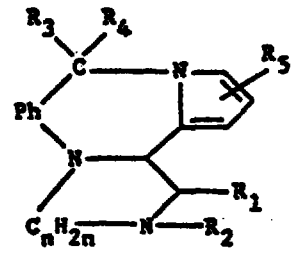
Piperazinopyrrolobenzodiazepines, a process for their preparation and pharmaceutical formulations containing these compounds

The invention relates to new 1,3,4,14b-tetrahydro-2H,10H-pyrazino[1,2-a]pyrrolo[2,1-c]-[1,4]benzodiazepines of the general formula I



(I)

wherein each of the symbols R_1, R_3 and R_4 denotes hydrogen or lower alkyl, R_1 represents hydrogen, lower alkyl, higher alkyl, lower alkenyl, lower alkinyl, cycloalkyl or cycloalkenyl having in each case 3 to 7 ring members or represents cycloalkyl-lower alkyl, hydroxy-lower alkyl, amino-lower alkyl, mono-lower alkylamino-lower alkyl, di-lower alkylamino-lower alkyl, carboxy-lower alkyl, lower carboalkoxy-lower alkyl, carbamoyl-lower alkyl, mono-lower alkylcarbamoyl-lower alkyl, Hph-lower alkyl, lower alkanoyl-lower alkyl or HphCO-lower alkyl, Ph denotes 1,2-phenylene which can be substituted by not more than 2 substituents belonging to the group comprising lower alkyl, lower alkoxy, lower alkylthio, halogen and tri-

fluoromethyl, C_nH_{2n} represents lower alkylene which separates the two nitrogen atoms by 2 or 3 carbon atoms, and R_5 denotes hydrogen, lower alkyl, carboxyl, lower carboalkoxy, hydroxy-lower alkyl, amino-lower alkyl, mono-lower alkylamino-lower alkyl or di-lower alkylamino-lower alkyl; the lower alkoxycarbonyl, lower alkanoyl, higher alkanoyl, adamantoyl, carbamoyl, mono-lower alkylcarbamoyl or di-lower alkylcarbamoyl derivatives or cycloalkylcarbonyl derivatives having 3 to 7 ring members or HphCO derivatives, the 2-N-oxides, the 2-lower alkyl or 2-Hph-lower alkyl quaternary ammonium derivatives and salts thereof, especially therapeutically usable salts, with acids or bases.

A lower alkyl group R_1, R_2, R_3, R_4, R_5 and/or a group of this type present in a substituted 1,2-phenylene Ph or phenyl Hph radical is, above all, methyl, but is also ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, n-heptyl, isopropyl, isobutyl, isopentyl, isohexyl or isoheptyl, for example 2-methylpropyl or 3-methylbutyl. A higher alkyl group R_2 is, for example, n-octyl, n-decyl, n-dodecyl, n-hexadecyl or n-octadecyl.

A lower alkenyl or lower alkinyl group R_2 is preferably a group of this type in which the multiple bond is separated from the nitrogen atom by at least two carbon atoms, for example allyl, 2-butenyl, 3-butenyl or 3-methyl-2-butenyl; or propargyl, 2-butinyl or 3-butinyl, respectively.

A cycloalkyl, cycloalkenyl or cycloalkyl-lower alkyl group R_2 containing 3 to 7 ring members is preferably cyclopropyl, cyclopentyl, cyclohexyl or cycloheptyl; 2-cyclopentenyl, 3-cyclopentenyl, 2-cyclohexenyl or 3-cyclohexenyl; or cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl, cyclobutylethyl, cyclopentylmethyl or cyclopentylethyl.

A hydroxy-lower alkyl, amino-lower alkyl, mono-lower alkylamino-lower alkyl, di-lower alkylamino-lower alkyl, carboxy-lower alkyl, carboalkoxy-lower alkyl, carbamoyl-lower alkyl, mono-lower alkylcarbamoyl-lower alkyl, di-lower alkylcarbamoyl-lower alkyl or lower alkanoyl-lower alkyl group R_2 is preferably a group of this type wherein the hetero-atoms

(O or N) are separated from the ring nitrogen atom by at least 2 carbon atoms, for example 2-hydroxyethyl, 2-hydroxypropyl, 2-aminoethyl, 2-aminopropyl, 2-methylaminoethyl, 2-methylaminopropyl, 2-ethylaminoethyl, 2-ethylaminopropyl, 2-dimethylaminoethyl, 2-dimethylaminopropyl, 2-diethylaminoethyl, 2-diethylaminopropyl, 2-carboxyethyl, 2-carboxypropyl, 2-carbomethoxyethyl, 2-carbomethoxypropyl, 2-carboethoxyethyl, 2-carboethoxypropyl, 2-carbamoylethyl, 2-carbamoylpropyl, 2-monomethylcarbamoylethyl, 2-monomethylcarbamoylpropyl, 2-dimethylcarbamoylethyl, 2-dimethylcarbamoylpropyl, 2-acetylethyl, 2-acetylpropyl, 2-propionylethyl, 2-propionylpropyl or 3-hydroxypropyl or carboxymethyl, carbomethoxymethyl, carboethoxymethyl, carbamoylmethyl, monomethylcarbamoylmethyl, dimethylcarbamoylmethyl or acetylmethyl.

A 1,2-phenylene radical Ph or the phenyl-lower alkyl or benzoyl-lower alkyl group (that is to say Hph-lower alkyl or HphCO-lower alkyl group) R_2 is preferably unsubstituted or monosubstituted in the benzene ring by one of the substituents mentioned, for example methyl or ethyl; methoxy, ethoxy or isopropoxy; methylthio or ethylthio; or fluorine, chlorine, bromine or trifluoromethyl.

A lower alkylene group C_nH_{2n} is especially ethylene but is also 1,2-propylene, 1,3-propylene, 1,2-butylene, 1,3-butylene or 2,3-butylene.

A carbo-lower alkoxy group or a hydroxy-lower alkyl, amino-lower alkyl, mono-lower alkylamino-lower alkyl or di-lower alkylamino-lower alkyl group R_5 is preferably carbomethoxy or carboethoxy or a hydroxymethyl, aminomethyl, monomethylamino, dimethylaminomethyl, monoethylaminomethyl or diethylaminomethyl group.

The said acyl derivatives of compounds of the formula I are either derived from compounds in which R_2 denotes hydrogen or from those in which R_2 and/or R_5 denotes hydroxy-lower alkyl, amino-lower alkyl or mono-lower alkylamino-lower alkyl. These derivatives are thus amides or esters which are derived from lower or higher aliphatic or cycloaliphatic acids, for example acetic, propionic, butyric, pivalic,

decanoic, palmitic, hexahydrobenzoic or adamantylcarboxylic acid, carbamic acid, monomethylcarbamic, dimethylcarbamic, monoethylcarbamic or diethylcarbamic acid or carbonic acid; benzoic acid, toluene (sic), amisic (sic) acid or halogeno-benzoic acids.

The N-oxides or lower alkyl or phenyl-lower alkyl quaternary derivatives are preferably derived from compounds of the formula I in which R_2 is not hydrogen and in which only the nitrogen atom in the 2-position has been substituted by functional groups. The anions or quaternary compounds and acid addition salts are preferably those of therapeutically usable acids, for example of the acids mentioned later in the text. Compounds of the formula I which have a carboxyl group in the radical R_2 and/or R_5 also form salts with such bases as, for example, ammonia, mono-, di- or tri-lower alkyl-amines, lower alkyleneamines, morpholine, piperazine, pyridine or lower alkyl derivatives of the said cyclic bases; or alkali metal or alkaline earth metal hydroxides.

In the organic radicals or compounds mentioned above or subsequently, the term "lower" defines those having not more than 7, preferably up to 4 and primarily 1 or 2 carbon atoms. The term "higher" defines radicals or compounds having 8 to 20, preferably 8 to 16, carbon atoms.

Tricyclic benzodiazepine derivatives which contain a piperazino-lower alkanoyl radical as well as a saturated pyrrolidine ring and which have a tranquillising action were known from U.S. Patent 3,984,562. Compared with these, the compounds according to the invention differ quite substantially in their structure (tetracyclic, no piperazino-lower alkanoyl radical and an unsaturated pyrrole ring) but also in respect of their action.

The compounds of the invention exhibit valuable pharmacological properties, primarily an antidepressive action, but also an analgesic, antihistamine and antiserotonergic action. These properties can be demonstrated in animal tests, preferably using mammals, such as mice, rats, guinea pigs and apes, as the test objects. The new compounds can be administered to these animals enterally or parenterally, preferably

orally, subcutaneously, intravenously or interperitoneally, for example by means of gelatine capsules or in the form of suspensions containing starch or aqueous solutions. The dose used can be within a range from approximately 0.01 to 100 mg/kg/day, preferably approximately 0.05 to 5 e (sic) mg/kg/day, especially approximately 0.1 to 0.5 mg/kg/day. The antidepressive properties can be demonstrated on mice by raising clonidine analgesia. In this test system the compounds of the invention are administered in the form of aqueous solutions orally or intraperitoneally to groups of at least 10 male mice, and 0.1 mg/kg of clonidine is intubated to them 30 minutes later. After 20 minutes, 3.75 mg/kg of phenyl-p-benzoquinone are injected intraperitoneally into the animals, and the number of writhing animals is determined 5 - 15 minutes after the injection. Every animal not writhing is designated favourable, and the ED_{50} value for the combination of the active compound tested and clonidine is determined by the Berkson logit method from the number of animals reacting favourably.

The said analgesic effects can be demonstrated similarly by the phenyl-p-benzoquinone writhing test. In this test, groups of at least 10 male mice receive the compound of the invention orally or intraperitoneally, and 50 minutes later receive 3.75 mg/kg of phenyl-p-benzoquinone intraperitoneally. The number of writhing animals is once more determined after 5 - 15 minutes, and the ED value for the animals not writhing is determined by the Berkson logit method.

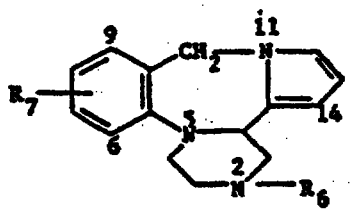
Finally, the antihistamine properties can be demonstrated in vitro by the method of Chasin et al., J. Neurochem. 22, 1031 (1974). Homogenates of a cell-free formulation are incubated beforehand with ^{3}H-adenine, in the course of which endogenous ^{3}-adenosine triphosphate is formed. The homogenates are then incubated with 50 micromolar histamine, in order to activate the synthesis of ^{3}H-cyclic adenosine monophosphate. This procedure is carried out in the presence or absence of the test compound, concentrations between 0.01

and 100 micromoles being employed. If the substance tested is active, the histamine activation of the adenylate-cyclase is inhibited.

The compounds of the invention can accordingly be used as antidepressives, analgesic and antihistamine formulations, for example in the treatment or handling of mental depressions, migraines and/or allergic conditions. They can, therefore, also be employed as intermediate products for the preparation of other valuable products, in particular pharmacologically active formulations.

Preferred compounds are those of the formula I wherein each of the symbols R_1, R_3 and R_4 denotes hydrogen, R_2 represents hydrogen, lower alkyl, lower alkenyl, lower alkinyl, hydroxy-lower alkyl, cycloalkyl or cycloalkyl-lower alkyl having in each case 3 to 7 ring carbon atoms, Ph denotes 1,2-phenylene, (lower alkyl)-1,2-phenylene, (lower alkoxy)-1,2-phenylene, (lower alkylthio)-1,2-phenylene, (halogen)-1,2-phenylene or (trifluoromethyl)-1,2-phenylene, n is an integer of 2 or 3 and R_5 denotes hydrogen, lower alkyl or hydroxy-lower alkyl, their lower alkanoyl, adamantoyl (sic), carbamoyl, mono-lower alkylcarbamoyl, di-lower alkylcarbamoyl or HphCO derivatives, 2-N-oxides, 2-lower alkyl or 2-Hph-lower alkyl quaternary derivatives and their therapeutically usable acid addition salts.

Compounds which should be singled out particularly are those of the general formula II



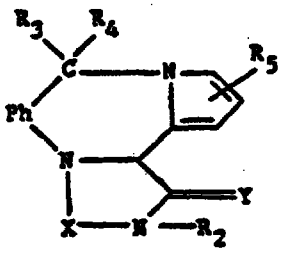
(II)

wherein R_6 denotes hydrogen, lower alkyl, lower alkenyl, lower alkinyl, hydroxy-lower alkyl or cycloalkyl-lower alkyl having 3 to 7 ring members, and R_7 represents hydrogen, halogen or trifluoromethyl, and their therapeutically usable acid addition salts.

Compounds which are particularly preferred are those

of the general formula II wherein R_6 denotes alkyl, alkenyl, alkinyl or hydroxyalkyl having in each case up to 4 carbon atoms, or denotes cyclopropylmethyl, and R_7 represents fluorine or chlorine, preferably in the 7-position, and their therapeutically usable acid addition salts.

The compounds of the invention can be prepared by methods which are in themselves known, preferably by reducing a compounds (sic) of the general formula III



(III),

wherein X denotes lower alkylene, monooxo-lower alkylene or dioxo-lower alkylene which separates the two nitrogen atoms by 2 or 3 carbon atoms and in which oxo is attached to the carbon atom adjacent to the nitrogen atom, and Y represents oxo, two hydrogen atoms or hydrogen and lower alkyl, subject to the proviso that at least one oxo group is present in X or Y, and, if desired, by converting a resulting compound of the formula I into another compound according to the invention.

The reduction of the said lactams of the formula III is preferably carried out by means of simple hydrides or complex light metal hydrides, such as boranes or alane, primarily by means of alkali metal aluminium hydrides or alkali metal lower alkoxy hydrides, for example lithium aluminium hydride, sodium tri-t.-butoxyaluminium hydride or sodium bos-2-methoxyethoxy)-aluminium hydride (sic).

The starting materials can be prepared by the methods described for their known analogues or as illustrated in the examples.

Thus the starting materials can be prepared by reacting appropriate compounds of the formula III in which X denotes two hydrogen atoms each of which is attached to a

different nitrogen atom, with reactive derivatives of appropriate glycols, glycollic acids or dicarboxylic acids, such as lower alkyl esters, halides or anhydrides thereof, or with reactive esters of the said glycols or glycollic acid derivatives, for example esters of hydrogen halide acids or aromatic sulfonic acids, such as 1,2-dibromoethane or 1,2-dibromopropane, ethyl or propyl bromoacetate, ethyl tosyloxyacetate, diethyl oxalate or malonate, oxalic acid hemiethyl ester-chloride, oxalyl bischloride or malonic anhydride. The said precursors, corresponding to the formula III, of the starting materials can be obtained analogously to Il Farmaco, Ed. Sc. 24, Fasc. 3, page 276 or as illustrated in the examples.

If it is desirable or necessary, the resulting compounds of the invention can be converted into one another by methods which are in themselves known. Thus, for example, resulting compounds of the formula I in which R_2 denotes hydrogen and/or R_5 represents amino-lower alkyl or mono-lower alkylamino-lower alkyl, or their alkali metal salts, for example sodium salts, can be converted into the corresponding N-substituted compounds or into the quaternary ammonium derivatives by being reacted with reactive esters of unsubstituted or appropriately substituted aliphatic or araliphatic alcohols, such as methanol, ethanol, allyl alcohol, propargyl alcohol or benzyl alcohol, depending on the molar amount of the alkylating agent used. The reactive esters are obtained by esterifying the alcohols with strong inorganic or organic acids, primarily with a hydrogen halide acid, for example hydrochloric, hydrobromic or hydriodic acid, sulfuric acid or an aromatic sulfonic acid, for example p-toluenesulfonic acid, or m-bromobenzenesulfonic acid.

Conversely, the resulting N-alkylated compounds can be converted into N-unsubstituted compounds, for example by catalytic hydrogenolysis of N-benzyl compounds. If N-lower alkyl, N-lower alkenyl or N-(CH_2-Hph) derivatives are reacted with lower alkyl halogenoformates, for example ethyl chloro-

formate, N-acyl derivatives are obtained. The latter can be converted, for example by means of aqueous bases, for example alkali metal hydroxide solutions, into the N-unsubstituted compounds, preferably into compounds in which R_2 is hydrogen. Other acyl derivatives, either amides or esters, can be prepared by reacting compounds of the formula I wherein R_2 denotes hydrogen or R_2 and/or R_5 represents hydroxy-lower alkyl, amino-lower alkyl or mono-lower alkylamino-lower alkyl, with appropriate acid derivatives, for example halides, simple or activated esters, such as alkyl or cyanoalkyl esters, anhydrides or cyanates. Resulting esters can be hydrolysed exactly as described for the N-acyl derivatives. Resulting unsaturated compounds, for example those in which R_2 denotes lower alkenyl, lower alkinyl or cycloalkenyl, can be hydrogenated as described above by means of catalytically activated hydrogen. Resulting esters can also be converted into amide (carbamoyl) compounds by reacting with ammonia or appropriate primary or secondary amines, or can be converted into the corresponding alcohols by reduction with complex light metal hydrides, for example lithium aluminium hydride.

Resulting compounds of the formula I wherein R_3 and/or R_4 denotes hydrogen can be converted into the corresponding lower alkyl derivatives by metallisation with reactive organometallic derivatives, for example n-butyllithium or lithium diisopropylamide, and reaction with reactive esters of lower alkanols.

Compounds of the formula I wherein R_5 denotes hydrogen can be converted into the corresponding 12-acyl derivatives, for example by acylation with corresponding derivatives of HO-X-OH wherein X has the meaning indicated above (analogously to the preparation of a starting material of the formula III), or by being reacted first with a trihalogenoacetyl halide and then with an alkali metal lower alkoxide. Resulting 12-carboalkoxy, 12-carboalkoxy-carbonyl or 12-hydroxymethyl derivatives can be hydrolysed in accordance with the methods indicated above and/or can be reduced by means of the above-mentioned simple hydrides or complex light metal hydrides to

give a 12-methyl, 12-hydroxymethyl or 12-(2-hydroxy)-ethyl compound. Resulting tertiary nitrogen compounds in which R_2 is not hydrogen can be converted into their N-oxides, for example by means of hydrogen peroxide or organic per-acids, such as lower peralkanoic acids or perbenzoic acid, for example peracetic acid or m-chloroperbenzoic acid, preferably at or below room temperature using the latter, or at temperatures up to 100°C using dilute hydrogen peroxide solution in the presence of lower alkanoic acids, for example acetic acid. In this case the reaction must be carried out carefully, particularly using the said per-acids, in order to avoid over-oxidation in the case of excessively long reaction times.

Finally, the compounds of the invention can be obtained in the form of free bases or as salts. The resulting free base can be converted into the corresponding acid addition salt, preferably by means of acids which produce therapeutically usable acid addition salts or by means of anion exchangers. Resulting salts can be converted into the corresponding free bases, for example by treatment with a fairly strong base, such as a metal hydroxide or ammonium hydroxide, a basic salt or a cation exchanger, for example by means of an alkali metal hydroxide or carbonate. Examples of acids which produce therapeutically usable acid addition salts are inorganic acids, such as a hydrogen halide acid, for example hydrochloric or hydrobromic acid, or sulfuric, phosphoric, nitric or perchloric acid; or organic acids, such as aliphatic or aromatic carboxylic or sulfonic acids, for example formic, acetic, propionic, succinic, glycollic, lactic, malic, tartaric, citric, maleic, fumaric, hydroxymaleic, pyruvic, phenylacetic, benzoic, 4-aminobenzoic, anthranilic, 4-hydroxybenzoic, salicylic, 4-aminosalicylic, pamoic, nicotinic, methanesulfonic, ethanesulfonic, hydroxyethanesulfonic, ethylenesulfonic, halogenobenzenesulfonic, toluenesulfonic, naphthalenesulfonic, sulfanilic or cyclohexylsulfamic acid; or ascorbic acid. These salts or others, for example the picrates, can also be used in the purification of free bases.

The bases are converted into their salts, the salts are separated off and the bases are liberated from the salts.

Because of the close relationships between the new compounds in the free form and in the form of their salts, in the preceding and following text free compounds and salts are to be understood, in terms of sense and intended use, as meaning, if appropriate, also the corresponding salts or free compounds.

Resulting mixtures of isomers of compounds, for example those of the formulae I to III, can be separated into the individual isomers by methods which are in themselves known, for example by fractional distillation, crystallisation and/or chromatography. Racemic products can be resolved into the optical antipodes, for example by separating their diastereoisomeric substance, for example by fractional crystallisation of the d- or 1-tartrates.

The reactions mentioned above are carried out by methods which are in themselves known, in the presence or absence of diluents, preferably in diluents which are inert towards the reactants and dissolve the latter, catalysts, condensation agents or other agents mentioned above and/or in an inert atmosphere, with cooling, at room temperature or at elevated temperatures, preferably at the boiling point of the solvent used, and under normal or elevated pressure.

The invention also relates to modifications of the present process in which an intermediate product obtained at any stage of the process is used as the starting material and the remaining process stages are carried out, or the process is discontinued at any stage, or a starting material is formed under the reaction conditions or a starting material is used in the form of a salt or optically pure antipodes.

In the process of the present invention, it is advantageous to use starting materials which result in the compounds described initially as particularly valuable, particularly those of the formula II.

The pharmacologically usable compounds of the present invention can be used for the preparation of pharmaceutical

formulations containing an effective amount of the active substance together, or mixed, with excipients suitable for enteral or parenteral administration. It is preferable to use tablets or gelatine capsules containing the active compound together with diluents, for example lactose, dextrose, cane sugar, mannitol, sorbitol, cellulose and/or glycine, and lubricants, for example silica, talc, stearic acid or salts thereof, such as magnesium or calcium stearate, and/or polyethylene glycol; tablets similarly contain binders, for example magnesium aluminium silicate, starch paste, gelatine, tragacanth, methylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone, and, if desired, disintegrating agents, for example starches, agar or alginic acid or a salt thereof, such as sodium alginate, enzymes of the binders (sic) and/or effervescent mixtures, or adsorbents, dyestuffs, flavouring substances and sweeteners. Injectable formulations are preferably isotonic aqueous solutions or suspensions, and suppositories are primarily fatty emulsions or suspensions. The pharmacological formulations can be sterilised and/or can contain auxiliary substances, for example preservatives, stabilisers, wetting agents and/or emulsifiers, solubilisers, salts for regulating the osmotic pressure and/or buffers. The present pharmaceutical formulations, which, if desired, can contain further pharmacologically valuable substances, are prepared in a manner which is in itself known, for example by means of conventional mixing, granulating or tablet-coating processes, and contain from about 0.1 % to about 75 %, in particular from about 1 % to about 50 %, of the active substance.

The examples which follow serve to illustrate the invention. Temperatures are quoted in degrees centigrade, and the data relating to parts are parts by weight. Unless otherwise defined, evaporation of solvents is carried out under reduced pressure, for example at between approximately 15 and 100 mm Hg.

Example 1

200 ml of 1-molar diborane in tetrahydrofuran are

added to a suspension of 12.8 g of 2-methyl-3,4-dioxo-1,3,4,14b-tetrahydro-2H,10H-pyrazino[1,2-a]pyrrolo[2,1-c][1,4]benzodiazepine in 460 ml of tetrahydrofuran with stirring and ice-cooling. The mixture is boiled under reflux for one hour and cooled again, and 25 ml of acetic acid are added. The reaction mixture is evaporated, a residue is taken up in 50 ml of 30 % strength aqueous sodium hydroxide solution, and the mixture is extracted with methylene chloride. The extract is dried and evaporated, the residue is dissolved in diethyl ether, the solution is filtered and the filtrate is evaporated. This gives 2-methyl-1,3,4,14b-tetrahydro-2H,10H-pyrazino[1,2-a]pyrrolo[2,1-c][1,4]benzodiazepine.

9.7 g of the last-mentioned compound are dissolved in a minimum amount of isopropanol, and the solution is acidified with a concentrated solution of 4.45 g of maleic acid in isopropanol. The resulting precipitate is separated off and recrystallised from methanol/diethyl ether. This gives the corresponding monomaleate, which melts at 176-178°.

It is also possible to reduce 2.35 g of the above-mentioned dioxo starting material in 50 ml of methylene chloride by means of 20 ml of 1-molar alane in triethylamine, and then to evaporate the mixture. The residue is triturated with ethyl acetate/diethyl ether, chromatographed over 70 g of silica gel and eluted with 1:9 methanol/chloroform. The eluate is evaporated and the residue is acidified as described above. This gives a somewhat purer maleate which melts at 180 - 182°.

The starting material is prepared as follows: a mixture of 54 g of potassium phthalimide, 50 g of o-nitrobenzyl chloride and 120 ml of dimethylformamides (sic) is boiled under reflux for 3 hours and poured into 900 ml of ice water with stirring. After 30 minutes the mixture is filtered, and the residue is washed with water. This gives N-o-nitrobenzyl-phthalimide which melts at 190 - 209°.

A mixture of 70 of the last-mentioned compound, 14.6 g of hydrazine hydrate and 600 ml of ethanol is boiled under reflux for 4 hours, and 50 ml of concentrated hydrochloric

acid are added. After 30 minutes, the reaction mixture is cooled to room temperature and filtered, and the residue is washed with water. The filtrate is concentrated, the aqueous concentrate is filtered, and the filtrate is rendered alkaline with 3-normal aqueous sodium hydroxide solution. The mixture is extracted with diethyl ether, and the extract is dried and evaporated. This gives o-nitrobenzylamine.

6.6 g of 2,5-dimethoxytetrahydrofuran are added to a solution of 7.6 g of the last-mentioned compound in 25 ml of glacial acetic acid, and the mixture is boiled under reflux for one hour. The reaction mixture is evaporated, the residue is poured into ice-water, and the mixture is extracted with ethyl acetate. The extract is washed with saturated aqueous sodium bicarbonate solution, dried and evaporated. The residue is taken up in diethyl ether, and the solution is decolourised with active charcoal, filtered and evaporated. This gives 1-(o-nitrobenzyl)-pyrrole.

A mixture of 13.42 g of the last-mentioned compound, 140 ml of diethyl ether and 6.85 g of chloroacetonitrile is cooled in an ice-salt bath and saturated with hydrogen chloride gas, with stirring. The saturated mixture is stirred overnight at room temperature and filtered, and the residue is suspended in 100 ml of water. The suspension is extracted three times with 100 ml of ethyl acetate, and the combined extracts are warmed on a steam bath, with stirring, in order to dissolve the precipitated material. The solution is dried and evaporated. This gives 1-o-nitrobenzyl-2-chloroacetylpyrrole.

14.1 g of N-methylbenzylamine are added to a solution of 16.2 g of the last-mentioned compound in 450 ml of ethanol, and the mixture is boiled under reflux for 3 hours. The reaction mixture is evaporated, the residue is taken up in methylene chloride, and the solution is washed with saturated aqueous sodium carbonate solution, dried, filtered and evaporated. The residue is triturated with diethyl ether. This gives 1-(o-nitrobenzyl)-2-(N-methyl-N-benzylaminoacetyl)-pyrrole.

A solution of 3 g of the last-mentioned compound in 30 ml of acetic acid is hydrogenated over 100 mg of platinum oxide at 2.7 atmospheres and room temperature until the theoretical amount of hydrogen has been absorbed. The mixture is filtered, the filtrate is evaporated, the residue is taken up in methylene chloride/diethyl ether, and the solution is washed with saturated aqueous sodium bicarbonate solution. The solution is dried and evaporated and the residue is chromatographed over 30 g of silica gel and eluted with 1:9 methanol/chloroform. This gives 11-(N-methyl-N-benzylaminomethyl)-10,11-dihydro-5H-pyrrolo[2,1-c][1,4]benzodiazepine, which melts at 147-149°.

A solution of 500 mg of the last-mentioned compound in 35 ml of ethanol and 5 ml of glacial acetic acid is hydrogenated over 250 mg of a 5 % strength palladium-on-charcoal catalyst for 7 hours at 40° and 2.7 atmospheres. The mixture is filtered, the filtrate is evaporated and the residue is taken up in methylene chloride. The solution is washed with saturated aqueous sodium carbonate solution, the aqueous phase is extracted with methylene chloride, and the combined organic solutions are dried and evaporated. This gives 11-(N-methylaminomethyl)-10,11-dihydro-5H-pyrrolo[2,1-c][1,4]-benzodiazepine.

A mixture of 300 mg of the last-mentioned compound and 232 mg of diethyl oxalate is heated slowly, to 140° in the course of 45 minutes and to 180° in the course of 15 minutes. The mixture is kept at the last-mentioned temperature for 30 minutes and is then cooled, diluted with benzene, chromatographed over silica gel and eluted with 1:9 methanol/chloroform. This gives 2-methyl-3,4-dioxo-1,3,4,14b-tetrahydro-2H,10H-pyrazino[1,2-a]pyrrolo[2,1-c][1,4]benzodiazepine, which melts at 178-179°.

Example 2

6 ml of 1-molar diborane in tetrahydrofuran is added to a suspension of 315 mg of 7-chloro-2-methyl-3,4-dioxo-1,3,4,14b-tetrahydro-2H,10H-pyrazino[1,2-a]pyrrolo[2,1-c]-[1,4]benzodiazepine in 20 ml of tetrahydrofuran, with stirring

and ice-cooling. The mixture is boiled under reflux for 2 hours and cooled again, and 1 ml of 6-normal hydrochloric acid is added. The reaction mixture is evaporated, the residue is taken up in 5 ml of 30% strength aqueous sodium hydroxide solution, and the mixture is extracted with methylene chloride. The extract is dried and evaporated, the residue is dissolved in diethyl ether, and 97 mg of maleic acid in a minimum amount of acetone are added to the solution. The resulting precipitate is separated off. This gives 7-chloro-2-methyl-1,3,4,14b-tetrahydro-2H,10H-pyrazino[1,2-a]pyrrolo-[2,1-c][1,4]benzodiazepine monomaleate, which melts at 200 - 202°.

The starting material is prepared as follows: A mixture of 9.4 g of potassium phthalimide, 31.35 g of p-chloro-o-nitrobenzyl chloride and 75 ml of dimethylformamide is boiled under reflux for 3 hours and poured into 180 ml of ice-water with stirring. After 30 minutes the mixture is filtered and the residue is washed with water. This gives N-p-chloro-o-nitrobenzylphthalimide, which melts at 190 - 194°.

A mixture of 29.6 g of the last-mentioned compound, 5.5 g of hydrazine hydrate and 300 ml of ethanol is boiled under reflux for 4 hours, and 21 ml of concentrated hydrochloric acid are then added. After 30 minutes the mixture is cooled to room temperature and filtered, and the residue is washed with water. The filtrate is concentrated, the aqueous concentrate is filtered and the filtrate is rendered alkaline with 3-normal aqueous sodium hydroxide solution. The filtrate is extracted with diethyl ether, and the extract is dried and evaporated. This gives p-chloro-o-nitrobenzylamine.

30.4 g of 2,5-dimethoxytetrahydrofuran are added to a solution of 42.8 g of the last-mentioned compound in 400 ml of glacial acetic acid, and the mixture is boiled under reflux for one hour. The mixture is evaporated, the residue is poured into ice-water, and the mixture is extracted with ethyl acetate. The extract is washed with saturated aqueous

sodium bicarbonate solution, dried and evaporated. The residue is taken up in diethyl ether, and the solution is decolourised with active charcoal, filtered and evaporated. This gives 1-(p-chloro-o-nitrobenzyl)-pyrrole.

A mixture of 4.26 g of the last-mentioned compound, 20 ml of diethyl ether and 1.46 g of chloroacetonitrile is cooled in an ice-salt bath and saturated with hydrogen chloride gas, with stirring. The saturated mixture is stirred overnight at room temperature and filtered, and the residue is suspended in 50 ml of water. The suspension is extracted with three times 50 ml of ethyl acetate. The extract is dried and evaporated. This gives 1-(p-chloro-o-nitrobenzyl)-2-chloroacetylpyrrole.

21.8 g of N-methylbenzylamine and 18.2 g of triethylamine are added to a suspension of 56.5 g of the last-mentioned compound in 960 ml of ethanol, and the mixture is boiled under reflux for 6 hours. The reaction mixture is evaporated, the residue is taken up in chloroform, and the solution is washed with saturated aqueous sodium carbonate solution, dried, filtered and evaporated. The residue is dissolved in diethyl ether, the solution is filtered, the filtrate is evaporated and the residue is triturated with methanol. This gives 1-(p-chloro-o-nitrobenzyl)-2-(N-methyl-N-benzylaminoacetyl)-pyrrole, which melts at 90 -93°.

0.545 g of ethyl chloroformate are added to a solution of 1 g of the last-mentioned compound in 30 ml of benzene, and the mixture is boiled under reflux for 4 hours. The reaction mixture is diluted with diethyl ether, washed with 1-normal hydrochloric acid and saturated aqueous sodium chloride solution, dried and evaporated. This gives 1-(p-chloro-o-nitrobenzyl)-2-(N-methyl-N-carboethoxyaminoacetyl)-pyrrole.

15 ml of titanium trichloride are added dropwise to a solution of 1.43 g of the last-mentioned compound in 20 ml of tetrahydrofuran, and the mixture is stirred overnight at room temperature. The reaction mixture is rendered alkaline with 60 ml of 10 % strength aqueous ammonia solution, and is filtered, and the residue is washed with methylene chloride.

The organic phase is separated off, washed with saturated aqueous sodium chloride solution, dried and evaporated. This gives 8-chloro-11-(N-methyl-N-carboethoxyaminomethyl-5H-pyrrolo[2,1-c][1,4]benzodiazepine.

760 mg of sodium borohydride are added to a solution of 430 mg of the last-mentioned compound in 10 ml of ethanol, and the mixture is stirred overnight at room temperature. The reaction mixture is acidified with 6-normal hydrochloric acid, diluted with methylene chloride, washed with water and saturated aqueous sodium chloride solution, dried and evaporated. The residue is chromatographed over silica gel and eluted with 1:19 ethyl acetate/methylene chloride. This gives 8-chloro-11-(N-methyl-N-carboethoxyaminomethyl)-10,11-dihydro-5H-pyrrolo[2,1-c][1,4]-benzodiazepine.

A mixture of 200 mg of the last-mentioned compound, 10 ml of ethanol and 3 ml of 20 % strength aqueous sodium hydroxide solution is boiled under reflux for 3 days and evaporated. The residue is taken up in water, the mixture is extracted with methylene chloride, and the extract is dried and evaporated. This gives 8-chloro-11-(N-methylaminomethyl)-10,11-dihydro-5H-pyrrolo[2,1-c][1,4]benzodiazepine.

A mixture of 960 mg of the last-mentioned compound and 600 mg of diethyl oxalate is heated slowly, to 140° in the course of 4 minutes and to 180° in the course of 15 minutes. The reaction mixture is kept at the last-mentioned temperature for 30 minutes, and is cooled and evaporated, and the residue is washed with diethyl ether and triturated with ethyl acetate. This gives 7-chloro-2-methyl-3,4-dioxo-1,3,4,14b-tetrahydro-2H,10H-pyrazino[1,2-a]pyrrolo[2,1-c]-[1,4]benzodiazepine, which melts at 203°.

Example 3

2.14 g of ethyl chloroformate are added to a solution of 1.9 g of 2-methyl-1,3,4,14b-tetrahydro-2H,10H-pyrazino-[1,2-a]pyrrolo[2,1-c][1,4]benzodiazepine in 50 ml of benzene, and the mixture is boiled under reflux for 3 days. The reaction mixture is diluted with diethyl ether, washed with 1-normal hydrochloric acid and with a saturated aqueous

solution of sodium chloride and sodium bicarbonate, dried and evaporated. This gives 2-carboethoxy-1,3,4,14b-tetrahydro-2H,10H-pyrazino[1,2-a]pyrrolo[2,1-c][1,4]benzodiazepine, which exhibits bands at 8.55(t), 6.60(m), 5.65(q) and 3.90(d) ppm in an MMR (sic) spectrum and a molecular ion of 311 in a mass spectrum.

Example 4

A mixture of 930 mg of 2-carboethoxy-1,3,4,14b-tetrahydro-2H,10H-pyrazino[1,2-a]pyrrolo[2,1-c][1,4]benzodiazepine, 40 ml of ethanol and 20 ml of 20 % aqueous potassium hydroxide solution is boiled under reflux for 2 days. After cooling, the reaction mixture is diluted with ethyl acetate, washed with water, dried and evaporated. The residue is taken up in diethyl ether, and 0.55 g of maleic acid in a minimum amount of acetone is added to the solution. The resulting precipitate is separated off and washed with diethyl ether. This gives 1,3,4,14b-tetrahydro-2H,10H-pyrazino[1,2-a]pyrrolo-[2,1-c][1,4]benzodiazepine maleate, which melts at 173 - 175°.

7-Chloro-1,3,4,14b-tetrahydro-2H,10H-pyrazino[1,2-a]-pyrrolo[2,1-c][1,4]benzodiazepine maleate, which melts at 184 - 186°, is also obtained analogously (by hydrolysis with 20 % strength aqueous sodium hydroxide solution).

Example 5

2.91 g of allyl bromide are added dropwise, with stirring, to a solution of 4.8 g of 1,3,4,14b-tetrahydro-2H,10H-pyrazino[1,2-a]pyrrolo[2,1-c][1,4]benzodiazepine in 20 ml of dimethylformamide and 2.44 g of triethylamine. After one hour the reaction mixture is diluted with diethyl ether, and is washed with water and saturated aqueous sodium chloride solution, and the aqueous phase is extracted with diethyl ether. The combined organic solutions are washed with saturated aqueous sodium bicarbonate solution, and dried ... (sic), and the residue is triturated with diethyl ether. This gives 2-allyl-1,3,4,14b-tetrahydro-2H,10H-pyrazino[1,2-a]pyrrolo[2,1-c][1,4]-benzodiazepine, which melts at 130 - 132°.

The following are also obtained analogously, starting

from equivalent quantities of corresponding bromide: a) 2-(3-methyl-2-butenyl)-1,3,4,14b-tetrahydro-2H,10H-pyrazino[1,2-a]-pyrrolo[2,1-c][1,4]benzodiazepine; b) 2-propargyl-1,3,4,14b-tetrahydro-2H,10H-pyrazino[1,2-a]pyrrolo[2,1-c][1,4]benzo-diazepine; c) 2-cyclopropylmethyl-1,3,4,14b-tetrahydro-2H,10H-pyrazino[1,2-a]pyrrolo[2,1-c][1,4]benzodiazepine; d) 2-carbo-methoxymethyl-1,3,4,14b-tetrahydro-2H,10H-pyrazino[1,2-a]-pyrrolo[2,1-c][1,4]benzodiazepine and e) 2-phenylethyl-1,3,4,14b-tetrahydro-2H,10H-pyrazino[1,2-a]pyrrolo[2,1-c]-[1,4]benzodiazepine. The compounds a) to d) of the invention are converted into their acid addition salts, mentioned below, in accordance with Examples 1 and 2, and the latter are re-crystallised from the solvents indicated. The salts melt at the following temperatures: a) maleate 152 - 153° (after re-crystallisation from isopropanol); b) fumarate, 138 - 140° (ethanol); c) maleate, 189 - 190° (isopropanol); d) maleate, 162 - 164° (isopropanol/diethyl ether), and the free base e) melts at 132 - 134° after recrystallisation from iso-propanol.

Example 6

A mixture of 1.5 g of 2-carbomethoxymethyl-1,3,4,14b-tetrahydro-2H,10H-pyrazino[1,2-a]pyrrolo[2,1-c][1,4]benzo-diazepine and 10 ml of 1-normal aqueous sodium hydroxide solution is boiled under reflux for 45 minutes, until a homo-geneous solution is formed. The solution is allowed to cool to room temperature. The resulting precipitate is separated off and washed with diethyl ether. This gives the sodium salt of 2-carboxymethyl-1,3,4,14b-tetrahydro-2H,10H-pyrazino-[1,2-a]pyrrolo[2,1-c][1,4]benzodiazepine, which melts at 249 - 250°.

Example 7

A solution of 300 mg of 2-carbomethoxymethyl-1,3,4,14b-tetrahydro-2H,10H-pyrazino[1,2-a]pyrrolo[2,1-c][1,4]benzo-diazepine in 5 ml of methanol is cooled to approximately -70°, and ammonia gas is passed into the solution at the tempera-ture mentioned for 2 hours. The mixture is stirred overnight at room temperature, then again saturated with ammonia and

allowed to stand for 2 days at room temperature. The reaction mixture is evaporated, and the residue is triturated with diethyl ether. This gives 2-carbamoylmethyl-1,3,4,14b-tetrahydro-2H,10H-pyrazino[1,2-a]pyrrolo[2,1-c][1,4]benzodiazepine, which melts at 198 - 200°.

Example 8

150 mg of lithium aluminium hydride are added to a solution of 780 mg of 2-carbomethoxymethyl-1,3,4,14b-tetrahydro-2H,10H-pyrazino[1,2-a]pyrrolo[2,1-c][1,4]benzodiazepine in 20 ml of tetrahydrofuran, and the mixture is stirred at room temperature for 2 days. 0.15 ml of water, 0.15 ml of 15 % strength aqueous sodium hydroxide solution and 0.15 ml of water are then added to the reaction mixture, in this sequence, the mixture is filtered, and the filtrate is evaporated. This gives 2-(2-hydroxyethyl)-1,3,4,14b-tetrahydro-2H,10H-pyrazino[1,2-a]pyrrolo[2,1-c][1,4]benzodiazepine, which is converted into its monofumarate. It melts at 187 - 189° with decomposition.

Example 9

A solution of 54.5 mg of sodium cyanate in 2 ml of water, followed by 2 ml of tetrahydrofuran, are added with stirring to a mixture of 100 mg of 1,3,4,14b-tetrahydro-2H,10H-pyrazino[1,2-a]pyrrolo[2,1-c][1,4]benzodiazepine, 1 ml of 1-normal hydrochloric acid and 10 ml of water. The reaction mixture is stirred overnight at room temperature and then extracted with methylene chloride, and the extract is washed with saturated aqueous sodium carbonate solution, dried and evaporated. This gives 2-carbamoyl-1,3,4,14b-tetrahydro-2H,10H-pyrazino[1,2-a]pyrrolo[2,1-c][1,4]benzodiazepine, which melts at 175 - 177°.

Example 10

A solution of 1.16 g of 2-allyl-1,3,4,14b-tetrahydro-2H,10H-pyrazino[1,2-a]pyrrolo[2,1-c][1,4]benzodiazepine in 25 ml of ethanol is hydrogenated over 40 mg of platinum oxide for 2 1/2 hours at room temperature and under atmospheric pressure. The reaction mixture is filtered, the filtrate is evaporated, the residue is taken up in isopropanol, and the

solution is acidified with maleic acid. This gives 2-n-propyl-1,3,4,14b-tetrahydro-2H,10H-pyrazino[1,2-a]pyrrolo-[2,1-c][1,4]benzodiazepine maleate, which melts at 157 - 159°.

2-(3-Methylbutyl)-1,3,4,14b-tetrahydro-2H,10H-pyrazino[1,2-a]pyrrolo[2,1-c][1,4]benzodiazepine maleate is also prepared analogously. It melts at 146 - 147°.

Example 11

470 mg of α-bromo-p-chloroacetophenone are added to a solution of 500 mg of 1,3,4,14b-tetrahydro-2H,10H-pyrazino-[1,2-a]pyrrolo[2,1-c][1,4]benzodiazepine in 7.5 ml of dimethylformamide and 350 mg of triethylamine, and the mixture is mixed for 2 hours at room temperature. The reaction mixture is diluted with 60 ml of diethyl ether, washed with water, dried and evaporated. The residue is taken up in 15 ml of chloroform, and the solution is evaporated again. This gives 2-(p-chlorobenzoylmethyl)-1,3,4,14b-tetrahydro-2H,10H-pyrazino[1,2-a]pyrrolo[2,1-c][1,4]benzodiazepine, which melts at 71 - 74°.

Example 12

12-Formyl-2-methyl-3,4-dioxo-1,3,4,14b-tetrahydro-2H,10H-pyrazino[1,2-a]pyrrolo[2,1-c][1,4]benzodiazepine is reduced with diborane in accordance with the methods illustrated in Examples 1 and 2 to give 2,12-dimethyl-1,3,4,14b-tetrahydro-2H,10H-pyrazino[1,2-a]pyrrolo[2,1-c][1,4]benzodiazepine. Its monomaleate melts at 173 - 175°.

The starting material is prepared as follows: a mixture of 170 mg of phosphorus oxychloride and 100 ml of dimethylformamide is stirred at room temperature for 30 minutes, and a solution of 281 mg of 2-methyl-3,4-dioxo-1,3,4,14b-tetrahydro-2H,10H-pyrazino[1,2-a]pyrrolo[2,1-c][1,4]benzodiazepine in 5 ml of methylene chloride is then added dropwise. After 30 minutes, the mixture is boiled under reflux for a further 30 minutes and is cooled to room temperature. 1.5 g of sodium acetate in 5 ml of water are added to the reaction mixture, the whole mixture is stirred for 30 minutes and the organic layer is separated off. It is washed with water and 5 % strength sodium bicarbonate solution, dried and

evaporated, and the residue is triturated with diethyl ether. This gives 12-formyl-2-methyl-3,4-dioxo-1,3,4,14b-tetrahydro-2H,10H-pyrazino[1,2-a]pyrrolo[2,1-c][1,4]benzodiazepine which melts at 300 - 302°.

Example 13

A mixture of 500 mg of 2-methyl-1,3,4,14b-tetrahydro-2H,10H-pyrazino[1,2-a]pyrrolo[2,1-c][1,4]benzodiazepine, 10 ml of methylene chloride and 0.5 ml of methyl iodide is stirred at room temperature for one hour. The reaction mixture is filtered and the residue is washed with methylene chloride. This gives 2,2-dimethyl-1,3,4,14b-tetrahydro-2H,10H-pyrazino[1,2-a]pyrrolo[2,1-c][1,4]benzodiazepinium iodide, which melts with decomposition at 258 - 260°.

Example 14

290 mg of m-chloroperbenzoic acid in 10 ml of methylene chloride are added to a solution of 300 mg of 2-methyl-1,3,4,14b-tetrahydro-2H,10H-pyrazino[1,2-a]pyrrolo[2,1-c]-[1,4]benzodiazepine in 10 ml of methylene chloride, and the mixture is stirred at room temperature for 5 hours. The reaction mixture is extracted by shaking with 5 ml of 10 % strength aqueous sodium sulfite solution, washed with saturated aqueous sodium bicarbonate solution, dried and evaporated. This gives 2-methyl-1,3,4,14b-tetrahydro-2H,10H-pyrazino[1,2-a]pyrrolo[2,1-c][1,4]benzodiazepine-2-N-oxide, which melts at 143 - 145°.

Example 15

2 ml of 1-molar diborane in tetrahydrofuran are added, with stirring and ice-cooling, to a solution of 140 mg of 2-methyl-1,4-dioxo-1,3,4,14b-tetrahydro-2H,10H-pyrazino[1,2-a]-pyrrolo[2,1-c][1,4]benzodiazepine in 5 ml of tetrahydrofuran. The reaction mixture is stirred overnight at room temperature and then boiled under reflux for 4 hours. After it has cooled to room temperature, 0.5 ml of glacial acetic acid are added, the mixture is evaporated and the residue is rendered alkaline with 3-normal aqueous sodium hydroxide solution. The mixture is extracted with methylene chloride, the extract is dried and evaporated, and the residue is taken up in diethyl

ether. The solution is filtered and the filtrate is evaporated. This gives 2-methyl-1,3,4,14b-tetrahydro-2H,10H-pyrazino[1,2-a]pyrrolo[2,1-c][1,4]benzodiazepine, identical with the product of Example 1. Its monomaleate melts at 176 - 178°.

The starting material is prepared as follows: a solution of 7.36 g of pyrrole in 30 ml of diethyl ether is added, with stirring and cooling to -50° (solid carbon dioxide/acetone bath), to a solution of 16 g of oxalyl chloride in 150 ml of diethyl ether at such a rate that the internal temperature of the reaction mixture remains at -50°. When the addition is complete, the mixture is stirred for one hour and then poured slowly into a solution of 27.5 g of sarcosine ethyl ester in 150 ml of diethyl ether. The resulting precipitate is filtered off and extracted carefully with methylene chloride, and the extract is evaporated. This gives N-(2-pyrrylglyoxy)-sarcosine ethyl ester, which melts at 114°.

1.07 g of a 50 % strength suspension in mineral oil of sodium hydride and 20 ml of dimethylformamide are added to a solution of 5.5 g of the last-mentioned compound in 30 ml of dimethylformamide. The mixture is heated at 60 - 70° for one hour and cooled to room temperature, and a solution of 5 g of o-nitrobenzyl bromide in 20 ml of dimethylformamide is added. The reaction mixture is stirred for one hour at 45 - 50°, cooled to room temperature, diluted with water and extracted with ethyl acetate. The extract is dried and evaporated and the residue is triturated with diethyl ether. This gives N-(1-o-nitrobenzyl-2-pyrrylglyoxy)-sarcosine ethyl ester, which melts at 105 - 108°.

A solution of 3 g of the last-mentioned compound in 30 ml of ethyl acetate is hydrogenated over 100 mg of platinum oxide at 3 atmospheres until 3 mole equivalents of hydrogen have been taken up. 1.5 ml of glacial acetic acid are added to the mixture, and the hydrogenation is discontinued at 3 atmospheres and 40°. The reaction mixture is filtered, the filtrate is evaporated and the residue is taken up in methylene chloride and purified by chromatography over silica

gel. 10 % strength methanol/methylene chloride is used as the mobile phase, giving N-(1,2-dihydro-5H-pyrrolo[2,1-c]-[1,4]benzodiazepin-2-ylcarbonyl)-sarcosine ethyl ester, which melts at 147 - 148°.

20 mg of sodium methoxide are added to a suspension of 100 mg of the last-mentioned compound in 10 ml of toluene, and the mixture is boiled under reflux for 1 hour. The reaction mixture is cooled, filtered and evaporated. This gives 2-methyl-1,4-dioxo-1,3,4,14b-tetrahydro-2H,10H-pyrazino-[1,2-a]pyrrolo[2,1-c][1,4]benzodiazepine, which melts at 165 - 167°.

Example 16

A hot solution of 3 g of d-tartaric acid in 50 ml of isopropanol is added to a hot solution of 10 g of 2-methyl-1,3,4,14b-tetrahydro-2H,10H-pyrazino[1,2-a]pyrrolo[2,1-c][1,4]-benzodiazepine (Example 1) in 300 ml of isopropanol. The mixture is allowed to cool to room temperature overnight. The resulting precipitate is filtered off and recrystallised from aqueous ethanol until (three times) the optical rotation of the base liberated is constant, that is to say $[\alpha]_D^{25}$ = +344.26° (c = 1 in methanol). The compound is converted into its monomaleate, which melts at 190 - 191°, with decomposition.

The corresponding 1-antipode, $[\alpha]_D^{25}$ =-358.89°, is obtained using 1-tartaric acid; the monomaleate melts at 188 - 189°, with decomposition.

Example 17

6.2 ml of 1-molar diborane in tetrahydrofuran are added to a solution of 800 mg of 2-methyl-5-oxo-1,2,3,4,5,15b-hexahydro-11H-[1,4]diazepino[1,2-a]pyrrolo[2,1-c][1,4]benzodiazepine in 50 ml of tetrahydrofuran. The mixture is boiled under reflux for 2 hours, cooled and stirred overnight at room temperature. 2 ml of glacial acetic acid are added to the reaction mixture, which is evaporated, and the residue is rendered alkaline with 3-normal aqueous sodium hydroxide solution. The resulting mixture is extracted with methylene chloride, the extract is dried and evaporated and the residue

is dissolved in a minimum amount of methylene chloride. The solution is chromatographed over silica gel and eluted with 10 % strength methanol/methylene chloride. This gives 2-methyl-1,2,3,4,5,15b-hexahydro-11H-[1,4]diazepino[1,2-a]-pyrrolo[2,1-c][1,4]benzodiazepine of the formula I in which $R_1=R_3=R_4=R_5=H$, R_2=methyl, Ph=1,2-phenylene and n=3. The product is converted into its monofumarate, which melts at 174 - 175°.

The starting material is prepared as follows: A solution of 1.5 g of 11-(N-methylaminomethyl)-10,11-dihydro-5H-pyrrolo[2,1-c][1,4]benzodiazepine (Example 1) in 7.5 ml of methyl acrylate is stirred at room temperature for 24 hours and the excess reagent is removed by evaporation. This gives N-methyl-N-(1,2-dihydro-5H-pyrrolo[2,1-c][1,4]benzodiazepin-2-ylmethylene)-β-alanine methyl ester in the form of an oil, which is chromatographed over silica gel and eluted with 2 % strength methanol/methylene chloride.

A solution of 1 g of the last-mentioned compound in 20 ml of tetrahydrofuran is added to a stirred solution in 10 ml of tetrahydrofuran of 475 mg of 2,2,6,6-tetramethyl-piperidine (which has been freshly distilled over calcium hydride), and 1.37 ml of 2.45-molar n-butyllithium in hexane is then added, at -75°. The mixture is stirred at this temperature for 30 minutes and is then allowed to warm up to 0°. The mixture is diluted with 2:1 acetic acid/water and evaporated, and the residue is dissolved in methylene chloride, chromatographed over silica gel and eluted with 5 % strength methanol/methylene chloride. This gives 2-methyl-5-oxo-1,2,3,4,5,15b-hexahydro-11H-[1,4]diazepino[1,2-a]pyrrolo-[2,1-c][1,4]benzodiazepine, which melts at 156 - 158°.

Example 18

4.5 ml of 2.45-molar n-butyllithium in hexane are added at room temperature, and with stirring, in an atmosphere of nitrogen, to a solution of 2.5 g of 2-methyl-1,3,4,14b-tetrahydro-2H,10H-pyrazino[1,2-a]pyrrolo[2,1-c][1,4]-benzodiazepine (Example 1) in 25 ml of tetrahydrofuran. The slightly yellow solution rapidly becomes cherry-red and the

temperature rises by about 7°. The mixture is stirred for a further 45 minutes and is then treated with methyl iodide until the solution has been decolourised. The reaction mixture is stirred for a further 30 minutes and is then poured into 100 ml of water, and the product is extracted with diethyl ether. The extract is washed successively with water and saturated aqueous sodium chloride solution, and is evaporated. The oil obtained as residue is chromatographed over silica gel and eluted with 2 % strength methanol/methylene chloride. This gives 2,10-dimethyl-1,3,4,14b-tetrahydro-2H,10H-pyrazino[1,2-a]pyrrolo[2,1-c][1,4]benzodiazepine, which is converted into its monomaleate, melting point 157°. The same product can also be obtained in accordance with the procedures of Examples 1 and 15, by using o-nitro-α-methylbenzyl chloride or bromide for the preparation of the starting material.

Example 19

765 mg of benzoyl chloride are added to a stirred solution in 15 ml of tetrahydrofuran of 1.3 g of 1,3,4,14b-tetrahydro-2H,10H-pyrazino[1,2-a]pyrrolo[2,1-c][1,4]benzodiazepine (Example 4) and 550 mg of triethylamine. The reaction mixture is stirred overnight at room temperature and is then evaporated, and the residue is taken up in 100 ml of water. The mixture is extracted with diethyl ether, and the extract is washed successively with water and saturated aqueous sodium chloride solution and is dried and evaporated. This gives 2-benzoyl-1,3,4,14b-tetrahydro-2H,10H-pyrazino-[1,2-a]pyrrolo[2,1-c][1,4]-benzodiazepine, which melts at 137 - 139° after recrystallisation from isopropanol.

Example 20

720 mg of acetyl chloride are added to a solution of 2.5 g of 2-(2-hydroxyethyl)-1,3,4,14b-tetrahydro-2H,10H-pyrazino[1,2-a]pyrrolo[2,1-c][1,4]benzodiazepine (Example 8) and 935 mg of triethylamine in 72 ml of tetrahydrofuran. The mixture is stirred at room temperature for 2 hours and is evaporated, and the residue is extracted with methylene chloride. The extract is washed successively with water and

saturated aqueous sodium chloride solution and is dried, filtered and evaporated. This gives 2-(2-acetoxyethyl)-1,3,4,14b-tetrahydro-2H,10H-pyrazino[1,2-a]pyrrolo[2,1-c]-[1,4]benzodiazepine, which is converted into its monofumarate, melting point 156 - 158° (with decomposition).

The monofumarates of 2-[2-(n-hexanoyloxy)-ethyl]-1,3,4,14b-tetrahydro-2H,10H-pyrazino[1,2-a]pyrrolo[2,1-c]-[1,4]benzodiazepine, 2-[2-(n-decanoyloxy)-ethyl]-1,3,4,14b-tetrahydro-2H,10H-pyrazino[1,2-a]pyrrolo[2,1-c][1,4]benzodiazepine, 2-[2-(n-hexadecanoyloxy)-ethyl]-1,3,4,14b-tetrahydro-2H,10H-pyrazino[1,2-a]pyrrolo[2,1-c][1,4]-benzodiazepine and 2-[2-(1-adamantylcarbonyloxy)-ethyl]-1,3,4,14b-tetrahydro-2H,10H-pyrazino[1,2-a]pyrrolo[2,1-c][1,4]benzodiazepine are prepared analogously. These compounds melt at 56 - 58°, 59 - 61°, 71 - 73° and 47 - 50°, respectively.

Example 21

348 g of 2-methyl-3,4-dioxo-1,3,4,14b-tetrahydro-2H,10H-pyrazino[1,2-a]pyrrolo[2,1-c][1,4]benzodiazepine are added, in portions in the course of one hour, to 4,500 ml of tetrahydrofuran and 7,410 ml of 1-molar diborane in tetrahydrofuran while the mixture is cooled with ice to 18° and stirred in an atmosphere of nitrogen. The mixture is boiled under reflux for 24 hours and cooled to 5°, and 1,200 ml of glacial acetic acid are added, followed by 900 ml of water. The solution is boiled under reflux for 24 hours and evaporated, and the residue is taken up in 10,500 ml of methanol. The solution is again boiled under reflux for 2 hours and evaporated, the residue is dissolved in 3,000 ml of water, and the pH of the solution is adjusted to a value of 14 with 1,200 ml of 10 % strength aqueous sodium hydroxide solution. The mixture is extracted with diethyl ether, and the extract is dried, filtered and evaporated. This gives 2-methyl-1,3,4,14b-tetrahydro-2H,10H-pyrazino[1,2-a]pyrrolo[2,1-c]-[1,4]benzodiazepine, which melts at 98 - 100°.

307 g of the last-mentioned compound are dissolved in 1,280 ml of absolute ethanol, under reflux, the solution is filtered and the filtrate is cooled to 28°, and 140.5 g

of maleic acid in 294 ml of ethanol are added. The resulting precipitate is separated off, washed with cold ethanol and recrystallised again from ethanol. This gives the corresponding monomaleate, which melts at 183 - 185°. The product is somewhat purer than that of Example 1.

The starting material is prepared as follows: a mixture of 3,078 g of o-nitrobenzylamine and 2,670 g of 2,5-dimethoxytetrahydrofuran is added rapidly to 10,000 ml of glacial acetic acid, while being stirred at 86° in an atmosphere of nitrogen. The mixture is stirred at 95° for 1 1/4 hours and cooled to 25°, and 30,000 ml of water are added. The reaction mixture is extracted with ethyl acetate, and the extract is washed with 10 % strength aqueous sodium hydroxide solution and with 10 % aqueous sodium chloride solution and is filtered and evaporated. This gives 1-(o-nitrobenzyl)-pyrrole.

A mixture of 3,468 g of the last-mentioned compound, 8,500 ml of tetrahydrofuran and 1,290 g of chloroacetonitrile is saturated with hydrogen chloride gas for three hours, while being stirred and cooled at 5 - 35°. The saturated suspension is stirred at 17° for a further hour and is filtered, and the residue is suspended in 1,000 ml of tetrahydrofuran, and the suspension is filtered again. This gives 1-o-nitrobenzyl-2-(1-imino-2-chloroethyl)-pyrrole hydrochloride, which melts with decomposition at 210 - 212°.

A suspension of 3,469 g of the last-mentioned compound in 3,500 ml of water is stirred for one hour at 80° and is then cooled to 25° and filtered. The residue is washed with water and dried. 6,000 g of the residue are dissolved in 60,000 ml of ethanol by boiling under reflux in an atmosphere of nitrogen. The solution is filtered hot, concentrated by distilling off 36,000 ml of ethanol and cooled overnight to 25°. The resulting suspension is filtered and the residue is dried. This gives 1-o-nitrobenzyl-2-chloroacetylpyrrole, which melts at 112 - 114°.

A suspension of 5,112 g of the last-mentioned compound, 26,400 ml of toluene, 2,445 g of N-methylbenzylamine

and 2,040 g of triethylamine is stirred in an atmosphere of nitrogen for 6 hours at 93° and overnight at room temperature. 20,000 ml of water are added to the reaction mixture, the aqueous phase is separated off and the organic phase is washed with 10 % strength aqueous sodium chloride solution and evaporated. The residue is dissolved in 20,000 ml of hot ethanol, the solution is concentrated by distilling off 2,000 ml of ethanol and stirred overnight at room temperature. The resulting crystals are filtered off, washed with ethanol and dried. This gives 1-(o-nitrobenzyl)-2-(N-methyl-N-benzyl-aminoacetyl)-pyrrole, which melts at 103 - 105°.

A solution of 300 g of the last-mentioned compound in 3,000 ml of ethyl acetate and 250 ml of glacial acetic acid is hydrogenated over 30 g of platinum oxide at room temperature and atmospheric pressure until the theoretical amount of hydrogen has been taken up. The reaction mixture is filtered, the residue is washed with ethyl acetate, and the filtrate is evaporated. The residue is taken up in methylene chloride, and the solution is washed with 2.5-normal aqueous sodium hydroxide solution and with saturated aqueous sodium chloride solution and is dried and evaporated. The residue is triturated with diethyl ether. This gives 11-(N-methyl-N-benzylaminomethyl)-10,11-dihydro-5H-pyrrolo[2,1-c]-[1,4]benzodiazepine, which melts at 151 - 152°.

61 g of oxalic acid hemiethyl ester-chloride in 850 ml of toluene is added, with stirring, at 10 - 20° and in the course of 90 minutes, to a solution of 142.5 g of the above-mentioned compound in 2,000 ml of toluene and 45 g of triethylamine. After 4 hours the mixture is poured into 750 ml of water, the mixture is stirred for 20 minutes and the organic layer is separated off. It is washed with saturated aqueous sodium bicarbonate solution and with saturated aqueous sodium chloride solution and is dried and evaporated. The residue is recrystallised from methanol. This gives 10-ethyl-oxalyl-11-(N-methyl-N-benzylaminomethyl)-10,11-dihydro-5H-pyrrolo[2,1-c][1,4]benzodiazepine, which melts at 99 - 101°. (If large amounts of oxalic acid hemiethyl ester-chloride

are used, the corresponding 3,10-bis-ethyloxalyl compound is obtained, which melts at 115 - 116°. This compound is less soluble in isopropanol than the compound previously mentioned and can be removed from concentrated solutions by filtration).

A solution of 6.9 g of the above 10-ethyloxalyl compound in 100 ml of ethanol and 27 ml of glacial acetic acid is hydrogenated over 1.65 g of a 5 % strength palladium-on-charcoal catalyst at 2.7 atmospheres and 40° for approximately one hour. The mixture is filtered and the filtrate is evaporated. This gives 2-methyl-3,4-dioxo-1,3,4,14b-tetrahydro-2H,10H-pyrazino[1,2-a]pyrrolo[2,1-c][1,4]benzodiazepine, which melts at 178 - 179°.

(2-Methyl-3,4-dioxo-1,3,4,14b-tetrahydro-2H,10H-pyrazino[1,2-a]pyrrolo[2,1-c][1,4]benzodiazepin-12-yl)-ethyl glycollate is obtained by hydrogenating the above 3,10-bis-ethyloxalyl compound analogously.

Example 22

Reducing 200 mg of (2-methyl-3,4-dioxo-1,3,4,14b-tetrahydro-2H,10H-pyrazino[1,2-a]pyrrolo[2,1-c][1,4]benzodiazepin-12-yl)-ethyl glycollate (Example 21) in accordance with Example 1 or 2 gives 2-methyl-12-(2-hydroxyethyl)-1,3,4,14b-tetrahydro-2H,10H-pyrazino[1,2-a]pyrrolo[2,1-c][1,4]benzodiazepine monomaleate, which melts at 153-156°.

Example 23

3.6 g of trichloroacetyl chloride are added to a solution of 5 g of 2-methyl-1,3,4,14b-tetrahydro-2H,10H-pyrazino[1,2-a]pyrrolo[2,1-c][1,4]benzodiazepine and 2 g of triethylamine in 50 ml of toluene. The mixture is stirred for one hour, and 30 ml of water and 50 ml of methylene chloride are then added. The organic phase is washed with water, dried and evaporated. This gives 2-methyl-12-trichloroacetyl-1,3,4,14b-tetrahydro-2H,10H-pyrazino[1,2-a]pyrrolo[2,1-c][1,4]-benzodiazepine.

100 mg of sodium are dissolved in 75 ml of ethanol, and 5.4 g of the 12-chloroacetyl compound previously mentioned are added to the solution. The resulting precipitate is filtered off, washed with water and dried. This gives

2-methyl-12-carboethoxy-1,3,4,14b-tetrahydro-2H,10H-pyrazino-[1,2-a]pyrrolo[2,1-c][1,4]benzodiazepine, which melts at 128 - 130°. Its monofumarate monohydrate melts at 147 - 150° with decomposition.

Example 24

The following compounds of the formula II are prepared, starting from equivalent amounts of corresponding starting materials, in accordance with the methods described in the preceding examples (preferably in Examples 1 and 21):

No.	R_6	R_7	Salt	Melting point (°C) (decomposition)
1	H	9-CH_3	Maleate	185–187
2	CH_3	9-CH_3	Maleate	172–174
3	CH_2-CH-CH_2	9-CH_3	Maleate	159–161
4	H	8-CH_3	Maleate	169–171
5	CH_3	8-CH_3	Maleate	162–164
6	CH_3	7-F	Maleate	179–181
7	H	7-CF_3	Maleate	172–174
8	CH_3	7-CF_3	Maleate	189–191
9	$(CH_2)_3$–OH	H	Fumarate	201–203
10	$(CH_2)_2$–CO–CH_3	H	Fumarate	155–157
11	$(CH_2)_{11}$–CH_3	H	Fumarate	144–148

Example 25

Preparation of 10,000 tablets each containing 5 mg of active substance:

Ingredients:

2-Methyl-1,3,4,14b-tetrahydro-2H,10H-pyrazino[1,2-a]pyrrolo[2,1-c][1,4]benzodiazepine monomaleate	50 g
Lactose	1157 g
Maize starch	75 g
Polyethylene glycol 6000	75 g
Talc powder	75 g

Magnesium stearate	18 g
Purified water	q.s.

Process: All the pulverulent ingredients are sieved using a sieve of mesh width 0.6 mm. The active compound is then mixed with lactose, talc, magnesium stearate and half the starch in a suitable mixer. The other half of the starch is suspended in 40 ml of water, and the suspension is added to a boiling solution of the polyethylene glycol in 150 ml of water. The resulting paste is added to the powder and, if desired, is granulated by adding a further amount of water. The granules are dried overnight at 35°, forced through a sieve of mesh width 1.2 mm and compressed to form tablets of diameter 6.4 mm, having a breaking groove.

Example 26

Preparation of 10,000 capsules each containing 10 mg of active substance:

Ingredients:

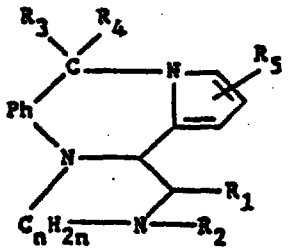
2-Methyl-1,3,4,14b-tetrahydro-2H,10H-pyrazino[1,2-a]pyrrolo[2,1-c][1,4]-benzodiazepine monomaleate	100 g
Lactose	1800 g
Talc powder	100 g

Process: All the pulverulent ingredients are sieved using a sieve of mesh width 0.6 mm. The active compound is then homogenised in a suitable mixer, first with talc and then with the lactose. No. 3 capsules are filled with 200 mg, in each case, of the mixture by means of a filling machine.

Tablets or capsules containing another compound of the invention, for the example the compound of the preceding examples, are prepared analogously.

Patent Claims

1. 1,3,4,14b-Tetrahydro-2H,10H-pyrazino[1,2-a]pyrrolo-[2,1-c][1,4]benzodiazepines of the general formula I



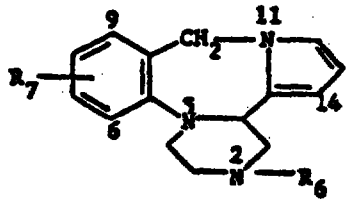
(I)

wherein each of the symbols R_1, R_3 and R_4 denotes hydrogen or lower alkyl, R_1 represents hydrogen, lower alkyl, higher alkyl, lower alkenyl, lower alkinyl, cycloalkyl or cycloalkenyl having in each case 3 to 7 ring members or represents cycloalkyl-lower alkyl, hydroxy-lower alkyl, amino-lower alkyl, mono-lower alkylamino-lower alkyl, di-lower alkylamino-lower alkyl, carboxy-lower alkyl, lower carboalkoxy-lower alkyl, carbamoyl-lower alkyl, mono-lower alkylcarbamoyl-lower alkyl, Hph-lower alkyl, lower alkanoyl-lower alkyl or HphCO-lower alkyl, Ph denotes 1,2-phenylene which can be substituted by not more than 2 substituents belonging to the group comprising lower alkyl, lower alkoxy, lower alkylthio, halogen and trifluoromethyl, C_nH_{2n} represents lower alkylene which separates the two nitrogen atoms by 2 or 3 carbon atoms, and R_5 denotes hydrogen, lower alkyl, carboxyl, lower carboalkoxy, hydroxy-lower alkyl, amino-lower alkyl, mono-lower alkylamino-lower alkyl or di-lower alkylamino-lower alkyl; the lower alkoxycarbonyl, lower alkanoyl, higher alkanoyl, adamantoyl, carbamoyl, mono-lower alkylcarbamoyl or di-lower alkoxycarbamoyl derivatives or cycloalkylcarbonyl derivatives having 3 to 7 ring members or HphCO derivatives, the 2-N-oxides, the 2-lower alkyl or 2-Hph-lower alkyl quaternary ammonium derivatives and their salts.

2. Compounds of the formula I indicated in claim 1, wherein each of the symbols R_1, R_3 and R_4 denotes hydrogen, R_2 represents hydrogen, lower alkyl, lower alkenyl, lower

alkinyl, hydroxy-lower alkyl, cycloalkyl or cycloalkyl-lower alkyl having 3 to 7 ring carbon atoms in each case, Ph denotes 1,2-phenylene, (lower alkyl)-1,2-phenylene, (lower alkoxy)-1,2-phenylene, (lower alkylthio)-1,2-phenylene, (halogen)-1,2-phenylene or (trifluoromethyl)-1,2-phenylene, n is an integer of 2 or 3, and R_5 denotes hydrogen, lower alkyl or hydroxy-lower alkyl, their lower alkanoyl, adamantoyl (sic), carbamoyl, mono-lower alkylcarbamoyl, di-lower alkylcarbamoyl or HphCO derivatives, 2-N-oxides or 2-lower alkyl or 2-Hph-lower alkyl quaternary derivatives and their therapeutically usable acid addition salts.

3. Compounds of the general formula II



(II)

wherein R_6 denotes hydrogen, lower alkyl, lower alkenyl, lower alkinyl, hydroxy-lower alkyl or cycloalkyl-lower alkyl having 3 to 7 ring members, and R_7 represents hydrogen, halogen or trifluoromethyl, and their therapeutically usable acid addition salts.

4. Compounds of the formula II shown in claim 3, wherein R_6 denotes alkyl, alkenyl, alkinyl or hydroxyalkyl having in each case up to 4 carbon atoms, or denotes cyclopropyl-methyl, R_7 represents fluorine or chlorine, and their therapeutically usable acid addition salts.

5. Compounds of the formula II shown in claim 3, wherein all the symbols have the meanings indicated in claim 4, R_7 being in the 7-position.

6. 2-Methyl-1,3,4,14b-tetrahydro-2H,10H-pyrazino[1,2-a]-pyrrolo[2,1-c][1,4]benzodiazepine, its d- and l-antipodes, its 2-N-oxides and its therapeutically usable acid addition salts.

7. 2-(2-Hydroxyethyl)-1,3,4,14b-tetrahydro-2H,10H-pyrazino[1,2-a]pyrrolo[2,1-c][1,4]benzodiazepine and its therapeutically usable acid addition salts.

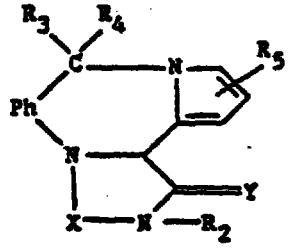
8. Pharmaceutical formulations containing a compound according to one of claims 1 to 7 together with a pharmaceutical excipient.

9. Compounds of the formula I indicated in claim 1 for use in a process for therapeutic treatment of a human or animal body.

10. The compounds of claims 1 to 7 for use as pharmaceutical products.

11. Compounds of the formula I indicated in claim 1 for use as antidepressives, analgesics and antihistamines.

12. Process for the preparation of new 1,3,4,14b-tetrahydro-2H,10H-pyrazino[1,2-a]pyrrolo[2,1-c][1,4]benzodiazepine (sic) according to the general formula I, of claim 1, characterised in that a compound of the general formula III



(III),

wherein X denotes lower alkylene, monooxo-lower alkylene or dioxo-lower alkylene which separates the two nitrogen atoms by 2 or 3 carbon atoms and wherein oxo is attached to the carbon atom adjacent to the nitrogen atom and Y represents two hydrogen atoms or hydrogen and lower alkyl, subject to the proviso that at least one oxo group is present in X or Y, is reduced and, if a compound wherein R_2 denotes lower alkyl, higher alkyl, lower alkenyl, lower alkinyl, cycloalkyl, cycloalkyl-lower alkyl, cycloalkenyl, Hph-lower alkyl or carboalkoxy-lower alkyl is desired, one of the radicals mentioned is introduced into a compound of the formula I wherein R_2 denotes hydrogen, and/or, if a compound wherein R_2 denotes carboxy-lower alkyl is desired, a compound of the formula I wherein R_2 denotes carboalkoxy-lower alkyl is hydrolysed, and/or, if a compound wherein R_2 denotes carbamoyl-lower alkyl, mono-lower alkylcarbamoyl-lower alkyl or di-lower

alkylcarbamoyl-lower alkyl is desired, the group carboalkoxy-lower alkyl in an end product wherein R_2 denotes this group is converted into one of the radicals mentioned, and/or, if a compound wherein R_2 is lower alkanoyl-lower alkyl or HphCO-lower alkyl is desired, one of the radicals mentioned is introduced into an end product wherein R_2 denotes hydrogen, and/or, if a compound wherein R_2 is mono-lower alkylcarbamoyl-lower alkyl or di-lower alkylcarbamoyl-lower alkyl is desired, an end product wherein R_2 is carbamoyl-lower alkyl or (mono-lower alkylcarbamoyl)-lower alkyl is alkylated, and/or, if a compound containing an abovementioned acyl radical in the 2-position is desired, a product wherein R_2 denotes hydrogen is acylated, and/or, if a compound wherein R_2 denotes lower alkylcarbonyl is desired, the groups lower alkyl, lower alkenyl or $-CH_2$-Hph in an end product wherein R_2 denotes these groups are converted into a lower alkoxycarbonyl group, and/or, if a compound wherein the substituent on the nitrogen atom is in the 2-position and/or R_5 is a lower alkanoyloxy-lower alkyl or higher alkanoyloxy-lower alkyl radical is desired, a product having one or two hydroxy-lower alkyl groups is esterified, and/or, if a compound wherein R_3 and/or R_4 denotes lower alkyl is desired, lower alkyl is introduced into a resulting compound wherein R_3 and/or R_4 denotes hydrogen, and/or, if a compound wherein R_5 in the 12-position is an acyl radical is desired, an end product is acylated in this position, and/or, if a compound wherein R_5 in the 12-position is a carboxyl group is desired, an end product wherein R_5 denotes lower alkoxycarbonyl is hydrolysed, and, if a quaternary compound is desired, a product which is substituted in the 2-position is quaternised by introducing a lower alkyl or Hph-lower alkyl radical into the 2-position, and/or, if an N-oxide is desired, a product wherein the nitrogen atom contains a substituent in the 2-position is N-oxidised, and/or, if desired, a resulting compound of the formula I is converted into another compound of the invention, and/or, if desired, a resulting free compound is converted into a salt, or a resulting salt is converted into the free

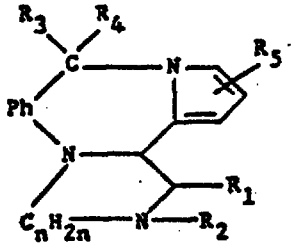
* C L M S *

compound or into another salt, and/or, if desired, a resulting mixture of isomers or racemates is separated into the individual isomers or racemates, and/or, if desired, resulting racemates are resolved into the optical antipodes.

* C L M S *

Patentansprüche

1. 1,3,4,14b-Tetrahydro-2H,10H-pyrazino[1,2-a]pyrrolo[2,1-c][1,4]benzodiazepine der allgemeinen Formel I

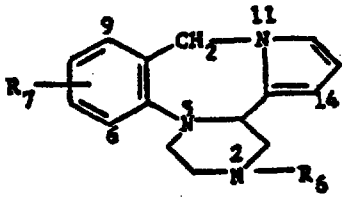


(I)

worin jedes der Symbole R_1, R_3 und R_4 Wasserstoff oder Niederalkyl bedeutet, R_2 für Wasserstoff, Niederalkyl, Höheralkyl, Niederalkenyl, Niederalkynyl, Cycloalkyl oder Cycloalkenyl mit jeweils 3 bis 7 Ringgliedern oder (Cycloalkyl, Hydroxy, Amino, Mono- oder Di-niederalkylamino, Carboxy, niederes Carbalkoxy, Carbamoyl, Mono- oder Di-niederalkyl-carbamoyl, HPh, Niederalkanoyl oder HPhCO)-niederalkyl steht, Ph 1,2-Phenylen bedeutet, welches durch höchstens 2 Substituenten der Gruppe bestehend aus Niederalkyl, Niederalkoxy, Niederalkylthio, Halogen und Trifluormethyl substituiert sein kann, C_nH_{2n} für Niederalkylen steht, welches die zwei Stickstoffatome durch 2 oder 3 Kohlenstoffatome trennt, und R_5 Wasserstoff, Niederalkyl, Carboxy, niederes Carbalkoxy oder (Hydroxy, Amino, Mono- oder Di-niederalkylamino)-niederalkyl bedeutet; die Niederalkoxycarbonyl-, Niederalkanoyl-, Höheralkanoyl-, Adamantoyl-, Carbamoyl-, Mono- oder Di-niederalkylcarbamoyl-, Cycloalkyl-carbonyl-, mit 3 bis 7 Ringgliedern, oder HPhCO-Derivate, die 2-N-Oxide, die 2-Niederalkyl- oder 2-HPh-Niederalkyl-quaternären Ammoniumderivate und ihre Salze.

2. Verbindungen der im Anspruch 1 angegebenen Formel I, worin jedes der Symbole R_1, R_3 und R_4 Wasserstoff bedeutet, R_2 für Wasserstoff, Niederalkyl, Niederalkenyl, Niederalkynyl, Hydroxy-niederalkyl, Cycloalkyl oder Cycloalkyl-niederalkyl mit jeweils 3 bis 7 Ringkohlenstoffatomen steht, Ph 1,2-Phenylen, (Niederalkyl)-1,2-phenylen, (Niederalkoxy)-1,2-phenylen, (Niederalkylthio)-1,2-phenylen, (Halogen)-1,2-phenylen oder (Trifluormethyl)-1,2-phenylen bedeutet, n eine ganze Zahl von 2 oder 3 ist, und R_5 Wasserstoff, Niederalkyl oder Hydroxy-niederalkyl bedeutet, ihre Niederalkanoyl-, Adamantoyl-, Carbamoyl-, Mono- oder Di-niederalkylcarbamoyl oder HPhCO-Derivate, 2-N-Oxide, 2-Niederalkyl- oder 2-HPh-Niederalkyl quaternären Derivate und ihre therapeutisch verwendbaren Säureadditionssalze.

3. Verbindungen der allgemeinen Formel II,



(II)

worin R_8 Wasserstoff, Niederalkyl, Niederalkenyl, Niederalkynyl, Hydroxy-niederalkyl oder Cycloalkyl-niederalkyl mit 3 bis 7 Ringgliedern bedeutet, und R_7 für Wasserstoff, Halogen oder Trifluormethyl steht, und ihre therapeutisch verwendbaren Säureadditionssalze.

4. Verbindungen der im Anspruch 3 gezeigten Formel II, worin R_8 Alkyl, Alkenyl, Alkynyl oder Hydroxyalkyl mit jeweils bis 4 Kohlenstoffatomen oder Cyclopropylmethyl bedeutet, R_7 für Fluor oder Chlor steht, und ihre therapeutisch verwendbaren Säureadditionssalze.

5. Verbindungen der im Anspruch 3 gezeigten Formel II, worin alle Symbole die im Anspruch 4 angegebenen Bedeutungen haben, wobei R_7 in 7-Stellung steht.

6. 2-Methyl-1,3,4,14b-tetrahydro-2H,10H-pyrazino[1,2-a]pyrrolo[2,1-c][1,4]benzodiazepin, seine d- und l-Antipoden, ihre 2-N-Oxide und ihre therapeutisch verwendbaren Säureadditionssalze.

7. 2-(2-Hydroxy-äthyl)-1,3,4,14b-Tetrahydro-2H,10H-pyrazino[1,2-a]pyrrolo[2,1-c][1,4]benzodiazepin und seine therapeutisch verwendbaren Säureadditionssalze.

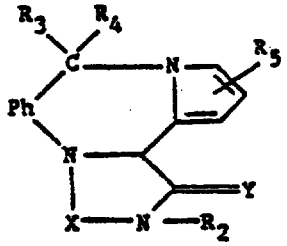
8. Pharmazeutische Präparate enthaltend eine Verbindung gemäss einem der Ansprüche 1 bis 7 zusammen mit einem pharmazeutischen Trägermaterial.

9. Verbindungen der im Anspruch 1 angegebenen Formel I zur Anwendung in einem Verfahren zur therapeutischen Behandlung des menschlichen oder tierischen Körpers.

10. Die Verbindungen der Ansprüche 1 bis 7 zur Verwendung als Pharmazeutika.

11. Verbindungen der im Anspruch 1 angegebenen Formel I zur Verwendung als Antidepressiva, Analgetika und Antihistaminika.

12. Verfahren zur Herstellung von neuen 1,3,4,14b-Tetrahydro-2H,10H-pyrazino[1,2-a]pyrrolo-[2,1-c][1,4]benzodiazepin gemäss der Allegemeinen Formel I, des Anspruches 1 dadurch gekennzeichnet, dass man eine Verbindung der allgemeinen Formel III

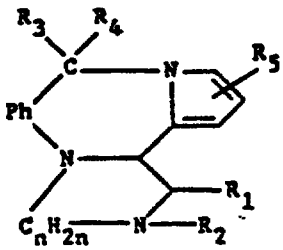


(III),

worin X Niederalkylen, Mono- oder Dioxo-niederalkylen bedeutet, welches die zwei Stickstoffatome durch 2 oder 3 Kohlenstoffatome trennt und worin Oxo zu dem mit dem Stickstoffatom benachbarten Kohlenstoffatom gebunden ist, und Y für Oxo, zwei Wasserstoffatome oder Wasserstoff und Niederalkyl steht, mit der Massgabe, dass mindestens eine Oxogruppe in X oder Y vorhanden ist, reduziert, und, wenn eine Verbindung erwünscht ist, worin R_2 Niederalkyl, Höheralkyl, Niederalkenyl, Niederalkynyl, Cycloalkyl, Cycloalkyl-niederalkyl, Cycloalkenyl, HPh-niederalkyl oder Carbalkoxy-niederalkyl bedeutet, in eine Verbindung der Formel I, worin R_2 Wasserstoff bedeutet, einen der genannten Reste einführt, und/oder, wenn eine Verbindung erwünscht ist, worin R_2 Carboxy-niederalkyl bedeutet, eine Verbindung der Formel I, worin R_2 Carbalkoxy-niederalkyl bedeutet, hydrolysiert, und/oder, wenn eine Verbindung erwünscht ist, worin R_2 Carbamoyl-niederalkyl, (Mono- oder Di-niederalkyl-carbamoyl)-niederalkyl bedeutet, in einem Endprodukt, worin R_2 Carbalkoxy-niederalkyl bedeutet, diese Gruppe in einen der genannten Reste umwandelt, und/oder, wenn eine Verbindung erwünscht ist, worin R_2 Niederalkanoyl-niederalkyl oder HPhCO-niederalkyl ist, in ein Endprodukt, worin R_2 Wasserstoff bedeutet, einen der genannten Reste einführt, und/oder, wenn eine Verbindung erwünscht ist, worin R_2 (Mono- oder Di-niederalkylcarbamoyl)-niederalkyl ist, ein Endprodukt, worin R_2 Carbamoyl-niederalkyl oder (Mono-niederalkylcarbamoyl)-niederalkyl ist, alkyliert, und/oder, wenn eine Verbindung erwünscht ist, die in 2-Stellung einen oben genannten Acylrest aufweist, ein Produkt, worin R_2 Wasserstoff bedeutet, acyliert, und/oder, wenn eine Verbindung erwünscht ist, worin R_2 Niederalkylcarbonyl bedeutet, in einem Endprodukt, worin R_2 Niederalkyl, Niederalkenyl oder —CH_2—HPh bedeutet, diese Gruppen in eine Niederalkoxycarbonylgruppe überführt, und/oder, wenn eine Verbindung erwünscht ist, worin der Substituent am Stickstoffatom in 2-Stellung und/oder R_5 ein Niederalkanoyloxy-niederalkyl oder ein Höheralkanoyloxy-niederalkylrest ist, ein Produkt, mit einer oder zwei Hydroxy-niederalkylgruppen verestert, und/oder, wenn eine Verbindung erwünscht ist, worin R_3 und/oder R_4 Niederalkyl bedeutet, in einer erhaltenen Verbindung, worin R_3 und/oder R_4 Wasserstoff bedeutet, Niederalkyl einführt, und/oder, wenn eine Verbindung erwünscht ist, worin R_5 in 12-Stellung ein Acylrest ist, ein Endprodukt in dieser Stellung acyliert, und/oder, wenn eine Verbindung erwünscht ist, worin R_5 in 12-Stellung eine Carboxygruppe ist, ein Endprodukt, worin R_5 Niederalkoxy-carbonyl bedeutet, hydrolysiert, und, wenn eine quaternäre Verbindung erwünscht ist, ein Produkt, das in 2-Stellung substituiert ist, durch Einführung eines Niederalkyl- oder HPh-niederalkylrestes in 2-Stellung quaternisiert, und/oder, wenn ein N-Oxyd erwünscht ist, ein Produkt, worin das Stickstoffatom in 2-Stellung einen Substituenten aufweist, N-oxydiert, und/oder wenn erwünscht, eine erhaltene Verbindung der Formel I in eine andere Verbindung der Erfindung umwandelt, und/oder, wenn erwünscht, eine erhaltene freie Verbindung in ein Salz oder ein erhaltenes Salz in die freie Verbindung oder in ein anderes Salz überführt, und/oder wenn erwünscht, ein erhaltenes Gemisch von Isomeren oder Razematen in die einzelnen Isomeren oder Razemate auftrennt, und/oder, wenn erwünscht, erhaltene Razemate in die optischen Antipoden aufspaltet.

Revendications

1. 1,3,4,14b-Tétrahydro-2H,10H-pyrazino[1,2-a]pyrrolo[2,1-c][1,4]benzodiazépines de formule générale (I)



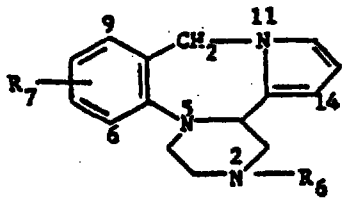
(I)

où chacun des symboles R_1, R_3 et R_4 représente un hydrogène ou un alcoyl inférieur, R_2 un hydrogène, un alcoyle inférieur, un alcoyle supérieur, un alcényle inférieur, un alcynyle inférieur, un cycloalcoyle ou un cycloalcényle ayant chacun de 3 à 7 chaînons dans le noyau ou un (cycloalcoyle, hydroxy, amino,

mono- ou di-alcoyle inférieur-amino, carboxy, carbalcoxy inférieur, carbamoyle, mono- ou dialcoyle inférieur-carbamoyle, HPh, alcanoyle inférieur ou HPhCO)-alcoyle inférieur, pH un 1,2-phénylène, qui peut être substitué par au plus deux substituants du groupe constitué par les alcoyles inférieurs, les alcoxy inférieurs, les alcoyle inférieur-thio, les halogènes et le trifluorométhyle, C_nH_{2n} représente un alcoylène inférieur qui sépare les deux atomes d'azote par deux ou trois atomes de carbone, et R_5 un hydrogène, un alcoyle inférieur, un carboxy, un carbalcoxy inférieur ou un (hydroxy, amino, mono- ou di-alcoyle inférieuramino)-alcoyle inférieur; les dérivés alcoxy inférieur-carbonyle, alcanoyle inférieur, alcanoyle supérieur, adamantoyle, carbamoyle, mono- ou di-alcoyle inférieur-carbamoyle, cycloalcoyl-carbonyle, ayant de 3 à 7 chaînons, ou les dérivés de HPhCO, les 2-N-oxydes, les dérivés de 2-alcoyle inférieur- ou de 2-HPh-alcoyle inférieur-ammonium quaternaire et leurs sels.

2. Composés de la formule I donnée dans la revendication 1 où chacun des symboles R_1, R_3 et R_4 représente un hydrogène, R_2 un hydrogène, un alcoyle inférieur, un alcényle inférieur, un alcynyle inférieur, un hydroxy-alcoyle inférieur, un cycloalcoyle ou un cycloalcoyl-alcoyle inférieur avec à chaque fois de 3 à 7 atomes de carbone dans le noyau, Ph un 1,2-phénylène, un (alcoyle inférieur)-1,2-phénylène, un (alcoxy inférieur)-1,2-phénylène, un (alcoyle inférieur-thio)-1,2-phénylène, un (halogène)-1,2-phénylène ou un (trifluorométhyl)-1,2-phénylène, n le nombre entier 2 ou 3, et R_5 un hydrogène, un alcoyle inférieur ou un hydroxy-alcoyle inférieur, leurs dérivés alcanoyle inférieurs, adamantoyle, carbamoyle, mono- ou di-alcoyle inférieur-carbamoyle ou HPhCO, 2-N-oxydes, dérivés 2-alcoyle inférieur ou 2-HPh-alcoyle inférieur quaternaires et leurs sels d'addition acides thérapeutiquement utilisables.

3. Composés de formule générale II



(II)

où R_6 représente un hydrogène, un alcoyle inférieur, un alcényle inférieur, un alcynyle inférieur, un hydroxy-alcoyle inférieur ou un cycloalcoyl-alcoyle inférieur ayant de 3 à 7 chaînons, et R_7 représente un hydrogène, un halogène ou un trifluorométhyle, et leurs sels d'addition acides thérapeutiquement acceptables.

4. Composés de formule II donnée dans la revendication 3, où R_6 représente un alcoyle, un alcényle, un alcynyle ou un hydroxyalcoyle avec à chaque fois jusqu'à 4 atomes de carbone ou un cyclopropylméthyle, et R_7 représente un fluor ou un chlore, et leurs sels d'addition acides thérapeutiquement utilisables.

5. Composés de formule II donnée dans la revendication 3, où tous les symboles ont la signification donnée dans la revendication 4, et où R_7 est en position 7.

6. 2 - Méthyl - 1,3,4,14b - térahydro - 2H,10H - pyrazino[1,2-a]pyrrolo[2,1-c][1,4]benzodiazépine, ses antipodes d et l, ses 2-N-oxydes et ses sels d'addition acides thérapeutiquement acceptables.

7. 2 - (2 - Hydroxy - éthyl) - 1,3,4,14b - tétrahydro - 2H,10H - pyrazino[1,2-a]pyrrolo[2,1-c][1,4]-benzodiazépine et ses sels d'addition acides thérapeutiquement acceptables.

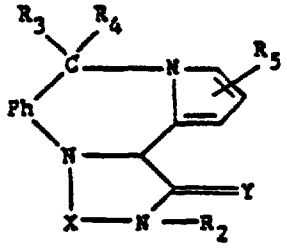
8. Préparations pharmaceutiques contenant un composé selon l'une des revendications 1 à 7 avec un support pharmaceutique.

9. Composés de formule I de la revendication 1 pour application dans un procédé de traitement thérapeutique du corps de l'homme ou de l'animal.

10. Les composés des revendications 1 à 7 aux fins d'application comme produits pharmaceutiques.

11. Composés de formule I données dans la revendication 1 aux fins d'application comme antidépresseurs, analgésiques et anti-histaminiques.

12. Procédé de préparation de nouvelles 1,2,4,14b-tétrahydro-2H,10H-pyrazino[1,2-a]-pyrrolo[2,1-c][1,4]benzodiazépines selon la formule I de la revendication 1, caractérisé en ce qu'on réduit un composé de formule générale III



(III)

où X représente un alcoylène inférieur, un mono- ou du dioxo-alcoylène inférieur qui sépare les deux atomes d'azote par 2 ou 3 atomes de carbone et où l'oxo est lié à l'atome de carbone voisin de l'atome d'azote, et Y représente un oxo, deux atomes d'hydrogène ou un hydrogène et un alcoyle inférieur, avec la précision qu'au moins un groupe oxo est présent en X ou Y, et, si on désire un composé où R_2 représente un alcoyle inférieur, un alcoyle supérieur, un alcényle inférieur, un alcynyle inférieur, un cycloalcoyle, un cycloalcoyl-alcoyle inférieur, un cycloalcényle, un HPh-alcoyle inférieur ou un carbalcoxy-alcoyle inférieur, dans un composé de formule I où R_2 représente un hydrogène, on introduit l'un des radicaux mentionnés, et/ou, lorsqu'on désire un composé où R_2 représente un carboxy-alcoyle inférieur, on hydrolyse un composé de formule I où R_2 représente un carbalcoxy-alcoyle inférieur, et/ou, lorsqu'on désire un composé où R_2 représente un carbamoyl-alcoyle inférieur, un (mono- ou dialcoyle inférieur-carbamoyl)-alcoyle inférieur, dans un produit final où R_2 représente un carbalcoxy-alcoyle inférieur, on transforme ce groupe dans un des radicaux mentionnés, et/ou lorsqu'on désire un composé où R_2 est un alcanoyle inférieur-alcoyle inférieur ou un HPhCO-alcoyle inférieur, on introduit dans un produit final où R_2 représente un hydrogène l'un des radicaux mentionnés, et/ou, lorsqu'on désire un composé où R_2 est un (mono- ou dialcoyle inférieur-carbamoyl)-alcoyle inférieur, on alcoyle un produit final où R_2 est un carbamoylalcoyle inférieur ou un (mono-alcoyle inférieur-carbamoyl)-alcoyle inférieur, et/ou lorsqu'on désire un composé qui présente en position 2 un radical acyle mentionné ci-dessus, on acyle un produit où R_2 représente un hydrogène, et/ou, lorsqu'on désire un produit où R_2 représente un alcoxy inférieur-carbonyle, dans un produit final où R_2 représente un alcoyle inférieur, un alcényle inférieur ou $—CH_2—HPh$, on transforme ces groupes en un groupe alcoxy inférieur-carbonyle, et/ou, lorsqu'on désire un composé où le substituant sur l'atome d'azote en position 2 et/ou R_5 est un alcanoyloxy inférieur-alcoyle inférieur ou un alcanoyloxy supérieur-alcoyle inférieur, on estérifie un produit avec un ou deux groupes hydroxy-alcoyle inférieur, et/ou, lorsqu'on désire un composé où R_3 et/ou R_4 représente un alcoyle inférieur, on introduit un alcoyle inférieur dans un composé obtenu où R_3 et/ou R_4 représente un hydrogène, et/ou, lorsqu'on désire un composé où R_5 en position 12 est un radical acyl, on cyle un produit final dans cette position, et/ou, lorsqu'on désire un composé où R_5 en position 12 est un groupe carboxy, on hydrolyse un produit final où R_5 représente un alcoxy inférieur-carbonyle, et, lorsqu'on désire un composé quaternaire, on quaternise un produit substitué en position 2 en introduisant un radical alcoyle inférieur ou HPh-alcoyle inférieur en position 2, et/ou, lorsqu'on désire un N-oxyde, on N-oxyde un produit où l'atome d'azote en position 2 présente un substituant, et/ou, si on le désire, on transforme un composé de formule I obtenu en un autre composé de l'invention, et/ou, si on le désire, on transforme un composé libre obtenu en un sel ou un sel obtenu en le composé libre ou en un autre sel, et/ou, si on le désire, on dédouble un mélange d'isomères ou de racémates obtenu en les isomères ou racémates isolés, et/ou, si on le désire, on dédouble les racémates obtenus en les antipodes optiques.