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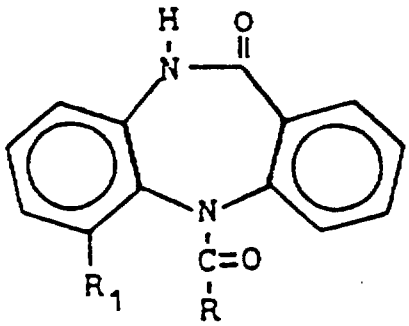
# Dibenzodiazepinones

The invention relates to new substituted dibenzodiazepinones and acid addition salts thereof, to processes for their preparation and to pharmaceutical compositions containing these compounds.

In German Offenlegungsschrift DE-OS 1 795 176, specific dibenzodiazepinones having an ulcer-inhibiting and secretion-inhibiting activity are described. From US Patent No. 3,953,430, substituted dibenzodiazepines with an antidepressant and analgesic activity are known.

We have now found, surprisingly, that dibenzodiazepinones with certain novel aminoacyl groups have valuable pharmacological effects superior to those of the compounds mentioned in the above Patent Specifications.

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



(I)

wherein

$R_1$ represents a hydrogen or chlorine atom and

R represents a (1-methyl-4-piperidinyl)methyl, (1-methyl-1,2,5,6-tetrahydro-4-pyridinyl)methyl, 1-methyl-1,2,5,6-tetrahydro-4-pyridinyl, (1-methyl-4-piperidinylidene)methyl, (2,3-dehydro-8-methyl-8-aza-

bicyclo[3.2.1]oct-3-yl)-methyl, (8-methyl-8-aza-bicyclo-[3.2.1]oct-3-ylidene)-methyl or an endo- or exo-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)methyl group, each group being optionally substituted by one or two further methyl groups in the heterocyclic ring), and optical isomers thereof and acid addition salts of the aforementioned compounds.

The compounds of the above mentioned general formula I and the physiologically compatible acid addition salts thereof possess valuable pharmacological properties, in particular anti-ulcerogenic and gastric acid-secretion inhibiting effects and favourable effects on various other disorders of the gastro-intestinal tract, including, in particular, irritable colon.

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

The expression "acid addition salts" used herein includes salts formed with inorganic and organic acids. Suitable acids include, for example, hydrochloric, hydrobromic, sulphuric, phosphoric, tartaric, fumaric, citric, maleic, succinic, gluconic, malic, p-toluene-sulphonic, methanesulphonic or amidosulphonic acids.

It will further be understood that various optical isomers of the compounds of general formula I and their acid addition salts are possible, and the invention includes within its scope all such isomeric, including diastereomeric and enantiomeric, forms.

The following compounds may be mentioned by way of example to illustrate the object of the invention:

5,10-dihydro-5-[(1-methyl-4-piperidinyl)acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one,

5,10-dihydro-5-[(1,3-dimethyl-4-piperidinyl)acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one,

5,10-dihydro-5-[(1,2-dimethyl-4-piperidinyl)acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one,

cis-5,10-dihydro-5-[(1,2-dimethyl-4-piperidinyl)acetyl]-11H-dibenzo[b,e][1,4]-diazepin-11-one,

trans-5,10-dihydro-5-[(1,2-dimethyl-4-piperidinyl)acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one,

cis-5,10-dihydro-5-[(1,3-dimethyl-4-piperidinyl)acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one,

trans-5,10-dihydro-5-[(1,3-dimethyl-4-piperidinyl)acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one,

5,10-dihydro-5-[(1-methyl-1,2,5,6-tetrahydro-4-pyridinyl)-acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one,

5,10-dihydro-5-[(1,2-dimethyl-1,2,5,6-tetrahydro-4-pyridinyl)acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one,

5,10-dihydro-5-[(1,3-dimethyl-1,2,5,6-tetrahydro-4-pyridinyl)acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one,

5,10-dihydro-5-[(1,5-dimethyl-1,2,5,6-tetrahydro-4-pyridinyl)acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one,

5,10-Dihydro-5-[(1,6-dimethyl-1,2,5,6-tetrahydro-4-pyridinyl)acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one,

5,10-dihydro-5-[(1,2,6-trimethyl-1,2,5,6-tetrahydro-4-pyridinyl)carbonyl]-11H-dibenzo[b,e][1,4]diazepin-11-one,

cis-5,10-dihydro-5-[(1,2,6-trimethyl-1,2,5,6-tetrahydro-4-pyridinyl)carbonyl]-11H-dibenzo[b,e][1,4]diazepin-11-one,

trans-5,10-dihydro-5-[(1,2,6-trimethyl-1,2,5,6-tetrahydro-4-pyridinyl)carbonyl]-11H-dibenzo[b,e][1,4]diazepin-11-one,

5,10-dihydro-5-[(1-methyl-1,2,5,6-tetrahydro-4-pyridinyl)-carbonyl]-11H-dibenzo[b,e][1,4]diazepin-11-one,

5,10-dihydro-5-[(1,2-dimethyl-1,2,5,6-tetrahydro-4-pyridinyl)carbonyl]-11H-dibenzo[b,e][1,4]diazepin-11-one,

5,10-dihydro-5-[(1,3-dimethyl-1,2,5,6-tetrahydro-4-pyridinyl)carbonyl]-11H-dibenzo[b,e][1,4]diazepin-11-one,

5,10-dihydro-5-[(1,5-dimethyl-1,2,5,6-tetrahydro-4-pyridinyl)carbonyl]-11H-dibenzo[b,e][1,4]diazepin-11-one,

5,10-dihydro-5-[(1,6-dimethyl-1,2,5,6-tetrahydro-4-pyridinyl)carbonyl]-11H-dibenzo[b,e][1,4]diazepin-11-one,

endo-5,10-dihydro-5-[(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one

exo-5,10-dihydro-5-[(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one

5,10-dihydro-5-[(1-methyl-4-piperidinylidene)acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one,

6-chloro-5,10-dihydro-5-[(1-methyl-4-piperidinyl)acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one,

6-chloro-5,10-dihydro-5-[(1-methyl-1,2,5,6-tetrahydro-4-pyridinyl)acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one,

6-chloro-5,10-dihydro-5-[(1-methyl-1,2,5,6-tetrahydro-4-pyridinyl)carbonyl]-11H-dibenzo[b,e][1,4]diazepin-11-one,

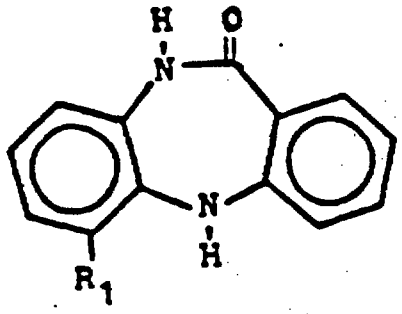
endo-6-chloro-5,10-dihydro-5-[(8-methyl-8-azabicyclo[3.2.1]-oct-3-yl)acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one,

exo-6-chloro-5,10-dihydro-5-[(8-methyl-8-azabicyclo[3.2.1]-oct-3-yl)acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one, and

6-chloro-5,10-dihydro-5-[(1,3-dimethyl-1,2,5,6-tetrahydro-4-pyridinyl)carbonyl]-11H-dibenzo[b,e][1,4]diazepin-11-one.

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

(a) reacting a compound of general formula II



(II)

(wherein $R_1$ is as hereinbefore defined), with a compound of general formula III

$$Z - \underset{\underset{O}{\|}}{C} - R \qquad \text{(III)}$$

(wherein R is as hereinbefore defined and Z represents a nucleophobic group or a leaving group).

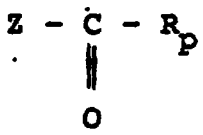
The reaction of the compound of general formula II with the compound of general formula III may be effected in a manner known per se. The leaving group Z is a group which, together with the carbonyl group to which it is bonded, forms a reactive carboxylic acid derivative. Examples of reactive carboxylic acid derivatives include acid halides, esters, anhydrides or mixed anhydrides, as obtained from salts of the corresponding acid (Z = OH) and acid chlorides, such as for example, phosphorus oxychloride, diphosphoric acid tetrachloride or chloroformates, or the N-alkyl-2-acyloxy-pyridinium salts formed by reacting the compound of formula III (Z=OH) with an N-alkyl-2-halo-pyridinium salt.

The reaction is preferably carried out with the mixed anhydrides of strong inorganic acids, particularly dichlorophosphoric acid. The reaction may optionally be carried out in the presence of an acid-binding agent (proton acceptor). Examples of suitable proton acceptors include alkali metal carbonates or alkali metal hydrogen carbonates, such as, for formula sodium carbonate or potassium hydrogen carbonate; tertiary organic amines, such as, for example pyridine, triethylamine, ethyldiisopropylamine, 4-dimethylaminopyridine; or sodium hydride. The reaction may be carried out at temperatures of between -25° and 130°C in an inert solvent. Examples of a suitable inert solvent include a chlorinated aliphatic hydrocarbon, such as methylene chloride or 1,2-dichloroethane; an open-chained or cyclic ether such as diethyl ether, tetrahydrofuran or 1,4-dioxan; an aromatic hydrocarbon such as benzene, toluene, xylene or o-dichlorobenzene; a polar aprotic

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solvent, such as acetonitrile, dimethylformamide or hexamethylphosphoric acid triamide; or mixtures thereof. The reaction times may be between 15 minutes and 80 hours, depending on the quantity and nature of the acylating agent of general formula III used. It is not necessary to prepare the compounds of general formula III in pure form; instead, they may be produced in situ in the reaction mixture in known manner;

(b) For the preparation of compounds of general formula I wherein R represents a (1-methyl-1,2,5,6-tetrahydro-4-pyridinyl)methyl or 1-methyl-1,2,5,6-tetrahydro-4-pyridinyl group, optionally substituted by one or two more methyl groups in the heterocyclic six-membered ring:
reacting a compound of general formula II (as hereinbefore defined) with a compound of general formula IV

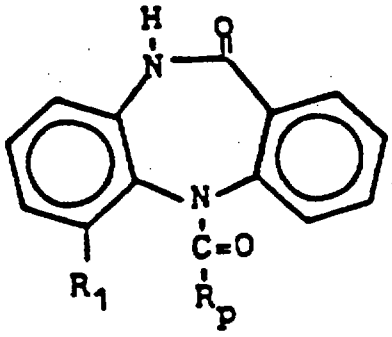


(IV)

(wherein Z has the meanings given for Z in formula III above and $R_p$ represents an optionally methyl-substituted or dimethyl-substituted 4-pyridinyl or (4-pyridinyl)-methyl group).

Acylation will generally be successful under the conditions mentioned for (a) above, but it is preferable to carry out the reaction in boiling dioxan in the presence of pyridine, 4-dimethylamino-pyridine or triethylamine.

The intermediate compound of general formula V

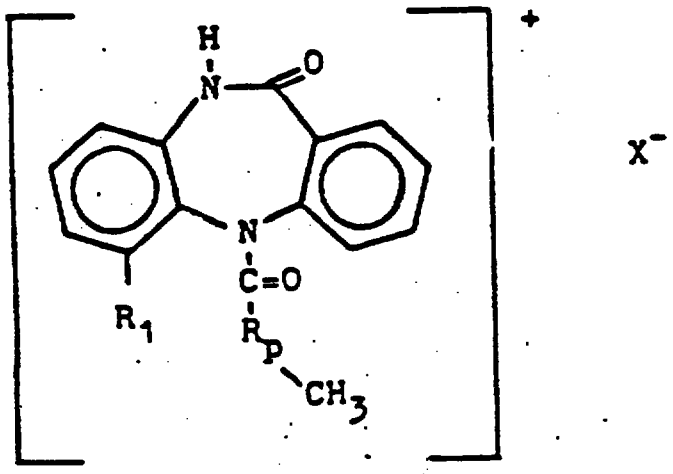


(V)

thus obtained, wherein $R_1$ and $R_p$ are as hereinbefore defined, is subsequently methylated using a methylating agent of general formula VI

$$H_3C - X \qquad (VI)$$

wherein X represents the acid group of a strong oxyacid, (for example of sulphuric, methylsulphuric, fluorosulphonic, trifluoromethanesulphonic, methanesulphonic, benzene-sulphonic, p-toluenesulphonic, p-bromobenzenesulphonic or phosphoric) acid or a halogen atom, preferably chlorine, bromine or iodine, to form a pyridinium salt of general formula Va



(Va)

wherein $R_1$, $R_p$ and X are as hereinbefore defined. The methylation may be carried out in an inert solvent, e.g. a chlorinated aliphatic hydrocarbon, such as, for example, methylene chloride or 1,2-dichloroethane; an open-chained or cyclic ether, such as, for example, diethyl ether or tetrahydrofuran, an aromatic hydrocarbon,

such as, for example, benzene, toluene, xylene or dichlorobenzene; but preferably in dioxan, acetonitrile or dimethylformamide and at temperatures of between -20 and +130°C, preferably between +30 and 100°C.

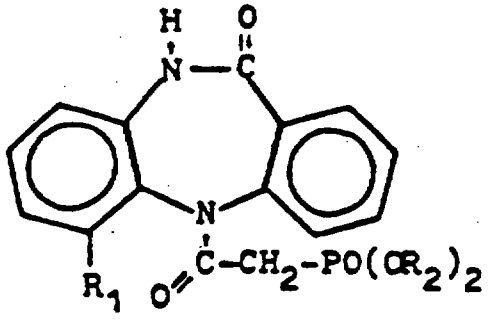
Subsequent reduction of the pyridinium salt of formula Va with a borohydride or alkoxy-borohydride, e.g. sodium or potassium tetrahydridoborate or sodium or potassium alkoxy, dialkoxy or trialkoxyborohydride, in protic solvents, for example in water, methanol, ethanol, 2-propanol or mixtures thereof at temperatures of between -40 and +50°C, preferably between -5 and +10°C produces the desired dibenzodiazepinones of general formula I wherein $R_1$ has the meanings given hereinbefore and R represents a (1-methyl-1,2,5,6-tetrahydro-4-pyridinyl)methyl or 1-methyl-1,2,5,6-tetrahydro-4-pyridinyl group.

The processes for preparing the pharmacologically active dibenzodiazepinones of general formula I are thus characterised in that dibenzodiazepinones of general formula II are acylated with compounds of general formula III or with pyridine alkanoic acid derivatives of general formula IV, and then methylated and reduced with borohydrides or alkoxyborohydrides and optionally the base initially obtained may subsequently be converted into a pharmacologically acceptable acid addition salt thereof or an acid addition salt initially obtained may subsequently be converted into a free base or into a pharmacologically acceptable acid addition salt;

(c) For the preparation of compounds of general formula I wherein R represents a (1-methyl-1,2,5,6-tetrahydro-4-pyridinyl)-methyl, (1-methyl-1,2,5,6-tetrahydro-4-piperidinylidene)-methyl, (2,3-dehydro-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-methyl or (8-methyl-8-aza-bicyclo[3.2.1]oct-3-ylidene)-methyl group, each group being optionally substituted by one or

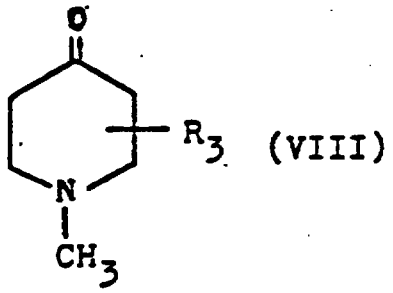
two further methyl groups in the heterocyclic six-membered ring:

reacting a compound of general formula VII

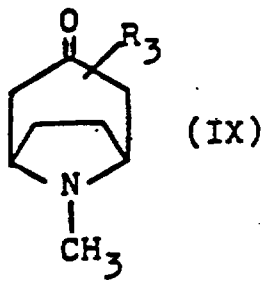


(VII)

(wherein $R_1$ is as hereinbefore defined and $R_2$ represents an alkyl group containing 1 to 10 carbon atoms, preferably an ethyl group), with a compound of general formula VIII or IX,



(VIII)



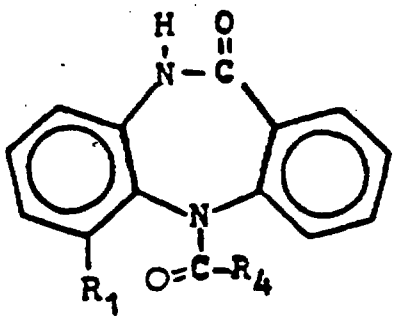
(IX)

(wherein $R_3$ represents a hydrogen atom or a methyl group), in the presence of an alkali metal hydride or of an alkali metal alkoxide (e.g. potassium tert.-butoxide) in a solvent at temperatures of from 20°C to the boiling point of the reaction mixture. Suitable solvents include ethers, such as, for example, diethyl ether or diisopropyl ether, and preferably tetrahydrofuran. Generally, mixtures are formed, e.g. when the tropinone of general formula IX is used, in addition to a compound of formula I wherein R represents an (8-methyl-8-aza-bicyclo[3.2.1]oct-3-ylidene)methyl group, a compound of formula I is also obtained wherein R represents a (2,3-dehydro-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)methyl

group. Mixtures of this kind can usually be separated into their individual components quite easily, e.g. by column chromatography;

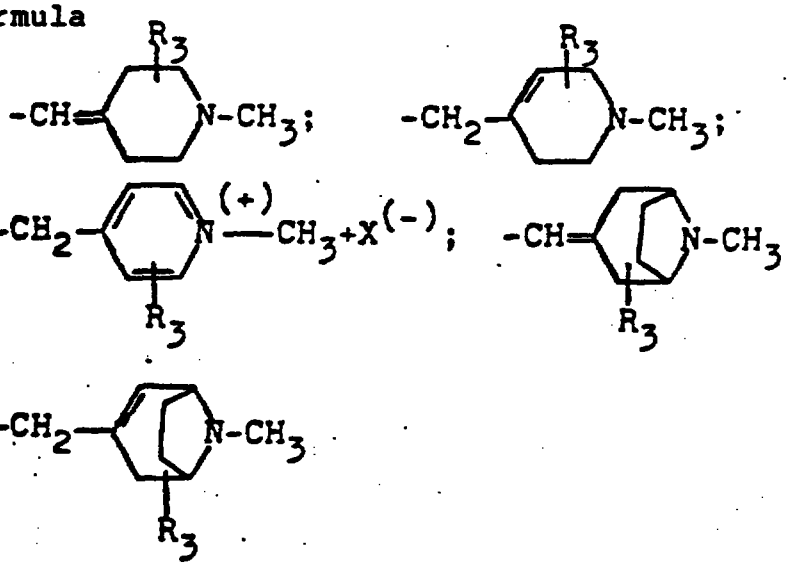
(d) For the preparation of compounds of general formula I wherein R represents a (1-methyl-4-piperidinyl)-methyl or an endo or exo-(8-methyl-8-aza-bicyclo[3.2.1]-oct-3-yl)methyl group, optionally substituted by one or two further methyl groups in the heterocyclic six-membered ring:

Catalytically hydrogenating a compound of general formula X



(X)

[wherein $R_1$ is as hereinbefore defined and $R_4$ represents a group of formula



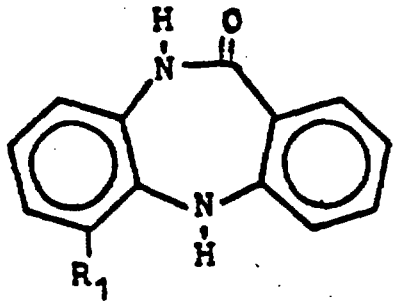
or



$R_3$ in these groups representing a hydrogen atom or a methyl group and X representing a halogen atom, preferably a chlorine or bromine atom]. Hydrogenation may, for example, be carried out with platinum dioxide as the catalyst at a pressure of between 1 and 50 bars, advantageously at 2 to 10 bars and at temperatures

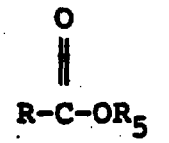
of between -20 and +100°C, advantageously at ambient temperature. Instead of platinum dioxide, it is also possible to use finely divided palladium on charcoal or Raney nickel or Raney cobalt. The compound to be hydrogenated is generally dissolved beforehand, e.g. in an alcohol such as ethanol;

(e) Initially converting a compound of general formula II



(II)

(wherein $R_1$ is as hereinbefore defined), into the di-lithium salt thereof with at least two equivalents of a lithium alkyl or lithium aryl or lithium amide and subsequently reacting this di-lithium salt with an ester of general formula XII



(XII)

(wherein R is as hereinbefore defined and $R_5$ represents an alkyl group containing 1 to 10 carbon atoms, preferably 1 to 6 carbon atoms, or an aralkyl group containing 7 to 13 carbon atoms, for example a phenylmethyl, phenylethyl or phenylpropyl group).

The conversion of the compound of general formula II into the di-lithium salt thereof may be effected, in particular, with n-butyl lithium, n-butyl lithium in the presence of tetramethyl ethylenediamine, tert.butyl

lithium, lithium diisopropylamide or lithium dicyclohexylamide or with lithium aryls such as lithium phenyl. The conversion into the lithium salt and the further reaction with a compound of general formula XII may be effected in an organic solvent at temperatures of between -60°C and 0°C, but preferably at -10°C. The organic solvents used are those conventionally used for reactions with lithium alkyls or aryls or amides; it is particularly advantageous to use tetrahydrofuran or an ether such as, for example diethyl ether; an aliphatic hydrocarbon such as, for example hexane, or a mixture thereof, optionally in the presence of hexamethyl phosphoramide as cosolvent. Shortly after the addition of the lithium alkyl, aryl or amide, a stoichiometric quantity or a slight excess of the ester of formula XII is added thereto and the reaction mixture is allowed to return slowly to ambient temperature, e.g. within 2 hours. The reaction product is isolated using methods known per se.

Bases of general formula I thus initially prepared may subsequently be converted into the acid addition salts thereof, for example by conventional methods such as reaction with the free acid, or an acid addition salt of a compound of general formula I initially obtained may subsequently be converted into the free base or another acid addition salt.

Some of the dibenzodiazepinones of general formula I according to the invention may contain one or two asymmetric carbon atoms in the group R. These compounds may therefore occur in two diastereomeric cis and trans forms or as the enantiomeric (+) and (-) forms. The invention includes the individual isomers and the mixtures thereof.

The diastereomers may be separated on the basis of their different physico-chemical properties, e.g. by fractional recrystallisation from suitable solvents or by chromatographic methods. Only one diastereomer is obtained if the method of synthesis (a) described

above is carried out with only one diastereomer of general formula III.

Any racemates of the compounds of general formula I may be separated according to known methods, for example using an optically active acid such as (+)- or (-)-tartaric acid or a derivative thereof, such as (+)- or (-)-diacetyl tartaric acid, (+)- or (-)-monomethyl tartrate or (+)-camphorsulphonic acid.

In a conventional method for separating isomers, the racemate of a compound of general formula I is reacted with an equimolar quantity of one of the above mentioned optically active acids in a solvent and the crystalline optically active salts obtained are separated on the basis of their different solubilities. This reaction may be carried out in any type of solvent provided that the salts have sufficiently different solubilities therein. Preferably, methanol, ethanol or a mixture thereof, for example in proportions of 50:50 by volume, is used. Then each of the optically active salts is dissolved in water and neutralised and in this way the corresponding free compound is obtained in the (+) or (-) form.

Only one enantiomer is obtained when the method of synthesis a) described above is carried out with only one enantiomer of general formula III.

The 5,10-dihydro-11H-dibenzo[b,e][1,4]diazepin-11-ones of general formula II required as starting materials are known from the literature (e.g. F. Hunziker et al., Arzneim. Forsch. 13, 324 [1963]).

Compounds of general formulae III and IV are known or may readily be obtained analogously to known methods of preparation. For example, by reacting the sodium salt of 4-hydroxy-1-methyl-4-piperidino-acetic acid with thionyl chloride, a mixture of 1-methyl-1,2,5,6-tetrahydro-4-pyridinoacetic acid chloride and (1-methyl-4-piperidinylidene)acetyl chloride is obtained, which can be reacted according to process a), without being separated, with a dibenzodiazepinone

of general formula II to form a mixture of the desired compounds of formula I, wherein R represents the (1-methyl-1,2,5,6-tetrahydro-4-pyridinyl)methyl and (1-methyl-4-piperidinylidene)methyl group. If desired, this mixture of double bond isomers can subsequently be separated into its components by the usual methods, for example fractional crystallisation, column chromatography or high pressure liquid chromatography.

Moreover, tropane-3α-acetic acid and tropane-3β-acetic acid can each be obtained, free from the other isomers, using the method described by W. Schneider et al., Arch. Pharm. 308, 365-375 (1975) and Ch. L. Zirkle et al., J. Org. Chem. 27, 1279-1285 (1962). The reactive acid derivatives of these compounds may be the acid chlorides, which can be prepared in the usual way from the carboxylic acids mentioned above by converting them into the potassium salt and subsequently treating them with purified thionyl chloride.

Optionally methyl- or dimethyl-substituted 4-pyridinoacetic acids or isonicotinic acids are commercially available or may be synthesised analogously to or by means of an Arndt-Eistert reaction via the substituted isonicotinic acids described by D. Jerchel et al., Liebigs Ann. Chem. 613, 153-170 (1958) or by R. Lukes et al., Collect. Czechoslov. Chem. Commun. 23, 1083-1089 (1958); 27, 2220-2222 (1962). The reactive acid derivatives used may be, for example, the acid chloride hydrochlorides, which may be obtained according to or analogously to the method described by H. Leditschke, Arch. Pharm. 295, 328 (1962).

As already mentioned hereinbefore, the new compounds of general formula I have valuable pharmacological properties; in particular, they have antiulcerogenic effects and they inhibit gastric acid secretion and they have favourable effects on various other disorders of the gastrointestinal tract, including, in particular, irritable colon.

A favourable relation between antiulcerogenic and anti-secretory effects, on the one hand, and the undesirable effects on pupil size and the secretion of tears and saliva, on the other hand, which occur particularly with therapeutic agents having an anti-cholinergic component, is of particular importance in the therapeutic use of the substances. The following tests show that the compounds according to the invention have surprisingly favourable characteristics in this respect.

Investigation of the selectivity of the antimuscarinic activity

Aims:

Oxotremorine, a specific agonist for muscarinic receptors, produces lesions in the mucous membrane of the stomach in rats and increases their secretion of saliva. This test method was chosen so that any selective activity of an antimuscarinic substance on the stomach could be identified.

Method:

10 female albino rats (of the Crl:COBS-CD (SD) BR strain) with a body weight of from 120 to 150 g were used in each treatment group and were kept without food for 24 hours before the start of the test but given free access to drinking water.

In order to determine, in preliminary tests, the muscarinic effect of oxotremorine on each of the symptoms studied, a dosage/activity curve was drawn up with at least three dosages for each symptom.

When testing the antimuscarinic substances, the dosage of oxotremorine which triggered the symptom in question in 90 to 100% of the animals in the preliminary tests was used.

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Lesions in mucous membrane of stomach: 0.62 mg/kg i.v.
Secretion of saliva: 0.083 mg/kg i.v.

Each antimuscarinic substance was administered intravenously in uniformly graduated doses 15 minutes before the oxotremorine was administered. Control groups were given corresponding quantities of the solvent and suspending agent instead of the test substance.

Immediately after the oxotremorine was administered, the animals were placed in a glass case for 15 minutes and observed.

The test for the effect on the oxotremorine-induced secretion of saliva was carried out as a blind test, i.e. the tester did not know which treatment the animals had been given.

The results were expressed as the percentage inhibition of the oxotremorine effect (the percentage of animals which did not show the symptom in question). The $ED_{50}$ values were determined using the method described by LITCHFIELD and WILCOXON (J. Pharmacol. Exp. Ther. 96, 99, 1949).

The effects on lesions of the mucous membrane of the stomach were evaluated as follows:

The lesions of the gastric mucous membrane were produced by intravenous injection of 0.62 mg/kg of oxotremorine 30 minutes after the oral administration of 1 mg/kg of neostigmine (a cholinesterase inhibitor). 60 minutes after the administration of the neostigmine, the animals were killed, the stomachs were removed and opened and examined for the presence of any lesions in the mucous membrane. The protective effect of the test substances was expressed as the percentage inhibition (percentage of animals without lesions). The $ED_{50}$ and $ED_{70}$ values were determined using the method of LITCHFIELD and WILCOXON (see above).

Mydriasis

The effect of the test substances on the pupil size in rats was investigated as follows:

The substances were administered intravenously to groups of 10 animals in at least three uniformly graduated doses. The pupil size was then observed for 10 minutes to see if there were any changes (mydriasis or miosis) and again the test was carried out blind, i.e. the tester did not know what preliminary treatment the animals had received. The percentage of test animals in which mydriasis occurred was determined. The $ED_{50}$ values were again determined using the method of LITCHFIELD and WILCOXON (see above).

2. Studies of bonding to muscarinic receptors: Determination of the $IC_{50}$ value

The organ donors were male Sprague-Dawley rats with a body weight of from 180 to 220 g. After the heart, stomach and cerebral cortex had been removed, the remainder of the operation was carried out in ice-cold Hepes-HCl buffer (pH 7.4; 100 m molar NaCl, 10 m molar $MgCl_2$). The smooth muscle of the fundus of the stomach was separated from the mucous membrane of the stomach and subjected to preliminary homogenisation. The whole heart was cut up with scissors. All the organs were then homogenised in a Potter apparatus.

For the bonding test, the homogenised organs were diluted as follows:

| | |
|---|---|
| Smooth muscle of the fundus of the stomach | 1:100 |
| Whole heart | 1:250 |
| Cerebral cortex | 1:3000 |

The homogenised organ preparations were incubated at a specific concentration of the radioligand and with a series of concentrations of the non-radioactive test substances in an Eppendorf centrifuge tube at 30°C. The duration of incubation was 45 minutes.

0.3 n molar $^3$H-N-methylscopolamine ($^3$H-NMS) was used as the radioligand. After incubation had been brought to an end by centrifuging at 14000 g, the radioactivity in the pellet was determined. It represents the sum of the specific and non-specific bonding of $^3$H-NMS. The proportion of non-specific bonding was defined as the radioactivity which was bonded in the presence of 1 µ molar quinuclidinylbenzylate. Four measurements were taken in each case. The $IC_{50}$ values of the non-labelled test substances were determined graphically. They represent the concentration of test substance at which the specific bonding of $^3$H-NMS to the muscarinic receptors in the various organs was inhibited by 50%.

The following compounds have been tested, for example, by the method described above:

A = 5,10-dihydro-5-[(1-methyl-1,2,5,6-tetrahydro-4-pyridinyl)carbonyl]-11H-dibenzo[b,e][1,4]diazepin-11-one,

B = 6-chloro-5,10-dihydro-5-[(1-methyl-4-piperidinyl)-acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one and

C = <u>endo</u>-5,10-dihydro-5-[(8-methyl-8-azabicyclo[3.2.1]-oct-3-yl)acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one.

**Results:**

| Substance | Receptor bonding tests $IC_{50}$ [n mol $l^{-1}$] | | | Oxotremorine Test [µg/kg] i.v. | | | |
|---|---|---|---|---|---|---|---|
| | Cortex | Smooth muscle fundus of stomach | Heart | Anti-ulcerative effect $ED_{50}$ | Anti-ulcerative effect $ED_{70}$ | Inhibition of salivation $ED_{50}$ | Mydriasis $ED_{50}$ i.v. [µg/kg] |
| A | 30 | 100 | 250 | 3.1 | 6.5 | 80 | 36.6 |
| B | 28 | 170 | 200 | 4.4 | 8.4 | 230 | 138 |
| C | 15 | 200 | 55 | 1.1 | 3.8 | 105 | 54 |

The results in the above table show that the compounds mentioned generally have a high affinity with muscarinic receptors. Moreover, the results show that the new compounds of general formula I differentiate between muscarinic receptors in different types of tissue. This is clear from the considerably lower $IC_{50}$ values in the tests on preparations from the cerebral cortex compared with those of the smooth muscle of the stomach and heart.

The pharmacological data in the above table show - in complete agreement with the receptor bonding studies - that the formation of oxotremorine-induced lesions in the mucous membrane of the stomach is inhibited by the above-mentioned compounds even at doses at which no restriction of salivation and no mydriasis can be observed.

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

For pharmaceutical administration, the physiologically compatible compounds according to the invention may be incorporated into conventional preparations in either solid or liquid form, optionally in combination with other active ingredients. The compositions may, for example, be presented in a form suitable for oral, rectal or parenteral administration. Preferred forms include, for example, solutions, suppositories, tablets, coated tablets, capsules or infusions.

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

Advantageously the compositions may be formulated as dosage units, each unit being adapted to supply a fixed dose of active ingredient.

The daily dose for oral administration is from 0.01 to 5, preferably from 0.02 to 2.5 more particularly from 0.05 to 1.0 mg/kg of body weight, generally administered in the form of several, preferably from 1 to 3, single doses. Depending on the kind and the body weight of the patient to be treated, on the kind and the seriousness of the disease, on the type of preparation and on the route of administration as well as on the period or interval over which the administration takes place, it may however be necessary to deviate from the above dosages. Thus, it may be sufficient in some cases to administer less than the above-mentioned amount of active ingredient, while in other cases the above-mentioned amount of active ingredient may have to be exceeded. The optimal dosage and type of administration of the active ingredients which are necessary in each case can easily be assessed by one skilled in the art.

The substituted dibenzodiazepinones of general formula I and the acid addition salts thereof have valuable properties which make them commercially viable, and are characterised in particular by an excellent protective effect on the stomach and intestines in warm-blooded animals; for example, they inhibit the formation of gastric ulcers. Moreover, they have a useful therapeutic range, thanks to their low toxicity and the absence of any significant side effects.

The excellent activity of the substituted dibenzodiazepinones of general formula I and of their pharmacologically, i.e. biologically, acceptable acid addition salts makes it possible to use them in both human and veterinary medicine, for the treatment and prophylaxis of diseases based on disorders of the stomach or intestines. They may be used, for example, to treat acute and

chronic gastric and duodenal ulcers, gastritis and gastric hyperacidity in humans and animals.

If the substituted dibenzodiazepinones of general formula I according to the invention and/or the pharmacologically acceptable acid addition salts thereof are to be used to treat the diseases mentioned above, the pharmaceutical preparations may also contain one or more pharmacologically active components from other groups of medicaments, such as antacids, e.g. aluminium hydroxide or magnesium aluminate; secretion-inhibitors, such as $H_2$ blockers, e.g. cimetidine or ranitidine; gastric and intestinal therapeutic agents, e.g. metoclopramide, bromoprid and tiaprid; tranquilizers such as benzodiazepines, for example diazepam and oxazepam; spasmolytics, e.g. bietamiverine, camylofine; anticholinergics, e.g. oxyphencyclimine and phencarbamide; glucocorticoids such as prednisolone, fluocortolone, and betamethasone; non-steroidal antiphlogistic agents such as arylacetic acids and arylpropionic acids, heteroarylacetic acids and heteroarylpropionic acids, benzothiazine carboxamide dioxides, pyrazolidinediones, quinazolinones, e.g. ibuprofen, naproxen, diclofenac, fenbufen, flurbiprofen, indomethacin, lonazolac, sudoxicam, piroxicam, phenylbutazone, bumadizon-calcium, proquazone; local anaesthetics such as tetracaine and procaine; and optionally also ferments, vitamins, amino acids, etc.

The following Examples serve to illustrate the invention. "M.p." indicates "melting point", "D." indicates "decomposition".

Example 1

5,10-Dihydro-5-[(1-methyl-1,2,5,6-tetrahydro-4-pyridinyl)-acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one

5.8 ml (0.081 mol) of thionyl chloride, dissolved in 20 ml of chloroform, were added dropwise to a suspension of 14.0 g (0.072 mol) of the potassium salt of 1-methyl-1,2,5,6-tetrahydro-4-pyridinoacetic acid in 150 ml of anhydrous chloroform, with external cooling and with the reaction temperature being maintained at +15°C. The mixture was stirred for a further 20 minutes and then concentrated to dryness in vacuo and the residue remaining was added to a suspension of 8.4 g (0.04 mol) of 5,10-dihydro-11H-dibenzo[b,e][1,4]diazepin-11-one in a mixture of solvents consisting of 300 ml of absolute dioxan and 20 ml of anhydrous pyridine. The mixture was heated to 80°C for 2 hours with vigorous stirring. After cooling, it was filtered and the filter residue was taken up in water. It was then made alkaline with solid sodium carbonate and the aqueous phase was extracted exhaustively with chloroform. The combined chloroform extracts were dried and the solvent was removed in vacuo. The residue was purified by column chromatography on silica gel using ethyl acetate/methanol (ratio of volumes 9:1) as eluent. The substance was isolated as an amorphous product. Yield: 3.5 g (25% of theory).

| $C_{21}H_{21}N_3O_2$ (347.42) | | | | |
|---|---|---|---|---|
| Calculated: | C 72.6 | H 6.09 | N 12.09 |
| Found: | 71.9 | 6.31 | 12.14 |

IR (KBr): C = O 1660, shoulder 1680 $cm^{-1}$

UV (ethanol): shoulder at $\lambda$ = 270 nm

(ethanol/KOH): $\lambda_{max}$ 290 nm (E = 0.08), shoulder at $\lambda$ = 260 nm (E = 0.105)

$^1$H-NMR ($d_6$-DMSO, 80 MH): $\delta$=7.1-7.9 (8H-m, aromat.H); 5.02 broad, 1H, olef.H); 2.95 broad (2H, C=C-$CH_2$-N) 2.68 (2H, N-$CH_2$); 2.15 to 2.5 (2H-m; CO-$CH_2$); 2.18 (3H-s; $NCH_3$); 1.84 broad (2H; c=c-$CH_2$), 12.00 broad (1H-s; exchangeable H).

Example 2

5,10-Dihydro-5-[(1-methyl-1,2,5,6-tetrahydro-4-pyridinyl)-acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one

and

5,10-Dihydro-5-[(1-methyl-4-piperidinylidene)acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one

A solution of 14.2 g (0.12 mol) of thionyl chloride in 50 ml of chloroform was added dropwise to a suspension of 16.8 g (0.08 mol) of the potassium salt of 4-hydroxy-1-methyl-4-piperidinoacetic acid in 300 ml of chloroform, with external cooling and with the reaction temperature being maintained at 15°C. After being stirred for 20 minutes, the mixture was concentrated by evaporation in vacuo, and the residue was then added to a suspension of 8.4 g (0.04 mol) of 5,10-dihydro-11H-dibenzo[b,e][1,4]-diazepin-11-one in a mixture of 400 ml of anhydrous dioxan and 20 ml of dry pyridine. The mixture was heated to 80°C for 2 hours with vigorous stirring. After cooling, the precipitate was filtered off and taken up in water. The aqueous solution was made alkaline with solid sodium carbonate and then extracted exhaustively with chloroform. The combined extracts were dried and concentrated by evaporation in vacuo, then the residue was purified by column chromatography on aluminium oxide (activity stage 1) using ethyl acetate/methanol (volume ratio 99:1) as eluent. 2.5 g

(18% of theory) of 5,10-dihydro-5-[(1-methyl-1,2,5,6-tetrahydro-4-pyridinyl)acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one were obtained (absolutely identical, according to thin layer chromatogram, IR and NMR spectra, to a product prepared according to Example 1), and 0.2 g (1.4% of theory) of 5,10-dihydro-5-[(1-methyl-4-piperidinylidene)acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one was obtained, m.p. 200-201°C.

The following were obtained analogously:

6-chloro-5,10-dihydro-5-[(1-methyl-1,2,5,6-tetrahydro-4-pyridinyl)acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one

and

6-chloro-5,10-dihydro-5-[(1-methyl-4-piperidinylidene)-acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one

by reacting 4-hydroxy-1-methyl-4-piperidinoacetic acid and 6-chloro-5,10-dihydro-11H-dibenzo[b,e][1,4]-diazepin-11-one in a yield of 31% of theory. The 6-chloro-5,10-dihydro-5-[(1-methyl-1,2,5,6-tetrahydro-4-pyridinyl)-acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one was obtained as an amorphous powder with a decomposition point of 180°C;

$C_{21}H_{20}ClN_3O_2$ (381.87)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Calculated: | C | 66.05 | H | 5.28 | Cl | 9.28 | N 11.01 |
| Found: | | 66.12 | | 5.07 | | 9.00 | 11.20 |

$^1$H-NMR($CDCl_3$, 80 MHz): $\delta$=7.9 (1H-m; aromat. H in the 1-position); 6.9-7.6 (6H-m; aromat. H); 4.9 and 5.15 (1H, olef. H); 2.8-3.05 (4H-m; $2CH_2$); 2.4-2.65 (2H-m, $CH_2$); 2.3 and 2.35 (3H, N-$CH_3$); 2.05 (2H, $CH_2$);

6-Chloro-5,10-dihydro-5-[(1-methyl-4-piperidinylidene)-acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one was also

obtained, in a yield of 10%, as an amorphous powder with a decomposition point of 155°C.

$C_{21}H_{20}ClN_3O_2$ (381.87)

Calculated: C 66.05 H 5.28 Cl 9.28 N 11.01

Found: 66.15 5.32 9.09 11.03

$^1$H-NMR($CDCl_3$): $\delta$ = 7.9-8.1 (1H-m; aromat. H in the 1-position); 6.9-7.65 (6H-m, aromat. H); 5.4 and 5.55 (1H, olef. H); 2.8-3.05 (2H-m, $CH_2$); 1.95-2.55 (6H-m; $3CH_2$); 2.2 (3H,N-$CH_3$).

Example 3

endo-5,10-Dihydro-5-[(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one

Prepared analogously to Example 2 from the potassium salt of tropane-3α-acetic acid and 5,10-dihydro-11H-dibenzo[b,e][1,4]diazepin-11-one in a yield of 33% of theory.

M.p. 226-227°C (ethyl acetate).

The following was obtained analogously:

endo-6-Chloro-5,10-dihydro-5-[(8-methyl-8-azabicyclo[3.2.1]-oct-3-yl)acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one

by reacting the potassium salt of tropan-3α-acetic acid and 6-chloro-5,10-dihydro-11H-dibenzo[b,e][1,4]-diazepin-11-one in a yield of 27% of theory as an amorphous powder;

$C_{23}H_{24}ClN_3O_2$ (409.93)

Calculated: C 67.39 H 5.90 Cl 8.65 N 10.25

Found: 67.42 5.85 8.60 10.08

$^1$H-NMR($CDCl_3$): $\delta$ = 7.8-8.0 (1H-m; aromat. H in the 1-position); 7.0-7.6(6H-m, aromat. H); 1.3-3.2 (16H-m, CH, $CH_2$ and N-$CH_3$ at 2.2).

IR(KBr): C=O 1665, shoulder 1675 $cm^{-1}$.

Example 4

5,10-Dihydro-5-[(1-methyl-4-piperidinyl)acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one

Prepared analogously to Example 2 from the potassium salt of 1-methyl-4-piperidinoacetic acid and 5,10-dihydro-11H-dibenzo[b,e][1,4]diazepin-11-one in a yield of 26% of theory. Waxy substance, m.p. $\geqslant$ 95°C.

$C_{21}H_{23}N_3O_2$ (349.43)

| | | | | | |
|---|---|---|---|---|---|
| Calculated: | C | 72.18 | H | 6.63 | N 12.03 |
| Found: | | 71.72 | | 7.07 | 14.90 |

MS: $\frac{m}{e}$ = 349 (210; 140; 96)

IR ($CH_2Cl_2$): NH 3375, CO 1660 and 1676 $cm^{-1}$

UV (ethanol): shoulder at $\lambda$ 270 nm

UV (ethanol/KOH): $\lambda_{max}$ 290 nm (E=0.095); shoulder at $\lambda$ 256 nm (E = 0.12)

$^1$H-NMR ($CDCl_3/D_2O$; 80 MHz): $\delta$ =7.7-8.0 (1H-m; aromat. H); 7.0-7.6 (7H-m; ar.H); 2.5-2.9 (2H-m); 0.8-2.4 (12H-m), then at =2.12 (3H-s; N-$CH_3$)

The following were obtained analogously:

5,10-dihydro-5-[(1,3-dimethyl-4-piperidinyl)acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one

from 5,10-dihydro-11H-dibenzo[b,e][1,4]diazepin-11-one

and the potassium salt of 1,3-dimethyl-4-piperidinoacetic acid in a yield of 45% of theory, m.p. 175°C;

MS: $\frac{m}{e}$ = 363;

5,10-dihydro-5-[(1,2-dimethyl-4-piperidinyl)acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one

from 5,10-dihydro-11H-dibenzo[b,e][1,4]diazepin-11-one

and the potassium salt of 1,2-dimethyl-4-piperidinoacetic acid in a yield of 38% of theory;

MS: $\frac{m}{e}$ = 363;

IR(KBr): C=O 1665 $cm^{-1}$.

exo-5,10-dihydro-5-[(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one
from 5,10-dihydro-11H-dibenzo[b,e][1,4]diazepin-11-one
and the potassium salt of tropan-3β-acetic acid in a yield of 48% of theory, m.p. 148-150°C;
and
exo-6-chloro-5,10-dihydro-5-[(8-methyl-8-azabicyclo-[3.2.1]oct-3-yl)acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one
from 6-chloro-5,10-dihydro-11H-dibenzo[b,e][1,4]diazepin-11-one
and the potassium salt of tropan-3β-acetic acid in a yield of 51% of theory;
$C_{23}H_{24}ClN_3O_2$ (409.93)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Calculated: | C | 67.39 | H | 5.90 | Cl | 8.65 | N 10.25 |
| Found: | | 67.30 | | 5.82 | | 8.91 | 10.09 |

IR(KBr): C=O 1665 $cm^{-1}$

Example 5
6-Chloro-5,10-dihydro-5-[(1-methyl-4-piperidinyl)acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one

A mixture of 1.7 g (21 mmol) of pyridine and 30 ml of dioxan was added dropwise at ambient temperature within 20 minutes to a suspension of 1.8 g (7 mmol) of 6-chloro-5,10-dihydro-11H-dibenzo[b,e][1,4]diazepin-11-one and 7.0 g (28 mmol) of 1-methyl-4-piperidinoacetic acid chloride hydrochloride in 200 ml of dioxan. The mixture was stirred at ambient temperature for 7 hours and then the reaction mixture was filtered. The solid portions were distributed between chloroform and an aqueous potassium carbonate solution. The organic phase was dried over magnesium sulphate, treated with animal charcoal, filtered and concentrated by evaporation. The residue was purified by column chromatography on silica gel (Macherey & Nagel MN 60; eluent:chloro-

form/ethyl acetate/methanol in a ratio by volume of 1:1:1) and after trituration with cyclohexane 0.85 g (32% of theory) of 6-chloro-5,10-dihydro-5-[(1-methyl-4-piperidinyl)acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one was obtained.

$C_{21}H_{22}ClN_3O_2$ (383.88)

Calculated: C 65.71 H 5.78 Cl 9.24 N 10.95

Found: 65.90 6.02 8.78 10.90

$^1$H-NMR ($CDCl_3$; 80 MHz): $\delta$ = 7.8-8.0 (1H-m; 1 ar.H in the 1-position); 7.0-7.6 (6H-m; ar.H); 2.2 (3H-s; N-$CH_3$); 2.6-2.9 and 1.1-2.3 (11H-m; aliph. H).

IR($CH_2Cl_2$): NH 3400 and 3200 $cm^{-1}$; C=O 1670 and shoulder 1690 $cm^{-1}$

UV (ethanol): $\lambda$ = 270 nm

(ethanol/KOH): $\lambda$ = 259 nm and 289 nm.

6-Chloro-5,10-dihydro-5-[(1-methyl-4-piperidinyl)acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one is crystallised from ethyl acetate with 1/2 mol of ethyl acetate: m.p. 147°C.

Example 6

5,10-Dihydro-5-[(1-methyl-1,2,5,6-tetrahydro-4-pyridinyl)-carbonyl]-11H-dibenzo[b,e][1,4]diazepin-11-one-hemihydrate

A mixture of 10.65 g (0.051 mol) of 5,10-dihydro-11H-dibenzo[b,e][1,4]diazepin-11-one, 19.6 g (0.10 mol) of 1-methyl-1,2,5,6-tetrahydroisonicotinic acid chloride hydrochloride, 20.7 g (0.15 mol) of potassium carbonate and 200 ml of anhydrous toluene were refluxed for 24 hours, with thorough stirring. After cooling, the mixture was stirred into 500 ml of ice-cold water, the organic layer was separated off and the aqueous layer was exhaustively extracted with ethyl acetate. The combined organic phases were dried over sodium sulphate then concentrated by evaporation in vacuo. The residue was purified by column chromatography,

first on silica gel with a particle size of 0.1 to 0.4 mm, using 1,2-dichloroethane/methanol as eluant (ratio by volume 9:1), and secondly on silica gel with a particle size of from 0.05 to 0.2 mm, using 1,2-dichloroethane/methanol (volume ratio 95:5) as eluant. When the appropriate fractions were worked up in the usual way, colourless crystals were obtained, m.p. 233-234°C (diisopropylether/ethyl acetate). Yield: 2.4 g (14% of theory).

Example 7

5,10-Dihydro-5-[(1-methyl-1,2,5,6-tetrahydro-4-pyridinyl)-carbonyl]-11H-dibenzo[b,e][1,4]diazepin-11-one hemihydrate

a) 5,10-Dihydro-5-[(4-pyridinyl)carbonyl]-11H-dibenzo[b,e][1,4]diazepin-11-one

A mixture of 21.0 g (0.1 mol) of 5,10-dihydro-11H-dibenzo[b,e][1,4]diazepin-11-one, 23.0 g (0.129 mol) of isonicotinic acid chloride hydrochloride, 21 ml (0.26 mol) of pyridine and 300 ml of anhydrous dioxan was refluxed for 3 hours. After cooling, the mixture was poured into 1 litre of ice-cold water, acidified with conc. hydrochloric acid and extracted twice, each time with 200 ml of dichloromethane. The aqueous phase was made alkaline with sodium carbonate and exhaustively extracted with methylene chloride. The combined methylene chloride extracts were washed with water, dried over sodium sulphate and the solvent was removed in vacuo. The residue was recrystallised from hot methanol. After washing with ether, the beige crystals melted at 277-279°C.
Yield 16.0 g (51% of theory).

b) 5,10-Dihydro-5-[(4-pyridinyl)carbonyl]-11H-dibenzo[b,e][1,4]diazepin-11-one methoiodide

6.3 g (0.02 mol) of 5,10-dihydro-5-[(4-pyridinyl)-carbonyl]-11H-dibenzo[b,e][1,4]diazepin-11-one were dissolved in 100 ml of anhydrous dimethylformamide

and, after the addition of 3.2 g (0.0227 mol) of iodomethane, the mixture was stirred overnight at ambient temperature. It was concentrated in vacuo down to one third of its original volume, then a mixture of equal parts by volume of methanol and ether was added until the salt formed began to crystallise out. After it had been left to stand for 2 hours at ambient temperature, it was suction filtered and the precipitate was washed thoroughly with ether. 7.2 g (79% of theory) of yellow crystals were obtained, m.p. 297°C (D).

c) 5,10-Dihydro-5-[(1-methyl-1,2,5,6-tetrahydro-4-pyridinyl)carbonyl]-11H-dibenzo[b,e][1,4]-diazepin-11-one hemihydrate

2.3 g (0.005 mol) of 5,10-dihydro-5-[(4-pyridinyl)-carbonyl]-11H-dibenzo[b,e][1,4]diazepin-11-one methoiodide were suspended in 200 ml of methanol and at 0°C 0.25 g (0.006 mol) of sodium borohydride were added in batches. The mixture was stirred for a further hour in the ice bath. It was then stirred into 1 litre of ice-cold water and extracted exhaustively with methylene chloride. The combined extracts were washed with water, dried over sodium sulphate and concentrated by evaporation in vacuo. After recrystallisation from diisopropylether/methanol, the colourless crystals melted at 233-234°C.

Yield: 0.9 g (53% of theory).

According to the thin layer chromatogram, IR and NMR spectra, the product was identical to a product prepared according to Example 6.

Example 8

5,10-Dihydro-5-[(1,2,6-trimethyl-1,2,5,6-tetrahydro-4-pyridinyl)carbonyl]-11H-dibenzo[b,e][1,4]diazepin-11-one

a) 5,10-Dihydro-5-[(2,6-dimethyl-4-pyridinyl)carbonyl]-11H-dibenzo[b,e][1,4]diazepin-11-one

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Prepared analogously to Example 7a) from 5,10-dihydro-11H-dibenzo[b,e][1,4]diazepin-11-one and 2,6-dimethylisonicotinic acid chloride hydrochloride (m.p. 135-138°C) in a yield of 54% of theory. Light beige crystals, m.p. 273-275°C (methanol, using active charcoal).

b) 5,10-Dihydro-5-[(2,6-dimethyl-4-pyridinyl)carbonyl]-11H-dibenzo[b,e][1,4]diazepin-11-one methoiodide

Prepared analogously to Example 7b) from 5,10-dihydro-5-[(2,6-dimethyl-4-pyridinyl)carbonyl]-11H-dibenzo[b,e][1,4]diazepin-11-one and iodomethane in a yield of 62% of theory. The yellow crystals melted, with decomposition, at 298-300°C.

c) 5,10-Dihydro-5-[(1,2,6-trimethyl-1,2,5,6-tetrahydro-4-pyridinyl)carbonyl]-11H-dibenzo[b,e][1,4]diazepin-11-one

Prepared analogously to Example 7c) from 5,10-dihydro-5-[(2,6-dimethyl-4-pyridinyl)carbonyl]-11H-dibenzo[b,e][1,4]diazepin-11-one methoiodide and sodium borohydride in methanol in a yield of 25% of theory. After purification by column chromatography on silica gel using dichloromethane/methanol (ratio by volume 9:1) as eluent and recrystallising from diisopropylether/methanol, the light beige crystals melted at 124-125°C.

The following were obtained analogously:

5,10-Dihydro-5-[(1,3-dimethyl-1,2,5,6-tetrahydro-4-pyridinyl)carbonyl]-11H-dibenzo[b,e][1,4]diazepin-11-one

and

5,10-dihydro-5-[(1,5-dimethyl-1,2,5,6-tetrahydro-4-pyridinyl)carbonyl]-11H-dibenzo[b,e][1,4]diazepin-11-one

by reacting 5,10-dihydro-11H-dibenzo[b,e][1,4]diazepin-11-one with 3-methylisonicotinic acid chloride (m.p.

155-156°C) via 5,10-dihydro-5-[3-methyl-4-pyridinyl)-carbonyl]-11H-dibenzo[b,e][1,4]diazepin-11-one, m.p. 223-224°C (diisopropylether/methanol) and 5,10-dihydro-5-[(3-methyl-4-pyridinyl)carbonyl]-11H-dibenzo[b,e][1,4]-diazepin-11-one methoiodide;

5,10-dihydro-5-[(1,2-dimethyl-1,2,5,6-tetrahydro-4-pyridinyl)carbonyl]-11H-dibenzo[b,e][1,4]diazepin-11-one
and
5,10-dihydro-5-[(1,6-dimethyl-1,2,5,6-tetrahydro-4-pyridinyl)carbonyl]-11H-dibenzo[b,e][1,4]diazepin-11-one;

from 5,10-dihydro-11H-dibenzo[b,e][1,4]diazepin-11-one and 2-methylisonicotinic acid chloride hydrochloride via 5,10-dihydro-5-[(2-methyl-4-pyridinyl)carbonyl]-11H-dibenzo[b,e][1,4]diazepin-11-one and 5,10-dihydro-5-[(2-methyl-4-pyridinyl)carbonyl]-11H-dibenzo[b,e][1,4]-diazepin-11-one methoiodide.

6-Chloro-5,10-dihydro-5-[(1-methyl-1,2,5,6-tetrahydro-4-pyridinyl)carbonyl]-11H-dibenzo[b,e][1,4]diazepin-11-one

from 6-chloro-5,10-dihydro-11H-dibenzo[b,e][1,4]diazepin-11-one and isonicotinic acid chloride hydrochloride via 6-chloro-5,10-dihydro-5-[(4-pyridinyl)carbonyl]-11H-dibenzo[b,e][1,4]diazepin-11-one and 6-chloro-5,10-dihydro-5-[(4-pyridinyl)carbonyl]-11H-dibenzo[b,e][1,4]-diazepin-11-one methoiodide; m.p. 296°C (from methanol) in a total yield of 53% of theory, obtained as an amorphous substance by treating with methanol and diisopropylether;
IR spectrum ($CH_2Cl_2$): NH 3380 $cm^{-1}$; C=O 1675 $cm^{-1}$,

5,10-Dihydro-5-[(1-methyl-1,2,5,6-tetrahydro-4-pyridinyl)-acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one

from 5,10-dihydro-11H-dibenzo[b,e][1,4]diazepin-11-one and 4-pyridinoacetic acid chloride hydrochloride via 5,10-dihydro-5-[(4-pyridinyl)acetyl]-11H-dibenzo[b,e]-[1,4]diazepin-11-one and 5,10-dihydro-5-[(4-pyridinyl)-acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one methoiodide.

Example 9

5,10-Dihydro-5-[(1-methyl-1,2,5,6-tetrahydro-4-pyridinyl)-acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one

A mixture of 0.97 g (6.25 mol) of 1-methyl-1,2,5,6-tetrahydro-4-pyridinoacetic acid and 0.20 g (6.25 mmol) of 75% sodium hydride (in paraffin oil) in 16 ml of dimethylformamide was heated to 50-80°C until the development of hydrogen had ceased (2 to 3 hours). 1.312 g (6.24 mmol) of 5,10-dihydro-11H-dibenzo[b,e][1,4]-diazepin-11-one was added to the sodium salt of the acid thus produced and at -10°C 0.99 g of 98% phosphorus oxytrichloride was added dropwise within 10 minutes. The resulting mixture was stirred at -10°C for 4 hours, at 0°C for 4 hours and at ambient temperature for 20 hours. The mixture was stirred into 200 g of crushed ice, adjusted to pH 3.5 with sodium hydroxide solution, extracted once with methylene chloride and then the aqueous phase was adjusted to pH 9 and exhaustively extracted with methylene chloride. The organic phase was washed with water, dried over sodium sulphate and concentrated by evaporation in vacuo. After purification by column chromatography on silica gel (using ethyl acetate/methanol in a volume ratio of 9:1 as eluent) 0.63 g (29% of theory) of a colourless amorphous product was obtained, which was identical, according to the thin layer chromatogram, elementary analysis and IR spectrum, to a preparation obtained according to Example 1.

The following were obtained analogously:

endo-5,10-dihydro-5-[(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one

exo-5,10-dihydro-5-[(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one

5,10-dihydro-5-[(1-methyl-4-piperidinyl)acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one

6-chloro-5,10-dihydro-5-[(1-methyl-4-piperidinyl)acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one

5,10-dihydro-5-[(1-methyl-1,2,5,6-tetrahydro-4-pyridinyl)-carbonyl]-11H-dibenzo[b,e][1,4]diazepin-11-one hemihydrate

Example 10

5,10-Dihydro-5-[(1-methyl-1,2,5,6-tetrahydro-4-pyridinyl)-acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one

1.1 g (10.14 mmol) of ethyl chlorocarbonate was added dropwise, at 0°C, to a suspension of 1.552 g (10 mmol) of 1-methyl-1,2,5,6-tetrahydro-4-pyridinoacetic acid in 20 ml of anhydrous tetrahydrofuran. 2.10 g (10 mmol) of 5,10-dihydro-11H-dibenzo[b,e][1,4]diazepin-11-one was added to the resulting mixture, which was then stirred for 1 hour at 0°C and then for 4 hours at ambient temperature. The mixture was then stirred into 160 ml of 2N sodium hydroxide solution, whilst external cooling with ice was carried out, and extracted exhaustively with dichloromethane and the organic phase was evaporated to dryness in vacuo. After purification by column chromatography on silica gel using ethyl acetate/methanol in a volume ratio of 9:1 as eluent, 0.87 g (25% of theory) of a colourless amorphous product was obtained, which was shown by thin layer chromatography and IR and NMR spectra to be identical to a preparation synthesised according to Example 1.

Analogously:

from 5,10-dihydro-11H-dibenzo[b,e][1,4]diazepin-11-one and 1-methyl-1,2,5,6-tetrahydro-isonicotinic acid,

5,10-dihydro-5-[(1-methyl-1,2,5,6-tetrahydro-4-pyridinyl)-carbonyl]-11H-dibenzo[b,e][1,4]diazepin-11-one hemihydrate was obtained, m.p. 233-234°C (diisopropylether/ethyl acetate;

from 5,10-dihydro-11H-dibenzo[b,e][1,4]diazepin-11-one and tropan-3α-acetic acid, endo-5,10-dihydro-5-[(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one was obtained, m.p. 226-227°C (ethyl acetate);

from 5,10-dihydro-11H-dibenzo[b,e][1,4]diazepin-11-one and 1-methyl-4-piperidinoacetic acid, 5,10-dihydro-5-[(1-methyl-4-piperidinyl)acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one was obtained, which was identical, according to thin layer chromatography, IR and $^1$H-NMR spectra, to a preparation obtained according to Example 4;

from 6-chloro-5,10-dihydro-11H-dibenzo[b,e][1,4]diazepin-11-one and 1-methyl-4-piperidinoacetic acid, 6-chloro-5,10-dihydro-5-[(1-methyl-4-piperidinyl)acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one was obtained, which was identical, according to thin layer chromatography and IR and NMR spectra, to a preparation obtained according to Example 5.

Example 11

5,10-Dihydro-5-[(8-methyl-2,3-dehydro-8-aza-bicyclo[3.2.1]-oct-3-yl)acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one

and

5,10-dihydro-5-[(8-methyl-8-aza-bicyclo[3,2,1]oct-3-ylidene)acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one

a) 5-bromoacetyl-5,10-dihydro-11H-dibenzo[b,e][1,4]-diazepin-11-one

93 g (0.55 mol) of bromoacetyl chloride were added dropwise, with stirring, to a suspension of 105 g (0.5 mol) of 5,10-dihydro-11H-dibenzo[b,e][1,4]-diazepine-11-one in 1 litre of toluene, at 90°C. The mixture was then refluxed for a further 30 minutes, during which there was a strong development of hydrogen chloride. After cooling, the dark blue crystal slurry obtained was suction filtered;
m.p. 215-216°C;
Yield: 143 g (86% of theory)

b) 5-diethylphosphono-acetyl-5,10-dihydro-11H-dibenzo-[b,e][1,4]diazepin-11-one

A mixture of 143 g (0.43 mol) of 5-bromoacetyl-5,10-dihydro-11H-dibenzo[b,e][1,4]diazepin-11-one and 400 ml of triethylphosphite was refluxed for 2 hours at 120°C, with stirring. In the course of the reaction, the 5-bromoacetyl compound went fully into solution and a grey precipitate began to settle out. After cooling, this was suction filtered and washed with ethyl acetate and 159 g (95% of theory) of 5-diethylphosphonoacetyl-5,10-dihydro-11H-dibenzo[b,e]-[1,4]diazepin-11-one were obtained; m.p. 195-197°C.

c) 5,10-dihydro-5-[(8-methyl-2,3-dehydro-8-aza-bicyclo[3.2.1]oct-3-yl)acetyl]-11H-dibenzo[b,e][1,4]-diazepin-11-one
and
5,10-dihydro-5-[(8-methyl-8-aza-bicyclo-[3,2.1]-oct-3-ylidene)acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one

15.9 g (0.041 mol) of 5-diethylphosphono-acetyl-5,10-dihydro-11H-dibenzo[b,e][1,4]diazepin-11-one were added in batches to a suspension of 3.92 g (0.082 mol) of sodium hydride (50% in paraffin oil) in 160 ml of tetrahydrofuran at ambient temperature, with stirring. The solution was then refluxed for 1 hour. Then a

solution of 5.7 g (0.041 mol) of tropinone in 10 ml of tetrahydrofuran was added dropwise to the reaction mixture and the resulting mixture was refluxed gently for 3 days. When the reaction had ended, the reaction solution was shaken with 100 ml of saturated sodium chloride solution. The resultant organic phase was diluted with 100 ml of ethyl acetate and extracted twice with 10% hydrochloric acid. The hydrochloric acid phase was made alkaline with solid potassium carbonate and extracted with ethyl acetate. The ethyl acetate solution was suction filtered over active charcoal and, after drying, the residue was concentrated by evaporation in a rotary evaporator. The residue obtained was a brown oil which contained the two products as its main components. This oil was separated by column chromatography on silica gel (MN silica gel 60; 0.063-0.2 mm particle size; eluent: methylene chloride/methanol/ammonia = 90:9:1). 5.1 g (33% of theory) of 5,10-dihydro-5-[(8-methyl-2,3-dehydro-8-aza-bicyclo[3.2.1]oct-3-yl)acetyl]-11H-dibenzo[b,e][1,4]-diazepin-11-one were obtained in the form of an amorphous powder; $C_{23}H_{23}N_3O_2$ (373.44)

| | | | | | |
|---|---|---|---|---|---|
| Calculated: | C | 73.98 | H | 6.21 | N 11.25 |
| Found: | | 74.12 | | 6.18 | 11.20 |

$R_f$ value: 0.3 (thin layer chromatography on silica gel, silical gel 60 $F_{254}$, layer thickness 0.25 mm; eluent: methylene chloride/methanol/cyclohexane/ammonia = 68:15:15:2);

and 4.3 g (28% of theory) of 5,10-dihydro-5-[(8-methyl-8-aza-bicyclo[3.2.1]oct-3-ylidene)acetyl]-11H-dibenzo[b,e]-[1,4]diazepin-11-one were obtained,

$C_{23}H_{23}N_3O_2$ (373.44)

| | | | | | |
|---|---|---|---|---|---|
| Calculated: | C | 73.98 | H | 6.21 | N 11.25 |
| Found: | | 73.90 | | 6.25 | 11.21 |

$R_f$ value: 0.25 (thin layer chromatography on silica gel, silica gel 60 $F_{254}$, layer thickness 0.25 mm; eluent: methylene chloride/methanol/cyclohexane/ammonia = 68:15:15:2).

The following were obtained analogously:
6-chloro-5,10-dihydro-5-[(8-methyl-2,3-dehydro-8-aza-bicyclo[3.2.1]oct-3-yl)acetyl]-11H-dibenzo[b,e][1,4]-diazepin-11-one
and
6-chloro-5,10-dihydro-5-[(8-methyl-8-aza-bicyclo-[3.2.1]oct-3-ylidene)acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one
from 5-bromoacetyl-6-chloro-5,10-dihydro-11H-dibenzo[b,e]-[1,4]diazepin-11-one, via
6-chloro-5-diethylphosphono-acetyl-5,10-dihydro-11H-dibenzo[b,e][1,4]diazepin-11-one;
and
5,10-dihydro-5-[(1-methyl-1,2,5,6-tetrahydro-4-pyridinyl)-acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one
from 5-diethylphosphono-acetyl-5,10-dihydro-11H-dibenzo-[b,e][1,4]diazepin-11-one and N-methyl-piperidin-4-one,
and
6-chloro-5,10-dihydro-5-[(1-methyl-1,2,5,6-tetrahydro-4-pyridinyl)acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one
from 6-chloro-5-diethylphosphono-acetyl-5,10-dihydro-11H-dibenzo[b,e][1,4]diazepin-11-one and N-methyl-piperidin-4-one.

Example 12

5,10-Dihydro-5-[(1-methyl-4-piperidinyl)acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one

3.5 g (0.01 mol) of 5,10-dihydro-5-[(1-methyl-1,2,5,6-tetrahydro-4-pyridinyl)acetyl]-11H-dibenzo[b,e]-[1,4]diazepin-11-one were dissolved in 100 ml of ethanol and hydrogenated in the presence of 0.5 g of platinum oxide at ambient temperature and under a pressure of 3 bar. After the uptake of hydrogen had ended, the catalyst was filtered off and the remaining mixture was concentrated by evaporation in vacuo. The residue was purified by column chromatography (NM silica gel

60; 0.063-0.2 mm particle size; eluent: ethyl acetate/-methanol = 9:1) and 3.2 g (91% of theory) of 5,10-dihydro-5-[(1-methyl-4-piperidinyl)acetyl]-11H-dibenzo-[b,e][1,4]-diazepin-11-one was obtained, which was identical, according to thin layer chromatography, elementary analysis and IR spectrum, to the product obtained according to Example 4.

The following were prepared analogously:

6-chloro-5,10-dihydro-5-[(1-methyl-4-piperidinyl)acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one
from
6-chloro-5,10-dihydro-5-[(1-methyl-1,2,5,6-tetrahydro-4-pyridinyl)acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one;

5,10-dihydro-5-[(1-methyl-4-piperidinyl)acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one
from
5,10-dihydro-5-[(1-methyl-4-piperidinylidene)acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one;

6-chloro-5,10-dihydro-5-[(1-methyl-4-piperidinyl)acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one
from
6-chloro-5,10-dihydro-5-[(1-methyl-4-piperidinylidene)-acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one;

endo-5,10-dihydro-5-[(8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one
and
exo-5,10-dihydro-5-[(8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one
from
5,10-dihydro-5-[(8-methyl-2,3-dehydro-8-aza-bicyclo[3.2.1]-oct-3-yl)acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one;

endo-5,10-dihydro-5-[(8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one
and
exo-5,10-dihydro-5-[(8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one
from
5,10-dihydro-5-[(8-methyl-8-aza-bicyclo[3.2.1]oct-3-ylidene)acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one;

endo-6-chloro-5,10-dihydro-5-[(8-methyl-8-aza-bicyclo-[3.2.1]oct-3-yl)-acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one
and
exo-6-chloro-5,10-dihydro-5-[(8-methyl-8-aza-bicyclo-[3.2.1]oct-3-yl)acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one
from
6-chloro-5,10-dihydro-5-[(8-methyl-2,3-dehydro-8-aza-bicyclo[3.2.1]oct-3-yl)acetyl]-11H-dibenzo[b,e][1,4]-diazepin-11-one;

endo-6-chloro-5,10-dihydro-5-[(8-methyl-8-aza-bicyclo-[3.2.1]oct-3-yl)acetyl]-11H-dibenzo[b,e][1,4-diazepin-11-one
and
exo-6-chloro-5,10-dihydro-5-[(8-methyl-8-aza-bicyclo[3.2.1]-oct-3-yl)acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one
from
6-chloro-5,10-dihydro-5-[(8-methyl-8-aza-bicyclo[3.2.1]oct-3-ylidene)acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one;

5,10-dihydro-5-[(1-methyl-4-piperidinyl)acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one
from

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5,10-dihydro-5-[(4-pyridinyl)acetyl]-11H-dibenzo[b,e]-[1,4]diazepin-11-one methoiodide.

Example 13

6-Chloro-5,10-dihydro-5-[(1-methyl-4-piperidinyl)-acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one

32 ml (0.05 mol) of n-butyl lithium (15% in hexane) were added dropwise, with stirring, to a suspension of 5 g (0.02 mol) of 6-chloro-5,10-dihydro-11H-dibenzo[b,-e][1,4]diazepin-11-one in 150 ml of tetrahydrofuran, at 0°C. The resulting mixture was then stirred for 30 minutes at ambient temperature. Then 5.6 g (0.03 mol) of ethyl 1-methylpiperidino-4-acetate, dissolved in 25 ml of tetrahydrofuran, were added dropwise, again at 0°C, with stirring, and the resulting mixture was stirred for 2 hours at ambient temperature. The reaction mixture was then concentrated to about one third of its volume in vacuo and mixed with ice/water. After acidification with dilute hydrochloric acid, the mixture was extracted three times with ethyl acetate and the aqueous phase was made alkaline with solid potassium carbonate under cold conditions. It was again extracted exhaustively with ethyl acetate. The extracts were dried, filtered and concentrated by evaporation in vacuo. After column chromatography on silica gel, 1.7 g (22% of theory) of 6-chloro-5,10-dihydro-5-[(1-methyl-4-piperidinyl)acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one was obtained, which was identical in its physical properties to the product of Example 5.

The preparation of some pharmaceutical forms will now be described with reference to some Examples:

Example I

Tablets containing 5 mg of 6-chloro-5,10-dihydro-5-[(1-methyl-4-piperidinyl)acetyl]-11H-dibenzo[b,e][1,4]-diazepin-10-one

Composition:

Tablet contains:

| | |
|---|---|
| Active substance | 5.0 mg |
| Lactose | 148.0 mg |
| Potato starch | 65.0 mg |
| Magnesium stearate | 2.0 mg |
| | 220.0 mg |

Method of preparation:

A 10% mucilage is prepared from potato starch by heating. The active substance, lactose and remaining potato starch are mixed together and granulated with the mucilage through a screen with a mesh size of 1.5 mm. The granulate is dried at 45°C, passed through the screen again, mixed with magnesium stearate and compressed to form tablets.

Weight of tablet: 220 mg

Punch: 9 mm

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Example II

Coated tablets containing 5 mg of 6-chloro-5,10-dihydro-5-[(1-methyl-4-piperidinyl)acetyl]-11H-dibenzo[b,e][1,4]-diazepin-10-one

The tablets prepared according to Example I are coated by a known method with a shell consisting essentially of sugar and talc. The finished coated tablets are polished with beeswax.
Weight of coated tablet: 300 mg

Example III

Ampoules containing 1 mg of 6-chloro-5,10-dihydro-5-[(1-methyl-4-piperidinyl)acetyl]-11H-dibenzo[b,e][1,4]-diazepin-10-one hydrochloride

Composition:
1 ampoule contains:

| | | |
|---|---|---|
| Active substance | | 1.0 mg |
| Sodium chloride | | 8.0 mg |
| Distilled water | ad | 1 ml |

Method of preparation

The active substance and sodium chloride are dissolved in distilled water and then topped up to the volume given. The solution is filtered sterile and transferred into 1 ml ampoules.
Sterilisation: 20 minutes at 120°C.

Example IV

Suppositories containing 5 mg of 6-chloro-5,10-dihydro-5-[(1-methyl-4-piperidinyl)acetyl]-11H-dibenzo[b,e]-[1,4]diazepin-11-one

Composition:
1 suppository contains:

| | |
|---|---|
| Active substance | 5.0 mg |
| Suppository mass (e.g. Witepsol W 45 ®) | 1 695.0 mg |
| | 1 700.0 mg |

Method of preparation:

The finely powdered active substance is suspended in the molten suppository mass which has been cooled to 40°C. At 37°C the mass is poured into slightly chilled suppository moulds.

Weight of suppository: 1.7 g

Example V

Drops containing 6-chloro-5,10-dihydro-5-[(1-methyl-4-piperidinyl)acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one

Composition:

100 ml of drops solution contain:

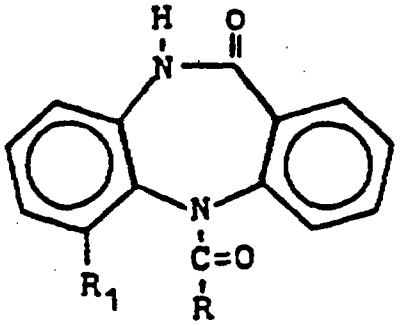
| | | |
|---|---|---|
| Methyl p-hydroxybenzoate | 0.035 | g |
| Propyl p-hydroxybenzoate | 0.015 | g |
| Anisole | 0.05 | g |
| Menthol | 0.06 | g |
| Pure ethanol | 10.0 | g |
| Active substance | 0.5 | g |
| Sodium cyclamate | 1.0 | g |
| Glycerol | 15.0 | g |
| Distilled water ad | 100.0 | ml |

Method of preparation:

The active substance and sodium cyclamate are dissolved in about 70 ml of water and glycerol is added thereto. The p-hydroxybenzoates, anisole and menthol are dissolved in the ethanol and this solution is added to the aqueous solution with stirring. Finally, the mixture is made up to 100 ml with water and filtered to remove any suspended particles.

Claims

1. Compounds of general formula I



(I)

(wherein $R_1$ represents a hydrogen or a chlorine atom and

R represents a (1-methyl-4-piperidinyl)methyl, (1-methyl-1,2,5,6-tetrahydro-4-pyridinyl)methyl, 1-methyl-1,2,5,6-tetrahydro-4-pyridinyl, (1-methyl-4-piperidinylidene)methyl, (2,3-dehydro-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-methyl, (8-methyl-8-aza-bicyclo-[3.2.1]oct-3-ylidene)-methyl or an endo- or exo-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)methyl group, each group being optionally substituted by one or two further methyl groups in the heterocyclic ring), and optical isomers thereof and acid addition salts of the afore-mentioned compounds.

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

3. Salts as claimed in claim 2 formed with hydrochloric, hydrobromic, sulphuric, phosphoric, tartaric, fumaric, citric, maleic, succinic, gluconic, malic, p-toluene-sulphonic, methanesulphonic or amidosulphonic acid.

4. Compounds as claimed in any preceding claim wherein $R_1$ represents a hydrogen or a chlorine atom and R represents a (1-methyl-4-piperidinyl)methyl,

* C L M S *



1-methyl-1,2,5,6-tetrahydro-4-pyridinyl or endo-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-methyl group.

5. 6-Chloro-5,10-dihydro-5-[(1-methyl-4-piperidinyl)-acetyl]-11H-dibenzo[b,e][1,4]diazepin-11-one and physiologically acceptable salts thereof.

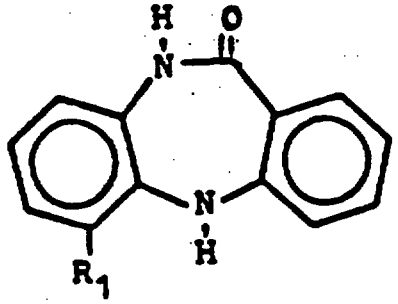
6. Compounds as claimed in claim 1 wherein $R_1$ represents a hydrogen or a chlorine atom and R represents a (1-methyl-4-piperidinyl)methyl, (1-methyl-1,2,5,6-tetrahydro-4-pyridinyl)methyl, 1-methyl-1,2,5,6-tetrahydro-4-pyridinyl, (1-methyl-4-piperidinylidene)methyl or endo- or exo- (8-methyl-8-azabicyclo [3.2.1]oct-3-yl)methyl group, each group being optionally substituted by one or two further methyl groups in the heterocyclic ring.

7. Compounds as claimed in claim 1 as herein specifically described.

8. Compounds as claimed in claim 1 as herein specifically described in any of Examples 1 to 13.

9. Compounds as claimed in claimed in claim 6 as herein described in any of Examples 1 to 10.

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



(II)

(wherein $R_1$ is as defined in claim 1) with a compound of general formula III

$$Z - \underset{\underset{O}{\|}}{C} - R \qquad \text{(III)}$$

(wherein R is as defined in claim 1 and Z represents a nucleophobic group).

11. A process as claimed in claim 10 wherein Z together with the carbonyl group to which it is bonded represent a reactive carbonyl derivative.

12. A process as claimed in claim 11 wherein the reactive carbonyl derivative is an acid halide, an ester, an anhydride, a mixed anhydride or an N-alkyl-2-acyloxy-pyridinium carboxylate.

13. A process as claimed in claim 11 or claim 12, wherein the reactive carbonyl derivative is a mixed anhydride with a strong inorganic acid.

14. A process as claimed in claim 13, wherein the strong inorganic acid is dichlorophosphoric acid.

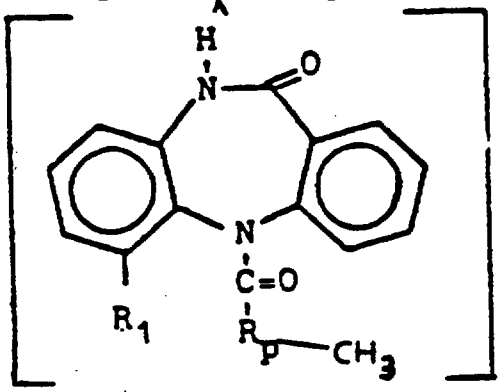
15. A process as claimed in any one of claims 10 to 14, wherein the reaction is carried out in an inert solvent.

16. A process as claimed in any one of claims 10 to 15 wherein the reaction is carried out at temperatures between -25 and +130°C.

17. A process as claimed in any one of claims 10 to 16 wherein the reaction is carried out in the presence of an acid-binding agent or proton acceptor.

18. A process as claimed in any of claims 10 to 17 wherein the compound of general formula III is prepared in situ in the reaction mixture.

19. A process for the preparation of compounds as claimed in claim 1 wherein R represents a (1-methyl-1,2,5,6-tetrahydro-4-pyridinyl)methyl or 1-methyl-1,2,5,6-tetrahydro-4-pyridinyl group optionally substituted by one or two further methyl groups in the heterocyclic ring, which comprises reducing a compound of general formula Va



(Va)

(wherein $R_1$ is as defined in claim 1, X represents the acid group of a strong oxyacid or a halogen atom and $R_p$ represents a 4-pyridinyl or (4-pyridinyl)methyl group optionally substituted by one or two further methyl groups), with a borohydride or alkoxyborohydride in a protic solvent at temperatures of between -40° and +50°C.

20. A process as claimed in claim 19 wherein X is the acid group of sulphuric, methylsulphuric, fluorosulphonic, trifluoromethylsulphonic, methanesulphonic, benzenesulphonic, p-toluenesulphonic, p-bromobenzenesulphonic or phosphoric acid or a chlorine, bromine or iodine atom.

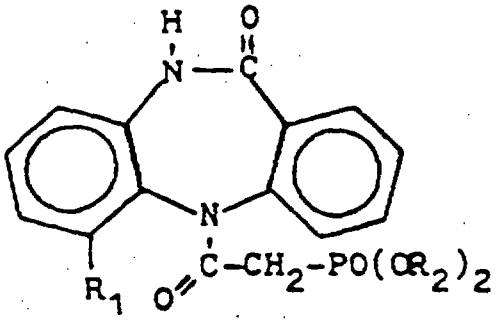
21. A process as claimed in claim 19 or claim 20, wherein the reduction is effected using sodium or potassium tetrahydridoborate or sodium or potassium alkoxy-, dialkoxy- or trialkoxy-borohydride.

22. A process as claimed in any one of claims 19 to 21 wherein the protic solvent is water, methanol, ethanol, or 2-propanol or a mixture of any of these solvents.

23. A process as claimed in any one of claims 19 to 22 wherein the reaction is carried out at temperatures of between -5 and +10°C.

24 A process for the preparation of compounds as claimed in claim 1

wherein R represents a (1-methyl-1,2,5,6-tetrahydro-4-pyridinyl)methyl, (1-methyl-1,2,5,6-tetrahydro-4-piperidinylidene)methyl, (2,3-dehydro-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)methyl or (8-methyl-8-aza-bicyclo [3.2.1]oct-3-ylidene)methyl group, each group being optionally substituted by one or two further methyl groups in the heterocyclic six-membered ring, which comprises reacting a compound of general formula VII

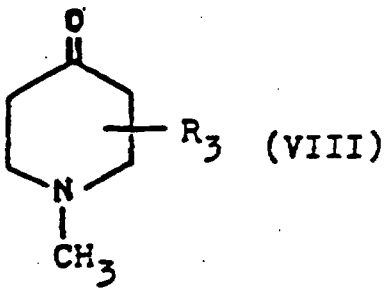


(VII)

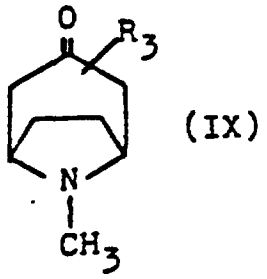
(wherein $R_1$ is as defined in claim 1 and $R_2$ represents an alkyl group containing 1 to 10 carbon atoms), with a compound of general formula VIII or IX

* C L M S *





(VIII)



(IX)

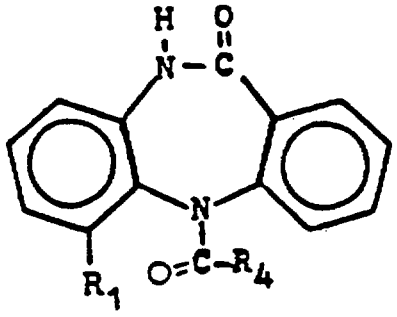
(wherein $R_3$ represents a hydrogen atom or a methyl group), in the presence of an alkali metal hydride or an alkali metal alkoxide in a solvent at temperatures of from 20°C up to the boiling point of the reaction mixture.

25. A process as claimed in claim 24, wherein the alkali metal alkoxide is potassium tert.butoxide.

26. A process as claimed in claim 24 or claim 25, therein the solvent is an ether.

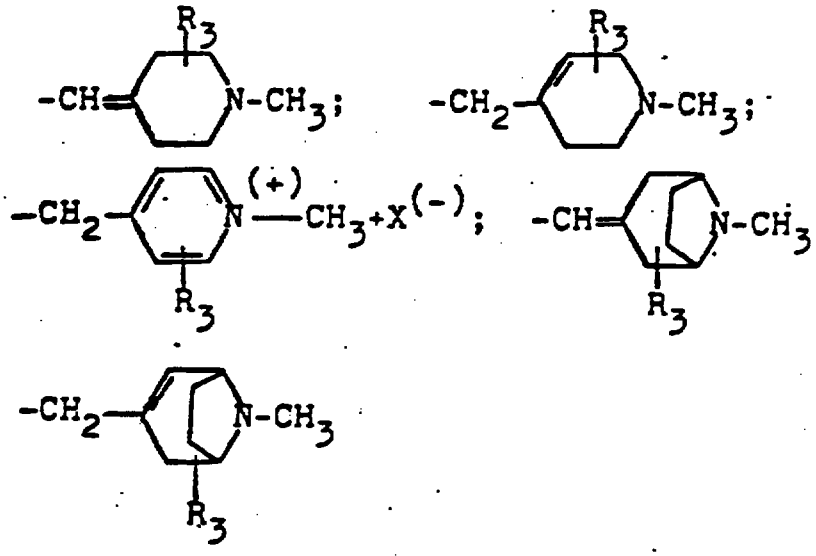
27. A process as claimed in claim 26 wherein the ether is diethyl ether, diisopropyl ether or tetrahydrofuran.

28. A process for the preparation of compounds as claimed in claim 1 wherein R represents a (1-methyl-4-piperidinyl)methyl or endo- or exo-(8-methyl-8-aza-bicyclo[3.2.1]-oct-3-yl)-methyl group, optionally substituted by one or two further methyl groups in the heterocyclic six-membered ring, which comprises catalytically hydrogenating a compound of general formula X



(X)

(wherein $R_1$ is as defined in claim 1 and $R_4$ represents a group of formula



or



wherein $R_3$ represents a hydrogen atom or a methyl group and X represents a halogen atom).

29. A process as claimed in claim 28 wherein X in $R_4$ represents a chlorine or bromine atom.

30. A process as claimed in claim 28 or claim 29 wherein the catalyst used is platinum dioxide, finely

* C L M S *



divided palladium on charcoal, Raney nickel or Raney cobalt.

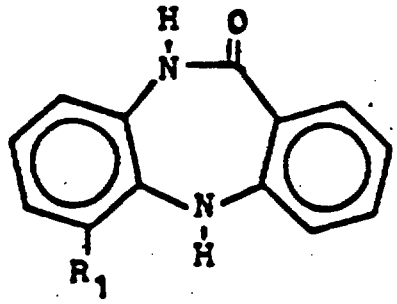
31. A process as claimed in any one of claims 28 to 30 wherein the hydrogenation is carried out at a hydrogen pressure of between 1 and 50 bars and at temperatures of between -20 and +100°C.

32. A process as claimed in claim 31 wherein the temperature is between +10 and +40°C.

33. A process as claimed in any one of claims 28 to 32 wherein the compound of formula X is present in solution.

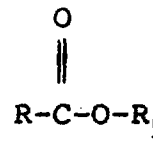
34. A process as claimed in claim 33 wherein an alcoholic solution of the compound of formula X is used.

35. A process for the preparation of compounds as claimed in claim 1, which comprises initially converting a compound of general formula II



(II)

(wherein $R_1$ is as defined in claim 1) into the di-lithium salt thereof and subsequently reacting the obtained di-lithium salt with an ester of general formula XII



(XII)

(wherein R is as defined in claim 1 and $R_5$ represents an alkyl group containing 1 to 10 carbon atoms or an aralkyl group containing 7 to 13 carbon atoms),

36. A process as claimed in claim 35 wherein $R_5$ represents an alkyl group containing 1 to 6 carbon atoms or a phenylmethyl, phenylethyl or phenylpropyl group.

37. A process as claimed in claim 35 or claim 36 wherein the initial conversion of the compound of general formula II into its di-lithium salt is effected with a lithium alkyl or a lithium aryl or a lithium amide.

38. A process as claimed in any one of claims 35 to 37 wherein the conversion of the compound of general formula II into its di-lithium salt is effected with n-butyl lithium, n-butyl lithium in the presence of tetramethyl ethylenediamine, tert.butyl lithium, lithium diisopropylamide, lithium dicyclohexylamide or lithium phenyl.

39. A process as claimed in claim 37 or 38 wherein the initial conversion of the compound of general formula II into its di-lithium salt is effected with at least two equivalents of a lithium alkyl or lithium aryl or lithium amide.

40. A process as claimed in any one of claims 35 to 39 wherein the reaction is carried out in a solvent at temperatures of between -60 and 0°C.

41. A process as claimed in claim 40 where the temperature is -10°C.

* C L M S *



42. A process as claimed in any one of claims 10 to 41 wherein a compound of general formula I initially obtained is subsequently converted into an acid addition salt thereof or an acid addition salt of a compound of general formula I initially obtained is subsequently converted into a compound of general formula I.

43. A process as claimed in any one of claims 10 to 42 for the preparation of compounds as claimed in claim 8.

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

45. A process for the preparation of compounds as claimed in claim 8 substantially as herein described in any one of Examples 1 to 10.

46. Compounds as claimed in claim 1 when prepared by a process as claimed in any one of claims 10 to 45.

47. Compounds as claimed in claim 8 when prepared by a process as claimed in claim 43 or 45.

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

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

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






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

52. Compositions as claimed in any one of claims 48 to 51 wherein the compound of formula I is as defined in claim 8.

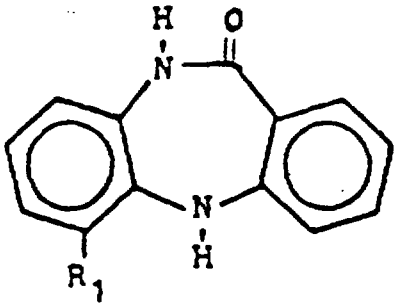
53. Compositions as claimed in any one of claims 48 to 52 containing additional active ingredients.

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

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

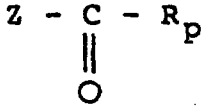
56. Compounds of general formula I as claimed in claim 1 and physiologically compatible acid addition salts thereof for use in a method of treatment of patients suffering from disorders of the stomach and intestines, including acute and chronic gastric and duodenal ulcers and related conditions.

57. A process as claimed in claim 19, in which the compounds of general formula Va are prepared by a process which comprises reacting a compound of formula II



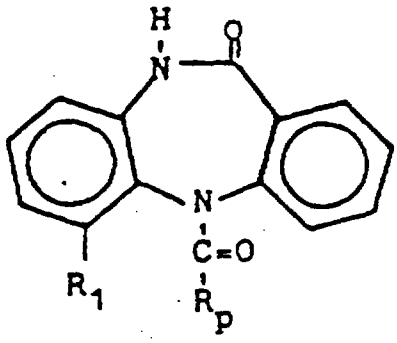
(II)

(wherein $R_1$ is as defined in claim 1) with a compound of general formula IV



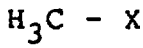
(IV)

(wherein Z represents a nucleophobic group and $R_p$ represents a 4-pyridinyl or (4-pyridinyl)methyl group optionally substituted by one or two methyl groups), to form a compound of general formula V



(V)

(wherein $R_1$ and $R_p$ are as defined above) and subsequently methylating the compound of general formula V thus initially obtained with a methylating agent of general formula VI



(VI)

* C L M S *



(wherein X represents the acid group of a strong oxyacid or a halogen atom), to form the corresponding compound of general formula Va.

58. A process as claimed in claim 57 wherein Z in the compound of formula IV represents a chlorine, bromine or iodine atom.

59. A process as claimed in claim 57 or claim 58 wherein the reaction is carried out in an inert solvent, the said solvent for the initial acylation step and the subsequent methylation step being the same or different.

60. A process as claimed in any one of claims 57 to 59 wherein the initial acylation step is effected at temperatures up to the boiling point of the reaction mixture, and the subsequent methylation step is effected at temperatures of between -20 and +130°C.