

PATENT SPECIFICATION

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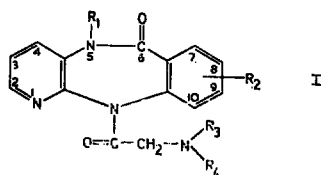


(54) PYRIDOBENZO-DIAZEPINE DERIVATIVES

(71) We, DR. KARL THOMAE G.M.B.H., a German Body Corporate of Biberach an der Riss, 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 11 - substituted 5,11 - dihydro - 6H - pyrido[2,3 - b][1,4]-benzodiazepine - 6 - ones having interesting physiological properties and processes for the preparation thereof.

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



[wherein R_1 represents a hydrogen atom or an alkyl group containing from 1 to 4 carbon atoms; R_2 represents a hydrogen or halogen atom or a methyl group; R_3 and R_4 which may be the same or different each represents a straight or branched alkyl group containing from 1 to 5 carbon atoms, or R_3 and R_4 together with the adjacent nitrogen atom form a 5 to 7 membered saturated monocyclic heterocyclic ring which, if desired, may further contain an oxygen atom or another nitrogen atom in the ring and/or be substituted by an alkyl or hydroxyalkyl group (each containing from 1 to 4 carbon atoms), by an unsubstituted or nuclear methyl substituted benzyl group or by a camphidino group] and acid addition salts thereof.

[Price 25p]

Compounds of formula I and physiologically acceptable acid addition salts thereof show interesting physiological activities. In particular, interesting ulcer-inhibiting, secretion-inhibiting, antitussive and antiemetic activity has been observed.

Preferred compounds of formula I by virtue of their particularly interesting physiological activities include those wherein R_1 represents a methyl or ethyl group whilst when R_2 represents a halogen atom it advantageously represents a chlorine atom. The symbols R_3 and R_4 preferably each represent a methyl, ethyl, n-propyl, n-butyl, iso-butyl or n-pentyl group although they may also represent together with the adjacent nitrogen atom a pyrrolidino, piperidino, piperazino, morpholino or hexamethyleneimino group. When R_3 , R_4 and the adjacent nitrogen atom form a heterocyclic ring, such a ring may carry substituents. Thus a piperidino group advantageously carries an alkyl substituent, e.g. a methyl or ethyl group which may be in the 2-, 3- and 4-position whilst a piperazino group preferably is substituted at the 4-position by for example, a methyl, 2-hydroxyethyl or 2-methylbenzyl group.

The particular compounds of formula I and physiologically acceptable acid addition salts thereof which are of especial interest by virtue of their physiological activities include:—

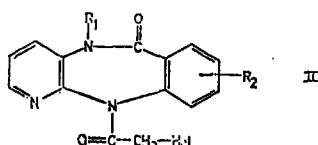
- 5-11 - dihydro - 11 - (4 - methylpiperazine - 1 - ylacetyl) - 6H - pyrido[2,3-b][1,4]benzodiazepine - 6 - one;
 5-11 - dihydro - 5 - methyl - 11 - (4 - methyl - piperazin - 1 - ylacetyl) - 6H - pyrido[2,3 - b][1,4]benzodiazepine - 6 - one;
 11 - (di - n - butylaminoacetyl) - 5,11 - dihydro - 6H - pyrido[2,3 - b][1,4]-benzodiazepine - 6 - one;

- 5,11 - dihydro - 11 - [4 - (2 - hydroxyethyl) - piperazin - 1 - ylacetyl] - 6H-pyrido[2,3 - b][4]benzodiazepine - 6-one;
- 5 5,11 - dihydro - 11 - piperazin - 1 - ylacetyl-6H - pyrido[2,3 - b][1,4] - benzodiazepine - 6 - one;
- 10 5,11 - dihydro - 11 - dimethylaminoacetyl-5 - methyl - 6H - pyrido - [2,3 - b][1,4] - benzodiazepine - 6 - one;
- 15 5,11 - dihydro - 11 - (2 - methylpiperidinoacetyl) - 6H - pyrido - [2,3 - b][1,4] - benzodiazepine - 6 - one;
- 20 5,11 - dihydro - 11 - (2 - ethylpiperidinoacetyl) - 6H - pyrido - [2,3 - b][1,4] - benzodiazepine - 6 - one; and
- 25 5,11 - dihydro - 5 - methyl - 11 - (2 - methylpiperidinoacetyl) - 6H - pyrido[2,3 - b][1,4]benzodiazepine - 6 - one.
- 30 The interesting physiological activity of some of the compounds of formula I and physiologically acceptable acid addition salts thereof has been demonstrated. Thus
- 35 5-11 - dihydro - 11 - (4 - methylpiperazin-1 - ylacetyl) - 6H - pyrido - [2,3 - b][1,4]benzodiazepine - 6 - one dihydrochloride,
- 40 5,11 - dihydro - 5 - methyl - 11 - (4 - methylpiperazin - 1 - ylacetyl) - 6H - pyrido[2,3 - b][1,4]benzodiazepine - 6 - one dihydrochloride,
- 45 5,11 - dihydro - 11 - [4 - (2 - methylbenzyl) - piperazin - 1 - ylacetyl] - 6H-pyrido[2,3 - b][1,4]benzodiazepine - 6-one and
- 50 5,11 - dihydro - 11 - piperazin - 1 - ylacetyl-6H - pyrido[2,3 - b][1,4]benzodiazepine - 6 - one dihydrochloride
- 55 when administered for example at a dose rate of 100 mg/kg show a 70 to 100% inhibition of ulcer induction in the rat when observed 22 hours after oral administration. Atropine possesses a substantially equal ulcer inhibiting action but the compounds according to the invention which have been tested are generally preferable to atropine since they usually exhibit certain specific symptomatic and organic effects. Thus the residual anticholinergic properties and the undesired side effects (peristalsis inhibiting effect on the intestines, accommodation disorder of the eyes and inhibiting of saliva-secretion) are generally lower. The spasmolytic action of the tested compounds is generally only 1/15 to 1/200 of that shown by atropine sulfate when the spasms are produced by acetylcholine in the intestines of guinea pigs.
- 60 The compounds mentioned above furthermore have been shown at a dosage rate of 40 mg/kg of rat, i.d. to reduce the quantity of separated gastric fluid by about 50 to 90% of normal and they decrease the quantity of free hydrochloric acid excreted into the stomach and the total hydrochloric acid
- 65 quite significantly.
- 5,11 - Dihydro - 11 - (4 - methylpiperazin - 1 - ylacetyl) - 6H - pyrido[2,3 - b][1,4]benzodiazepine - 6 - one and 11 - (di-n-butylaminoacetyl) - 5,11 - dihydro - 6H-pyrido[2,3 - b][1,4]benzodiazepine - 6 - one for example, show particularly interesting and apparently greater antitussive properties in awake white rats than those of codeine.
- 70 Toxicity studies in white mice on the above compounds administered orally showed L.D.₅₀ values in excess of 1500 mg/kg. 5,11-Dihydro - 11 - (4 - methylpiperazin - 1 - ylacetyl) - 6H - pyrido[2,3 - b][1,4]benzodiazepine - 6 - one dihydrochloride, for example, shows an L.D.₅₀ of 3100 mg/kg mouse p.o.
- 75 The inhibitory effect on the formation of stress induced ulcers was examined in male FW 49-rats having a body weight of 140 and 150 g in a manner similar to that of G. Rossi, S. Bonfils *et al.*, C. R. Soc. Biol. 150, 2124 (1956). The rats were starved for 24 hours and then anaesthetised using ether applied by means of plaster bandages. The compounds according to the invention were administered orally 5 minutes before the narcosis. Ten animals were used to test each compound. The control animals received 1 ml of 0.9% physiological sodium chloride solution in a similar manner. After 22 hours
- 80 the rats were killed by ether inhalation, the stomachs removed and opened by cutting along the great curvature and opened out on a cork sheet. The evaluation of the stomachs was carried out according to the method described in Med.Exp. 4, 284—292 (1961).
- 85 The influence on gastric fluid secretion was determined by the method of Shay *et al.*, Gastroenterology 5, 43—61 (1945). The pylorus of sober male rats of the FW-49 strain weighing 140 to 150 g, was tied under Evipan induced anaesthesia (100 mg/kg i.p.), the word 'Evipan' being a registered Trade Mark. The compounds were administered intraduodenally immediately after the pylorus ligation at a dose rate of 40 mg/kg. Ten animals were used to test each compound. The control animals received 0.15 ml of 0.9% physiological sodium chloride solution i.d. After 5 hours the rats were killed by
- 90 chloroethyl narcosis, the stomachs removed, opened along the great curvature and the gastric fluid was collected. The free and the total hydrochloric acid in the gastric fluid was determined by titration against N/50 sodium hydroxide solution.
- 95 The spasmolytic action was determined *in vitro* on the colon of the guinea pig in the test procedure of R. Magnus, Pflugers Archive 102—123 (1904). Acetylcholine was used to induce spasms for comparison with atropine sulfate. The acetyl - choline was administered one minute before the spasmolytic, the time of action of the spasmolytic being one minute.
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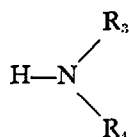
The antitussive activity was determined according to the method of Engelhorn and Puschmann, *Arzneimittelforschung* 13, 474—480 (1963). 50 mg/kg of active compound were administered perorally to each of a group of 5 awake white rats. Coughing was induced by inhalation of a 7.5% citric acid spray.

The toxicity was determined by oral administration of the active compounds to sober white mice of 18 to 20 g. body weight. The LD₅₀ was calculated according to the method of Litchfield and Wilcoxon. The animals were observed for 14 days. For each dose rate a group of 5 to 10 mice was used.

According to a further feature of the invention there is provided a process for the preparation of compounds of the formula I and acid addition salts thereof wherein a compound of formula



(wherein R₁ and R₂ are as hereinbefore defined and Hal represents a halogen atom) is reacted with an amine of formula



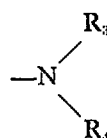
III

(wherein R₃ and R₄ are as hereinbefore defined) and the compound of formula I produced is, if desired, subsequently converted into an acid addition salt thereof.

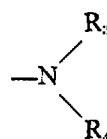
The reaction is preferably effected in a solvent advantageously one which is substantially inert under the conditions used and conveniently in the presence of an acid binding agent. The reaction may, for example, be effected at an elevated temperature, preferably at the boiling point of the solvent when used. Suitable solvents include, for example alkanols such as ethanol, acetone and dioxan, however, aromatic hydrocarbons such as benzene or toluene may be used. It is advantageous to use the amine of formula III in a sufficient excess to bind the liberated hydrogen halide although other hydrogen halide binding agents such as alkali metal carbonates or alkali metal hydrogen carbonates may be used. When a readily volatile amine is used for example, the reaction is conveniently effected in a closed vessel.

In order to shorten the reaction time and to decrease the reaction temperature used it is advantageous in some cases to use a compound of formula II, wherein Hal represents an iodine atom as starting material. These iodoacetyl compounds may conveniently be prepared by reacting the corresponding chloroacetyl compound of formula II with sodium iodide in acetone, for example according to a conventional method.

If a compound of formula I is desired wherein the substituent



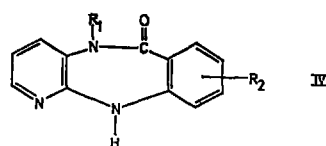
represents an unsubstituted piperazin - 1 - yl group, it is often convenient first to prepare a compound of formula I, wherein the substituent



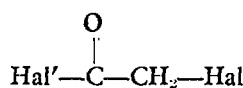
represents a 4 - aralkylpiperazin - 1 - yl group and subsequently to split off the aralkyl group of this compound by a convenient method such as is conventionally used for example by hydrogenation in the presence of a catalyst such as palladium on active charcoal.

The compounds of formula I produced may, if desired, be converted, for example by reaction with an inorganic or organic acid into an acid addition salt thereof, for example according to a known method. Advantageously these acid addition salts are physiologically acceptable acid addition salts. The following acids may be used for the formation of physiologically acceptable acid addition salts:— hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, tartaric acid, fumaric acid, citric acid, maleic acid, succinic and oxalic acid.

The starting compounds of formula II, which are also new may, for example, be prepared by a method analogous to a known method such as the reaction of a 5,11 - dihydro - 6H - pyrido[2,3 - b][1,4]benzodiazepine - 6 - one of formula



(wherein R₁ and R₂ are as hereinbefore defined) with a haloacetyl halide of formula



V

wherein Hal and Hal', which may be the same or different, each represent a chlorine, bromine or iodine atom. The reaction is preferably effected in a solvent advantageously in the presence of a hydrogen halide binding agent for example at an elevated temperature, preferably at the boiling point of the solvent used. Suitable solvents include, for example aromatic hydrocarbons such as benzene, toluene, xylene, or an ether such as diethyl ether, dipropyl ether or preferably a cyclic ether such as dioxan. The acid binding agents which act as hydrogen halide binding agents may, for example, be tertiary organic bases such as triethylamine, N,N - dimethylaniline or pyridine, or inorganic bases such as alkali metal or alkaline earth metal carbonates or hydrogen carbonates. The reaction mixture may be worked up in a conventional manner, the yields frequently amounting to as high as 90% of theory. The haloacetyl compounds of formula II which are formed are generally readily crystallizable compounds, which may be used for the reaction as crude products without further purification. Preparations A to F herein illustrate the preparation of these compounds.

The compounds of formula IV may be prepared, for example, according to the method described in German Patents Nos. 1,179,943 and 1,204,680.

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

The compositions according to the invention may be presented in forms suitable for oral, rectal or parenteral administration using carriers and excipients conventionally used in the pharmaceutical art. Thus the compositions may take the form of solutions, infusions, tablets, sugar coated tablets or suppositories. The compositions may conveniently be presented in single dose, dosage unit form, each dosage unit for adults conveniently containing for example 5 to 30 mg, advantageously 10 to 20 mg, of active ingredient according to the invention. The daily dose for adults may, for example, be from 20 to 100 mg, preferably 30 to 60 mg, of active ingredient according to the invention.

The compositions may also contain further physiologically active ingredients such as 7-chloro - 1,3 - dihydro - 3 - hydroxy - 5-phenyl - 2H - 1,4 - benzodiazepine - 2 - one, diethyl - aminoacet - 2,6 - xylidide or dimagnesium aluminium trisilicate and preserv-

ing agents such as *p* - hydroxybenzoates. Flavouring agents such as aniseed oil, menthol or vanillin and a sweetening agent e.g. an artificial sweetener may, if desired also be used.

The following preparations and examples are given by way of illustration only:—

Preparation of the starting materials of formula II:

PREPARATION A

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

48.4 g. of 5,11 - dihydro - 6H - pyrido[2,3 - b][1,4]benzodiazepine - 6 - one were refluxed in 900 ml of absolute dioxan for 15 minutes. Within 45 minutes, 28 ml of chloroacetyl chloride and 52 ml of triethylamine were simultaneously added dropwise to the mixture. The mixture was heated under reflux for 8 hours and filtered with suction after cooling. The filtrate was evaporated *in vacuo*. The crystalline residue was recrystallized from acetonitrile using active charcoal.

M.p.: 212—213°C (under decomposition)
Yield: 85% (of theory).

PREPARATION B

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

9.0 g (0.04 mol) of 5,11 - dihydro - 5-methyl - 6H - pyrido[2,3 - b][1,4] - benzodiazepine - 6 - one and 4.0 g (0.04 mol) of triethylamine were heated to boiling in 300 ml of absolute benzene. 8.8 g (0.08 mol) of chloroacetyl chloride were added dropwise over 10 minutes and the mixture was heated under reflux for 3 hours. The mixture was filtered with suction while still hot and the filtrate was evaporated *in vacuo*. The residue was recrystallized from ethanol.

M.p.: 203—205°C (with decomposition)
Yield: 80% (of theory).

PREPARATION C

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

4.8 g 8 - chloro - 5,11 - dihydro - 6H-pyrido[2,3 - b][1,4]benzodiazepine - 6 - one were heated to boiling in 100 ml of absolute dioxan. 2.4 ml of chloroacetyl chloride and 4.5 ml of triethylamine were added dropwise simultaneously. After 6 hours' heating the mixture was processed as described in Preparation A. The compound obtained was recrystallized from ethanol.

M.p.: 211—212°C (with decomposition)
Yield: 65% (of theory).

PREPARATION D

- 9 - Chloro - 11 - chloroacetyl - 5,11 - dihydro - 6H - pyrido[2,3 - b][1,4] - benzodiazepine - 6 - one
- 5 24.5 g of 9 - chloro - 5,11 - dihydro - 6H - pyrido[2,3 - b][1,4] - benzodiazepine - 6 - one were reacted in 500 ml of absolute dioxan with 12 ml of chloroacetyl chloride and 22.5 ml of triethylamine as described in Preparation C. When the reaction was complete, the mixture was filtered with suction while still hot. The content of the filter was washed with water. The residue was recrystallized from dimethylformamide.
- 10 M.p.: 223—225°C (under decomposition)
- 15 Yield: 25% (of theory).

PREPARATION E

- 5 - Ethyl - 11 - chloroacetyl - 5,11 - dihydro - 6H - pyrido[2,3 - b][1,4] - benzodiazepine - 6 - one
- 20 12.0 g of 5 - ethyl - 5,11 - dihydro - 6H - pyrido[2,4 - b][1,4] - benzodiazepine - 6 - one and 7.3 g of N,N - dimethylaniline were heated to boiling in 200 ml of absolute dioxan.
- 25 6.7 g. of chloroacetyl chloride were added dropwise over 10 minutes. The mixture was refluxed for 4.5 hours and when cool, 1 ltr. of water was poured in. The substance first separated as an oil which crystallized and was
- 30 filtered with suction.
- M.p.: 169—170°C.
- Yield: 60% (of theory).

PREPARATION F

- 11 - Chloroacetyl - 5,11 - dihydro - 8 - methyl - 6H - pyrido[2,3 - b][1,4] - benzodiazepine - 6 - one
- 35 Prepared from 5,11 - dihydro - 8 - methyl - 6H - pyrido[2,3 - b][1,4]benzodiazepine - 6 - one, chloroacetyl chloride and dimethylaniline in absolute dioxan, according to the manner described in Preparation E.
- 40 M.p.: 120—124°C (from ethanol)
- Yield: 55% (of theory).

- 45 Examples of the preparation of compounds and compositions according to the invention:

EXAMPLE 1

- 11 - Diethylaminoacetyl - 5,11 - dihydro - 6H - pyrido[2,3 - b][1,4]benzodiazepine - 6 - one
- 50 5.0 g (0.0174 mol) of 11 - chloroacetyl - 5,11 - dihydro - 6H - pyrido - [2,3 - b][1,4] - benzodiazepine - 6 - one (prepared as described in Preparation A), and 2.55 g (0.0358 mol) of diethylamine were refluxed in 200 ml of absolute benzene for 70 hours.
- 55 After distilling off the solvent *in vacuo*, the residue was recrystallized from cyclohexane.
- M.p.: 152—153°C,
- Yield: 54% (of theory).
- 60 $C_{18}H_{20}N_4O_2$ (324.4)
- Calculated: C 66.64%, H 6.21%, N 17.27%
- Found: 66.60 6.39 17.24

EXAMPLE 2

- 11 - Diethylaminoacetyl - 5,11 - dihydro - 5 - methyl - 6H - pyrido[2,3 - b][1,4] - benzodiazepine - 6 - one
- 65 9.5 g (0.0316 mol) of 11 - chloroacetyl - 5,11 - dihydro - 5 - methyl - 6H - pyrido[2,3 - b][1,4]benzodiazepine - 6 - one (prepared according to Preparation B) and 4.6 g (0.0632 mol) of diethylamine were re-
- 70 fluxed in 300 ml of absolute benzene for 15 hours. After the solvent had been distilled off *in vacuo*, the residue was recrystallized from isopropanol.
- 75 M.p.: 137—138°C
- Yield: 30% (of theory).

$C_{19}H_{22}N_4O_2$ (338.4)

Calculated: C 67.43%, H 6.55%, N 16.56%

Found: 67.35 6.68 16.75 80

EXAMPLE 3

- 5,11 - Dihydro - 11 - (di - n - propylaminoacetyl) - 6H - pyrido[2,3 - b][1,4] - benzodiazepine - 6 - one
- 85 4.2 g of 11 - chloroacetyl - 5,11 - dihydro - 6H - pyrido[2,3 - b][1,4] - benzodiazepine - 6 - one and 15 ml of di - n - propylamine were refluxed in 100 ml of ethanol for 18 hours. The solvent was distilled off *in vacuo* and the residue was dissolved in dilute hydrochloric acid. This solution was washed with chloroform and rendered alkaline with potassium hydroxide solution. The alkaline solution was extracted with methylene chloride and the organic phase evaporated
- 90 *in vacuo*. The residue was recrystallized from isopropanol.
- M.p.: 212—213°C
- Yield: 30% (of theory).

$C_{20}H_{24}N_4O_2$ (352.4)

Calculated: C 68.16%, H 6.86%, N 15.90%

Found: 68.50 6.94 15.95 100

EXAMPLE 4

- 11 - (Di - n - butylaminoacetyl) - 5,11 - dihydro - 6H - pyrido[2,3 - b][1,4]benzodiazepine - 6 - one
- 105 6.3 g of 11 - chloroacetyl - 5,11 - dihydro - 6H - pyrido[2,3 - b][1,4]benzodiazepine - 6 - one and 30 ml of di - n - butylamine were heated in 150 ml of ethanol at 80°C in an autoclave for 18 hours. The mixture was further processed as described in Example 3.
- 110 After recrystallization from ethanol m.p. 177—179°C.
- Yield: 33% (of theory).
- 115

$C_{22}H_{28}N_4O_2$ (380.5)

Calculated: C 69.45%, H 7.42%, N 14.72%

Found: 69.50 7.50 14.70

EXAMPLE 5

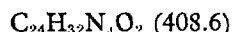
- 5,11 - Dihydro - 11 - (diisobutylaminoacetyl)-
6H - pyrido[2,3 - b][1,4] - benzodiazepine - 6 - one
- 5 4.2 g of 11 - chloroacetyl - 5,11 - dihydro-
6H - pyrido[2,3 - b][1,4]benzodiazepine - 6 - one and 15 ml of di - iso - butylamine were refluxed in 150 ml of ethanol for 18 hours and processed as described in Example 3.
- 10 After recrystallization from isopropanol:
M.p. 226—227°C
Yield: 37% (of theory).



- 15 Calculated: C 69.45% H 7.42% N 14.72%
Found: 69.25 7.38 14.72

EXAMPLE 6

- 5,11 - Dihydro - 11 - (di - n - pentylamino-
acetyl) - 6H - pyrido[2,3 - b][1,4]-
benzodiazepine - 6 - one
- 20 4.2 g of 11 - chloroacetyl - 5,11 - dihydro-
6H - pyrido[2,3 - b][1,4]benzodiazepine - 6 - one and 15 ml of di - n - pentylamine were refluxed in 100 ml of ethanol for 18 hours and processed as described in Example 3.
- 25 After recrystallization from ethylene chloride/
benzene:
M.p.: 157—158°C
Yield: 35% (of theory).



- 30 Calculated: C 70.56% H 7.89% N 13.72%
Found: 70.80 7.81 13.68

EXAMPLE 7

- 5,11 - Dihydro - 11 - piperidinoacetyl - 6H-
pyrido[2,3 - b][1,4]benzodiazepine - 6 - one
- 35 4.0 g. of 11 - chloroacetyl - 5,11 - dihydro-
6H - pyrido[2,3 - b][1,4]benzodiazepine - 6 - one and 2.55 g of piperidine were refluxed in 100 ml of absolute benzene for 28 hours.
- 40 After distilling off the solvent, the residue was recrystallized from ethanol:
M.p. 217—218°C
Yield: 43% (of theory).



- 45 Calculated: C 67.84% H 5.99% N 16.69%
Found: 67.95 6.19 16.80

EXAMPLE 8

- 5,11 - Dihydro - 11 - (4 - methylpiperazin-
1 - ylacetyl) - 6H - pyrido - [2,3 - b]-
[1,4]benzodiazepine - 6 - one
- 50 67.5 g of 11 - chloroacetyl - 5,11 - dihydro-
6H - pyrido[2,3 - b][1,4]benzodiazepine - 6 - one and 183 ml of N - methylpiperazine were refluxed in 1.37 ltr. of absolute benzene for 18 hours. The crystalline precipitate was filtered off with suction, dissolved in 20% hydrochloric acid and the solution evaporated *in vacuo*. The crystalline residue was dissolved in 250 ml of water with

heating, the solution was mixed with 150 ml of isopropanol and active charcoal and filtered. 2.5 ltr. of isopropanol were added to the filtrate. After cooling, the precipitate was filtered off with suction. The dihydrochloride of m.p. 257—259°C (decomposition) was obtained in a yield of 70% (of theory).



Calculated:

C 53.78% H 5.47% N 16.50% Cl 16.71%

Found:

53.50 5.49 16.25 16.70

The base obtained from the dihydrochloride by rendering the aqueous solution alkaline with dilute sodium hydroxide solution and extracting with chloroform melted after recrystallization from methanol ether at M.p. 226—228°C.



Calculated: C 64.94% H 6.02% N 19.93%

Found:

64.50 6.29 19.90

The fumarate with 1-1/2 mol of fumaric acid per mol base melted at 219—220°C with decomposition.

EXAMPLE 9

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

5.0 g of 11 - chloroacetyl - 5,11 - dihydro-
5 - methyl - 6H - pyrido[2,3 - b][1,4]benzodiazepine - 6 - one (produced according to Preparation B) and 15 ml of N - methylpiperazine were refluxed in 200 ml of absolute dioxan for 18 hours. The mixture was evaporated *in vacuo* the residue was dissolved in 20% hydrochloric acid and it was processed as described in Example 8. The dihydrochloride melted after recrystallization from aqueous isopropanol at 227°C under recombination.



Calculated:

C 54.80% H 5.75% N 15.97% Cl 16.18%

Found:

54.50 5.88 15.70 16.25

EXAMPLE 10

- 8 - Chloro - 5,11 - dihydro - 11 - (4 - methylpiperazin - 1 - ylacetyl) - 6H - pyrido-
[2,3 - b][1,4]benzodiazepine - 6 - one
- 110 7.3 g of 8 - chloro - 11 - chloroacetyl-
5,11 - dihydro - 6H - pyrido[2,3 - b][1,4]-
benzodiazepine - 6 - one (produced according to preparation C) and 15 ml of N - methylpiperazine were reacted in 200 ml of absolute ethanol analogously to the manner described in Example 3 and processed accordingly. The

substance melted after recrystallization from ethanol at 254—256°C with decomposition. Yield: 56% (of theory).

$C_{19}H_{20}ClN_5O_2$ (385.9)

5 Calculated: C 59.14% H 5.23% N 18.15% Cl 9.19%
Found: 59.20 5.23 18.25 9.12

EXAMPLE 11

10 9 - Chloro - 5,11 - dihydro - 11 - (4 - methylpiperazin - 1 - ylacetyl) - 6H - pyrido[2,3 - b][1,4]benzodiazepine - 6 - one
3.0 g of 9 - chloro - 11 - chloroacetyl - 5,11 - dihydro - 6H - pyrido[2,3 - b][1,4]benzodiazepine - 6 - one (produced according to Preparation D) and 10 ml of N-methylpiperazine were reacted in 100 ml of ethanol analogously to the method described in Example 9 and processed accordingly. After recrystallization from ethanol the dihydrochloride was obtained of
M.p. 205—207°C (decomposition)
Yield: 36% (of theory).

Dihydrochloride: $C_{19}H_{22}Cl_2N_5O_2$ (458.8)

25 Calculated: C 49.74% H 4.83% N 15.26% Cl 23.20%
Found: 49.20 5.08 15.30 22.60

EXAMPLE 12

30 5,11 - Dihydro - 11 - [4 - (2 - hydroxyethyl) - piperazin - 1 - ylacetyl] - 6H - pyrido[2,3 - b][1,4]benzodiazepine - 6 - one
8.6 g of 11 - chloroacetyl - 5,11 - dihydro - 6H - pyrido[2,3 - b][1,4] - benzodiazepine - 6 - one and 25 ml of N - (2 - hydroxyethyl) - piperazine were reacted with 300 ml of ethanol as described in Example 3 and processed accordingly. After recrystallization from isopropanol/cyclohexane:
M.p. 213—214°C
Yield: 25% of theory.

$C_{20}H_{29}N_5O_3$ (381.4)

45 Calculated: C 62.98% H 6.08% N 18.36%
Found: 63.00 6.04 18.35

EXAMPLE 13

50 5,11 - Dihydro - 11 - (4 - benzylpiperazin - 1 - ylacetyl) - 6H - pyrido[2,3 - b][1,4]benzodiazepine - 6 - one
4.2 g of 11 - chloroacetyl - 5,11 - dihydro - 6H - pyrido[2,3 - b][1,4]benzodiazepine - 6 - one and 8 g of N - benzylpiperazine were refluxed in 200 ml of absolute benzene for 18 hours. The cooled solution was mixed with ethanol, rendered alkaline with concentrated ammonia and evaporated *in vacuo*. The residue was recrystallized from isopropanol/water,
M.p. 216—217°C
Yield: 40% (of theory).

$C_{25}H_{28}N_5O_2$ (427.5)

Calculated: C 70.24% H 5.89% N 16.38%
Found: 70.45 6.05 16.36

EXAMPLE 14

5,11 - Dihydro - 11 - [4 - (2 - methylbenzyl) - piperazin - 1 - ylacetyl] - 6H - pyrido[2,3 - b][1,4]benzodiazepine - 6 - one
6.8 g of 11 - chloroacetyl - 5,11 - dihydro - 6H - pyrido[2,3 - b][1,4] - benzodiazepine - 6 - one and 10.0 g of N - (2 - methylbenzyl) - piperazine were reacted in 300 ml of absolute dioxan as described in Example 3 and processed accordingly. The compound melted after recrystallization from ethanol at 218—220°C with decomposition.
Yield: 35% of theory.

$C_{26}H_{27}N_5O_2$ (441.5)

Calculated: C 70.73% H 6.16% N 15.85%
Found: 70.90 6.23 15.55 80

EXAMPLE 15

5,11 - Dihydro - 11 - piperazin - 1 - ylacetyl - 6H - pyrido[2,3 - b][1,4]benzodiazepine - 6 - one
10.0 g of 5,11 - dihydro - 11 - (4 - benzylpiperazin - 1 - ylacetyl) - 6H - pyrido[2,3 - b][1,4]benzodiazepine - 6 - one (produced according to example 13) were hydrogenated over 1 g of 10% palladium on charcoal in 120 ml of methanol containing 3 drops of glacial acetic acid at 50°C and 50 atmospheres pressure. After 8 hours, the calculated quantity of hydrogen was taken up. After cooling, the product was filtered off with suction and the filtrate was evaporated *in vacuo*. The residue was dissolved in 20 ml of isopropanol and mixed with ethereal hydrochloric acid. The dihydrochloride separated which melted after recrystallization from ethanol with the addition of active charcoal at 229—230°C with decomposition.
Yield: 30% of theory.

Dihydrochloride hydrate: $C_{18}H_{23}Cl_2N_5O_3$ (428.3)

Calculated: C 50.48% H 5.41% N 16.35% Cl 16.55%
Found: 50.85 5.16 16.45 16.10 105

EXAMPLE 16

5,11 - Dihydro - 11 - pyrrolidinoacetyl - 6H - pyrido[2,3 - b][1,4]benzodiazepine - 6 - one
4.2 g of 11 - chloroacetyl - 5,11 - dihydro - 6H - pyrido[2,3 - b][1,4] - benzodiazepine - 6 - one and 15 ml of pyrrolidine were refluxed in 200 ml of absolute benzene for 18 hours. The hot solution was mixed with animal charcoal and filtered. The filtrate was evaporated

ated *in vacuo* and the residue was recrystallized from isopropanol.
M.p. 202—203°C
Yield: 50% of theory.

- 5 $C_{18}H_{18}N_4O_2$ (322.4)
Calculated: C 67.07% H 4.63% N 17.38%
Found: 67.20 5.72 17.15

EXAMPLE 17

- 10 5,11 - Dihydro - 11 - (4 - methylpiperidinoacetyl) - 6H - pyrido[2,3 - b][1,4] - benzodiazepine - 6 - one
4.2 g. of 11 - chloroacetyl - 5,11 - dihydro - 6H - pyrido[2,3 - b][1,4]benzodiazepine - 6 - one and 15 ml of 4 - methylpiperidine were reacted in 200 ml of absolute benzene according to the method described in Example 16 and processed accordingly. After recrystallization from ethanol:

- 20 M.p. 249—250°C
Yield: 40% of theory.

$C_{20}H_{22}N_4O_2$ (350.4)
Calculated: C 68.80% H 6.40% N 16.10%
Found: 68.44 6.33 15.99

EXAMPLE 18

- 25 5,11 - Dihydro - 11 - morpholinoacetyl - 6H - pyrido[2,3 - b][1,4]benzodiazepine - 6 - one
4.2 g of 11 - chloroacetyl - 5,11 - dihydro - 6H - pyrido[2,3 - b][1,4]benzodiazepine - 6 - one and 15 ml of morpholine were reacted in 200 ml of absolute benzene as described in Example 16 and processed accordingly. After recrystallization from ethanol/ether:

- 35 M.p. 222°C under decomposition.
Yield: 35% of theory.

$C_{18}H_{18}N_4O_3$ (338.4)
Calculated: C 63.89% H 5.36% N 16.56%
Found: 63.70 5.43 16.50

EXAMPLE 19

- 40 5,11 - Dihydro - 11 - (hexahydroazepin - 1 - ylacetyl) - 6H - pyrido[2,3 - b][1,4] - benzodiazepine - 6 - one
From 11 - chloroacetyl - 5,11 - dihydro -

- 45 6H - pyrido[2,3 - b][1,4]benzodiazepine - 6 - one and hexahydroazepine (i.e. hexamethyleneimine) in benzene according to the method described in Example 16.
M.p. 207—209°C (from ethanol).

- 50 Yield: 70% of theory.

$C_{20}H_{22}N_4O_2$ (350.4)
Calculated: C 68.55% H 6.33% N 15.99%
Found: 68.60 6.86 15.50

EXAMPLE 20

- 55 5 - Ethyl - 5,11 - dihydro - 11 - (4 - methylpiperazin - 1 - ylacetyl) - 6H - pyrido[2,3 - b][1,4]benzodiazepine - 6 - one
From 5 - ethyl - 11 - chloroacetyl - 5,11 -

dihydro - 6H - pyrido[2,3 - b][1,4] - benzodiazepine - 6 - one (produced according to preparation E) and N - methylpiperazine in absolute dioxan in the manner described in Example 9. When the reaction was finished, the mixture was evaporated *in vacuo*, the residue was dissolved in ammonia containing ethanol and the solution evaporated. The residue was recrystallized from acetonitrile.
M.p. 174—175°C.
Yield: 60% of theory.

$C_{21}H_{25}N_5O_2$ (379.5)
Calculated: C 66.47% H 6.64% N 18.46%
Found: 66.50 6.62 18.40

EXAMPLE 21

- 75 5,11 - Dihydro - 8 - methyl - 11 - (4 - methylpiperazin - 1 - ylacetyl) - 6H - pyrido[2,3 - b][1,4]benzodiazepine - 6 - one

From 11 - chloroacetyl - 5,11 - dihydro - 8 - methyl - 6H - pyrido[2,3 - b][1,4]benzodiazepine - 6 - one (produced according to preparation F) and N - methylpiperazine in absolute dioxan in the manner described in Example 20.

- M.p. 236—237°C under decomposition (from ethanol).
Yield: 30% of theory.

$C_{20}H_{23}N_5O_2$ (365.4)
Calculated: C 65.74% H 6.34% N 19.16%
Found: 66.00 6.45 18.80

The monohydrochloride-hemihydrate melted at 169—170°C with decomposition (recrystallized from ethanol.)

EXAMPLE 22

- 95 5,11 - Dihydro - 11 - (4 - ethylpiperazin - 1 - ylacetyl) - 6H - pyrido[3,3 - b][1,4]benzodiazepine - 6 - one

Prepared from 11 - chloroacetyl - 5,11 - dihydro - 6H - pyrido[2,3 - b][1,4] - benzodiazepine - 6 - one and N - ethylpiperazine in absolute dioxan as described in Example 20.

Yield: 80% of theory.

M.p. of the dihydrochloride: 253—254°C from isopropanol and a small quantity of hydrochloric acid) with decomposition.

Dihydrochloride: $C_{20}H_{25}Cl_2N_5O_2$ (438.4)
Calculated: C 54.80% H 5.75% N 15.98% Cl 16.18%
Found: 54.60 5.85 15.78 15.85

EXAMPLE 23

- 115 5,11 - Dihydro - 11 - dimethylaminoacetyl - 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 50 ml of 40% aqueous dimethylamine solution in 50 ml of ethanol were stirred for 8 hours at room temperature. After evaporating the solution *in vacuo*, the residue was chromatographed on a column of silica gel eluted with chloroform and ethyl acetate (1:1). The column was then eluted with method and the eluate was evaporated. After adding ethereal hydrochloric acid, the hydrochloride precipitated and was recrystallized twice from ethanol/ethyl acetate (1:10).
M.p.: 241—242°C (decomp.);
Yield: 45% of theory.
- Hydrochloride: $C_{16}H_{17}ClN_4O_2$ (332.8)
Calculated: Cl 10.65
Found: 10.81
- EXAMPLE 24
- 5,11 - Dihydro - 11 - dimethylaminoacetyl - 5 - methyl - 6H - pyrido[2,3 - b][1,4] - benzodiazepine - 6 - one
4.8 g of 11 - chloroacetyl - 5,11 - dihydro - 5 - methyl - 6H - pyrido[2,3 - b][1,4]benzodiazepine - 6 - one and 30 ml of a 40% aqueous solution of dimethylamine in 30 ml of acetone were stirred for 8 hours at room temperature. The mixture was further processed as described in Example 23. The hydrochloride was recrystallized from ethyl acetate/absolute ethanol (10:1).
M.p.: 251—252°C (decomp.);
Yield: 55% theory.
- Hydrochloride: $C_{17}H_{19}ClN_4O_2$ (346.8)
Calculated: C 58.88% H 5.52% N 16.15% Cl 10.22%
Found: 58.90 5.78 15.98 10.27
- EXAMPLE 25
- 5,11 - Dihydro - 11 - (2 - methylpiperidinoacetyl) - 6H - pyrido[2,3 - b][1,4]benzodiazepine - 6 - one
4.3 g of 11 - chloroacetyl - 5,11 - dihydro - 6H - pyrido - [2,3 - b][1,4]benzodiazepine - 6 - one and 15 ml of 2 - methylpiperidine were dissolved in 200 ml of absolute benzene and treated according to the method described in Example 16. After recrystallisation from absolute ethanol:
M.p.: 203—204°C;
Yield: 45% of theory.
- EXAMPLE 26
- 5,11 - Dihydro - 11 - (3 - methylpiperidinoacetyl) - 6H - pyrido[2,3 - b][1,4] - benzodiazepine - 6 - one
4.3 g of 11 - chloroacetyl - 5,11 - dihydro - 6H - pyrido[2,3 - b][1,4]benzodiazepine - 6 - one and 15 ml of 3 - methylpiperidine were dissolved in 200 ml of absolute benzene and treated according to the method described in Example 16. The residue from the evaporated filtrate was triturated with water and recrystallized from acetonitrile.
M.p.: 214—215°C;
Yield: 58% of theory.
- $C_{20}H_{22}N_4O_2$ (350.4)
Calculated: C 68.55% H 6.33% N 15.99%
Found: 69.10 6.14 16.35
- EXAMPLE 27
- 5,11 - Dihydro - 11 - (2 - ethylpiperidinoacetyl) - 6H - pyrido - [2,3 - b][1,4] - benzodiazepine - 6 - one
From 11 - chloroacetyl - 5,11 - dihydro - 6H - pyrido - [2,3 - b][1,4]benzodiazepine - 6 - one and 2 - ethyl - piperidine in absolute benzene according to the method described in Example 16. After recrystallisation from isopropanol:
M.p.: 218—219°C;
Yield: 62% of theory.
- $C_{21}H_{24}N_4O_2$ (364.5)
Calculated: C 69.21% H 6.64% N 15.37%
Found: 69.10 6.65 15.20
- EXAMPLE 28
- 5,11 - Dihydro - 5 - methyl - 11 - (2 - methylpiperidinoacetyl) - 6H - pyrido - [2,3 - b][1,4]benzodiazepine - 6 - one
From 11 - chloroacetyl - 5,11 - dihydro - 5 - methyl - 6H - pyrido[2,3 - b][1,4] - benzodiazepine - 6 - one and 2 - methylpiperidine in absolute benzene according to the method described in Example 26. After recrystallisation from ethanol/absolute ether:
M.p.: 173—174°C;
Yield: 68% of theory.
- $C_{21}H_{24}N_4O_2$ (364.5)
Calculated: C 69.21% H 6.64% N 15.37%
Found: 69.10 6.74 15.15
- EXAMPLE 29
- 5,11 - Dihydro - 5 - methyl - 11 - [4 - (2 - methylbenzyl) - piperazin - 1 - ylacetyl] - 6H - pyrido[2,3 - b][1,4]benzodiazepine - 6 - one
From 11 - chloroacetyl - 5,11 - dihydro - 5 - methyl - 6H - pyrido[2,3 - b][1,4] - benzodiazepine - 6 - one and N - (2 - methylbenzyl) piperazine in absolute benzene according to the method described in Example 16.
M.p.: 191—192°C (from ethanol);
Yield: 85% of theory.

EXAMPLE 30

Tablets with 10 mg of 5,11 - dihydro - 11 -
(4 - methyl - piperazin - 1 - ylacetyl) -
6H - pyrido[2,3 - b][1,4]benzodiazepine - 6 - one dihydrochloride

Composition:

1 tablet contains:
5,11 - dihydro - 11 - (4 - methyl -
piperazin - 1 - ylacetyl) - 6H -
pyrido[2,3 - b][1,4]benzo-
diazepine - 6 - one dihydro
chloride 10.0 mg
lactose 148.0 mg
potato starch 60.0 mg
magnesium stearate 2.0 mg
220.0 mg

Preparation:

A 10% - paste is prepared from potato
starch by heating. The active ingredient,
lactose and the remaining potato starch are
mixed with the above paste and granulated
through a screen of 1.5 mm mesh-size. The
granulate is dried at 45°C, triturated once
more through the above screen, mixed with
magnesium stearate and pressed to tablets.
Tablet weight 220 mg.
Dic: 9 mm.

EXAMPLE 31

Sugar-coated tablets with 10 mg of 5,11 - di-
hydro - 11 - (4 - methylpiperazin - 1 -
ylacetyl) - 6H - pyrido[2,3 - b][1,4] -
benzodiazepine - 6 - one dihydrochloride

The tablets prepared as described in Ex-
ample 30 are coated with a shell according to
a known process, the shell consisting essen-
tially of sugar and talcum. The finished sugar-
coated tablets are polished with beeswax.
Weight of sugar-coated tablet: 300 mg.

EXAMPLE 32

Ampoules with 2 mg of 5,11 - dihydro - 11 -
(4 - methylpiperazin - 1 - ylacetyl) - 6H -
pyrido[2,3 - b][1,4]benzodiazepine - 6 -
one dihydrochloride

Composition:

1 ampoule contains;
5,11 - dihydro - 11 - (4 - methyl -
piperazin - 1 - ylacetyl) - 6H -
pyrido[2,3 - b][1,4]benzo-
diazepine - 6 - one dihydro-
chloride 2.0 mg
sodium chloride 8.0 mg
distilled water ad 1 ml

Preparation:

The active ingredient and sodium chloride
are dissolved in distilled water and subse-
quently filled to the indicated volume. The
solution is filtered sterile and filled into 1 ml
ampoules.

Sterilization: 20 minutes at 120°C.

EXAMPLE 33

Suppositories with 15 mg of 5,11 - dihydro-
11 - (4 - methylpiperazin - 1 - ylacetyl) -
6H - pyrido[2,3 - b][1,4]benzodiazepine - 6 - one dihydrochloride

Composition:

1 suppository contains:
5,11 - dihydro - 11 - (4 - methyl -
piperazin - 1 - ylacetyl) - 6H -
pyrido[2,3 - b][1,4]benzo-
diazepine - 6 - one dihydro-
chloride 15.0 mg
suppository base (c.g. 'Witepsol'
W 45, the word "Witepsol"
being a registered Trade Mark 1685.0 mg
1700.0 mg

Preparation:

The finely pulverized active ingredient is
suspended in the molten suppository base,
cooled to 40°C. At 37°C the molten mass is
poured into slightly precooled suppository
moulds.

Weight of suppository: 1.7 g.

EXAMPLE 34

Drops with 10 mg of 5,11 - dihydro - 11 -
(4 - methylpiperazin - 1 - ylacetyl) - 6H -
pyrido[2,3 - b][1,4]benzodiazepine - 6 -
one dihydrochloride

Composition:

100 ml of drop solution comprise
methyl *p* - hydroxybenzoate 0.035 g
propyl *p* - hydroxybenzoate 0.015 g
aniseed oil 0.05 g
menthol 0.06 g
ethanol pure 10.0 g
5,11 - dihydro - 11 - (4 - methyl -
piperazin - 1 - ylacetyl) - 6H -
pyrido[2,3 - b][1,4]benzo-
diazepine - 6 - one dihydro-
chloride 1.0 g
artificial sweetener 1.0 g
glycerin 15.0 g
distilled water ad 100.0 ml

Preparation:

The active ingredient and artificial
sweetener are dissolved in approximately 70
ml of water and glycerin added. The *p* -
hydroxybenzoates, aniseed oil and menthol
are dissolved in ethanol and the solution
added to the aqueous solution with stirring.
Finally the solution is made up with water
to 100 ml and filtered free of particles.

1 ml of drop solution = 10 mg. of 5,11 - di-
hydro - 11 - (4 - methylpiperazin - 1 -
ylacetyl) - 6H - pyrido[2,3 - b][1,4] -
benzodiazepine - 6 - one dihydrochloride.

EXAMPLE 35

Tablets with 10 mg of 5,11 dihydro - 11 - (4-methylpiperazin - 1 - ylacetyl) - 6H-pyrido[2,3 - b][1,4]benzodiazepine - 6-one dihydrochloride and 5 mg of 7-chloro - 1,3 - dihydro - 3 - hydroxy - 5-phenyl - 2H - 1,4 - benzodiazepine - 2-one [Adumbran (registered Trade Mark)]

10 Composition:

1 tablet contains:
 5,11 - dihydro - 11 - (4 - methylpiperazin - 1 - ylacetyl) - 6H-pyrido[2,3 - d][1,4]benzodiazepine - 6 - one dihydrochloride 10.0 mg
 7 - chloro - 1,3 - dihydro - 3 - hydroxy - 5 - phenyl - 2H - 1,4 - benzodiazepine - 2 - one 5.0 mg
 20 lactose 135.0 mg
 potato starch 60.0 mg
 polyvinylpyrrolidone 8.0 mg
 magnesium stearate 2.0 mg
 220.0 mg

25 Preparation:

A mixture of the active ingredient, lactose and potato starch is moistened with a 15% ethanolic solution of polyvinylpyrrolidone, granulated through a screen of 1.5 mm mesh-size, dried at 45°C and triturated once more through the above screen. The granulate obtained is mixed with magnesium stearate and pressed into tablets.

Weight of table: 220 mg

35 Die: 9 mm, flat.

EXAMPLE 36

Sugar-coated tablets with 10 mg of 5,11-dihydro - 11 - (4 - methylpiperazin - 1 - ylacetyl) - 6H - pyrido[2,3 - b][1,4]benzodiazepine - 6 - one dihydrochloride and 25 mg of phenylethylbarbituric acid.

40 Composition:

1 sugar-coated table core contains:
 5,11 - dihydro - 11 - (4 - methylpiperazin - 1 - ylacetyl) - 6H-pyrido[2,3 - b][1,4]benzodiazepine - 6 - one dihydrochloride 10.0 mg
 phenylethyl barbituric acid 25.0 mg
 45 lactose 50.0 mg
 corn starch 30.0 mg
 polyvinylpyrrolidone 4.0 mg
 magnesium stearate 1.0 mg
 120.0 mg

55 Preparation:

A mixture of the active ingredients, lactose and corn starch is granulated with a 10% ethanolic solution of the polyvinylpyrrolidone

through screen of 1 mm mesh-size. The granulate is mixed with magnesium stearate and pressed to tablet cores.

Weight of core: 120 mg.

Die: 7 mm, arched.

The tablet cores thus obtained are coated with a shell according to a known method, the shell consisting essentially of talcum and sugar. The finished sugar coated tablets are polished with beeswax.

Weight of sugar coated tablet: 180 mg.

EXAMPLE 37

Sugar coated tablets with 10 mg of 5,11-dihydro - 11 - (4 - methylpiperazin - 1 - ylacetyl) - 6H - pyrido[2,3 - b][1,4]benzodiazepine - 6 - one dihydrochloride and 50 mg of diethylaminoacet - 2,6-xylidide

Composition:

1 tablet-core contains:
 5,11 - dihydro - 11 - (4 - methylpiperazin - 1 - ylacetyl) - 6H-pyrido[2,3 - b][1,4]benzodiazepine - 6 - one dihydrochloride 10.0 mg
 diethylaminoacet - 2,6 - xylidide 50.0 mg
 lactose 98.0 mg
 85 corn starch 50.0 mg
 polyvinylpyrrolidone 10.0 mg
 magnesium stearate 2.0 mg
 220.0 mg

Preparation

The mixture of active ingredients, lactose and corn starch is granulated with a 20% alcoholic solution of the polyvinylpyrrolidone through a screen of 1.5 mm mesh-size dried at 45°C and triturated once more through the above screen. The granulate mixed with magnesium stearate is pressed into tablet cores.

Weight of core: 220 mg.

Die: 9 mm, arched.

The sugar coated tablets are prepared as described in Example 36.

Weight of sugar coated tablet: 300 mg.

EXAMPLE 38

"Roll-cure" (patient ingests the preparation and changes position (rolls) from side to side, so that the preparation reaches all parts of his stomach)
 10 mg of 5,11 - dihydro - 11 - (4 - methylpiperazin - 1 - ylacetyl) - 6H - pyrido[2,3 - b][1,4]benzodiazepine - 6 - one dihydrochloride and 300 mg of Targisin^(R) (diacetyltanninalbumin with 6% of silver)

The substances are intimately mixed and the mixture is sealed into aluminium foil.

Filling per single dose: 310 mg.

For administration, the content of one portion is dissolved in water.

EXAMPLE 39

- Milk powder chewing tablets with 10 mg of 5,11 - dihydro - 11 - (4 - methyl-piperazin - 1 - ylacetyl) - 6H - pyrido[2,3 - b][1,4]benzodiazepine - 6 - one dihydrochloride and 500 mg of Masigel^(R) (dimagnesium aluminium trisilicate)

Composition:

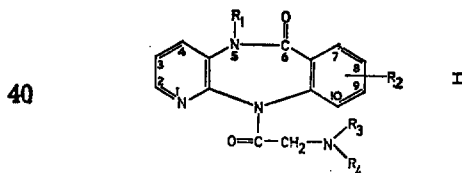
- 1 tablet contains:
- | | | |
|----|---|-----------------|
| 10 | 5,11 - dihydro - 11 - (4 - methyl-piperazin - 1 - ylacetyl) - 6H - pyrido[2,3 - b][1,4]benzodiazepine - 6 - one dihydrochloride | 10.0 mg |
| 15 | Masigel ^(R) | 500.0 mg |
| | skim milk powder | 300.0 mg |
| | mannitol | 113.0 mg |
| | suppository base (e.g. 'Witepsol' H 15, the word 'Witepsol' being a registered Trade Mark) | 70.0 mg |
| 20 | vanillin, ground | 1.0 mg |
| | artificial sweetener, ground | 1.0 mg |
| | magnesium stearate | 5.0 mg |
| | | <hr/> 1000.0 mg |

Preparation:

- A mixture of active ingredients, skim milk powder and mannitol is moistened first with a 30% ethanolic solution of the suppository base and then with 500 g of distilled water (per 1000 tablets) and granulated through a screen of 2.0 mm mesh-size. The mixture is dried at 45°C, triturated once more through a screen of 1.5 mm mesh size and then intimately mixed with the remaining excipients. The mixture is pressed into tablets.
- Weight of tablet: 1.0 g.
Die: 16 mm, flat.

WHAT WE CLAIM IS:—

1. Compounds of the general formula



- [wherein R₁ represents a hydrogen atom or an alkyl group containing from 1 to 4 carbon atoms; R₂ represents a hydrogen or halogen atom or a methyl group; R₃ and R₄, which may be the same or different each represents a straight or branched alkyl group containing from 1 to 5 carbon atoms, or R₃ and R₄ together with the adjacent nitrogen atom form a 5 to 7 membered saturated monocyclic heterocyclic ring which, if desired, may further contain an oxygen atom or another nitrogen atom in the ring and/or be

substituted by an alkyl or hydroxyalkyl group (each containing from 1 to 4 carbon atoms), by an unsubstituted or nuclear methyl substituted benzyl group or by a camphidino group] and acid addition salts thereof.

2. Compounds as claimed in claim 1 wherein R₁ represents a methyl or ethyl group.

3. Compounds as claimed in claim 1 or claim 2 wherein R₂ represents a chlorine atom.

4. Compounds as claimed in any of the preceding claims wherein R₃ and R₄ each represents a methyl, ethyl, n-propyl, n-butyl, iso-butyl or n-pentyl group or together with the adjacent nitrogen atom R₃ and R₄ represent a pyrrolidino, piperidino, piperazino, morpholino or hexamethyleneimino group.

5. Compounds as claimed in any of claims 1 to 3 wherein R₃ and R₄ together with the adjacent nitrogen atom represent an alkyl substituted piperidino group or a piperazino group substituted in the 4-position by a methyl, 2-hydroxyethyl or 2-methylbenzyl group.

6. Compounds as claimed in claim 5 wherein R₃ and R₄ together with the adjacent nitrogen atom form a 2-, 3- or 4- position methyl or ethyl substituted piperidino group.

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

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

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

10. 5,11 - Dihydro - 11 - [4 - (2 - hydroxyethyl) - piperazin - 1 - ylacetyl] - 6H - pyrido[2,3 - b][1,4]benzodiazepine - 6 - one and acid addition salts thereof.

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

12. 5,11 - Dihydro - 11 - dimethylaminoacetyl - 5 - methyl - 6H - pyrido[2,3 - b][1,4]benzodiazepine - 6 - one and acid addition salts thereof.

13. 5,11 - Dihydro - 11 - (2 - methylpiperidinoacetyl) - 6H - pyrido[2,3 - b][1,4]benzodiazepine - 6 - one and acid addition salts thereof.

14. 5,11 - Dihydro - 11 - (2 - ethylpiperidinoacetyl) - 6H - pyrido[2,3 - b][1,4]benzodiazepine - 6 - one and acid addition salts thereof.

15. 5,11 - Dihydro - 5 - methyl - 11 - (2 - methylpiperidinoacetyl) - 6H - pyrido[2,3 - b][1,4]benzodiazepine - 6 - one and acid addition salts thereof.

16. Compounds as claimed in any of the

EXAMPLE 39

Milk powder chewing tablets with 10 mg of 5,11 - dihydro - 11 - (4 - methyl-piperazin - 1 - ylacetyl) - 6H - pyrido[2,3 - b][1,4]benzodiazepine - 6 - one dihydrochloride and 500 mg of Masigel^(R) (dimagnesium aluminium trisilicate)

Composition:

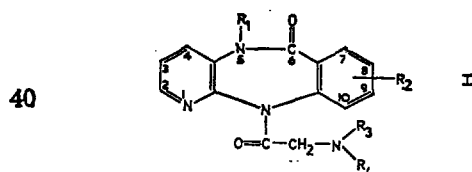
1 tablet contains:	
10 5,11 - dihydro - 11 - (4 - methyl-piperazin - 1 - ylacetyl) - 6H - pyrido[2,3 - b][1,4]benzodiazepine - 6 - one dihydrochloride	10.0 mg
15 Masigel ^(R)	500.0 mg
skim milk powder	300.0 mg
mannitol	113.0 mg
suppository base (e.g. 'Witepsol' H 15, the word 'Witepsol' being a registered Trade Mark)	
20 vanillin, ground	70.0 mg
artificial sweetener, ground	1.0 mg
magnesium stearate	5.0 mg
	1000.0 mg

Preparation:

- 25 A mixture of active ingredients, skim milk powder and mannitol is moistened first with a 30% ethanolic solution of the suppository base and then with 500 g of distilled water (per 1000 tablets) and granulated through a screen of 2.0 mm mesh-size. The mixture is dried at 45°C, triturated once more through a screen of 1.5 mm mesh size and then intimately mixed with the remaining excipients. The mixture is pressed into tablets.
- 30 Weight of tablet: 1.0 g.
Die: 16 mm, flat.

WHAT WE CLAIM IS:—

1. Compounds of the general formula



[wherein R₁ represents a hydrogen atom or an alkyl group containing from 1 to 4 carbon atoms; R₂ represents a hydrogen or halogen atom or a methyl group; R₃ and R₄, which may be the same or different each represents a straight or branched alkyl group containing from 1 to 5 carbon atoms, or R₃ and R₄ together with the adjacent nitrogen atom form a 5 to 7 membered saturated monocyclic heterocyclic ring which, if desired, may further contain an oxygen atom or another nitrogen atom in the ring and/or be

substituted by an alkyl or hydroxyalkyl group (each containing from 1 to 4 carbon atoms), by an unsubstituted or nuclear methyl substituted benzyl group or by a camphidino group] and acid addition salts thereof.

2. Compounds as claimed in claim 1 wherein R₁ represents a methyl or ethyl group.

3. Compounds as claimed in claim 1 or claim 2 wherein R₂ represents a chlorine atom.

4. Compounds as claimed in any of the preceding claims wherein R₃ and R₄ each represents a methyl, ethyl, n-propyl, n-butyl, iso-butyl or n-pentyl group or together with the adjacent nitrogen atom R₃ and R₄ represent a pyrrolidino, piperidino, piperazino, morpholino or hexamethyleneimino group.

5. Compounds as claimed in any of claims 1 to 3 wherein R₃ and R₄ together with the adjacent nitrogen atom represent an alkyl substituted piperidino group or a piperazino group substituted in the 4-position by a methyl, 2-hydroxyethyl or 2-methylbenzyl group.

6. Compounds as claimed in claim 5 wherein R₃ and R₄ together with the adjacent nitrogen atom form a 2-, 3- or 4- position methyl or ethyl substituted piperidino group.

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

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

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

10. 5,11 - Dihydro - 11 - [4 - (2 - hydroxyethyl) - piperazin - 1 - ylacetyl] - 6H - pyrido[2,3 - b][1,4]benzodiazepine - 6 - one and acid addition salts thereof.

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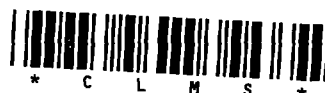
12. 5,11 - Dihydro - 11 - dimethylaminoacetyl - 5 - methyl - 6H - pyrido[2,3 - b][1,4]benzodiazepine - 6 - one and acid addition salts thereof.

13. 5,11 - Dihydro - 11 - (2 - methylpiperidinoacetyl) - 6H - pyrido[2,3 - b][1,4]benzodiazepine - 6 - one and acid addition salts thereof.

14. 5,11 - Dihydro - 11 - (2 - ethylpiperidinoacetyl) - 6H - pyrido[2,3 - b][1,4]benzodiazepine - 6 - one and acid addition salts thereof.

15. 5,11 - Dihydro - 5 - methyl - 11 - (2 - methylpiperidinoacetyl) - 6H - pyrido[2,3 - b][1,4]benzodiazepine - 6 - one and acid addition salts thereof.

16. Compounds as claimed in any of the



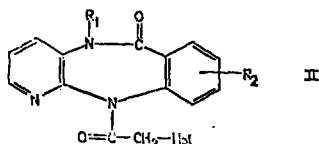


preceding claims in the form of physiologically acceptable acid addition salts.

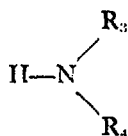
17. Compounds as claimed in claim 16 wherein the physiologically acceptable acid addition salts are salts with hydrochloric, hydrobromic, sulfuric, phosphoric, tartaric, fumaric, citric, maleic, succinic or oxalic acid.

18. Compounds as claimed in claim 1 as herein specifically described with the exception of those as claimed in any of claims 7 to 15.

19. A process for the preparation of compounds as claimed in claim 1 wherein a compound of formula



(wherein R_1 and R_2 are as defined in claim 1 and Hal represents a halogen atom) is reacted with an amine of formula



19 to 26 wherein the compound of formula II is a compound wherein Hal represents an iodine atom.

28. A process for the preparation of compounds as claimed in claim 1 (wherein R_1 and R_2 together with the adjacent nitrogen atom represent an unsubstituted piperazin-1-yl group) wherein a compound of formula I (wherein R_1 and R_2 together with the adjacent nitrogen atom represent a 4-aralkyl-piperazin-1-yl group) is reacted to convert the 11-(4-aralkylpiperazin-1-ylacetyl) group into an 11-piperazin-1-ylacetyl group and the compound of formula I produced is, if desired, converted into an acid addition salt thereof.

29. A process as claimed in claim 28 wherein the reaction is effected by hydrogenation in the presence of a catalyst.

30. A process as claimed in claim 29 wherein the catalyst comprises palladium on active charcoal.

31. A process as claimed in claim 19 substantially as herein described.

32. A process for the preparation of compounds as claimed in claim 1 substantially as herein described in any of Examples 1 to 14 and 16 to 29.

33. A process as claimed in claim 28 substantially as herein described.

34. A process for the preparation of compounds as claimed in claim 1 substantially as herein described in Example 15.

35. Compounds as claimed in claim 1 when prepared by a process as claimed in any of claims 19 to 34.

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

37. Compositions as claimed in claim 36 in a form suitable for oral, rectal or parenteral administration.

38. Compositions as claimed in claim 36 or claim 37 in the form of solutions, infusions, tablets, sugar coated tablets or suppositories.

39. Compositions as claimed in any of claims 36 to 38 in the form of dosage units.

40. Compositions as claimed in claim 39 wherein each dosage unit contains from 5 to 30 mg of active ingredient.

41. Compositions as claimed in claim 40 wherein each dosage unit contains from 10 to 20 mg. of active ingredient.

42. Compositions as claimed in any of claims 36 to 41 which contain a further active ingredient.

43. Compositions as claimed in claim 42 wherein the further active ingredient comprises 7-chloro-1,3-dihydro-3-hydroxy-5-phenyl-2H-1,4-benzodiazepine-2-one, diethyl-aminoacet-2,6-xylidide or dimagnesium aluminium trisilicate.

wherein R_3 and R_4 are as defined in claim 1) and the compound of formula I produced is, if desired, converted into an acid addition salt thereof.

20. A process as claimed in claim 19 wherein the reaction is effected in a solvent.

21. A process as claimed in claim 20 wherein the solvent comprises an alkanol, acetone, dioxan or an aromatic hydrocarbon.

22. A process as claimed in claim 21 wherein the solvent comprises ethanol, benzene or toluene.

23. A process as claimed in any of claims 19 to 22 wherein the reaction is effected at an elevated temperature.

24. A process as claimed in any of claims 20 to 22 wherein the reaction is effected at a temperature up to the boiling point of the solvent used.

25. A process as claimed in any of claims 19 to 24 wherein the reaction is effected in the presence of an acid binding agent.

26. A process as claimed in claim 25 wherein the acid binding agent comprises an excess of the compound of formula III or an alkali metal carbonate or alkali metal hydrogen carbonate.

27. A process as claimed in any of claims

44. Compositions as claimed in claim 36 substantially as herein described.

45. Pharmaceutical compositions substantially as herein described in any of Examples 5 30 to 39.

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