 188°C).

Pharmaceutical formulation Examples

A) Tablets	per tablet
Active substance	100 mg
Lactose (powdered)	140 mg
Corn starch	240 mg
Polyvinylpyrrolidone	15 mg
Magnesium stearate	5 mg
	500 mg

The finely ground active ingredient, lactose and part of the corn starch are mixed together. The mixture is screened and then moistened with a solution of polyvinylpyrrolidone in water, kneaded, granulated whilst moist and then dried. The granulate, the remaining corn starch and the magnesium stearate are screened and mixed together. The mixture is compressed to form tablets of suitable shape and size.

B) Tablets	per tablet
Active substance	80 mg
Corn starch	190 mg
Lactose	55 mg
Microcrystalline cellulose	35 mg
Polyvinylpyrrolidone	15 mg
Sodium carboxymethyl starch	23 mg
Magnesium stearate	2 mg
	400 mg

The finely ground active substance, some of the corn starch, lactose, microcrystalline cellulose and polyvinylpyrrolidone are mixed together, the mixture is screened and processed with the remaining corn starch and water to form a granulate which is dried and screened. The sodium carboxymethyl starch and the magnesium stearate are added and the mixture is compressed to form tablets of suitable

size.

C) Ampoules

4-Aminomethyl-1-(4-fluorobenzyl)-pyrrolidin-2-one fumarate	50.0 mg
Sodium chloride	10.0 mg
Doubly distilled water q.s. ad	1.0 ml

Method

The active substance and sodium chloride are dissolved in doubly distilled water and the solution is transferred into ampoules under sterile conditions.

D) Drops

4-Aminomethyl-1-(4-fluorobenzyl)-pyrrolidin-2-one fumarate	5.0 g
methyl p-hydroxybenzoate	0.1 g
propyl p-hydroxybenzoate	0.1 g
dimineralised water q.s. ad	100.0 ml

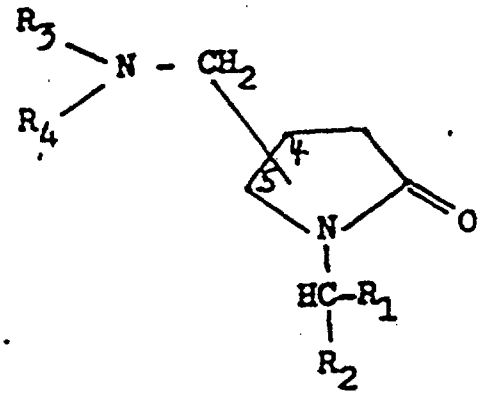
Method

The active substance and preservatives are dissolved in demineralised water and the solution is filtered and transferred into 100 ml vials.

* C L M S *

Patent Claims

1. 1-benzyl-aminoalkyl-pyrrolidinones of general formula



wherein

R_1 represents hydrogen or methyl,

R_2 represents a phenyl group which may be mono- or disubstituted by alkoxy with 1 to 2 carbon atoms, branched or unbranched alkyl with 1 to 4 carbon atoms, fluorine, chlorine, bromine, trifluoromethyl, hydroxy or nitro, or a pyridyl group and

R_3 and R_4, which may be identical or different, represent hydrogen or an alkyl group with 1 to 2 carbon atoms,

R_3 and R_4 together with the nitrogen atom form a saturated 5- or 6-membered ring which may contain an O or N atom as a further heteroatom and may optionally be substituted by methyl, or they form an imidazole ring and the aminoalkyl group is in the 4 or 5 position,

and the acid addition salts thereof,

subject to the proviso that in the case of the base, when R_1 represents methyl, R_2 represents phenyl and the aminomethyl group is in the 5 position, R_3 and R_4 cannot both represent hydrogen.

2. 1-Benzyl-4-aminoalkyl-pyrrolidinones of general formula I wherein R_1 represents hydrogen, R_2 represents

a phenyl group optionally substituted by fluorine or methoxy in the p position and R_3 and R_4 represent hydrogen or methyl, and the acid addition salts thereof.

3. 4-Aminomethyl-1-benzyl-pyrrolidin-2-one and the acid addition salts thereof.

4. 4-Aminomethyl-1-(p-fluorobenzyl)-pyrrolidin-2-one and the acid addition salts thereof.

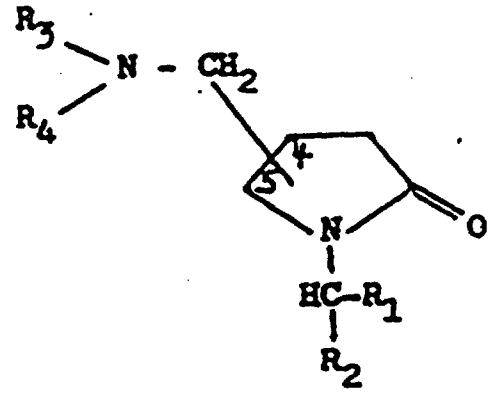
5. 4-Aminomethyl-1-(p-methoxybenzyl)-pyrrolidin-2-one and the acid addition salts thereof.

6. 4-Diethylaminomethyl-1-benzyl-pyrrolidin-2-one and the acid addition salts thereof.

7. 5-Diethylaminomethyl-1-benzyl-pyrrolidin-2-one and the acid addition salts thereof.

8. 5-Aminomethyl-1-benzyl-pyrrolidin-2-one and the acid addition salts thereof.

9. Process for preparing compounds of general formula I



(I)

wherein

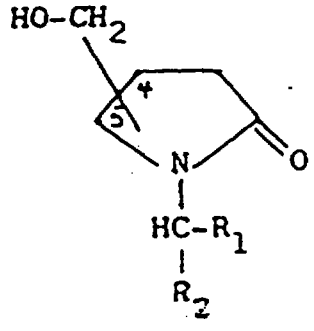
R_1 represents hydrogen or methyl,

R_2 represents a phenyl group which may be mono- or disubstituted by alkoxy with 1 to 2 carbon atoms, fluorine, chlorine, bromine, trifluoromethyl, branched or unbranched alkyl with 1 to 4 carbon atoms, hydroxy or nitro or a pyridyl group and

R_3 and R_4, which may be identical or different, represent hydrogen, however, they do not both represent hydrogen or an alkyl group with 1 to 2 carbon atoms or both groups, R_3 and R_4,

together with the nitrogen atom form a saturated 5- or 6-membered ring which may contain an O or N atom as a further heteroatom and may optionally be substituted by methyl, or they form an imidazole ring and the aminoalkyl group is in the 4 or 5 position,

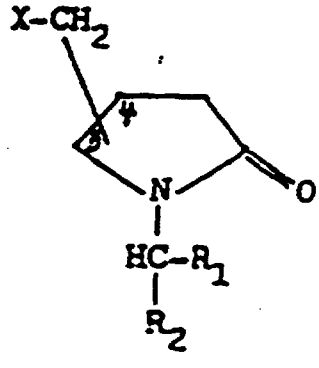
characterised in that a hydroxymethylpyrrolidin-2-one of general formula



(II)

wherein

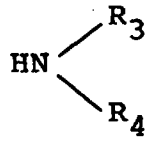
R_1 and R_2 are as hereinbefore defined is reacted with a thionyl or a phosphorus halide or a tosyl or mesyl halide and the resulting compound of general formula III



(III)

wherein

R_1 and R_2 are as hereinbefore defined and X represents a halogen atom or the tosyloxy or mesyloxy group, are reacted with a primary or secondary amine of general formula

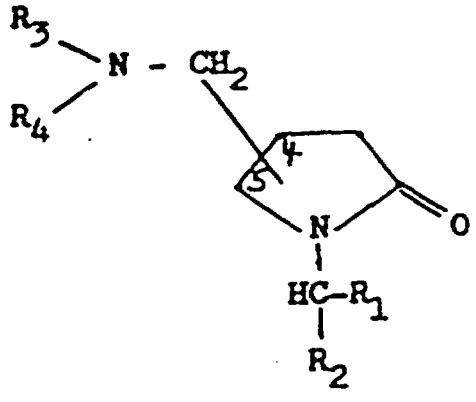


(IV)

wherein

R_3 and R_4 are as hereinbefore defined, and if desired an end product of general formula I thus obtained is converted by conventional methods into a physiologically acceptable acid addition salt.

10. Process for preparing new compounds of general formula I



(I)

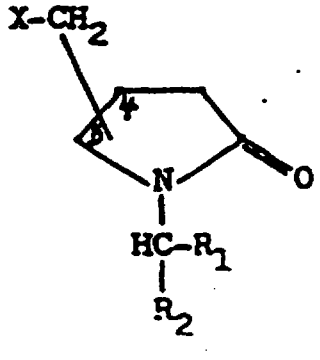
wherein

R_1 represents hydrogen or methyl,

R_2 represents a phenyl group which may be mono- or disubstituted by alkoxy with 1 to 2 carbon atoms, fluorine, chlorine, bromine, trifluoromethyl, branched or unbranched alkyl with 1 to 4 carbon atoms, hydroxy or nitro or a pyridyl group and

R_3 and R_4 represent hydrogen, characterised in that

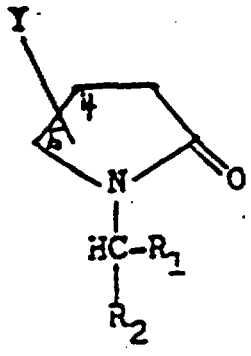
α) a compound of general formula III



(III)

is reacted with phthalimide or an alkaline salt of phthalimide and the 4-phthalimidomethyl compound thus obtained is reacted with hydrazine or

β) a compound of general formula V



(V)

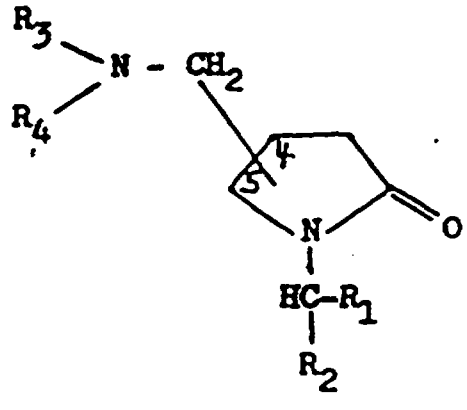
wherein

R_1 and R_2 are as hereinbefore defined and Y represents one of the groups $-CH_2N_3$ or -CN, is hydrogenated, and if desired an end product of general formula I thus obtained is converted by conventional methods into a physiologically acceptable acid addition salt.

11. Pharmaceutical preparations containing as an active substance one or several compounds of general formula I or the physiologically tolerant acid addition salts thereof in conjunction with conventional excipients and/or carriers.

12. Process for producing pharmaceutical preparations as claimed in claim 11, characterised in that compounds of general formula I are processed with the usual galenic excipients and/or carriers to form conventional pharmaceutical preparations.

13. Use of 1-benzyl-aminoalkylpyrrolidinones of general formula



(I)

wherein

R_1 represents hydrogen or methyl,

R_2 represents a phenyl group which may be mono- or disubstituted by alkoxy with 1 to 2 carbon atoms, fluorine, chlorine, bromine, trifluoromethyl, branched or unbranched alkyl with 1 to 4 carbon atoms, hydroxy or nitro or a pyridyl group and

R_3 and R_4, which may be identical or different, represent hydrogen or an alkyl group with 1 to 2 carbon atoms or the two groups, R_3 and R_4, together with the nitrogen atom form a saturated 5- or 6-membered ring which may contain an O or N atom as a further heteroatom and if desired may be substituted by methyl or may form an imidazole ring and the aminoalkyl group is in the 4 or 5 position, and the acid addition salts thereof, for the preparation of a medicament for treating conditions of restricted cerebral performance.