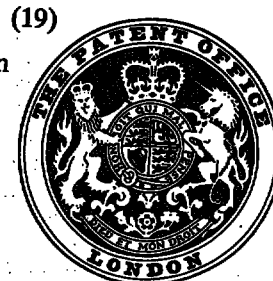


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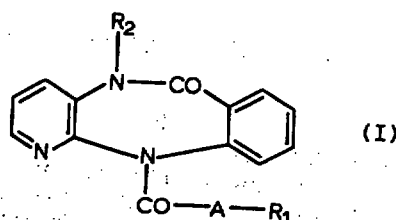


(52) Index at Acceptance

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(54) PYRIDOBENZODIAZEPINES/

(71) We, DR. KARL THOMAE Gesellschaft mit beschränkter 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 new 5,11-dihydro-6H-pyrido-[2,3-b][1,4]benzodiazepine-6-ones, 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,



wherein,

R₁ represents a free amino, tert.butylamino, N-cyclohexyl-N-methylamino, dibenzylamino, benzylamino, trimethoxybenzylamino, dimethylamino, diethylamino, dipropylamino, di-isopropylamino, di-n-butylamino, di-isobutylamino or pyrrolidino group; a piperidino group optionally substituted by a methyl or ethyl group; a morpholino, 1-ethylpyrrolidin-2-ylmethylamino or 1-ethylpiperidin-3-ylamino group; a 9-methyl-3,9-diazabicyclo [3.3.1]nonan-3-yl, 1,2,5,6-tetrahydropyrid-1-yl or 4-benzylpiperidino group; a 1,2,3,6,7,8,9a-octahydro-4H-pyrazino[1,2-a]pyrimidin-1- or -8-yl group; a 3- or 4-hydroxypiperidino or methoxypiperidino group; a 1,2,3,4-tetrahydroisoquinol-2-yl or 3-azaspiro[5.5]undecan-3-yl group; a 4-oxopiperidino group or the ethylene ketal thereof; a hexahydro-3-methyl-pyrimidin-1-yl, thiomorpholino or 1-oxido-thiomorpholino group; a hexahydro-4-methyl-1H-1,4-diazepin-1-yl or 2,6-dimethylmorpholino group; a 1,4-diazabicyclo[4.3.0]nonan-4-yl, (1-methylpyrrolidin-2-yl)-ethylamino, (1-methylpyrrolidin-2-yl)-methylamino, (1-n-propylpyrrolidin-2-yl)-methylamino, (1-allylpyrrolidin-2-yl)-methylamino, (1-n-butylpyrrolidin-2-yl)-methylamino or (1-benzylpyrrolidin-2-yl)-methylamino group; or a (furan-2-yl)-methylamino, (tetrahydrofuran-2-yl)-methylamino, N-[(1-ethylpyrrolidin-2-yl)-methyl]-methylamino, (1-ethylpyrrolidin-3-yl)-methylamino or (1-allylpyrrolidin-3-yl)-methylamino group;

3 MAR 1981

A represents a straight or branched chain alkylene group containing from 1 to 5 carbon atoms; and

R₂ represents a hydrogen atom or a methyl or ethyl group; and acid addition salts thereof,

with the proviso that, when R₁ represents a dimethylamino, diethylamino, dipropylamino, di-isopropylamino, di-n-butylamino, di-isobutylamino or pyrrolidino group; a piperidino group optionally substituted by a methyl or ethyl group; or a morpholino or 4-benzylpiperidino group, A represents a straight or branched chain alkylene group containing from 2 to 5 carbon atoms.

The compounds according to the invention possess interesting pharmacological properties and in particular, in general, an 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.

Particular preferred compounds according to the invention are the following:

5,11-dihydro-11[(4-methoxypiperidino)acetyl]-6H-pyrido[2,3-b][1,4]benzodiazepine-6-one,

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

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

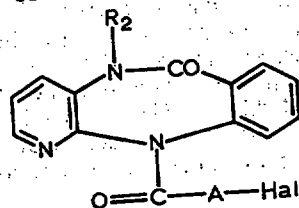
5,11-dihydro-11-(4-pyrrolidinobutyryl)-6H-pyrido[2,3-b][1,4]benzodiazepine-6-one,

11-[(1-ethylpiperid-3-yl)aminoacetyl]-5,11-dihydro-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,



(wherein A and R² are as hereinbefore defined and Hal represents a halogen atom) with a compound of formula III,

R₁ - H

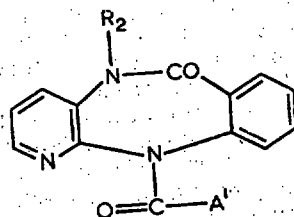
(III)

(wherein R₁ is as hereinbefore defined).

The reaction is preferably effected in the presence of an inert solvent such as, for example, 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. Preferred temperatures for the reaction are elevated temperatures, most preferred being the boiling point of the reaction mixture. Also preferred is 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, a tertiary amine e.g. triethylamine, pyridine or trimethylaniline, or an excess of the compound of formula III.

B. for the preparation of compounds of general formula I wherein A represents an alkylene group containing from 2 to 5 carbon atoms:

Reaction of a compound of formula VI,



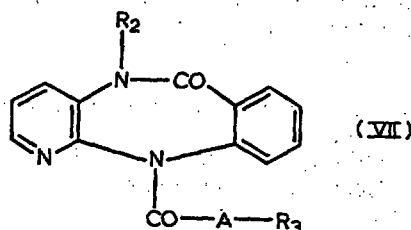
(wherein R₂ is as hereinbefore defined and A' represents an alkenyl group containing from 2 to 5 carbon atoms) with a compound of formula III as hereinbefore defined whereby the desired compound of formula I is obtained.

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

When the above-described processes A and B are used to prepare compounds of general formula I wherein R_1 represents a free amino group, the reaction of the compound of formula II or VI with the compound of formula II (i.e. ammonia) is desirably effected under pressure in a closed vessel. Such compounds are, however, produced more easily and in higher yields by process C described below.

C. for the preparation of compounds of general formula I wherein R_1 represents a free amino group;

Catalytic hydrogenation of a compound of formula VII,



[wherein A and R_2 are as hereinbefore defined and R_3 represents an (optionally substituted benzyl)amino group].

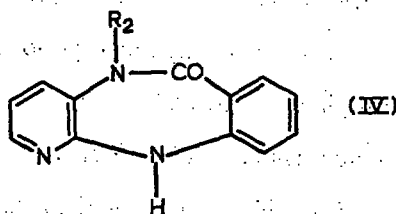
The catalyst for the hydrogenation may, for example, be palladium on charcoal. In the compound of formula VII, R_3 may, for example, be a benzylamino or trimethoxybenzylamino group in which case the compound of formula VII corresponds to a compound of formula I.

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

The compounds of general formula VI, useful as starting materials in process B described above, may be obtained, if desired, by heating a compound of formula II as hereinbefore defined wherein A represents an alkylene group containing from 2 to 5 carbon atoms 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 organic amines e.g. triethylamine, pyridine and dimethylaniline. Heating 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 and is preferably effected to the boiling point of the reaction mixture.

The compounds of general formula VII, useful as starting materials in process C described above, may also if desired, be obtained from compounds of general formula II by reaction with (optionally substituted benzyl)amine in a process analogous to process A described above.

The compounds of general formula II may themselves be obtained, for example, by reaction of a compound of formula IV,



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



(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. Preferred temperatures are elevated temperatures, most preferred being the boiling point of the reaction mixture. Suitable solvents include, for example, aromatic hydrocarbons e.g. benzene and xylene and ethers e.g. diethyl ether, dipropyl ether and preferably cyclic ethers e.g. dioxan. Hydrogen halide-binding agents which may be used include, for example, tertiary organic amines e.g. triethylamine, N,N-dimethylaniline and pyridine and inorganic bases e.g. alkali metal carbonates and alkali metal hydrogen carbonates. Further processing of the reaction mixture is carried out in conventional manner, the yield generally amounting to up to 90% of theory. The compounds of general formula II thus formed are generally easily crystallized substances, which can be used for subsequent reaction without further purification. For example, by reaction of the corresponding compounds of general formula IV

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

M.p.: 170-172°C (from n-propanol),

e) with 6-chlorocaproyl chloride in xylene, 11-(6-chlorocaproyl)-5,11-dihydro-6H-pyrido[2,3-b][1,4]benzodiazepine-6-one

M.p.: 128-130°C (decomp.),

were obtained.

From such compounds of general formula II may be obtained, as described above, compounds of general formula VI. Thus, for example, by refluxing 11-(3-chloropropionyl)-5,11-dihydro-6H-pyrido[2,3-b][1,4]benzodiazepine-6-one for 1 hour in the presence of excess triethylamine and of dioxan as solvent, 11-(acryloyl)-5,11-dihydro-6H-pyrido[2,3-b][1,4]benzodiazepine-6-one, M.p.: 235°C (decomp) (from acetonitrile) may be obtained in high yield (compare DT-PS 1,936,670).

The compounds of general formula V are well-known from the literature. (compare DT-PS 1,179,943 and 1,204,680).

As mentioned above the compounds according to the invention possess 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 ulcus ventriculi et duodeni, against gastritis and other disturbances of the stomach and intestines.

The following substances, i.e.

11-[(1-ethylpyrrolidin-2-yl)methylamino]acetyl - 5,11-dihydro-5-methyl-6H-pyrido[2,3-b][1,4]benzodiazepine-6-one

= A,

5,11-dihydro-11-[(4-methoxypiperidino)acetyl]-6H-pyrido-[2,3-b][1,4]benzodiazepine-6-one

= B,

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

= C,

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

= D,

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

= E,

were examined with regard to their inhibitory effect on the formation of stress-ulcers in rats and on their spasmolytic effect on atropine, as well as with regard to their acute toxicity.

The inhibitory effect on the formation of stress-ulcers 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 a small wire-cage and subsequently kept vertically in a water-bath, maintained constantly at a temperature of 23°C, for 16 hours, so that only the heads and breastbones of the animals were above the water surface.

The test compounds were administered orally about 5 to 10 minutes before this procedure. Five animals were used per test compound.

(12)

In an analogous way 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. 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 carried out according to the method of Marazzi-Uberti and Turba, Takagi and Okabe as described in Med. Exp. 4, pp. 284-292 (1961).

The spasmolytic effect was determined *in vitro* by means of guinea-pig colons according to the test of R. Magnus, Pflugers Archiv 102, pp. 123 (1904). Acetylcholine was used for spasm-provocation and the control substance was atropine sulfate. The spasticum was administered one minute before administration of the spasmolyticum and the effective period of the spasmolyticum was 1 minute. In rats it was observed that the atropinic side-effects such as retardation of saliva secretion, were missing completely or were remarkably decreased by compounds A to E.

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

The following table shows the values obtained:

Test Compound	Ulcer-inhibition in % (rat) after oral administr. of			Spasmolysis (acetylcholine) with regard to Atropine = 1	LD ₅₀
	50	25	12.5		
	mg/kg				
A	95	90	90	1/250	~1500*
B	89	79	53	1/125	>1000**
C	95	84	79	1/50	>1000***
D	84	69	58	1/125	~2000****
E	79	58	18	1/190	>1500*****

* at 1500 mg/kg 2 out of 4 animals died;

** at 1000 mg/kg 2 out of 5 animals died;

*** at 1000 mg/kg 1 out of 5 animals died;

**** at 2000 mg/kg 3 out of 5 animals died;

***** at 1500 mg/kg 1 out of 6 animals died;

The spasmolytic effect of compounds A to E in comparison with that of atropine sulfate is remarkably lower and therefore also the atropinic side-effects.

According to yet a 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 parenteral 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 from 30 to 100 mg per day in adults.

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

EXAMPLE 1

11-[(1-Ethylpyrrolidin-2-yl)methylamino]acetyl-5,11-dihydro-5-methyl-6H-pyrido[2,3-b][1,4]benzodiazepine-6-one

9.0 g of 11-chloroacetyl-5,11-dihydro-5-methyl-6H-pyrido[2,3-b][1,4]benzodiazepine-6-one, 3.5 g of sodium carbonate and 4 g of 1-ethyl-2-aminomethyl-pyrrolidine were refluxed in 100 ml of ethanol for 1.5 hours. The hot mixture thus obtained was filtered with suction and the filtrate was evaporated *in vacuo* to dryness. The residue was recrystallized from acetonitrile and then from ethyl acetate.

M.p.: 169-171°C

Yield: 48 % of theory

Dihydrochloride: M.p.: 196-198°C (from ethanol).

EXAMPLE 2

5,11-Dihydro-11-[(4-methoxypiperidino)acetyl]-6H-pyrido[2,3-b]-[1,4]benzodiazepine-6-one

5.8 g of 11-chloroacetyl-5,11-dihydro-6H-pyrido[2,3-b][1,4] benzodiazepine-6-one and 15 ml of 4-methoxypiperidine were refluxed in 200 ml of benzene for 15 hours. The resultant hot mixture was filtered with suction. The solvent was distilled off from the filtrate and the residue was recrystallized from isopropanol.

M.p.: 219-220°C

Yield: 55% of theory.

EXAMPLE 3

11-Dibenzylaminoacetyl-5,11-dihydro-6H-pyrido[2,3-b][1,4]-benzodiazepine-6-one

6 g of 11-chloroacetyl-5,11-dihydro-6H-pyrido[2,3-b][1,4]-benzodiazepine-6-one, 4.2 g of dibenzylamine and 2.1 g of triethylamine were refluxed in 100 ml of abs. dioxan for 15 hours. After cooling of the resultant mixture the triethylamine hydrochloride formed was separated off and the filtrate was evaporated *in vacuo* to dryness. The residue was then recrystallized twice from ethanol.

M.p.: 187-189°C

Yield: 60% of theory.

EXAMPLE 4

5,11-Dihydro-11-[3-(2-methylpiperidino)Propionyl]-6H-pyrido-[2,3-b][1,4]benzodiazepine-6-one

16 g of 11-(3-chloropropionyl)-5,11-dihydro-6H-pyrido[2,3-b]-[1,4]benzodiazepine-6-one and 20 ml of 1-methylpiperidine were refluxed for 1 hour in 200 ml of isopropanol. The mixture obtained was evaporated *in vacuo* to dryness and the residue was mixed with water. The resultant mixture was made alkaline by addition of ammonia and then extracted with chloroform. The residue of the chloroform extract after evaporation was purified on a silica gel column. The eluate was evaporated *in vacuo* to dryness and the residue recrystallized from isopropanol.

M.p.: 197-199°C (under decomposition)

Yield: 65% of theory.

EXAMPLE 5

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

4.9 g of 11-acryloyl-5,11-dihydro-6H-pyrido [3-b][1,4]benzodiazepine-6-one and 15 ml of piperidine were refluxed in 150 ml of dioxan for 2 hours. The solvent and excess amine were then distilled off *in vacuo* and the residue was recrystallized from n-propanol.

M.p.: 230°C (under decomposition)

Yield: 72% of theory.

EXAMPLE 6

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

6.0 g of 11-(3-chloropropionyl)-5,11-dihydro-6H-pyrido[2,3-b]-[1,4]benzodiazepine-6-one, 2.3 g of sodium carbonate and 4.4 g of benzylamine were refluxed in 80 ml of ethanol for 4 hours. The resultant hot mixture was filtered with suction. The alcohol was distilled off from the filtrate and the residue was purified on a silica gel column. The evaporated eluate was twice recrystallized from n-propanol.

M.p.: 155-158°C

Yield: 41% of theory.

EXAMPLE 7

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

16.4 g of 11-[3-(benzylamino)propionyl]-5,11-dihydro-6H-pyrido[2,3-b][1,4]benzodiazepine-6-one (prepared according to Example 6) together with 3 g of palladium on charcoal were hydrogenated in 300 ml of abs. ethanol for 7 hours at 70°C and 5 The catalyst was then filtered off and the alcohol was distilled off from the filtrate. The residue was purified on a column. After evaporation of the eluate, the residue obtained was recrystallized from ethanol.

M.p.: 198-200°C

Yield: 37% of theory.

EXAMPLE 8

11-[4-(Diethylamino)butyryl]-5,11-dihydro-5-methyl-6H-pyrido-[2,3-b][1,4]benzodiazepine-6-one hydrochloride

4.3 g of 11-(4-chlorobutyryl)-5, 11-dihydro-5-methyl-6H-pyrido-[2,3-b][1,4]benzodiazepine-6-one and 1.9 g of diethylamine in 70 ml of dimethylformamide were allowed to stand for 3 weeks at room temperature. The resultant mixture was then evaporated *in vacuo* to dryness and the residue was recrystallized from isopropanol. The hydrochloride of M.p.: 233-235°C was obtained.

Yield: 54% of theory.

EXAMPLE 9

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

5.5 g of 11-(4-chlorobutyryl)-5,11-dihydro-6H-pyrido[2,3-b][1,4]-benzodiazepine-6-one, 1.4 g of pyrrolidine and 2.1 g of sodium carbonate were refluxed in a mixture of 80 ml of abs. ethanol and 20 ml of abs. dioxan for 10 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 *in vacuo* to dryness and the residue was recrystallized from acetonitrile.

M.p.: 163-165°C

Yield: 55% of theory.

EXAMPLE 10

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

7.2 g of 11-chloroacetyl-5, 11-dihydro-6H-pyrido[2,3-b][1,4]benzodiazepine-6-one, 2.8 g of sodium carbonate and 3.8 g of 1-ethyl-3-amino-piperidine were refluxed in 100 ml of ethanol for 5 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 evaporated eluate was recrystallized from ethyl acetate.

M.p. 147-148°C

Yield: 58% of theory.

EXAMPLE 11

5,11-Dihydro-11-[hexahydro-4-methyl-1H-1,4-diazepin-1-yl)-acetyl]-6H-pyrido[2,3-b][1,4]benzodiazepine-6-one dihydrochloride

8.6 g of 11-chloroacetyl-5,11-dihydro-6H-pyrido[2,3-b][1,4]-benzodiazepine-6-one, 3.5 g of sodium carbonate and 4.5 g of hexahydro-1-methyl-1H-1,4-diazepine were refluxed in 100 ml of ethanol for 2.5 hours. The resultant hot mixture was filtered with suction. The alcohol was distilled off from the filtrate and the residue was triturated with dioxan. The crystals thus precipitated were dissolved in ethanol and converted into the dihydrochloride by addition of concentrated hydrochloric acid.

After recrystallization from 94% ethanol:

M.p.: 241-243°C (under decomposition)

Yield: 47% of theory.

EXAMPLE 12

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

4.5 g of 11-(5-chlorovaleryl)-5,11-dihydro-6H-pyrido[2,3-b][1,4]-benzodiazepine-6-one and 10 ml of pyrrolidine were refluxed in 100 ml of ethanol for 12 hours. The alcohol was then distilled off and the residue dissolved in chloroform/water. The organic phase was separated and evaporated *in vacuo* to dryness. The residue was recrystallized from ethyl acetate.

M.p. 157-159°C

Yield: 45% of theory.

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EXAMPLE 13

11-[(1-Benzylpyrrolidin-2-yl)-methylamino]acetyl-5,11-dihydro-5-methyl-6H-pyrido[2,3-b][1,4]benzodiazepine-6-one

14.3 g of 11-chloroacetyl-5,11-dihydro-5-methyl-6H-pyrido[2,3-b][1,4]benzodiazepine-6-one, 5.3 g of sodium carbonate and 11.4 g of 2-aminomethyl-1-benzyl-pyrrolidine, dissolved in 300 ml of absolute dioxan, were refluxed together for 2 hours. The resultant mixture was filtered while still hot, then the dioxan was evaporated off from the filtrate and the residue was purified on a silica gel column. The eluate was evaporated and the residue recrystallized twice using ethyl acetate.

M.p.: 123-124°C;

Yield: 47% (of theory).

The column-chromatographical purifications of the crude products were carried out in the above Examples using a silica gel column and a mixture of chloroform, methanol, cyclohexane and activated ammonia in a proportion of 68:15:15:2 as both solvent and eluant.

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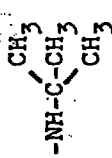
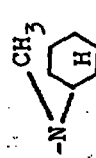
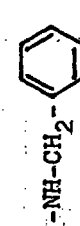
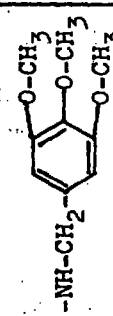
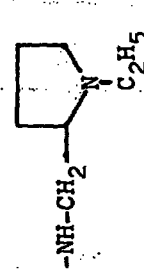
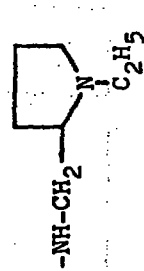
Example	R ₁	R ₂	A	M.p. (recryst. from)	Yield %	prepared acc. to Example
14	$\begin{array}{c} \text{CH}_3 \\ \diagup \\ -\text{N} \\ \diagdown \\ \text{CH}_3 \end{array}$	H	$-(\text{CH}_2)_3-$	Hydrochloride; M.p.: 207-209°C (decomp.) (acetone trile)	48	8
15	$\begin{array}{c} \text{C}_2\text{H}_5 \\ \diagup \\ -\text{N} \\ \diagdown \\ \text{C}_2\text{H}_5 \end{array}$	CH ₃	$-\text{CH}_2-\text{CH}_2-$	Hydrochloride; M.p.: 230-232°C (ethanol/isopropanol)	39	2
16	$\begin{array}{c} \text{C}_2\text{H}_5 \\ \diagup \\ -\text{N} \\ \diagdown \\ \text{C}_2\text{H}_5 \end{array}$	H	$-(\text{CH}_2)_3-$	Hydrochloride; M.p.: 209-211°C (acetone trile)	44	8
17	$\begin{array}{c} \text{CH}_3 \qquad \text{CH}_3 \\ \diagup \quad \diagdown \\ \text{CH}_2-\text{CH} \qquad \text{CH}_2-\text{CH} \\ \diagdown \quad \diagup \\ \text{N} \qquad \text{CH}_3 \qquad \text{CH}_3 \end{array}$	CH ₃	$-(\text{CH}_2)_3-$	M.p.: 145-147°C (cyclohexane)	30	3

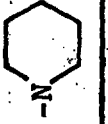
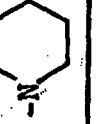
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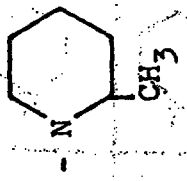
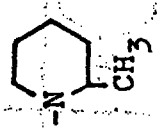
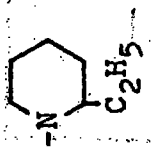
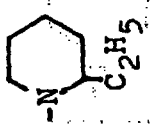
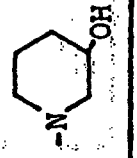
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Example	R ₁	R ₂	A	M.p. (recryst. from)	Yield %	prepared acc. to Example
18		H	-CH ₂ -	M.p.: 198-200°C (ethyl acetate/ chloroform)	37	6
19		H	-CH ₂ -	M.p.: 213-215°C (isopropanol)	63	2
20		H	-CH ₂ -	M.p.: 170-174°C (acetonitrile)	35	6
21		H	-CH ₂ -	M.p.: 198-200°C (decomp.) (n-propanol)	36	6
22		H	-CH ₂ -	M.p.: 173-174°C (isopropanol)	79	6
23		H	-CH ₂ -CH ₂ -	M.p.: 140-143°C (ethyl acetate)	48	6

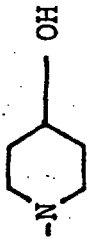
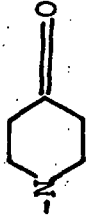
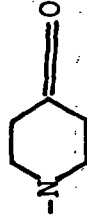
Example	R ₁	R ₂	A	M.p. (recryst. from)	Yield %	prepared acc. to Example
24		H	-CH ₂ -CH ₂ -	M.p.: 204-207°C (decomp.) (acetonitrile)	83	4
25		CH ₃	-CH ₂ -CH ₂ -	M.p.: 155-156°C (xylene)	88	4
26		CH ₃	-(CH ₂) ₃ -	M.p.: 122-123°C (butylacetate)	21	3
27		CH ₃	-CH ₂ -CH ₂ -	M.p.: 160-162°C (xylene)	53	4
28		H	-(CH ₂) ₃ -	M.p.: 157-158°C (acetonitrile)	33	3
29		CH ₃	-(CH ₂) ₃ -	M.p.: 124-125°C (isopropanol)	26	3

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Example	R ₁	R ₂	A	M.p. (recryst. from)	Yield %	prepared acc. to Example
30		CH ₃	-CH ₂ -CH ₂ -	M.p.: 104-106°C (isopropanol) Hydrochloride: M.p.: 260-262°C (methanol/ethanol)	90	4
31		H	-(CH ₂) ₃ -	M.p.: 174-175°C (acetonitrile)	29	8
32		H	-CH ₂ -CH ₂ -	M.p.: 185-187°C (decomp.) (acetonitrile)	78	4
33		CH ₃	-CH ₂ -CH ₂ -	M.p.: 115-116°C (cyclohexane)	53	4
34		H	-CH ₂ -	M.p.: 218-219°C (ethanol/ether)	63	2

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Example	R ₁	R ₂	A	M.p. (recryst. from)	Yield %	Prepared acc. to Example
35		H	-CH ₂ -	M.p.: 247-248°C (ethanol/ether)	54	2
36		H	-CH ₂ -	M.p.: 216-218°C (acetonitrile)	59	2
37		H	-CH ₂ -	M.p.: 223-225°C {decomp.} {ethanol}	43	6
38		CH ₃	-CH ₂ -	M.p.: 177-178°C (i.sopropanol)	39	6
39		H	-CH ₂ -CH ₂ -	M.p.: 210-212°C {decomp.} {ethanol}	24	6

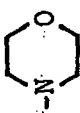
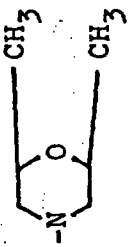
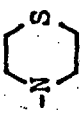
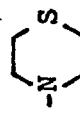
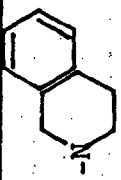
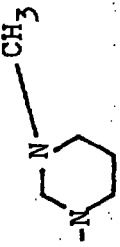
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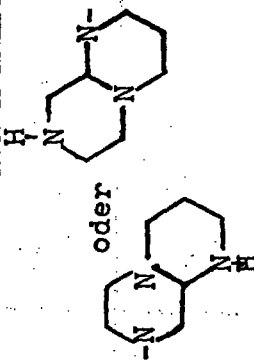
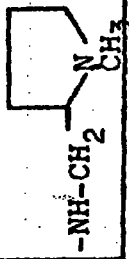
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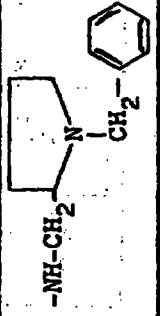
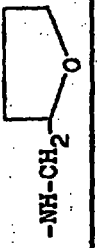
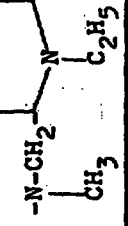
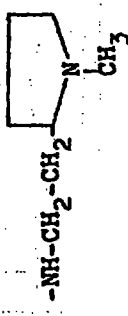
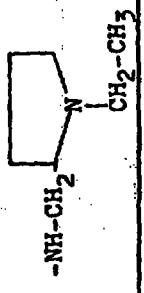
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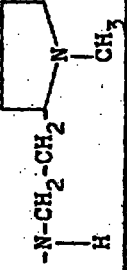
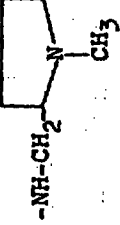
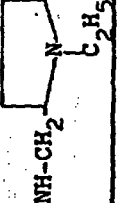
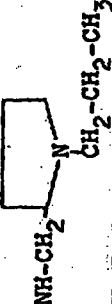
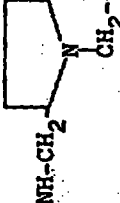
Example	R ₁	R ₂	A	M.p. (recryst. from)	Yield %	Prepared acc. to Example
40		H	-CH ₂ -	M.p.: 219-221°C (isopropanol)	72	6
41		CH ₃	-CH ₂ -	M.p.: 191-192°C (ethanol)	83	6
42		H	-CH ₂ -CH ₂ -	M.p.: 228-230°C (ethanol)	18	2
43		H	-(CH ₂) ₃ -	M.p.: 138-140°C (ethyl acetate)	27	6
44		H	-CH ₂ -	M.p.: 217-219°C (isopropanol)	58	6
45		H	-CH ₂ -CH ₂ -	M.p.: 208-210°C (decomp.) (acetonitrile)	85	4

Example	R ₁	R ₂	A	M.p. (recryst. from)	Yield %	Prepared acc. to Example
46		CH ₃	-CH ₂ -CH ₂ -	M.p.: 200-202°C (xylene)	55	4
47		H	-CH ₂ -	M.p.: 262-264°C (isopropanol)	51	4
48		H	-CH ₂ -	M.p.: 246-248°C (n-propanol)	62	6
49		H	-CH ₂ -	M.p.: 245-246°C (n-propanol)	59	6
50		H	-CH ₂ -	M.p.: 210-211°C (isopropanol)	72	2
51		H	-CH ₂ -	M.p.: 214-216°C (isopropanol)	45	6

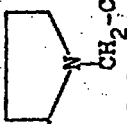
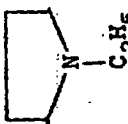
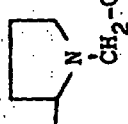
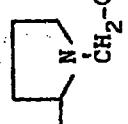
Example	R ₁	R ₂	A	M.p.: (recryst. from)	Yield %	Prepared acc. to Example
52		H	-CH ₂ -	M.p.: 237-240°C (decomp.) (isopropanol)	57	6
53		H	-CH ₂ -	M.p.: 237-239°C (ethanol)	46	6
54		CH ₃	-CH ₂ -CH ₂ -	Hydrochloride: M.p.: 220-221°C (acetonitrile)	47	3
55		H	-CH ₂ -	168-170°C (ethyl acetate)	49	6

Example	R ₁	R ₂	A	M.p.: (recryst. from)	Yield	Prepared acc to Example
56	 -NH-CH ₂ -	H	-CH ₂ -	181-183°C (ethanol)	50	1
57	 -NH-CH ₂ -	H	-CH ₂ -	179-180°C (ethanol)	30	13
58	 -NH-CH ₂ -	H	-CH ₂ -	169-171°C (acetonitrile)	51	5
59	 -N-CH ₂ -	H	-CH ₂ -	143-145°C (cyclohexane/ethyl acetate)	43	13
60	 -NH-CH ₂ -CH ₂ -	H	-CH ₂ -	154-156°C (butyl acetate)	31	13
61	 -NH-CH ₂ -	CH ₃	-CH ₂ -CH ₂ -	84-86°C (cyclohexane/ ethyl acetate)	49	13
62	 -N-	H	-CH ₂ -	219-221°C (isopropanol)	63	1

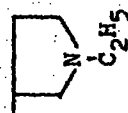
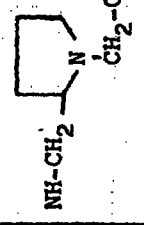
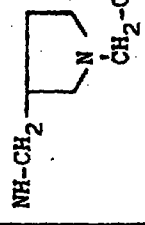
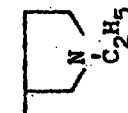
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Example	R ₁	R ₂	A	M.p.: (recryst. from)	Yield	Prepared acc. to Example
63		CH ₃	-CH ₂ -	162-163°C (isopropanol)	81	1
64		H	-CH ₂ -CH ₂ -	207-209°C (ethanol)	65	1
65		CH ₃	-CH ₂ -	141-144°C (ethyl acetate)	32	1
66		CH ₃	-CH ₂ -	179-181°C (isopropanol)	54	1
67		C ₂ H ₅	-CH ₂ -	119-120°C (acetonitrile)	46	1
68		CH ₃	-CH ₂ -	147-148°C (ethyl acetate)	52	1
69		CH ₃	-CH ₂ -	123-125°C (ethyl acetate/ cyclohexane)	45	6

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Example	R ₁	R ₂	A	M.p.: (recryst. from)	Yield	Prepared acc. to Example
70	$\text{NH-CH}_2\text{-}$ 	CH ₃	-CH ₂ -	64-67°C (ethyl acetate/ cyclohexane)	34	6
71	$\text{NH-CH}_2\text{-}$ 	CH ₃	-(CH ₂) ₅ -	Hydrobromide 186-188°C (isopropanol/etha- nol)	50	5
72		H	-(CH ₂) ₅ -	140-142°C (ethyl acetate)	58	5
73	$\text{NH-CH}_2\text{-}$ 	H	-CH ₂ -	150-152°C (acetonitrile)	41	6
74	$\text{NH-CH}_2\text{-}$ 	H	-CH ₂ -	126-128°C (ethyl acetate/ cyclohexane)	35	6

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Example	R ₁	R ₂	A	M.p.: (recryst. from)	Yield	Prepared acc. to Example
75	NH-CH ₂ - 	CH ₃	-CH ₂ -	97-100°C (diethyl ether)	41	6
76	NH-CH ₂ - 	H	-CH ₂ -	114-116°C (butyl acetate)	31	6
77	NH-CH ₂ - 	CH ₃	-CH ₂ -	78-81°C (diethyl ether)	27	6
78	NH-CH ₂ - 	H	-CH ₂ -	86-88°C (diethyl ether)	32	6

EXAMPLE I

Tablets containing 10 mg of 11-[(1-ethylpyrrolidin-2-yl)methylamino]acetyl-5,11-dihydro-5-methyl-6H-pyrido[2,3-b][1,4]benzodiazepine-6-one

Composition:

1 tablet contains:

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

Method of preparation:

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

Weight of tablet:	220 mg
Punch:	9 mm

EXAMPLE II

Coated tablets containing 10 mg of 11-[(1-ethylpyrrolidin-2-yl)methylamino]acetyl-5,11-dihydro-5-methyl-6H-pyrido[2,3-b][1,4]benzodiazepine-6-one

The tablets prepared according to Example I were covered with a coating consisting essentially of sugar and talcum according to known methods. The coated tablets were finally polished with bees-wax.

Weight of coated tablet	300 mg
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EXAMPLE III

Ampoules containing 2 mg of 11-[(1-ethylpyrrolidin-2-yl)methylamino]acetyl-5,11-dihydro-5-methyl-6H-pyrido[2,3-b][1,4]benzodiazepine-6-one dihydrochloride

Composition:

1 ampoule contains:

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

Method of preparation:

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

Sterilisation: 20 minutes at 120°C

Example IV

Suppositories containing 15 mg of 11-[(1-ethylpyrrolidin-2-yl)methylamino]acetyl-5,11-dihydro-5-methyl-6H-pyrido[2,3-b][1,4]benzodiazepine-6-one

Composition:

1 suppository contains:

active ingredient	15.0 mg
suppository mass (e.g. "Witepsol" [registered Trade Mark] W45)	1 685.0 mg 1 700.0 mg

Method of preparation:

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

Weight of suppository:	1.7 g
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EXAMPLE V

Drop solution containing 10 mg/ml of 11-[(1-ethylpyrrolidin-2-yl)methylamino]acetyl]-5,11-dihydro-5-methyl-6H-pyrido[2,3-b]-[1,4]benzodiazepine-6-one dihydrochloride

Composition:

100 ml of drop solution contain:

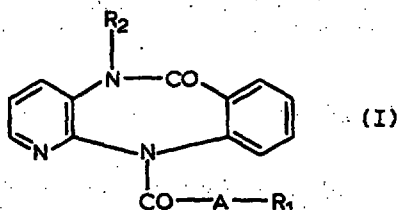
	methyl <i>p</i> -hydroxybenzoate	0.035 g	
	propyl <i>p</i> -hydroxybenzoate	0.015 g	
	anise oil	0.05 g	
10	menthol	0.06 g	10
	ethanol pure	10.0 g	
	active ingredient	1.0 g	
	sodium cyclamate	1.0 g	
	glycerine	15.0 g	
15	dist. water ad.	100.0 ml	15

Method of preparation:

The active ingredient and sodium cyclamate were dissolved in about 70 ml of water and glycerine was added thereto. The *p*-hydroxybenzoates, anise oil and menthol were dissolved in ethanol and added while stirring to the aqueous solution obtained above. Finally, the resultant solution was made up with water to a volume of 100 ml and suspended particles were filtered off.

WHAT WE CLAIM IS:—

1. Compounds of general formula I,



wherein,

R₁ represents a free amino, tert, butylamino, N-cyclohexyl-N-methyl-amino, dibenzylamino, benzylamino, trimethoxybenzylamino, dimethylamino, diethylamino, dipropylamino, di-isopropylamino, di-n-butylamino, diisobutylamino or pyrrolidino group; a piperidino group optionally substituted by a methyl or ethyl group; a morpholino, 1-ethylpyrrolidin-2-ylmethylamino or 1-ethylpiperidin-3-ylamino group; a 9-methyl-3,9-diazabicyclo[3.3.1]nonan-3-yl, 1,2,5,6-tetrahydro-pyrid-1-yl or 4-benzylpiperidino group; a 1,2,3,6,7,8,9,9a-octahydro-4H-pyrazino[1,2-a]pyrimidin-1-or -8-yl group; a 3- or 4-hydroxypiperidino or methoxypiperidino group; a 1,2,3,4-tetrahydroisoquinol-2-yl or 3-azaspiro[5.5]undecan-3-yl group; a 4-oxopiperidino group or the ethylene ketal thereof; a hexahydro-3-methyl-pyrimidin-1-yl, thiomorpholino or 1-oxido-thiomorpholino group; a hexahydro-4-methyl-1H-1,4-diazepin-1-yl or 2,6-dimethylmorpholino group; a 1,4-diazabicyclo[4.3.0]nonan-4-yl, (1-methylpyrrolidin-2-yl)-ethylamino, (1-methylpyrrolidin-2-yl)-methylamino, (1-n-propylpyrrolidin-2-yl)-methylamino, (1-allylpyrrolidin-2-yl)-methylamino, (1-n-butylpyrrolidin-2-yl)-methylamino or (1-benzylpyrrolidin-2-yl)-methylamino group; or a (furan-2-yl)-methylamino, (tetrahydrofuran-2-yl)-methylamino, N-[(1-ethylpyrrolidin-2-yl)-methyl]-methylamino, (1-ethylpyrrolidin-3-yl)-methylamino or (1-allylpyrrolidin-3-yl)-methylamino group;

A represents a straight or branched chain alkylene group containing from 1 to 5 carbon atoms; and

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

and acid addition salts thereof, with the proviso that, when R₁ represents a diethylamino, diethylamino, dipropylamino, di-isopropylamino, di-n-butylamino, di-isobutylamino or pyrrolidino group; a piperidino group optionally substituted by a methyl or ethyl group; or a morpholino or 4-benzylpiperidino group, A represents a straight or branched chain alkylene group containing from 2 to 5 carbon atoms.

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

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

EXAMPLE V

Drop solution containing 10 mg/ml of 11-[(1-ethylpyrrolidin-2-yl)methylamino]-acetyl]-5,11-dihydro-5-methyl-6H-pyrido[2,3-b]-[1,4]benzodiazepine-6-one dihydrochloride

Composition:

5 100 ml of drop solution contain:

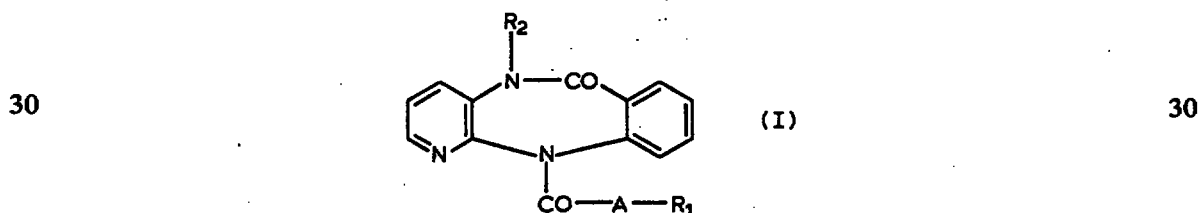
	methyl <i>p</i> -hydroxybenzoate	0.035 g	
	propyl <i>p</i> -hydroxybenzoate	0.015 g	
	anise oil	0.05 g	
10	menthol	0.06 g	10
	ethanol pure	10.0 g	
	active ingredient	1.0 g	
	sodium cyclamate	1.0 g	
	glycerine	15.0 g	
15	dist. water ad.	100.0 ml	15

Method of preparation:

The active ingredient and sodium cyclamate were dissolved in about 70 ml of water and glycerine was added thereto. The *p*-hydroxybenzoates, anise oil and menthol were dissolved in ethanol and added while stirring to the aqueous solution obtained above. Finally, the resultant solution was made up with water to a volume of 100 ml and suspended particles were filtered off.

WHAT WE CLAIM IS:—

25 1. Compounds of general formula I,



35 wherein,

R_1 represents a free amino, tert, butylamino, N-cyclohexyl-N-methyl-amino, dibenzylamino, benzylamino, trimethoxybenzylamino, dimethylamino, diethylamino, dipropylamino, di-isopropylamino, di-n-butylamino, diisobutylamino or pyrrolidino group; a piperidino group optionally substituted by a methyl or ethyl group; a morpholino, 1-ethylpyrrolidin-2-ylmethylamino or 1-ethylpiperidin-3-ylamino group; a 9-methyl-3,9-diazabicyclo[3.3.1]nonan-3-yl, 1,2,5,6-tetrahydro-pyrid-1-yl or 4-benzylpiperidino group; a 1,2,3,6,7,8,9a-octahydro-4H-pyrazino[1,2-a]pyrimidin-1-or -8-yl group; a 3- or 4-hydroxypiperidino or methoxypiperidino group; a 1,2,3,4-tetrahydroisoquinol-2-yl or 3-azaspiro[5.5]undecan-3-yl group; a 4-oxopiperidino group or the ethylene ketal thereof; a 45 hexahydro-3-methyl-pyrimidin-1-yl, thiomorpholino or 1-oxido-thiomorpholino group; a hexahydro-4-methyl-1H-1,4-diazepin-1-yl or 2,6-dimethylmorpholino group; a 1,4-diazabicyclo[4.3.0]nonan-4-yl, (1-methylpyrrolidin-2-yl)-ethylamino, (1-methylpyrrolidin-2-yl)-methylamino, (1-n-propylpyrrolidin-2-yl)-methylamino, (1-allylpyrrolidin-2-yl)-methylamino, (1-n-butylpyrrolidin-2-yl)-methylamino or (1-benzylpyrrolidin-2-yl)-methylamino group; or a (furan-2-yl)-methylamino, (tetrahydrofuran-2-yl)-methylamino, 50 N-[(1-ethylpyrrolidin-2-yl)-methyl]-methylamino, (1-ethylpyrrolidin-3-yl)-methylamino or (1-allylpyrrolidin-3-yl)-methylamino group;

A represents a straight or branched chain alkylene group containing from 1 to 5 carbon atoms; and

55 R_2 represents a hydrogen atom or a methyl or ethyl group; and acid addition salts thereof.

with the proviso that, when R_1 represents a diethylamino, diethylamino, dipropylamino, di-isopropylamino, di-n-butylamino, di-isobutylamino or pyrrolidino group; a piperidino group optionally substituted by a methyl or ethyl group; or a morpholino or 4-benzylpiperidino group, A represents a straight or branched chain alkylene group 60 containing from 2 to 5 carbon atoms.

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

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





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

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

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

7. 11-[1-Ethylpiperid-3-yl)aminoacetyl]-5, 11-dihydro-6H-pyrido[2,3-b][1,4]benzodiazepine-6-one and acid addition salts thereof.

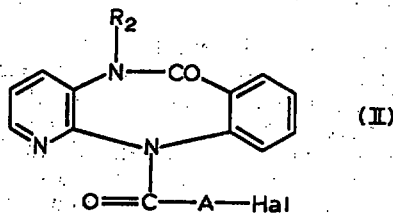
8. Physiologically compatible acid addition salts of compounds of general formula I as defined in claim 1.

9. Compounds of general formula I as defined in claim 1 wherein R_1 represents a free amino, tert. butylamino, N-cyclohexyl-N-methyl-amino, dibenzylamino, benzylamino, trimethoxybenzylamino, dimethylamino, diethylamino, dipropylamino, di-isopropylamino, di-n-butylamino, di-isodutylamino or pyrrolidino group; a piperidino group optionally substituted by a methyl or ethyl group, a morpholino, 1-ethylpyrrolidin-2-ylmethylamino or 1-ethylpiperidin-3-ylamino group; a 9-methyl-3, 9-diazabicyclo-[3.3.1]nonan-3-yl, 1,2,5,6-tetrahydropyrid-1-yl or 4-benzylpiperidino group; a 1,2,3,6,7,8,9,9a-octahydro-4H-pyrazino[1,2-a]pyrimidin-1- or -8-yl group; a 3- or 4-hydroxypiperidino or methoxypiperidino group; a 1,2,3,4-tetrahydroisoquinol-2-yl or 3-azaspiro[5.5]undecan-3-yl group; a 4-oxopiperidino group or the ethylene ketal thereof; a hexahydro-3-methyl-pyrimidin-1-yl, thiomorpholino or 1-oxido-thiomorpholino group; or a hexahydro-4-methyl-1H-1,4-diazepin-1-yl or 2,6 dimethylmorpholino group and the physiologically compatible acid addition salts thereof.

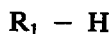
10. Compounds as claimed in claim 1, other than those claimed in any one of claims 2 to 7, as herein specifically disclosed in any one of Examples 1 to 78.

11. Compounds as claimed in claim 9, other than those claimed in any one of claims 3 to 7, as herein specifically disclosed in any one of Examples 1 to 12 and 14 to 53.

12. 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 A and R_2 are as defined in claim 1 and Hal represents a halogen atom) with a compound of formula III,



(III)

(wherein R_1 is as defined in claim 1).

13. A process as claimed in claim 12 wherein the reaction is effected in the presence of an inert solvent.

14. A process as claimed in claim 13 wherein the solvent comprises an alcohol, ketone, ether or aromatic hydrocarbon.

15. A process as claimed in claim 14 wherein the solvent comprises ethanol, n-propanol, isopropanol, acetone, dioxan, tetrahydrofuran, benzene or toluene.

16. A process as claimed in any one of claims 12 to 15 wherein the reaction is effected at elevated temperatures.

17. A process as claimed in claim 16 wherein the reaction is effected at the boiling point of the reaction mixture.

18. A process as claimed in any one of claims 12 to 17 wherein the reaction is effected in the presence of a hydrogen halide-binding agent.

19. A process as claimed in claim 18 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.

20. A process as claimed in claim 19 wherein the hydrogen halide-binding agent is triethylamine, pyridine or dimethylaniline.

21. A process for the preparation of compounds of general formula I as defined in claim 1 wherein A represents an alkylene group containing from 2 to 5 carbon atoms which comprises reacting a compound of formula VI,

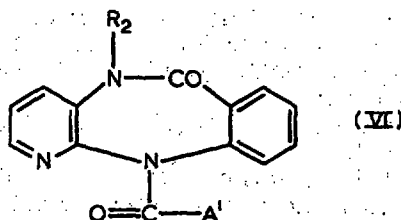
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(wherein R_2 is as defined in claim 1 and A' represents an alkenyl group containing from 2 to 5 carbon atoms) with a compound of formula III as defined in claim 12 whereby the desired compound of formula I is obtained.

22. A process as claimed in claim 21 wherein the reaction is effected in the presence of an alcohol, ketone, ether or aromatic hydrocarbon as solvent.

23. A process as claimed in claim 22 wherein the reaction is effected in the presence of ethanol, n-propanol, isopropanol, acetone, dioxane, tetrahydrofuran, benzene or toluene as solvent.

24. A process as claimed in any one of claims 21 to 23 wherein the reaction is effected at temperatures of from ambient temperature to the boiling point of the reaction mixture.

25. A process as claimed in any one of claims 21 to 24 wherein the compound of formula VI is obtained by heating a compound of formula II as defined in claim 12 wherein A represents an alkylene group containing from 2 to 5 carbon atoms in the presence of a hydrogen halide-binding agent.

26. A process as claimed in claim 25 wherein the hydrogen halide-binding agent is an alkali metal carbonate, alkali metal hydrogen carbonate or tertiary organic amine.

27. A process as claimed in claim 26 wherein the hydrogen halide-binding agent is triethylamine, pyridine or dimethylaniline.

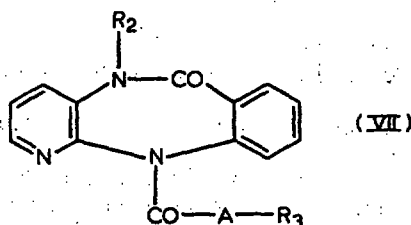
28. A process as claimed in any one of claims 25 to 27 wherein the heating of the compound of formula II is effected in the presence of a high boiling ether or aromatic hydrocarbon as solvent.

29. A process as claimed in claim 28 wherein the heating of the compound of formula II is effected in the presence of dioxane, tetrahydrofuran, benzene or toluene as solvent.

30. A process as claimed in any one of claims 25 to 29 wherein the heating of the compound of formula II is effected to the boiling point of the reaction mixture.

31. A process as claimed in any one of claims 12 to 30, for the preparation of compounds of general formula I wherein R_1 represents a free amino group, wherein the reaction of the compound of formula II or VI with the compound of formula III is effected under pressure in a closed vessel.

32. A process for the preparation of compounds of general formula I as defined in claim 1 wherein R_1 represents a free amino group which comprises catalytically hydrogenating a compound of formula VII.



[wherein A and R_2 are as defined in claim 1 and R_3 represents an (optionally substituted benzyl) amino group].

33. A process as claimed in claim 32 wherein the catalyst is palladium on charcoal.

34. A process as claimed in claim 32 or claim 33 wherein, in the compound of formula VII, R_3 represents a benzylamino or trimethoxybenzylamino group.

35. A process as claimed in any one of claims 32 to 34 wherein the compound of formula VII is obtained by reaction of a compound of formula II as defined in claim 12 with (optionally substituted benzyl)amine.

36. 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.

37. A process as claimed in claim 36 wherein the acid is hydrochloric, hydrobromic, sulfuric, phosphoric, acetic, citric, fumaric, maleic, succinic or oxalic acid.

38. A process as claimed in any one of claims 12 to 37 for the preparation of compounds as claimed in claim 9.
39. A process for the preparation of compounds as claimed in claim 1 substantially as herein described.
- 5 40. A process for the preparation of compounds as claimed in claim 1 substantially as herein described in any of Examples 1 to 78.
41. A process for the preparation of compounds as claimed in claim 9 substantially as herein described in any one of Examples 1 to 12 and 14 to 53.
- 10 42. Compounds as claimed in claim 1 whenever prepared by a process as claimed in any one of claims 12 to 37, 39 and 40.
43. Compounds as claimed in claim 9 whenever prepared by a process as claimed in claim 38 or claim 41.
- 15 44. 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.
45. Compositions as claimed in claim 44 in a form suitable for oral, rectal or parenteral administration.
- 20 46. Compositions as claimed in claim 44 or claims 45 in the form of tablets, coated tablets, ampoules, suppositories, infusions and solutions.
47. Compositions as claimed in any one of claims 44 to 46 in the form of dosage units.
- 20 48. Compositions as claimed in claim 47 wherein each dosage unit contains from 5 to 50 mg of active ingredient.
49. Compositions as claimed in claim 48 wherein each dosage unit contains from 10 to 30 mg of active ingredient.
- 25 50. Compositions as claimed in any one of claims 44 to 49 wherein the active ingredient comprises a compound as claimed in any one of claims 2 to 7.
51. Compositions as claimed in claim 44 wherein the active ingredient comprises a compound as claimed in claim 9.
- 30 52. Pharmaceutical compositions as claimed in claim 44 substantially as herein described.
53. Pharmaceutical compositions substantially as herein described in any one of Examples I to V.

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