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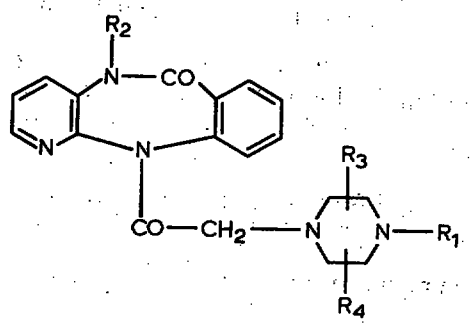


(54) PYRIDOBENZODIAZEPINES

(71) We, DR. KARL THOMAE Gesellschaft mit beschrankter Haftung, a Body Corporate organised under the laws of the Federal Republic of Germany of Biberach an de 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,



(I)

wherein

R_1 represents a straight or branched chain alkyl group containing from 1 to 12 carbon atoms, an unsaturated straight or branched chain aliphatic hydrocarbyl group containing from 3 to 20 carbon atoms and including from 1 to 3 double bonds and/or a triple bond, a phenylalkyl group in which the alkylene moiety may be straight or branched and contain from 2 to 4 carbon atoms, a methylenedioxybenzyl group, a chlorobenzyl group, an indan-5- or indan-3-ylmethyl group, a phenylalkenyl group in which the alkenyl moiety contains from 2 to 4 carbon atoms, a cycloalkyl group containg from 5 to 7 carbon atoms, a cycloalkylmethyl group in which the cycloalkyl ring contains from 3 to 10 carbon atoms and may optionally be substituted by a methyl group; or a morpholino-, pyrrolidino-, piperidino- or 4-methylpiperazino-alkyl group in which the alkylene moiety contains 2 or 3 carbon atoms;

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

R_3 and R_4, which may be the same or different, each represents a hydrogen atom or a methyl or ethyl group,

with the proviso that, when R_1 represents a methyl or ethyl group, R_3 and/or R_4 represents a methyl or ethyl group;

and acid addition salts thereof.

The compounds according to the invention possess interesting

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pharmacological properties and in particular in general, an ulcus inhibiting and secretion inhibiting effect.

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, sec.butyl, isobutyl, tert.butyl, neopentyl, isopentyl, n-pentyl, 1-methylbutyl, 3-methylbutyl, n-hexyl, 4-methylpentyl, 2-ethylbutyl, 3,3-dimethylbutyl, heptyl, octyl, nonyl, decyl, undecyl or dodecyl group; a 2-methylallyl, allyl, but-2-enyl, 1-methylallyl, pent-4-enyl, 3-methyl-but-2-enyl, n-hex-5-enyl, n-hept-6-enyl, farnesyl, neryl, geranyl, citronellyl, phytyl or propargyl group; a 2-phenylethyl, 1-phenylethyl, 3-phenylpropyl, 2-phenylpropyl, 1-phenylpropyl, phenylisopropyl or 4-phenylbutyl group; a cinnamyl or phenylethylenyl group; a 4-phenyl-but-2-or -3-enyl group or an isomer thereof in which the phenyl group is in 2- or 3-positions; a cyclopentyl, cyclohexyl or cycloheptyl group; or an adamantyl, cycloheptyl, cyclohexyl, cyclopentyl, cyclobutyl, cyclopropyl or bicyclo[2,2,1]hept-2-yl-methyl group.

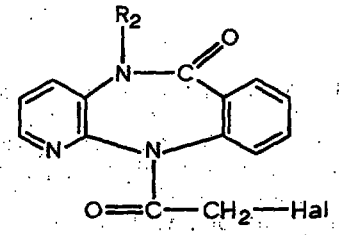
Particularly preferred compounds according to the invention are the following:

5,11 - dihydro - 11{[4 - (2 - methylallyl) - piperazin - 1 - yl] - acetyl} - 6H - pyrido [2,3-b][1-4]benzodiazepine-6-one,
5,11 - dihydro - 11 - {[4 - (3 - methylbut - 2 - enyl) - piperazin - 1 - yl]acetyl} - 6H - pyrido[2,3-b][1,4]benzodiazepine-6-one,
5,11 - dihydro - 11 - {[4 - (2,2 - dimethylpropyl) - piperazine - 1 - yl]acetyl} - 6H - pyrido[2,3-b][1,4]benzodiazepine-6-one,
11 - {[4 - (adamantylmethyl) - piperazin - 1 - yl]acetyl} - 5,11 - dihydro - 6H - pyrido - [2,3 - b] [1,4]benzodiazepine - 6 - one,
5,11 - dihydro - 11 - {[3,4 - methylenedioxybenzyl) - piperazin - 1 - yl]acetyl} - 6H - pyrido[2,3-b][1,4]benzodiazepine-6-one,
5,11 - dihydro - 11[2,4 - dimethylpiperazin - 1 - yl)acetyl] - 6H - pyrido[2,3-b][1,4] benzodiazepine-6-one,
5,11 - dihydro - 5 - methyl - 11 -{[4 - (3,4 - methylenedioxybenzyl) - piperazin - 1 - yl]acetyl} - 6H - pydrido[2,3][1,4]benzodiazepine - 6 - one,
11 - [(4 - cinnamylpiperazin - 1 - yl)acetyl] - 5,11 - dihydro - 6H - pyrido[2,3-b][1,4] benzodiazepine-6-one

and acid addition salts thereof.

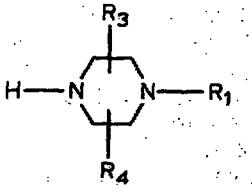
The compounds of general formula I may, for example, be prepared by the following processes, which processes constitute further features of the present invention:

A. Reaction of a compound of forumla II,



(II)

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

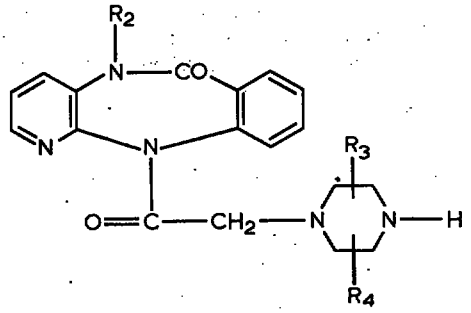


(III)

(wherein R_1, R_3 and R_4 are 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. The reaction is preferably effected at elevated temperatures, most preferably at the boiling point of the reaction mixture. It is preferred to effect the reaction in the presence of a hydrogen halide-binding agent which may, for example, be an alkali metal carbonate or hydrogen carbonate, a tertiary organic amine e.g. methylamine, pyridine or dimethylaniline, or an excess of the compound of formula III.

B. Reaction of a compound of formula IV,



(IV)

(wherein R_2, R_3 and R_4 are as hereinbefore defined) with a compound of formula V,

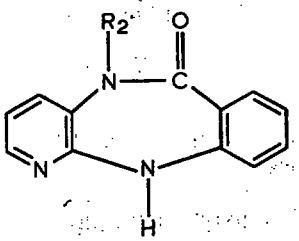
$$R_1—Hal \qquad (V)$$

(wherein R_1 and Hal are as hereinbefore defined).

The reaction is preferably effected in the presence of an alcohol e.g. ethanol, n-propanol or is opropanol, an ether e.g. dioxan or tetrahydrofuran, or a ketone e.g. acetone as solvent and preferably at the boiling point of the reaction mixture. It is preferred to effect the reaction in the presence of a hydrogen halide-binding agent such as, for example, an alkali metal carbonate or hydrogen carbonate, or a tertiary organic amine e.g. methylamine, pyridine or dimethylaniline.

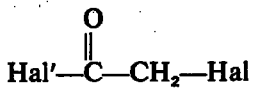
The compounds of general formula I may, if desired, be converted into their acid addition salts by reaction with an appropriate acid. Suitable acids include, for example, hydrochloric, hydrobomic, sulfuric, phosphoric, acetic, fumaric, citric, maleic, succinic and oxalic acid.

The compounds of general formula II, useful as starting materials in process A described above, may for example, be obtained by reaction of a compound of formula VI,



(VI)

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

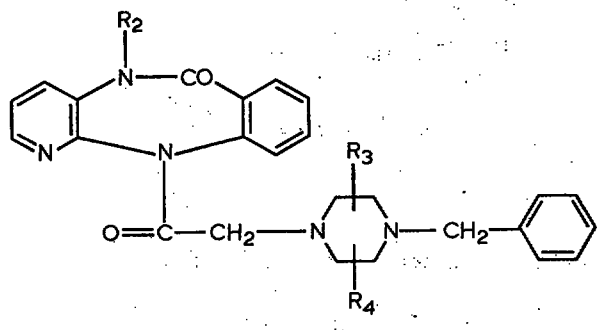


(VII)

(wherein Hal and Hal', which may be the same or different, each represents a chlorine, bromine or iodine atom). The reaction is preferably carried out in the presence of an inert solvent and of a hydrogen halide-binding agent and at elevated temperatures, most preferably at the boiling point of the reaction mixture. Suitable

solvents include, for example aromatic hydrocarbons, e.g. benzene, toluene and xylene ethers, e.g. diethyl ether and dipropyl ether and especially cyclic ethers, e.g. dioxan. As hydrogen halide-binding agents may be used tertiary organic bases, e.g. triethylamine, N-N-dimethylaniline and pyridine, or also inorganic bases, e.g. alkali metal carbonates or alkali metal hydrogen carbonates. Processing of the reaction mixture is carried out according to conventional methods and the yield generally amounts to up to 90% of theory. The compounds of general formula II thus formed are mostly easily crystallizable substances (compare as well DT—PS 1,795,183). The compounds of general formula VI are well known from the literature (see German Patent Specification Nos. 1,179,943 and 1,204,680).

The compounds of general formula IV, useful as starting materials in process B described above, may for example be obtained from compound of general formula II by reaction under reflux with N-benzyl-piperazine in a solvent such as, for example ether, dioxan, ethanol, propanol or benzene. A crystalline precipitate is obtained, which may be filtered off with suction and isolated, for example, as its hydrochloride. The thus formed compound of general formula VIII,



(VIII)

(wherein R_2, R_3 and R_4 are hereinbefore defined) may subsequently be dissolved as a free base in an alcohol, for example, in methanol, and hydrogenated by means of hydrogen in the presence of palladium on charcoal at 20° to 80°C, preferably at 50°C and at a hydrogen pressure of 1 to 100 atm, preferably 50 atm; the desired compound of formula IV may then be isolated from the reaction mixture.

As mentioned above, the compounds of general formula I and their physiologically compatible acid addition salts possess interesting pharmacological properties. Those compounds which we have tested exhibit an ulcus 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

5,11-dihydro-11{[4-(2-methylallyl)-piperazin-1-yl]-acetyl}-6H-pyrido[2,3-b][1,4]benzodiazepine-6-one = A

5,11-dihydro-11-{[4-(3-methyl-but-2-enyl)-piperazin-1-yl]acetyl}-6H-pyrido[2,3-b][1,4]benzodiazepine-6-one dihydrochloride

5,11-dihydro-11-{[4-(2,2-dimethylpropyl)-piperazin-1-yl]acetyl}-6H-pyrido[2,3-b][1,4]benzodiazepine-6-one = C

11-{[4-(1-adamantylmethyl)-piperazin-1-yl]acetyl}-5,11-dihydro-6H-pyrido[2,3-b][1,4]benzodiazepine-6-one = D

5,11-dihydro-11{[4-(3,4-methylendioxybenzyl)-piperazin-1-yl]acetyl}-6H-pyrido[2,3-b][1,4]benzodiazepine-6-one = E

5,11-dihydro-11-[2,4-dimethylpiperazin-1-yl)-acetyl]-6H-pyrido[2,3-b][1,4]benzodiazepine-6-one hydrochloride = F

5,11-dihydro-5-methyl-11{[4-(3,4-methylene-dioxybenzyl)-piperazin-1-yl[acetyl]-6H-pyrido[2,3-b][1,4]benzodiazepine-6-one = G

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

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

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 to 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 suspended vertically in a water-bath which was kept constant at a temperature of 23°C for 16 hours, so that only the heads and the breastbones of the animals were above water level. The test compounds were administered orally 5 to 10 minutes before. Five animals were treated with each test compund 1 ml of a 0.09% physiological sodium chloride solution or 1 ml of a 1% tylose solution was administered to each of a control group of animals in the same way. After 18 hours the animals were killed by an overdose of chloroethane and 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 and Takagi and Okabe described in Med.Exp.*4*, pp. 284 to 292 (1961).

The spasmolytic effect was determined *in vitro* in guinea-pig colons using an experimental technique according to R. Magnus, Pflugers Archiv, *102*, pp. 123 (1904). Acetylcholine was used to cause spasms. The effect of the test compounds was compared with that of atropine sulfate. The spasticum was administered one minute before the administration of the spasmolytic substance, the effective period of the spasmolytic substance was 1 minute. In rats it was also observed that the atropinic side-effects, such as inhibition of salivary secretion, were completely missing or remarkably decreased after prior administration of compounds A to H. 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. For each dosage a group of six mice was used.
The following table show the values obtained:

Test Compound	Ulcus-inhibition in % (rat) after peroral administration of 50 25 12.5 mg/kg			Spasmolysis (acetylcholine) with respect to Atropine) = 1	LD_{50} peroral mg/kg mouse
A	90	52	32	1/330	$>3000^{+}$
B	84	63	52	1/200	$>1500^{+}$
C	95	61	39	1/70	$>1500^{+}$
D	79	47	26	1/86	$>3000^{+}$
E	95	73	37	1/78	$>3000^{+++}$
F	95	90	84	1/130	$>3000^{++}$
G	90	58	21	1/290	$>1500^{+++}$
H	95	69	53	1/700	$\sim 3000^{+++}$

+ means, 0 of 6 animals died;

++ means, 1 of 6 animals died;

+++ means, 2 of 6 animals died;

++++ means, 4 of 6 animals died;

The spasmolytic effect of the compounds A to H as compared with atropine sulfate is remarkably weak, as are the atropinic side-effects.

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. 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 90 mg per day in adults.

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

Example 1.

5,11 - Dihydro - 11 - {[4-(2-methylallyl) - piperazin - 1 - yl]acetyl} - 6H - pyrido[2,3-b] [1,4]benzodiazepine - 6 - one

8.62 g of 11-chloroacetyl-5,11-dihydro-6H-pyrido[2,3b][1,4]-benzodiazepine-6-one, 3.5 g of sodium carbonate and 4.6g of 1-(2-methylallyl)-piperazine were refluxed together in 100 ml of absolute ethanol for 2 hours. The mixture obtained was filtered with suction while still hot and the filtrate evaporated to a volume of 40 ml then cooled. The crystals thus precipitated were recrystallized from ethanol with addition of active charcoal.

M.p.: 205—207°C.

The yield was 75% of theory.

Example 2.

5,11 - Dihydro - 11 - {[4-(3 - methylbut - 2 - enyl) - piperazin - 1 yl]acetyl} - 6H - pyrido[2,3-b][1,4]benzodiazepine - 6 - one dihydrochloride

8.62 g of 11 - chloroacetyl - 5,11 - dihydro - 6H - pyrido[2,3 - b][1,4] - benzo - diazepine-6-one, 3.5 g of sodium carbonate and 5.07 g of 1-(3-methylbut-2-enyl)-piperazine ($R_1 = -CH_2-CH=C(CH_3)_2$) were refluxed together in 100 ml of isopropanol for 2.5 hours. The mixture obtained was filtered with suction while still hot and the filtrate was evaporated to a volume of 40 ml then cooled. The crystals thus precipitated were dissolved while heating in 100 ml of absolute ethanol and the calculated quantity of concentrated hydrochloric acid necessary to form the hydrochloride was added. On cooling the dihydrochloride crystallized out.

M.p.: 208—211°C.

Yield: 70% of theory.

Example 3.

5,11 - Dihydro - 11 - {[4 - (2,2 - dimethylpropyl) - piperazin - 1 - yl] - acetyl} - 6H - pyrido[2,3-b][1,4]benzodiazepine - 6 - one

7.15 g of 11-chloroacetyl-5,11-dihydro-6H-pyrido[2,3-b][1,4]benzodiazepine-6-one, 2.9 g of potassium carbonate and 4.5 g of 1-(2,2-dimethylpropyl)-piperazine were refluxed for 5 hours in 100 ml of absolute ethanol. The hot resultant mixture was then filtered with suction. The crystals, precipitated out of the filtrate, were recrystallized from isopropanol using active charcoal.

M.p.: 232—234°C.

Yield: 40% of theory.

Example 4.

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

8.62 g of 11-chloroacetyl-5,11-dihydro-6H-pyrido[2,3-b][1,4]benzodiazepine-6-one and 8.3 g of 1-allylpiperazine were refluxed in 100 ml of ethanol for 2 hours. The mixture obtained was evaporated and the crystalline residue obtained was sub-

sequently recrystallized from 30 ml of isopropanol and then from 94% ethanol using active charcoal.
M.p.: 230—233°C.
Yield: 47% of theory.

Example 5.

11 - {[4 - (n - But - 2 - enyl) - piperazin - 1 - yl]acetyl} - 5,11 - dihydro - 6H - pyrido [2,3-b][1,4]benzodiazepine-6-one dihydrochloride dihydrate

8.62 g of 11-chloroacetyl-5,11-dihydro-6H-pyrido[2,3-b][1,4]benzodiazepine-6-one and 8.7 g of 1-(n-but-2-enyl)-piperazine ($R = -CH_2—CH=CH—CH_3$) were refluxed in 100 ml of dioxan for 3 hours and then the resultant mixture was evaporated *in vacuo*. The residue was purified on a silica gel column and the obtained oily base was diluted while hot with 70 ml of isopropanol. The mixture thus obtained was acidified with hydrochloric acid whereupon the dihydrochloride crystallized out. The reaction mixture was recrystallized from 94% ethanol. The crystals obtained included 2 mol of water of crystallisation and melted at 207—210°C.
Yield: 35% of theory.

Example 6.

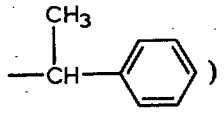
5,11 - Dihydro - 11 - [4 - nerylpiperazin - 1 - yl)acetyl] - 6H - pyrido - [2,3-b][1,4] benzodiazepine - 6 - one dihydrochloride

Produced from 5.8 g of 11-chloroacetyl-5,11-dihydro-6H-pyrido[2,3-b][1,4]benzodiazepine-6-one, 2.4 g of sodium carbonate and 5.3 g of 1-nerylpiperazine in 100 ml of absolute ethanol analogously to Example 1. The crude product obtained was purified on a silica gel column and converted to the dihydrochloride in absolute ethanol with concentrated hydrochloric acid. After recrystallization from absolute ethanol.
M.p.: 188—191°c.
Yield: 65% of theory.

Example 7.

5,11 - Dihydro - 11 - {[4 - (α - methylbenzyl) - piperazin - 1 - yl]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, 3 ml of triethylamine and 4.2 g of 1-(α-methylbenzyl)piperazine ($R_1 =$



) were stirred in 40 ml of dioxan for 2 hours at 80°C. The dark solution obtained was then evaporated *in vacuo* and the residue dissolved in chloroform/water by shaking. The organic phase was then cleared with active charcoal, dried over sodium sulfate and evaported *in vacuo*. The residue was recrystallized from a mixture of ethyl acetate and cyclohexane.
M.p.: 204—206°C.
Yield: 62% of theory.

Example 8.

5,11 - Dihydro - 11 - {[4 - (2 - morpholinoethyl) - piperazin - 1 - yl] - acetyl} - 6H - pyrido[2,3-b][1,4]benzodiazepine - 6 - one

Produced from 8.62 g of 11-chloroacetyl-5,11-dihydro-6H-pyrido[2,3-b][1,4]benzodiazepine-6-one, 3.5 g of sodium carbonate and 6.1 g of 1-(2-morpholinoethyl)-piperazine in 100 ml of absolute ethanol analogously to Example 1.
M.p.: 227—229°C (from n-propanol).
Yield: 63% of theory.

Example 9.

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

4.4 g of 11-chloroacetyl-5,11-dihydro-6H-pyrido[2,3-b][1,4]benzodiazepine-6-

one, 1.8 g of sodium carbonate and 3.75 g of 1-(1-adamantylmethyl)-piperazin were reacted together in 80 ml of absolute ethanol and worked up analogously to Example 1. After recrystallization from a mixture of n-propanol and dimethylformamide.
M.p.: 284—287°C (decomposition).
Yield: 64% of theory.

Example 10.

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

8 g of 11-chloroacetyl-5,11-dihydro-6H-pyrido[2,3-b][1,4]benzodiazepine-6-one and 14 g of 1-(3,4-methylenedioxybenzyl)-piperazine were refluxed in 400 ml of absolute benzene for 18 hours. The resultant mixture was cooled then mixed with ethanol. Ammonia was added to the mixture obtained and the resultant mixture was evaporated *in vacuo*. The precipitate thus formed was recrystallized from aqueous isopropanol and subsequently from isopropanol.
M.p.: 192—193°C.
Yield: 51% of theory.

Example 11.

5,11 - Dihydro - 11 - [2,4 - dimethylpiperazin - 1 - yl)acetyl] - 6H - pyrido[2,3-b][1,4] benzodiazepine - 6 - one hydrochloride

8.6 g of 11-chloroacetyl-5,11-dihydro-6H-pyrido[2,3-b][1,4]benzodiazepine-6-one, 3.1 g of sodium carbonate and 4.5 g of 1,3-dimethylpiperazine were refluxed in 100 ml of absolute ethanol for 3.5 hours. After filtration of the mixture obtained the filtrate was evaporated to dryness. The residue was purified on a silica gel column. The obtained base was dissolved in ethanol followed by addition of hydrochloric acid to form the hydrochloride. After recrystallization from ethanol.
M.p.: 301—303°C.
Yield: 20% of theory.

Example 12.

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

10.5 g of 11-chloroacetyl-5,11-dihydro-5-methyl-6H-pyrido[2,3-b][1,4]benzodiazepine-6-one, 3.8 g of sodium carbonate and 8 g of 1-[(3,4-methylenedioxy)benzyl]-piperazine were reacted in 200 ml of absolute ethanol analogously to Example 1 and likewise processed.
M.p.: 200—202°C.
Yield: 52% of theory.

Example 13.

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

5.05 g of 5,11-dihydro-11-(piperazin-1-ylacetyl)-6H-pyrido[2,3-b][1,4]benzodiazepine-6-one, 2.07 ml of triethylamine and 2.5 ml of cyclohexylmethyl bromide were refluxed for 16 hours in 150 ml of absolute ehtanol. After evaporation *in vacuo* the residue obtained was purified on a silica gel column and then recrystallized from ethanol. The dihydrate was obtained:
M.p.: 222—224°C.
Yield: 33% of theory.

Example 14.

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

8.4 g of 5,11-dihydro-11-(piperazine-1-ylacetyl)-6H-pyrido[2,3-b][1,4]benzodiazepine-6-one, 3.45 ml of triethylamine and 10.5 g of farnesyl bromide were refluxed in 140 ml of n-propanol for 6 hours. The resultant mixture was evaporated and the residue was dissolved in chloroform/water. The organic phase was separated and dried over sodium sulfate. The chloroform was distilled off and the residue was purified on a silica gel column. The base obtained was then dissolved in isopropanol, to which concentrated hydrochloric acid was added. The dihydrochloride crystallized out and was recrystallized from absolute ethanol.
M.p.: 164—170°C (decomposition).
Yield: 29% of theory.

Example 15.

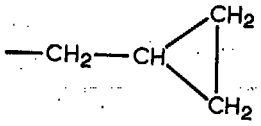
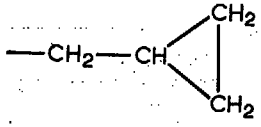
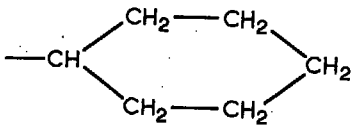
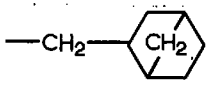
11 - [(4 - Cinnamylpiperazin - 1 - yl)acetyl] - 5,11 - dihydro - 6H - pyrido[2,3-b][1,4] benzodiazepine - 6 - one

5.05 g of 5,11-dihydro-11-(piperazin-1-ylacetyl)-6H-pyrido[2,3-b][1,4]benzodiazepine-6-one, 1.6 g of sodium carbonate and 3.7 g of cinnamyl bromide were refluxed in 80 ml of n-propanol for 3.5 hours. After evaporation of the resultant mixture, the residue was dissolved in chloroform/water. The organic phase was separated and dried over sodium sulfate. The chloroform was distilled off and the residue purified on a silica gel column. After recrystallization from ethyl acetate. M.p.: 196—198°C.
Yield: 41% of theory.

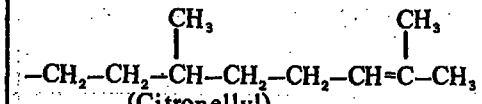
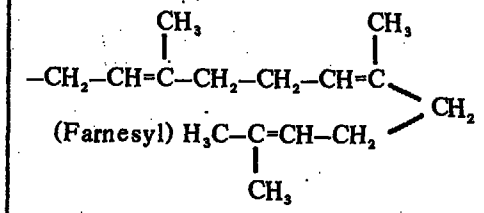
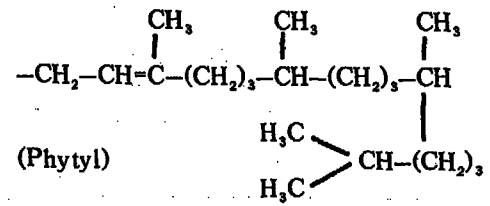
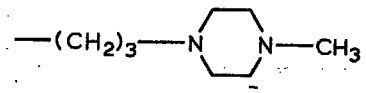
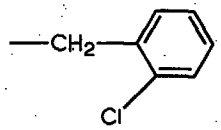
Analogously to Examples 1—15 the compound in the following table were produced:

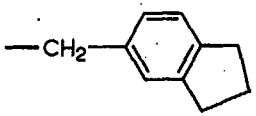
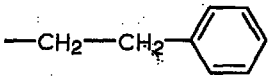
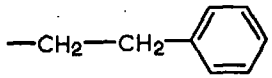
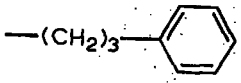
Example	R_1	R_2	R_3	R_4	M.p. (recryst.)	Yield % of theory	Produced acc. to Example
16	$-CH_2-CH_2-CH_3$	H	H	H	Dihydrochloride: 252–254°C, (decomp.) (aqueous Isopropanol)	51	1
17	$-CH(CH_3)_2$	H	H	H	Dihydrochloride: 239–241°C, (decomp.) (absol. ethanol)	44	1
18	$-CH_2-CH_2-CH_2-CH_3$	H	H	H	Dihydrochloride: 240–242°C, (decomp.) (ethanol)	53	5
19	$-CH(CH_3)-CH_2-CH_3$	H	H	H	Dihydrochloride-hydrate 210–213°C (absol. ethanol)	48	14
20	$-CH_2-CH(CH_3)_2$	H	H	H	Dihydrochloride: 235–237°C (methanol)	52	1
21	$-(CH_2)_4-CH_3$	H	H	H	Dihydrochloride: 242–245°C (methanol)	32	1
22	$-CH(CH_3)-CH_2-CH_2-CH_3$	H	H	H	Dihydrochloride-dihydrate: 226–229°C (methanol)	46	1
23	$-CH(CH_3)-CH_2-CH_2-CH_3$	CH_3	H	H	130–131°C (cyclohexane)	82	1

Example	R_1	R_2	R_3	R_4	M.p. (recryst.)	Yield % of theory	Produced acc. to Example
24	$-CH_2-CH_2-CH(CH_3)(CH_3)$	H	H	H	Dihydrochloride: 243–245°C (isopropanol)	72	1
25	$-(CH_2)_5-CH_3$	H	H	H	Dihydrochloride: 239–241°C (decomp.) (ethanol)	44	14
26	$-CH_2-C(CH_3)(CH_3)(CH_3)$	CH_3	H	H	136–138° (cyclohexane)	24	14
27	$-(CH_2)_3-CH(CH_3)(CH_3)$	H	H	H	Dihydrochloride-hydrate: 246–248°C (decomp.) (methanol)	73	14
28	$-CH_2-CH(C_2H_5)(C_2H_5)$	H	H	H	Dihydrochloride: 232–234°C (ethanol)	41	14
29	$-CH_2-CH_2-C(CH_3)(CH_3)(CH_3)$	H	H	H	Dihydrochloride: 235–237°C (methanol)	61	1
30	$-(CH_2)_6-CH_3$	H	H	H	Dihydrochloridedihydrate 228–230°C (decomp.) (methanol)	56	14
31	$-(CH_2)_{11}-CH_3$	H	H	H	Dihydrochloride: 195–198°C (decomp.) (ethanol)	42	14

Example	R_1	R_2	R_3	R_4	M.p. (recryst.)	Yield % of theory	Produced acc. to Example
32	$-CH_3$	H	3-CH_3	H	Dihydrochloride: 257–259°C (methanol)	62	1
33	$-CH_3$	H	3-CH_3	5-CH_3	Dihydrochloride: 253–255°C (methanol)	60	1
34	$-CH_3$	H	3-CH_3	6-CH_3	Hydrochloride: 275–276°C (isopropanol)	33	1
35		H	H	H	Dihydrochloride: 233–235°C (ethanol)	70	14
36		CH_3	H	H	135–136°C (cyclohexane)	43	14
37		H	H	H	218–220°C ethyl acetate	20	1
38		H	H	H	248–250°C (ethanol)	34	1

Example	R_1	R_2	R_3	R_4	M.p. (recryst.)	Yield % of theory	Produced acc. to Example
39	$-CH_2-CH=CH_2$	CH_3	H	H	164–166°C (acetonitril)	33	14
40	$-CH_2-C\equiv CH$	H	H	H	248–250°C (n-propanol)	61	13
41	$-CH_2-\underset{\displaystyle CH_3}{\overset{}{C}}=CH_2$	CH_3	H	H	135–140°C hydrochloride: 250–252°C (decomp.) (dimethylformamide)	65	1
42	$-\underset{\displaystyle CH_3}{\overset{}{CH}}-CH=CH_2$	H	H	H	140–142°C (ethyl acetate cyclohexane)	51	1
43	$-(CH_2)_3-CH=CH_2$	H	H	H	dihydrochloride-hydrate: 216–218°C (abs. ethanol)	62	14
44	$-CH_2-CH=C\begin{matrix}\nearrow CH_3\\ \searrow CH_3\end{matrix}$	CH_3	H	H	dihydrochloride: 229–233°C (decomp.) (abs. ethanol)	58	1
45	$-(CH_2)_4-CH=CH_2$	H	H	H	dihydrochloridehydrate 231–234°C (decomp.) (methanol)	40	13
46	$-CH_2-\underset{\displaystyle CH_3}{\overset{}{CH}}=\underset{\displaystyle CH_3}{\overset{}{C}}-CH_2-CH_2-CH=\underset{\displaystyle CH_3}{\overset{}{C}}-CH_3$ (Geranyl)	H	H	H	dihydrochloride: 188–190°C (decomp.) (abs. ethanol)	71	1

Example	R_1	R_2	R_3	R_4	M.p. (recryst.)	Yield % of theory	Produced acc. to Example
47	 (Citronellyl)	H	H	H	Dihydrochloride: 200–204°C (decomp.) (ethanol)	68	1
48	 (Farnesyl)	CH_3	H	H	Dihydrochloride: 208–210°C (isopropanol)	61	1
49	 (Phytyl)	H	H	H	Dihydrochloride: 180°C (decomp.) (abs. ethanol)	75	1
50		H	H	H	194–197°C (ethyl acetate)	36	15
51		H	H	H	238–240°C (n-propanol)	61	5

Example	R_1	R_2	R_3	R_4	M.p. (recryst.)	Yield % of theory	Produced acc. to Example
52		H	H	H	Dihydrochloride hydrate: 209–212°C (ethanol)	47	14
53		H	H	H	Hydrochloride: 263–264°C (n-propanol)	68	7
54		CH_3	H	H	173–175°C (n-propanol)	67	7
55		H	H	H	210–212°C (n-propanol)	64	1

Purification of the crude product was carried out in all examples on a silica gel column with a mixture of chloroform, methanol, cyclohexane and concentrated ammonia in a proportion of 68:15:15:2 as solvent and eluant.

Example I.

Tablets containing 10 mg of 5,11 - dihydro - 11 - {[4 - (2 - methylallyl)piperazin - 1 - yl]acetyl} - 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:

Potato starch is used to prepare a 10% pulp by heating. The active ingredient, lactose and the remaining potato starch are mixed and granulated together with the above pulp through a sieve of 1.5 mm of mesh size. The granulate thus obtained is dried at 45°C and again passed through the same sieve. The resultant granulate is mixed with magnesium stearate and finally pressed into tablets.

Weight of tablet: 220 mg

Punch: 9 mm

Example II.

Coated tablets containing 10 mg of 5,11 - dihydro - 11 - {[4 - (2 - methylallyl) - piperazin - 1 - yl]acetyl} - 6H - pyrido[2,3-b][1,4]benzodiazepine - 6 - one

The tablets prepared according to Example I are coated with a coating consisting of mainly sugar and talcum according to known methods. The coated tablets are polished with bees-wax.

Weight of coated tablet: 300 mg

Example III.

Ampoules containing 2 mg of 5,11 - dihydro - 11 - {[4 - (3 - methyl - but - 2 - enyl)-piperazin - 1 - yl]acetyl} - 6H - pyrido[2,3-b][1,4]benzodiazepine - 6 - one dihydrochloride

Compositon:

1 ampoule contains:

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

Method of preparation:

The active ingredient and sodium chloride and diluted in distilled water and subsequently made up to the desired volume. Then the solution is sterile-filtered and filled into 1 ml ampoules.

Sterilisation: 20 minutes at 120°C

Example IV.

Suppositories containing 15 mg of 5,11 - dihydro - 11 - {[4 - (2,2 - dimethyl - propyl)-piperazin - 1 - yl]acetyl} - 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 is suspended in the molten suppository mass cooled down to 40°C. The resultant mass is poured at 37°C into slightly pre-cooled suppository moulds.

Weight of suppository: 1.7 g

Example V.

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

Composition:

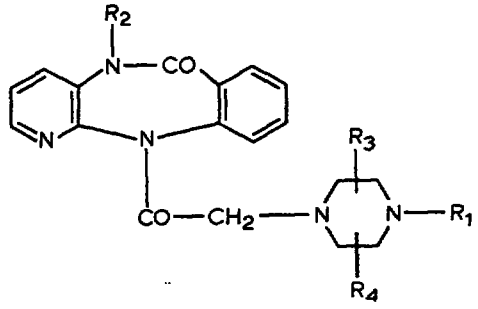
100 ml of drop solution contain:

methyl *p*-hydroxybenzoate	0.035 g
propyl *p*-hydroxybenzoate	0.015 g
anise oil	0.05 g
menthol	0.06 g
pure ethanol	10.0 g
active ingredient	1.0 g
sodium cyclamate	1.0 g
glycerine	15.0 g
distilled water ad.	100.0 g

Method of preparation:
The active ingredient and sodium cyclamate are dissolved in about 70 ml of water and glycerine is added thereto. Then the *p*-hydroxybenzoates, the anise oil and menthol are dissolved in ethanol and subsequently poured whilst stirring into the aqueous solution. Subsequently the resultant solution is made up with water to a volume of 100 ml and filtered free of suspended particles.

WHAT WE CLAIM IS:—

1. Compounds of general formula I,



(I)

wherein

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 is suspended in the molten suppository mass cooled down to 40°C. The resultant mass is poured at 37°C into slightly pre-cooled suppository moulds.

Weight of suppository: 1.7 g

Example V.

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

Composition:

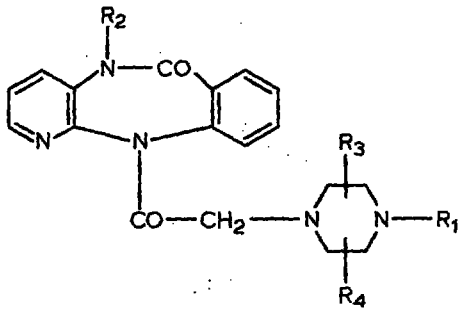
100 ml of drop solution contain:

methyl *p*-hydroxybenzoate	0.035 g
propyl *p*-hydroxybenzoate	0.015 g
anise oil	0.05 g
menthol	0.06 g
pure ethanol	10.0 g
active ingredient	1.0 g
sodium cyclamate	1.0 g
glycerine	15.0 g
distilled water ad.	100.0 g

Method of preparation:
The active ingredient and sodium cyclamate are dissolved in about 70 ml of water and glycerine is added thereto. Then the *p*-hydroxybenzoates, the anise oil and menthol are dissolved in ethanol and subsequently poured whilst stirring into the aqueous solution. Subsequently the resultant solution is made up with water to a volume of 100 ml and filtered free of suspended particles.

WHAT WE CLAIM IS:—

1. Compounds of general formula I,



(I)

wherein

R_1 represents a straight or branched chain alkyl group containing from 1 to 12 carbon atoms, an unsaturated straight or branched chain aliphatic hydrocarbyl group containing from 3 to 20 carbon atoms and including from 1 to 3 double bonds and/or a triple bond, a phenylalkyl group in which the alkylene moiety may be straight or branched and contain from 2 to 4 carbon atoms, a methylenedioxybenzyl group, a chlorobenzyl group, an indan-5- or indan-3-ylmethyl group, a phenylalkyl group in which the alkenyl moiety contains from 2 to 4 carbon atoms, a cycloalkyl group containing from 5 to 7 carbon atoms, a cycloalkylmethyl group in which the cycloalkyl ring contains from 3 to 10 carbon atoms and may optionally be substituted by a methyl group; or a morpholino-, pyrrolidino-, piperidino- or 4-methylpiperazino-alkyl group in which the alkylene moiety contains 2 or 3 carbon atoms;

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

R_3 and R_4, which may be the same or different, each represents a hydrogen atom or a methyl or ethyl group,

with the proviso that, when R_1 represents a methyl or ethyl group, R_3 and/or R_4 represents a methyl or ethyl group,

and acid addition salts thereof.

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

3. 5,11 - Dihydro - 11 - {[4 - (3 - methylbut - 2 - enyl) - piperazin - 1 - yl]acetyl} - 6H - pyrido[2,3-b][1,4]benzodiazepine - 6 - one and acid addition salts thereof.

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

5. 11 - {[4 - (1 - Adamantylmethyl) - piperazin - 1 - yl]acetyl} - 5,11 - dihydro - 6H - pyrido[2,3-b][1,4]benzodiazepine - 6 - one and acid addition salts thereof.

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

7. 5,11 - Dihydro - 11 - [(2,4 - dimethylpiperazin - 1 - yl)acetyl] - 6H - pyrido[2,3-b][1,4]benzodiazepine - 6 - one and acid addition salts thereof.

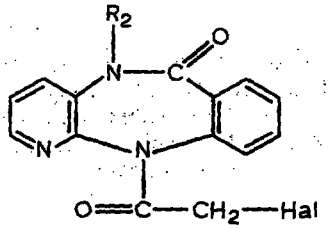
8. 5,11 - Dihydro - 5 - methyl - 11 - {[4 - (3,4 - methylenedioxybenzyl) - piperazin - 1 - yl]acetyl} - 6H - pyrido[2,3-b][1,4]benzodiazepine - 6 - one and acid addition salts thereof.

9. 11 - [(4 - Cinnamylpiperazin - 1 - yl)acetyl] - 5,11 - dihydro - 6H - pyrido[2,3-b][1,4]benzodiazepine - 6 - one and acid addition salts thereof.

10. Physiologically compatible acid solution salts of compounds of general formula I as defined in claim 1.

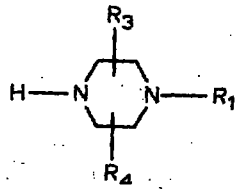
11. Compounds as claimed in claim 1, other than those claimed in any one of claims 2 to 9, as herein specifically disclosed in any one of Examples 1 to 55.

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.



(II)

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



(III)

(wherein R_1, R_3 and R_4 are 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.

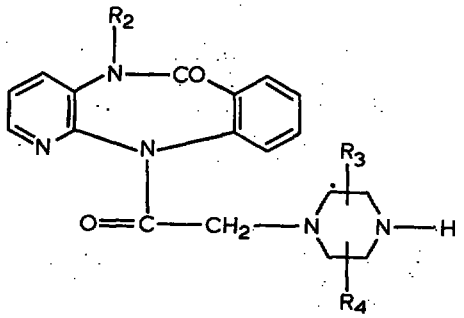
17. A process as claimed in claim 16 wherein the reaction is effected at the boiling point of the reaction mixture.

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, an alkali metal hydrogen carbonate, a 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 which comprises reacting a compound of formula IV,



(IV)

(wherein R_2, R_3 and R_4 are as defined in claim 1) with a compound of formula V,

$$R_1\text{–Hal} \qquad \text{(V)}$$

(wherein R_1 is as defined in claim 1 and Hal represents a halogen atom).

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

23. A process as claimed in claim 22 wherein the reaction is effected in the presence of ethanol, n-propanol, isopropanol, dioxan, teterahydrofuran or acetone.

24. A process as claimed in any one of claims 21 to 23 wherein the reaction is effected at elevated temperatures.

25. A process as claimed in claim 24 wherein the reaction is effected at the boiling point of the reaction mixture.

26. A process as claimed in any one of claims 21 to 25 wherein the reaction is effected in the presence of a hydrogen halide-binding agent.

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

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

29. 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.

30. A process as claimed in claim 29 wherein the acid is hydrochloric, hydrobromic, sulfuric, phosphoric, acetic, fumaric, citric, maleic, succinic or oxalic acid.

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

32. A process for the preparation of compounds as claimed in claim 1 substantially as herein described in any one of Examples 1 to 35.

33. Compounds as claimed in claim 1 whenever prepared by a process as claimed in any one of claims 12 to 32.

34. 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.

35. Compositions as claimed in claim 34 in a form suitable for oral, rectal or parenteral administration.

36. Compositions as claimed in claim 34 or claim 35 in the form of tablets, coated tablets, ampoules, suppositories, infusions and solutions.

37. Compositions as claimed in any one of claims 34 to 36 in the form of dosage units.

38. Compositions as claimed in claim 37 wherein each dosage unit contains from 5 to 50 mg of active ingredient.

39. Compositions as claimed in claim 38 wherein each dosage unit contains from 10 to 30 mg of active ingredient.

40. Compositions as claimed in any one of claims 34 to 39 wherein the active ingredient comprises a compound as claimed in any one of claims 2 to 9.

41. Pharmaceutical compositions as claimed in claim 34 substantially as herein described.

42. Pharmaceutical compositions substantially as herein described in any one of Examples I to V.

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SPECIFICATION NO 1571781

The following amendments were allowed under Section 29 on 23 October 1981:

Page 1, line 29, Page 18, line 16, *delete* a methyl or ethyl group *insert* an alkyl group containing from 1 to 4 carbon atoms

Page 2, line 29, *after* 11 – { [insert 4 – (

Page 10, *delete* whole of Example 16 to 20 *for* 21 to 33 *read* 16 to 18

Page 11, *for* Example 24 to 31 *read* 19 to 26

Page 12, *for* Example 32 to 38 *read* 27 to 33

Page 13, *for* Example 39 to 46 *read* 34 to 41

Page 14, *for* Example 47 to 51 *read* 42 to 46

Page 15, *for* Example 52 to 55 *read* 47 to 50

Page 18, line 40, *for* 55 *read* 50

Page 19, line 48, *for* 35 *read* 50

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16 November 1981

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