

PATENT SPECIFICATION

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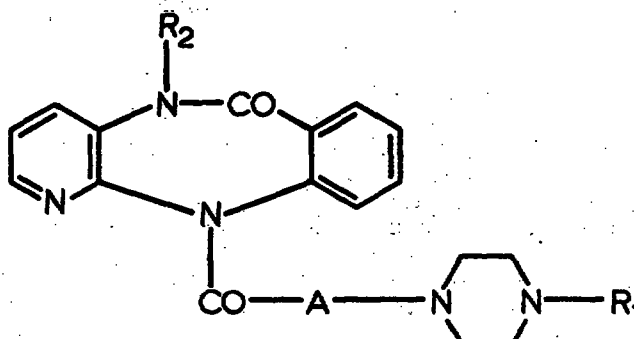


(54) PYRIDOBENZODIAZEPINES

(71) We, DR. KARL THOMAE GESSELLSCHAFT MIT BESCHRANKTER HAFTUNG, a Body Corporate organised under the laws of the Federal Republic of Germany, of Biberach an der Riss, Federal Republic of Germany, 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 invention relates to novel 11-substituted derivatives of 5,11-dihydro-6H-pyrido[2,3-b][1,4]benzodiazepin-6-one, to processes for their preparation and to pharmaceutical compositions containing them.

According to one feature of the present invention there are provided compounds of general formula I,



(I)

wherein

R_1 represents a hydrogen atom, an alkyl group containing from 1 to 6 carbon atoms, a straight or branched chain, mono- or polyunsaturated aliphatic hydrocarbyl group containing from 3 to 20 carbon atoms, a phenylalkyl group in which the alkylene moiety contains from 1 to 4 carbon atoms or a cinnamyl group;

R_2 represents a hydrogen atom or a methyl or ethyl group; and

A represents a straight or branched chain alkylene radical containing from 2 to 5 carbon atoms;

and acid addition salts thereof.

The compounds according to the invention possess interesting pharmacological properties and in particular, in general, ulcer inhibiting and secretion inhibiting activity.

It will be appreciated that, for pharmaceutical use, the salts referred to above will be physiologically compatible acid addition salts but other acid addition salts may find use, for example in the preparation of compounds of general formula I and their physiologically compatible acid addition salts.

In the compounds according to the invention R_1 may, for example, represent a methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, sec.butyl, tert.butyl, neopentyl, isopentyl, n-pentyl, n-hexyl, allyl, 2-methylallyl, 3-methylbut-2-enyl (prenyl), 1-methylallyl, pent-4-enyl, n-hex-5-enyl, n-hept-6-enyl, farnesyl, neryl, geranyl, citronellyl, phytol, benzyl, 2-phenylethyl, 1-phenylpropyl, 2-phenyl-propyl,

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2'

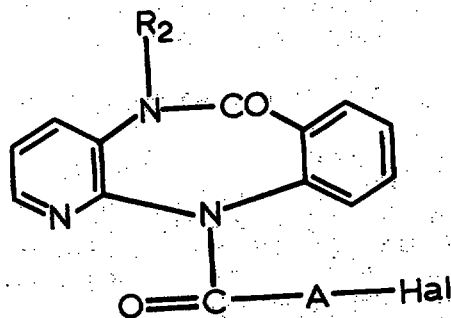
3-phenylpropyl or phenylbutyl group or a hydrogen atom.

Particularly preferred compounds according to the invention are the following:

11 - [3 - (4 - benzylpiperazin - 1 - yl)propionyl] - 5,11 - dihydro - 6H - pyrido-
[2,3 - b][1,4]benzodiazepine - 6 - one,
5,11 - dihydro - 11 - [3 - [4 - (2 - phenylethyl) - piperazin - 1 - yl]propionyl]-
6H - pyrido[2,3 - b][1,4]benzodiazepine - 6 - one
and acid addition salts thereof.

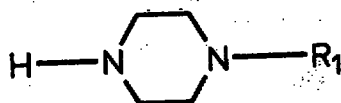
The compounds of general formula I may, for example, be prepared by the following processes, which processes constitute further features of the present invention:

A. Reaction of a compound of formula II,



(II)

(wherein R_2 and A are as hereinbefore defined and Hal represents a halogen atom) with a compound of formula III,

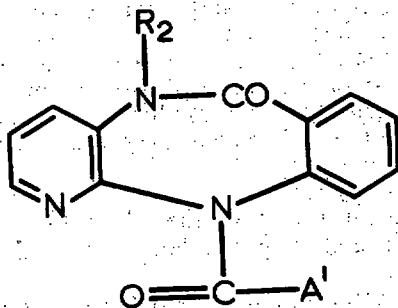


(III)

(wherein R_1 is as hereinbefore defined).

The reaction is preferably effected in the presence of an inert solvent, suitable solvents including, for example, alcohols, e.g. ethanol, n-propanol and isopropanol, ketones, e.g. acetone, ethers, e.g. dioxan and tetrahydrofuran, and aromatic hydrocarbons, e.g. benzene and toluene. The reaction is also preferably effected in the presence of a hydrogen halide-binding agent, for example, an alkali metal carbonate, an alkali metal hydrogen carbonate, a tertiary amine, e.g. triethylamine, pyridine or dimethylaniline, or an excess of the compound of formula III. Preferred reaction temperatures are elevated temperatures, most preferred being the boiling point of the reaction mixture.

B. Reaction of a compound of formula IV,



(IV)

(wherein R_2 is as hereinbefore defined and A' represents a straight or branched chain alkenyl group containing from 2 to 5 carbon atoms) with a compound of formula III as hereinbefore defined whereby the desired compound of formula I is obtained.

The reaction is preferably effected in the presence of an alcohol, e.g. ethanol, n-propanol or isopropanol, a ketone, e.g. acetone, an ether, e.g. dioxan or tetrahydrofuran, or an aromatic hydrocarbon, e.g. benzene or toluene as solvent.

Preferred temperatures are from ambient temperature to the boiling point of the reaction mixture.

When process A or B described above is used to prepare compounds of general formula I wherein R_1 represents a hydrogen atom then desirably the compound of formula III is present in large excess. Thus, in process A described above, when the reaction is effected in the presence of a hydrogen halide-binding agent, preferably the compound of formula III will be present in at least a 2 molar excess. The yields obtained in such processes are not always satisfactory and generally it is desirable to use an alternative method to prepare compounds of general formula I wherein R_1 represents a hydrogen atom such as, for example, process C described below.

C. for the preparation of compounds of general formula I wherein R_1 represents a hydrogen atom:

Debenzylation of a compound of formula I as hereinbefore defined wherein R_1 represents a benzyl group.

Debenzylation is preferably effected by means of hydrogen in the presence of palladium on active charcoal. Preferred hydrogen pressures are from 1 to 100 atmospheres, most preferred being about 50 atmospheres. The debenzylation is preferably effected in the presence of an alcohol, e.g. methanol or ethanol, as solvent and preferably at temperatures of from 20 to 80°C, most preferably about 50°C.

D. for the preparation of compounds of general formula I wherein R_1 is other than hydrogen:

Reaction of a compound of formula I as hereinbefore defined wherein R_1 represents a hydrogen atom with a compound of formula V,



(wherein R'_1 is as hereinbefore defined for R_1 , other than a hydrogen atom and Hal represents a halogen atom).

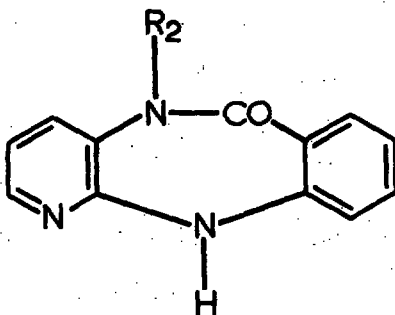
The reaction is preferably effected in the presence of an alcohol, e.g. ethanol, n-propanol or isopropanol, an ether, e.g. dioxan or tetrahydrofuran, or a ketone, e.g. acetone as solvent. Preferred reaction temperatures are elevated temperatures, most preferred being the boiling point of the reaction mixture.

It is also preferred to effect the reaction in the presence of a hydrogen halide-binding agent such as, for example, an alkali metal carbonate, an alkali metal hydrogen carbonate or a tertiary organic amine, e.g. triethylamine, pyridine or dimethylaniline.

The compounds of general formula I may, if desired, be converted into their acid addition salts by reaction with an appropriate acid. Suitable acids include, for example, hydrochloric, hydrobromic, sulfuric, phosphoric, tartaric, fumaric, citric, maleic, succinic and oxalic acid.

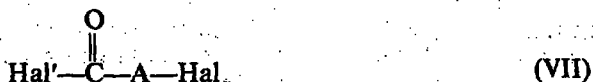
The compounds of general formula IV, useful as starting materials in process B described above, may, for example, be obtained by heating a compound of formula II as hereinbefore defined in the presence of a hydrogen halide-binding agent. Suitable hydrogen halide-binding agents include, for example, alkali metal carbonates, alkali metal hydrogen carbonates and tertiary amines, e.g. triethylamine, pyridine and dimethylaniline. The heating of the compound of formula II is preferably effected in the presence of a high boiling ether, e.g. dioxan or tetrahydrofuran, or an aromatic hydrocarbon, e.g. benzene or toluene, as solvent. A preferred temperature to which the compound of formula II is heated is the boiling point of the reaction mixture.

The compounds of general formula II may if desired be obtained by reaction of a compound of formula VI,



(VI)

(wherein R_2 is as hereinbefore defined) with a compound of formula VII,



(wherein A is as hereinbefore defined and Hal and Hal', which may be the same or different, each represents a halogen atom, e.g. chlorine, bromine or iodine). The reaction is preferably carried out in the presence of an inert solvent and of a hydrogen halide-binding agent. Elevated temperatures are preferred, most preferred being the boiling point of the reaction mixture. Suitable solvents include, for example, aromatic hydrocarbons, e.g. benzene, toluene and xylene and ethers, e.g. diethyl ether, dipropyl ether and preferably cyclic ethers e.g. dioxan. The hydrogen halide-binding agent may, for example be a tertiary organic amine, e.g. triethylamine, N,N-dimethylaniline or pyridine or an inorganic base e.g. an alkali metal carbonate or an alkali metal hydrogen carbonate. Processing of the reaction mixture is carried out according to conventional methods and the yield is generally up to 90% of theory. The compounds of general formula II thus formed are mostly well-crystallizable substances which may be used for subsequent reaction without further purification. For example, by reaction of the corresponding compound of formula VI the following were prepared:

- a) with 2-chloropropionyl chloride in dioxan as solvent:
 11 - (2 - chloropropionyl) - 5,11 - dihydro - 6H - pyrido[2,3-b][1,4]benzodiazepine - 6 - one
 M.p.: 215—218°C (from ethanol)
 and
 11 - (2 - chloropropionyl) - 5 - methyl - 5,11 - dihydro - 6H - pyrido[2,3-b][1,4]benzodiazepine - 6 - one
 M.p.: 210—212°C (from acetonitrile);
- b) with 3-chloropropionyl chloride in dioxan as solvent:
 11 - (3 - chloropropionyl) - 5,11 - dihydro - 6H - pyrido[2,3-b][1,4]benzodiazepine - 6 - one
 M.p.: 216—218°C (decomp.);
- c) with 4-chlorobutyryl chloride in xylene as solvent:
 11 - (4 - chlorobutyryl) - 5,11 - dihydro - 6H - pyrido[2,3-b][1,4]benzodiazepine - 6 - one,
 M.p.: 205—207°C (from ethyl acetate);
- d) with 5-chlorovaleryl chloride in xylene as solvent:
 11 - (5 - chlorovaleryl) - 5,11 - dihydro - 6H - pyrido[2,3-b][1,4]benzodiazepine - 6 - one,
 M.p.: 170—172°C (from n-propanol)
 and
- e) with 6-chlorocaproyl chloride in xylene as solvent:
 11 - (6 - chlorocaproyl) - 5,11 - dihydro - 6H - pyrido[2,3-b][1,4]benzodiazepine - 6 - one,
 M.p.: 128—130°C
 (see also DT—PS 1 936 670)

As described above, from the compounds of general formula II thus formed may easily be obtained compounds of general formula IV. Thus, for example, by refluxing 11-(3-chloropropionyl)-5,11-dihydro-6H-pyrido[2,3-b][1,4]benzodiazepine-6-one in dioxan as solvent, for 1 hour in the presence of excess triethylamine, 11-(acryloyl)-5,11-dihydro-6H-pyrido[2,3-b][1,4]benzodiazepine-6-one is obtained in a good yield. M.p.: 235°C (decomp.) (from acetonitrile).

The compounds of general formula VI are well-known from literature (see DT—PS 1 179 943 and 1 204 680).

As mentioned above the compounds of general formula I and their physiologically compatible acid addition salts have interesting pharmacological properties. Those compounds which we have tested exhibit an ulcer inhibiting and secretion inhibiting effect. Such compounds are thus useful in the treatment of ulcer ventriculi et duodeni, against gastritis and other disturbances of the stomach and intestines.

The following compounds were examined with regard to their inhibitory effect

on the formation of stress-ulcera in rats, on their spasmolytic effect on atropine and on their acute toxicity.

11 - [3 - (4 - benzylpiperazin - 1 - yl)propionyl] - 5,11 - dihydro - 6H - pyrido-
[2,3-b][1,4]benzodiazepine - 6 - one = A

and
5,11 - dihydro - 11 - [3 - [4 - (2 - phenylethyl) - piperazin - 1 - yl]propionyl]-
6H - pyrido[2,3-b][1,4]benzodiazepine - 6 - one = B

The inhibitory effect on the formation of stress-ulcera in rats was examined according to the method of K. Takagi and S. Okabe, Jap. Journ. Pharmac. 18, pp. 9—18 (1968). Well-fed female rats with a body-weight between 220 and 260 g were put each into small wire cages and subsequently kept vertically in a waterbath, which was kept constant at a temperature of 23°C for 16 hours, so that only the heads and breast-bones of the animals were above the water-surface. About 5 to 10 min. before this procedure, the test compounds were administered perorally to the animals. Five animals were treated with each compound. In an analogous manner 1 ml of a 0.9% physiological sodium chloride solution or 1 ml of a 1% solution of tylose was administered to a control group of animals. After 18 hours the rats were killed by an overdose of chloroethane, the stomachs were extracted, cut along the big curvature and extended on a cork disc. The evaluation was executed according to the method of Marazzi-Uberti and Turba and according to Takagi and Okabe, as described in Med. Exp. 4, pp. 284—292 (1961).

The spasmolytic effect was determined *in vitro* in guinea-pig colons using an experimental technique according to R. Magnus, Pflügers Archiv, 102, pp. 123 (1904). Acetylcholine was used to cause spasms—control substance was atropine sulfate. The spasticum was administered one minute before the administration of the spasmolyticum, the effective period of the spasmolyticum was 1 minute. Also in rats it was observed that the atrophinic side-effects like retardation of saliva-secretion, are completely suppressed or remarkably decreased by compounds A and B.

The acute toxicity was determined after oral administration of the test compounds to starved white mice with a body-weight of 18 to 20 g. The observation period was 14 days. A group of six mice was used for each dosage.

The following table shows values obtained:

Test compound	Ulcus-inhibition in % (rat) after oral administration of			Spasmolysis (acetylcholine) with reference to Atropine = 1	LD ₅₀ peroral mg/kg mouse
	50	25	12.5 mg/kg		
A	90	68	58	1/43	3000*
B	87	56	34	1/700	1500**

* at 3000 mg/kg 1 animal out of 5 died;

** at 1500 mg/kg 3 animals out of 6 died;

The spasmolytic effect of the compounds A and B in comparison to atropine sulfate is remarkably low as are also the atropinic side-effects.

Compounds A and B have a very low toxicity.

According to a yet further feature of the present invention there are provided pharmaceutical compositions comprising, as active ingredient, at least one compound of formula I as hereinbefore defined or a physiologically compatible acid addition salt thereof in association with a pharmaceutical carrier or excipient.

For pharmaceutical administration the compounds of general formula I and their physiologically compatible acid addition salts may be incorporated into the conventional pharmaceutical preparations in either solid or liquid form, optionally in combination with other active ingredients. The compositions may, for example, be presented in a form suitable for oral, rectal or perantral administration. Preferred forms include, for example, tablets, coated tablets, ampoules,

suppositories, infusions and solutions e.g. for injection.

The active ingredient may be incorporated in excipients customarily employed in pharmaceutical compositions such as, for example, talc, gum arabic, lactose, starch, magnesium stearate, cocoa butter, aqueous or non-aqueous vehicles, fatty substances of animal or vegetable origin, paraffin derivatives, glycols, various wetting, dispersing or emulsifying agents and/or preservatives.

Advantageously the compositions may be formulated as dosage units, each unit being adapted to supply a fixed dose of active ingredient. Suitable dosage units for adults contain from 5 to 50, preferably from 10 to 30 mg of active ingredient. The oral daily dosage, which may be varied according to the compound used, the subject treated and the complaint concerned, may for example, be from 20 to 100, preferably 30 to 100 mg per day in adults.

The following non-limiting examples serve to illustrate the present invention.

Example 1.

5,11 - Dihydro - 11 - [3 - (4 - prenylpiperazin - 1 - yl)propionyl] - 6H - pyrido[2,3-b]-[1,4]benzodiazepine - 6 - one

6.6 g of 11 - (3 - chloropropionyl) - 5,11 - dihydro - 6H - pyrido[2,3-b]-[1,4]benzodiazepine - 6 - one, 2.56 g of sodium carbonate and 4.0 g of 1-prenylpiperazine were refluxed together in 90 ml of absolute ethanol for 2 hours. The resultant mixture was filtered with suction while still hot and the filtrate was then evaporated to a volume of about 20 ml. The precipitate thus crystallized out was filtered off with suction and recrystallized from isopropanol.

M.p.: 199—201°C,

Yield: 62% of theory.

Example 2.

11 - [3 - (4 - Benzylpiperazin - 1 - yl)propionyl] - 5,11 - dihydro - 6H - pyrido[2,3-b]-[1,4]benzodiazepine - 6 - one

8.0 g of 11 - (3 - chloropropionyl) - 5,11 - dihydro - 6H - pyrido[2,3-b]-[1,4]benzodiazepine - 6 - one and 30 ml of 1-benzylpiperazine were refluxed together in 100 ml of isopropanol for 1 hour. The mixture obtained was evaporated *in vacuo* to dryness. The residue was treated with sodium hydroxide solution and the base formed was extracted with chloroform. The chloroform was distilled off and the residue was recrystallized from xylene.

M.p.: 205—207°C,

M.p.: of the dihydrochloride: 212—214°C (methanol),

Yield: 78% of theory.

Example 3.

5,11 - dihydro - 11 - [3 - (piperazin - 1 - yl)propionyl] - 6H - pyrido[2,3-b]-[1,4]benzodiazepine - 6 - one

The compound was obtained according to 2 methods:

a) 8.5 g of 11 - [3 - (4 - benzylpiperazin - 1 - yl)propionyl] - 5,11 - dihydro - 6H - pyrido[2,3-b]-[1,4]benzodiazepine - 6 - one were hydrogenated in 100 ml of absolute ethanol at 60°C and 50 atm with palladium on charcoal as catalyst. After 5 hours the calculated quantity of hydrogen had been absorbed. After filtering off the catalyst, the alcohol was distilled off and the residue was recrystallized from acetonitrile.

M.p.: 280—282°C,

Yield: 54% of theory.

b) A warm solution of 6.0 g of 11 - (3 - chloropropionyl) - 5,11 - dihydro - 6H - pyrido[2,3-b]-[1,4]benzodiazepine - 6 - one in 12 ml of dimethylacetamide and 40 ml of ethanol was added dropwise with stirring to a boiling solution of 8.6 g of piperazine in 50 ml of ethanol. The resultant mixture was refluxed for 1 hour and then evaporated *in vacuo* to dryness. The residue was purified using a silica gel column. The eluate was evaporated *in vacuo* to dryness and the residue recrystallized from acetonitrile.

M.p.: 280—282°C (decomp.),

Yield: 70% of theory.

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Example 4.

5,11 - Dihydro - 11 - [3 - (4 - benzylpiperazin - 1 - yl)propionyl] - 6H - pyrido[2,3-b]-[1,4]benzodiazepine - 6 - one

3.5 g of 5,11 - dihydro - 11 - [3 - (piperazin - 1 - yl)propionyl] - 6H - pyrido - [2,3-b]-[1,4]benzodiazepine - 6 - one, 1.1 g of triethylamine and 2 g of prenyl bromide were refluxed in 50 ml of n-propanol for 3 hours. The mixture obtained was evaporated *in vacuo* to dryness. The residue was triturated with water and the dissolved portion was recrystallized from isopropanol.

M.p.: 199—201°C,

Yield: 38% of theory.

Example 5.

5,11 - Dihydro - 11 - [3 - [4 - (2 - phenylethyl) - piperazin - 1 - yl]propionyl] - 6H - pyrido[2,3-b][1,4]benzodiazepine - 6 - one

5.4 g of 11 - (3 - chloropropionyl) - 5,11 - dihydro - 6H - pyrido[2,3-b][1,4]benzodiazepine - 6 - one and 3.8 g of 1 - (2 - phenylethyl)piperazine were stirred for 2.5 hours at 80°C in 25 ml of dioxan. The red solution thus obtained was evaporated *in vacuo* to dryness and the residue was dissolved in a mixture of chloroform and sodium hydrogen carbonate. The chloroform phase was subsequently evaporated *in vacuo* to dryness. The residue was recrystallized twice from n-propanol.

M.p.: 192—194°C,

Yield: 65% of theory.

Example 6.

5,11 - Dihydro - 11 - [3 - (4 - benzylpiperazin - 1 - yl)propionyl] - 6H - pyrido[2,3-b]-[1,4]benzodiazepine - 6 - one

2.65 g of 11 - acryloyl - 5,11 - dihydro - 6H - pyrido[2,3-b][1,4]benzodiazepine - 6 - one and 5.4 g of 1-benzylpiperazine were refluxed in 90 ml of absolute dioxan for 2 hours. After evaporation of the mixture obtained *in vacuo*, the residue was recrystallized from isopropanol.

M.p.: 205—207°C,

Yield: 54% of theory.

Example 7.

5,11 - Dihydro - 11 - [2 - (4 - methylpiperazin - 1 - yl)propionyl] - 6H - pyrido[2,3-b][1,4]benzodiazepine - 6 - one

9.5 g of 5 - methyl - 11 - (2 - chloropropionyl) - 5,11 - dihydro - 6H - pyrido[2,3-b][1,4]benzodiazepine - 6 - one, 3.2 g of sodium carbonate and 4 ml of 1 - methylpiperazine were refluxed for 7 hours in 120 ml of ethanol. The hot resultant solution was then filtered with suction and the filtrate was evaporated to a volume of about 50 ml. The crystalline precipitate thus formed was separated off. The filtrate was evaporated *in vacuo* to dryness and the residue recrystallized from isopropanol.

M.p.: 206—208°C,

Yield: 36% of theory.

Example 8.

5,11 - Dihydro - 11 - [4 - methylpiperazin - 1 - yl]butyryl - 6H - pyrido[2,3-b]-[1,4]benzodiazepine - 6 - one dihydrogen fumarate

6 g of 11 - (4 - chlorobutyryl) - 5,11 - dihydro - 6H - pyrido[2,3-b][1,4]benzodiazepine - 6 - one and 6 g of 1-methylpiperazine were refluxed for 10 hours in 200 ml of absolute dioxan. The resultant hot solution was filtered with suction and the filtrate was evaporated *in vacuo* to dryness. The residue was washed with water and purified on a silica gel column. The base obtained was then heated with a calculated quantity of fumaric acid in 60 ml of ethanol for 3 hours. On cooling the dihydrogen fumarate separated out. The precipitate was recrystallized from ethanol.

M.p.: 199—201°C (under decomposition)

Yield: 31% of theory.

Example 9.

5,11 - Dihydro - 11 - [5 - (4 - methylpiperazin - 1 - yl)valeryl] - 6H - pyrido[2,3-b]-[1,4]benzodiazepine - 6 - one

5.0 g of 11 - (5 - chlorovaleryl) - 5,11 - dihydro - 6H - pyrido[2,3-

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b)[1,4]benzodiazepine - 6 - one, 1.6 g of sodium carbonate and 3 ml of 1-methylpiperazine were refluxed in 100 ml of ethanol for 20 hours. The resultant hot mixture was filtered with suction and the filtrate was evaporated *in vacuo* to dryness. The residue was purified on a silica gel column.

M.p.: 151—153°C (after recrystallization from ethyl acetate)

Yield: 37% of theory.

Example 10.

11 - [3 - (4 - Benzylpiperazin - 1 - yl)propionyl] - 5,11 - dihydro - 6H - pyrido[2,3-b]-[1,4]benzodiazepine - 6 - one

3.51 g of 5,11 - dihydro - 11 - [3 - (piperazin - 1 - yl)propionyl] - 6H - pyrido[2,3-b][1,4]benzodiazepine - 6 - one and 1.6 g of sodium carbonate were mixed with 2.14 g of benzyl bromide in 100 ml of absolute ethanol and refluxed for 6 hours. The resultant hot mixture was filtered with suction and the filtrate was evaporated *in vacuo* to dryness. The residue was purified on a silica gel column. The eluate was evaporated and the residue was recrystallized from xylene.

M.p.: 205—207°C

Yield: 42% of theory.

The column chromatographic purification of the crude products was executed in all Examples by means of a silica gel column using as solvent and eluant chloroform:methanol:cyclohexane:concentrated ammonia (68:15:15:2).

Analogously to Examples 1—10 the following compounds of Examples 11 to 17 were prepared:

Example	R ₁	R ₂	A	Melt. Point (recr. from)	Yield	prepared acc. to Example
11	-CH ₃	H	$\begin{array}{c} \text{---CH---} \\ \\ \text{CH}_3 \end{array}$	223-224°C (ethyl acetate)	49	5
12	-CH ₃	H	-(CH ₂) ₂ -	232-233°C (ethyl acetate ethanol) dihydrochloride: M.p.: 235°C (ethanol)	51	2
13	-CH ₃ -CH=CH ₂	H	-(CH ₂) ₂ -	205-207°C (ethanol)	39	7
14	$\begin{array}{c} \text{CH}_3 \\ \\ \text{---CH}_2\text{---C---CH}_2 \end{array}$	H	-(CH ₂) ₂ -	210-211°C (ethanol)	45	2
15	$\begin{array}{c} \text{CH}_3 \\ \\ \text{---CH}_2\text{---CH=CH---C---CH}_2\text{---CH=CH---CH}_2\text{---CH}_2 \\ \quad \quad \\ \text{H}_3\text{C} \quad \text{H}_3\text{C} \quad \text{H}_3\text{C} \end{array}$ (Farnesyl)	H	-(CH ₂) ₂ -	Dihydrochloride: 207-209°C (abs. ethanol)	48	7

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Example	R ₁	R ₂	A	Melt. Point (recr. from)	Yield	prepared acc. to Example
16	$ \begin{array}{c} \text{CH}_3 \\ \\ \text{---CH}_2\text{---CH=C---}(\text{CH}_2)_3\text{---CH---}(\text{CH}_2)_3\text{---CH---CH}_3 \\ \qquad \qquad \qquad \qquad \\ \text{CH}_3 \qquad \text{H}_3\text{C} \qquad \text{H}_3\text{C} \end{array} $ (Phytyl)	H	-(CH ₂) ₂ -	Dihydrochloride: 204-210°C (decomp.) (ethanol)	62	7
17	-CH ₃	H	-(CH ₂) ₅ -	179-181°C (ethyl acetate)	36	9

Example I.
Tablets containing 10 mg of 11 - [3 - (4 - benzylpiperazin - 1 - yl)propionyl]-
5,11 - dihydro - 6H - pyrido[2,3-b][1,4]benzodiazepine - 6 - one

5 Composition:
1 tablet contains:

active ingredient	10.0 mg	5
lactose	148.0 mg	
potato starch	60.0 mg	
magnesium stearate	2.0 mg	10
	220.0 mg	

Method of preparation

By heating of the potato starch a 10% pulp was prepared. The active
ingredient, lactose and the remaining potato starch were admixed and granulated
together with the above prepared pulp through a sieve of mesh size 1.5 mm. The
granulate was then dried at 45°C and again passed through the above sieve. The
resultant granulate was mixed with magnesium stearate and pressed into tablets.

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Weight of tablet: 220 mg
Punch: 9 mm

Example II.

5 Coated tablets containing 10 mg of 11 - [3 - (4 - benzylpiperazin - 1 - yl)propionyl]-
5,11 - dihydro - 6H - pyrido[2,3-b][1,4]benzodiazepine - 6 - one 5
The tablets prepared according to Example I were coated according to known
methods with a coating consisting essentially of sugar and talcum. The coated
tablets were polished with bees-wax.

Weight of coated tablet: 300 mg

Example III.

10 Ampoules containing 2 mg of 11 - [3 - (4 - benzylpiperazin - 1 - yl)propionyl]-
5,11 - dihydro - 6H - pyrido[2,3-b][1,4]benzodiazepine - 6 - one dihydro-
chloride 10

15 Composition:
1 ampoule contains: 15

active ingredient 2.0 mg
sodium chloride 8.0 mg
dist. water ad. 1 ml

Method of preparation

20 The active ingredient and sodium chloride were dissolved in distilled water
and subsequently the solution obtained was made up to the desired volume. The
solution was then sterile-filtered and filled into 1 ml ampoules. 20

Sterilization: 20 minutes at 120°C.

Example IV.

25 Suppositories containing 15 mg of 11 - [3 - (4 - benzylpiperazinyl)propionyl]-
5,11 - dihydro - 6H - pyrido[2,3-b][1,4]benzodiazepine - 6 - one 25

Composition:
1 suppository contains:

active ingredient 15.0 mg
30 suppository mass (e.g. "Witepsol" [Registered
Trade Mark] W 45) 1 685.0 mg 30
1 700.0 mg

Method of preparation

35 The highly pulverized active ingredient was suspended in the molten sup-
pository mass cooled down to 40°C. The resultant mass was poured into slightly
pre-cooled moulds at 37°C. 35

Weight of suppository: 1.7 g

Example V.

40 Drop solution containing 10 mg/ml of 11 - [3 - (4 - benzylpiperazin - 1 - yl)pro-
pionyl] - 5,11 - dihydro - 6H - pyrido[2,3-b][1,4]benzodiazepine - 6 - one
dihydrochloride 40

Composition:
100 ml of drop solution contain:

methyl *p*-hydroxybenzoate 0.035 g

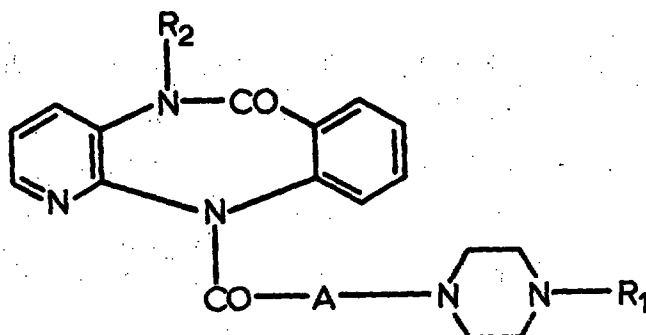
	propyl <i>p</i> -hydroxybenzoate	0.015 g
	anise oil	0.05 g
	menthol	0.06 g
	ethanol pure	10.0 g
5	active ingredient	1.0 g
	sodium cyclamate	1.0 g
	glycerine	15.0 g
	dist. water	ad. 100.0 ml

Method of preparation

The active ingredient and sodium cyclamate were dissolved in about 70 ml of water and the glycerine was added thereto. The *p*-hydroxybenzoates and anise oil as well as the menthol were then dissolved in the ethanol and added, while stirring, to the aqueous solution obtained above. Subsequently water was added up to 100 ml and the resultant solution was filtered clear of suspended particles.

WHAT WE CLAIM IS:—

1. Compounds of general formula I,



(I)

wherein

R₁ represents a hydrogen atom, an alkyl group containing from 1 to 6 carbon atoms, a straight or branched chain, mono- or polyunsaturated aliphatic hydrocarbyl group containing from 3 to 20 carbon atoms, a phenylalkyl group in which the alkylene moiety contains from 1 to 4 carbon atoms or a cinnamyl group;

R₂ represents a hydrogen atom or a methyl or ethyl group; and

A represents a straight or branched chain alkylene radical containing from 2 to 5 carbon atoms; and acid addition salts thereof.

2. 11 - [3 - (4 - Benzylpiperazin - 1 - yl)propionyl] - 5,11 - dihydro - 6H - pyrido[2,3-b][1,4]benzodiazepine - 6 - one and acid addition salts thereof.

3. 5,11 - Dihydro - 11 - [3 - [4 - (2 - phenylethyl) - piperazin - 1 - yl] - propionyl] - 6H - pyrido[2,3-b][1,4]benzodiazepine - 6 - one and acid addition salts thereof.

4. Physiologically compatible acid addition salts of compounds of general formula I as defined in claim 1.

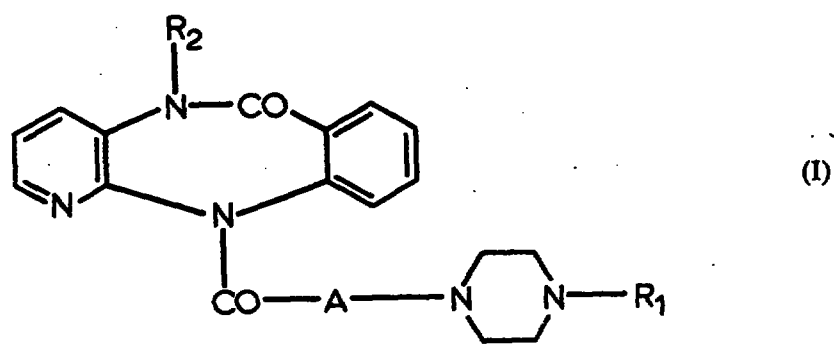
5. Compounds as claimed in claim 1, other than those claimed in claim 2 or claim 3, as herein specifically disclosed in any one of Examples 1 to 17.

6. A process for the preparation of compounds of general formula I as defined in claim 1 which comprises reacting a compound of formula II,

	propyl <i>p</i> -hydroxybenzoate	0.015 g	
	anise oil	0.05 g	
	menthol	0.06 g	
	ethanol pure	10.0 g	
5	active ingredient	1.0 g	5
	sodium cyclamate	1.0 g	
	glycerine	15.0 g	
	dist. water	ad. 100.0 ml	

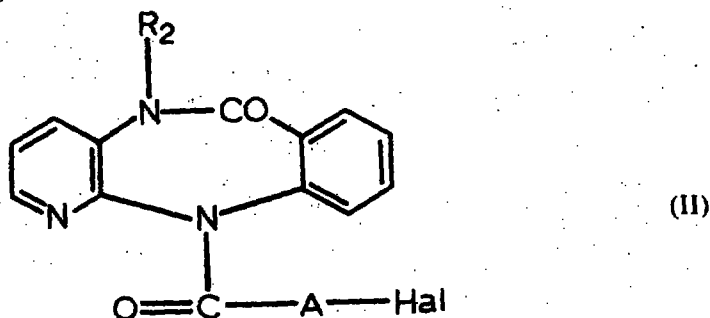
10 *Method of preparation*
The active ingredient and sodium cyclamate were dissolved in about 70 ml of water and the glycerine was added thereto. The *p*-hydroxybenzoates and anise oil as well as the menthol were then dissolved in the ethanol and added, while stirring, to the aqueous solution obtained above. Subsequently water was added up to 100 ml and the resultant solution was filtered clear of suspended particles.

15 **WHAT WE CLAIM IS:—**
1. Compounds of general formula I,

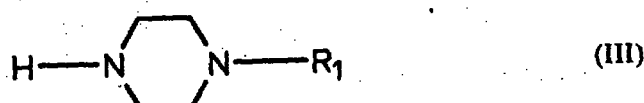


wherein
20 R_1 represents a hydrogen atom, an alkyl group containing from 1 to 6 carbon atoms, a straight or branched chain, mono- or polyunsaturated aliphatic hydrocarbyl group containing from 3 to 20 carbon atoms, a phenylalkyl group in which the alkylene moiety contains from 1 to 4 carbon atoms or a cinnamyl group;
25 R_2 represents a hydrogen atom or a methyl or ethyl group; and
A represents a straight or branched chain alkylene radical containing from 2 to 5 carbon atoms;
and acid addition salts thereof.
2. 11 - [3 - (4 - Benzylpiperazin - 1 - yl)propionyl] - 5,11 - dihydro - 6H - pyrido[2,3-b][1,4]benzodiazepine - 6 - one and acid addition salts thereof.
30 3. 5,11 - Dihydro - 11 - [3 - [4 - (2 - phenylethyl) - piperazin - 1 - yl -]propionyl] - 6H - pyrido[2,3-b][1,4]benzodiazepine - 6 - one and acid addition salts thereof.
4. Physiologically compatible acid addition salts of compounds of general formula I as defined in claim 1.
35 5. Compounds as claimed in claim 1, other than those claimed in claim 2 or claim 3, as herein specifically disclosed in any one of Examples 1 to 17.
6. A process for the preparation of compounds of general formula I as defined in claim 1 which comprises reacting a compound of formula II,

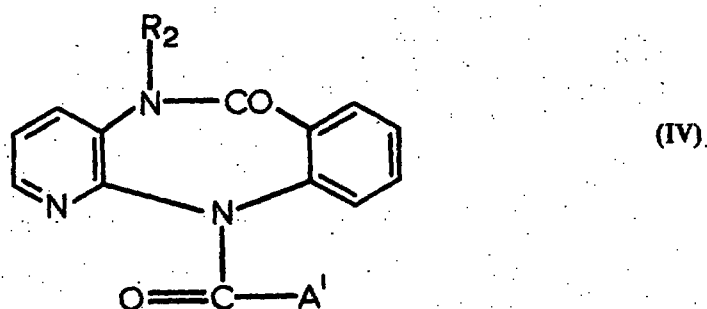




(wherein R_2 and A are as defined in claim 1 and Hal represent a halogen atom) with a compound of formula III,



- 5 (wherein R_1 is as defined in claim 1). 5
7. A process as claimed in claim 6 wherein the reaction is effected in the presence of an inert solvent. 5
8. A process as claimed in claim 7 wherein the solvent comprises an alcohol, ketone, ether or aromatic hydrocarbon. 5
- 10 9. A process as claimed in claim 8 wherein the solvent comprises ethanol, n-propanol, isopropanol, acetone, dioxan, tetrahydrofuran, benzene or toluene. 10
10. A process as claimed in any one of claims 6 to 9 wherein the reaction is effected in the presence of a hydrogen halide-binding agent. 10
- 15 11. A process as claimed in claim 10 wherein the hydrogen halide-binding agent is an alkali metal carbonate, alkali metal hydrogen carbonate, tertiary organic amine or an excess of the compound of formula III. 15
12. A process as claimed in claim 11 wherein the hydrogen halide-binding agent is triethylamine, pyridine or dimethylaniline. 15
- 20 13. A process as claimed in any one of claims 6 to 12 wherein the reaction is effected at elevated temperatures. 20
14. A process as claimed in claim 13 wherein the reaction is effected at the boiling point of the reaction mixture. 20
15. A process for the preparation of compounds of general formula I as defined in claim 1 which comprises reacting a compound of formula IV,



(wherein R_2 is as defined in claim 1 and A' represents a straight or branched chain alkenyl group containing from 2 to 5 carbon atoms) with a compound of formula III as defined in claim 6 whereby the desired compound of formula I is obtained.

- 30 16. A process as claimed in claim 15 wherein the reaction is effected in the presence of an alcohol, ketone, ether or aromatic hydrocarbon as solvent. 30
17. A process as claimed in claim 16 wherein the reaction is effected in the presence of ethanol, n-propanol, isopropanol, acetone, dioxan, tetrahydrofuran, benzene or toluene as solvent. 30
- 35 18. A process as claimed in any one of claims 15 to 17 wherein the reaction is effected at temperatures of from ambient temperature to the boiling point of the reaction mixture. 35



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19. A process as claimed in any one of claims 15 to 18 wherein the compound of formula IV is obtained by heating a compound of formula II as defined in claim 6 in the presence of a hydrogen halide-binding agent.

5 20. A process as claimed in claim 19 wherein the hydrogen halide-binding agent is an alkali metal carbonate, alkali metal hydrogen carbonate or tertiary amine.

21. A process as claimed in claim 20 wherein the hydrogen halide-binding agent is triethylamine, pyridine or dimethylaniline.

10 22. A process as claimed in any one of claims 19 to 21 wherein the heating of the compound of formula II is effected in the presence of a high boiling ether or aromatic hydrocarbon as solvent.

23. A process as claimed in claim 22 wherein the heating of the compound of formula II is effected in the presence of dioxan, tetrahydrofuran, benzene or toluene as solvent.

15 24. A process as claimed in any one of claims 19 to 23 wherein heating of the compound of formula II is effected to the boiling point of the reaction mixture.

25. A process as claimed in any one of claims 6 to 24, for the preparation of compounds of general formula I wherein R₁ represents a hydrogen atom, wherein the compound of formula III is present in large excess.

20 26. A process as claimed in any one of claims 6 to 14, for the preparation of compounds of general formula I wherein R₁ represents a hydrogen atom, wherein the reaction is effected in the presence of a hydrogen-halide binding agent and at least a 2 molar excess of the compound of formula III.

25 27. A process for the preparation of compounds of general formula I as defined in claim 1 wherein R₁ represents a hydrogen atom which comprises debenzylating a compound of formula I as defined in claim 1 wherein R₁ represents a benzyl group.

28. A process as claimed in claim 27 wherein debenzylation is effected by means of hydrogen in the presence of palladium on active charcoal.

30 29. A process as claimed in claim 28 wherein the debenzylation is effected in the presence of an alcohol as solvent.

30. A process as claimed in claim 29 wherein the alcohol is methanol or ethanol.

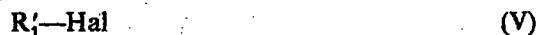
35 31. A process as claimed in claim 29 or claim 30 wherein the debenzylation is effected at temperatures of from 20 to 80°C.

32. A process as claimed in claim 31 wherein the debenzylation is effected at temperatures of about 50°C.

33. A process as claimed in any one of claims 28 to 32 wherein the debenzylation is effected with a hydrogen pressure of from 1 to 100 atmospheres.

40 34. A process as claimed in claim 33 wherein the debenzylation is effected with a hydrogen pressure of about 50 atmospheres.

35. A process for the preparation of compounds of general formula I as defined in claim 1 wherein R₁ is other than hydrogen which comprises reacting a compound of formula I as defined in claim 1 wherein R₁ represents a hydrogen atom with a compound of formula V,



(wherein R₁' is as defined for R₁ in claim 1 other than a hydrogen atom and Hal represents a halogen atom).

50 36. A process as claimed in claim 35 wherein the reaction is effected in the presence of an alcohol, ether or ketone as solvent.

37. A process as claimed in claim 36 wherein the reaction is effected in the presence of ethanol, n-propanol, isopropanol, dioxan, tetrahydrofuran or acetone as solvent.

55 38. A process as claimed in any one of claims 35 to 37 wherein the reaction is effected at elevated temperatures.

39. A process as claimed in claim 38 wherein the reaction is effected at the boiling point of the reaction mixture.

40. A process as claimed in any one of claims 35 to 39 wherein the reaction is effected in the presence of a hydrogen halide-binding agent.

60 41. A process as claimed in claim 40 wherein the hydrogen halide-binding agent is an alkali metal carbonate, alkali metal hydrogen carbonate or tertiary organic amine.

42. A process as claimed in claim 41 wherein the hydrogen halide-binding



* C L M S *

agent is triethylamine, pyridine or dimethylaniline.

43. A process for the preparation of acid addition salts of compounds of general formula I as defined in claim 1 which comprises reacting a compound of formula I as defined in claim 1 with an appropriate acid.

44. A process as claimed in claim 43 wherein the acid is hydrochloric, hydrobromic, sulfuric, phosphoric, tartaric, fumaric, citric, maleic, succinic or oxalic acid.

45. A process for the preparation of compounds as claimed in claim 1 substantially as herein described.

46. A process for the preparation of compounds as claimed in claim 1 substantially as herein described in any one of Examples 1 to 17.

47. Compounds as claimed in claim 1 whenever prepared by a process as claimed in any one of claims 6 to 46.

48. Pharmaceutical compositions comprising, as active ingredient, at least one compound of formula I as defined in claim 1 or a physiologically compatible acid addition salt thereof in association with a pharmaceutical carrier or excipient.

49. Compositions as claimed in claim 48 in a form suitable for oral, rectal or parenteral administration.

50. Compositions as claimed in claim 48 or claim 49 in the form of tablets, coated tablets, ampoules, suppositories, infusions and solutions.

51. Compositions as claimed in any one of claims 48 to 50 in the form of dosage units.

52. Compositions as claimed in claim 51 wherein each dosage unit contains from 5 to 50 mg of active ingredient.

53. Compositions as claimed in claim 52 wherein each dosage unit contains from 10 to 30 mg of active ingredient.

54. Compositions as claimed in any one of claims 48 to 53 wherein the active ingredient comprises a compound as claimed in claim 2 or claim 3.

55. Pharmaceutical compositions as claimed in claim 48 substantially as herein described.

56. Pharmaceutical compositions substantially as herein described in anyone of Examples I to V.

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