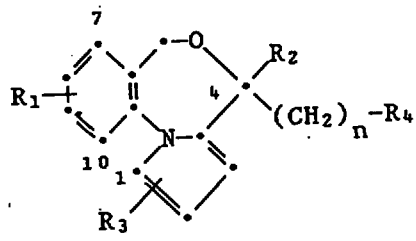
4-15722/CGC 1176
EP

Pyrrolo[1,2-a][4,1]benzoxazepines, a process for the preparation thereof, pharmaceutical compositions comprising those compounds, and the therapeutic use thereof

The present invention relates to novel substituted pyrrolo[1,2-a][4,1]benzoxazepines, especially pyrrolo-[1,2a]-[4,1]benzoxazepines substituted at C-4, to the preparation thereof, to pharmaceutical compositions comprising those novel compounds, and also to the use thereof.

4H,6H-pyrrolo[1,2-a][4,1]benzoxazepines that are unsubstituted at C-4 and are CNS-active are known from Farmaco, Ed. Sci. (1983) 38, 893-903 and C-4-substituted, structurally isomeric pyrrolo[2,1-c][1,4]benzoxazepines that have analgesic, anticonvulsive and sedative properties or antihypertensive properties are known from US-A-4 096 672 and US-A-4 053 599. Also, C-4-substituted structurally isomeric pyrrolo[2,1-c][1,4]benzoxazepines that have antipsychotic and analgesic properties are described in EP-A-0 144 729.

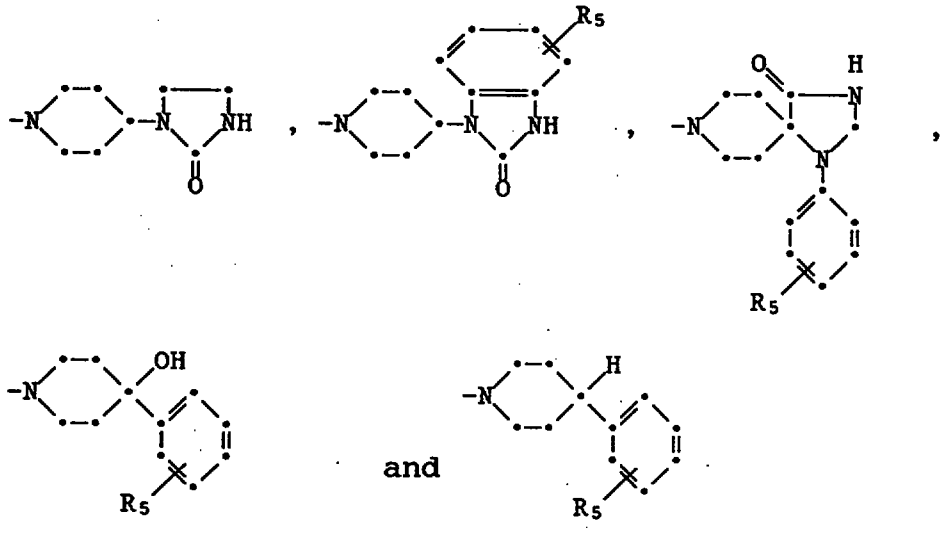
It has surprisingly now been found that the novel 4-substituted 4H,6H-pyrrolo[1,2-a][4,1]benzoxazepines of the general formula I



(I)

wherein n represents the integer 1 or 2; R_1 represents hydrogen, lower alkyl, halogen, trifluoromethyl, hydroxy

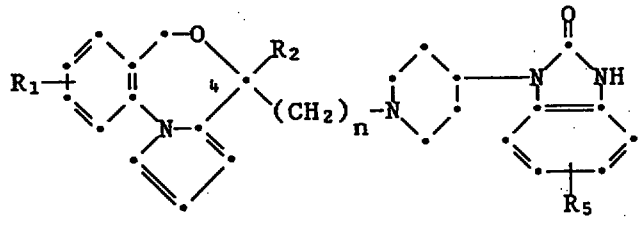
or lower alkoxy; R_2 represents hydrogen or lower alkyl; R_3 represents hydrogen, lower alkyl or halogen; R_4 represents N-lower alkylpiperazino, N-phenylpiperazino that is unsubstituted or substituted in the phenyl moiety by halogen or by lower alkyl, or piperidino or substituted piperidino selected from



and

in which R_5 represents hydrogen, halogen or lower alkyl; and salts thereof, have gastrointestinal antisecretory effects, especially anti-diarrhoeal effects.

Preferred are compounds of the general formula II



(II)

wherein R_1 represents hydrogen, lower alkyl, halogen, trifluoromethyl, hydroxy or lower alkoxy; R_2 represents hydrogen or lower alkyl; n represents the integer 1 or 2; and R_5 represents hydrogen, halogen or lower alkyl; and pharmaceutically acceptable salts thereof.

Also preferred are compounds of formula II wherein n

represents the integer 1 or 2; R_2 represents straight-chain lower alkyl having from 1 to 4 carbon atoms; R_1 and R_5 represent hydrogen or halogen, and pharmaceutically acceptable salts thereof.

Particularly preferred are compounds of formula II wherein R_1 and R_5 represent hydrogen, R_2 represents methyl or ethyl, and n represents 1, and pharmaceutically acceptable salts thereof.

The general definitions used herein have the following meaning within the scope of the present invention.

Halogen is preferably chlorine or fluorine, but may also be bromine or iodine.

The term "lower" referred to above and hereinafter in connection with organic radicals or compounds defines such radicals or compounds having up to and including 7, preferably up to and including 4, and advantageously one or two, carbon atoms.

Lower alkyl contains 1 to 7 carbon atoms, preferably 1 to 4 carbon atoms, is advantageously straight-chain and represents methyl, ethyl, propyl or butyl, advantageously methyl.

Lower alkoxy is preferably straight-chain and represents, for example, methoxy, ethoxy or propoxy, advantageously methoxy.

Phenyl is unsubstituted or may be monosubstituted by lower alkyl or by halogen.

Pharmaceutically acceptable salts are acid additon salts, which are preferably derived from therapeutically

acceptable inorganic or organic acids, such as strong mineral acids, for example hydrohalic acids, e.g. hydrochloric or hydrobromic acid; sulfuric, phosphoric or nitric acid; aliphatic or aromatic sulfonic acids, e.g. methanesulfonic acid, ethanesulfonic acid, hydroxyethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid or naphthalenesulfonic acid; aliphatic or aromatic carboxylic acids, e.g. acetic, propionic, succinic, glycolic, lactic, malic, tartaric, gluconic, citric, maleic, fumaric, pyruvic, phenylacetic, benzoic, 4-aminobenzoic, anthranilic, 4-hydroxybenzoic, salicylic, 4-aminosalicylic, pamoic, nicotinic acid; or ascorbic acid.

The compounds of the present invention exhibit valuable pharmacological properties, e.g. gastrointestinal antisecretory effects, particularly anti-diarrhoeal effects; inter alia they inhibit calmodulin activity in mammals.

The above-mentioned properties can be demonstrated by in vitro and in vivo tests, advantageously using mammals, e.g. mice, rats, or dogs, as test subjects. The compounds of the invention may be administered enterally or parenterally, advantageously orally, or subcutaneously, intravenously or intraperitoneally, for example, within gelatin capsules or in the form of aqueous solutions or suspensions. The applied dosage may range between about 0.10 and 100 mg/kg/day, preferably between about 0.50 and 50 mg/kg/day, advantageously between about 5 and 30 mg/kg/day.

The dosage that can be administered in vitro may range between about 10^{-4} and 10^{-8} M concentration, preferably between about 10^{-5} and 10^{-7} M.

The calmodulin inhibitory properties shown by the antisecretory activity of the novel compounds of the invention can be demonstrated *in vivo* by measuring the activation, induced by calmodulin inhibition, of bovine c-AMP phosphodiesterase, according to the method described by J.A. Norman *et al.*, Mol. Pharmacology 16, 1089 (1979).

1,3-Dihydro-1-{1-[(4-methyl-4H,6H-pyrrolo[1,2-a][4,1]-benzoxazepin-4-yl)-methyl]-4-piperidinyl}-2H-benzimidazol-2-one maleate, which as a result of calmodulin inhibition induces the activation of phosphodiesterase *in vitro* by 50 % at about 3×10^{-6} molar concentration, may be mentioned as an example to illustrate the invention.

The anti-diarrhoeal effect of the compounds of formula I of the invention can be demonstrated by measuring the inhibition of diarrhoea that has been induced in rats by the intraperitoneal administration of prostaglandin E_2.

The test is carried out as follows: Female Sprague-Dawley rats weighing 200-250 g and fasted for 18 hours are employed. The test compounds are diluted in dimethyl sulfoxide with water to a 30-50 % dimethyl sulfoxide concentration and administered to the rats orally by gastric lavage in a volume of 1 ml/kg. Thirty or sixty minutes later, prostaglandin E_2 (150 μg) is administered in a volume of 0.5 ml of water. The decrease in faecal excretion compared to untreated animals is measured for a period of 30 minutes after administration of prostaglandin E_2.

1,3-dihydro-1-{1-[(4-methyl-4H,6H-pyrrolo[1,2-a][4,1]-benzoxazepin-4-yl)-methyl]-4-piperidinyl}-2H-benzimidazol-2-one maleate, which exhibits the described activity at a dose of 10 mg/kg p.o. in rats, may be

mentioned as an example to illustrate the invention.

Inhibition of gastric acid secretion, indicative of anti-ulcer activity, was determined in vitro in rat stomach parietal cells as follows:

Approximately 1 x 10^6 parietal cells (18-22 % enriched) are incubated in a glucose-containing salt solution, BSA (bovine serum albumin), 0.1 uCi of ^{14}C-aminopyrine, histamine (1 mM), isobutyl methylxanthine (0.1 mM) and the test compound is tested under 95 % oxygen at 37°C for a period of 40 minutes. The cells are then washed, ruptured with distilled water and analyzed by scintillation spectrometry. A decrease in the accumulation of ^{14}C-aminopyrine in the cells is an indirect indication of the level of gastric acid inhibition.

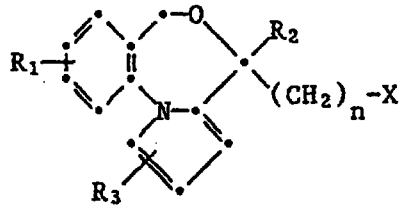
1,3-dihydro-1-{1-[(4-methyl-4H,6H-pyrrolo[1,2-a][4,1]-benzoxazepin-4-yl)-methyl]-4-piperidinyl}-2H-benz-imidazol-2-one maleate, which inhibits gastric acid secretion in rat stomach parietal cells, showing an IC_{50} of about 3 x 10^{-7} M, may be mentioned as an example to illustrate the invention,

The compounds of formula I of the invention can be used as gastro-intestinal active compounds, e.g. as gastro-intestinal antisecretory agents, for example for the treatment of diarrhoea, ulcers, excess gastric acid secretion, inflammatory bowel diseases and dehydration.

The compounds of the invention of formula I or II, and salts thereof, are prepared by
a) condensing an amine of formula III

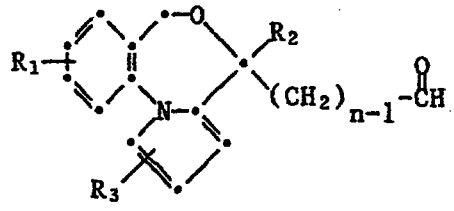
$$R_4\text{-H} \qquad \text{(III)},$$

wherein R_4 is as defined above and H is attached to the nitrogen atom of the group R_4, with a compound of formula IV



(IV),

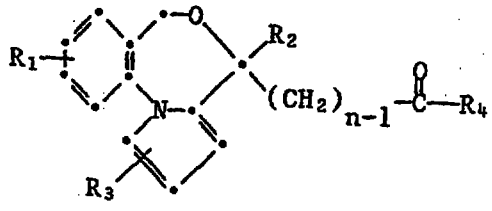
wherein n, R_1, R_2 and R_3 are as defined for formula I and X represents reactive esterified hydroxy, or with a compound of formula V



(V),

wherein n, R_1, R_2 and R_3 are as defined for formula I, under conditions of reductive amination; or

b) reducing a compound of formula VI



(VI),

wherein R_1, R_2, R_3, R_4 and n are as defined for formula I, and, if desired, in all of these processes temporarily protecting an interfering reactive group, and isolating the resulting compound of formula I; and, if desired, converting a resulting compound of formula I into another compound of formula I of the invention and/or, if desired, converting a resulting compound of formula I into a salt or a resulting salt into the free compound or into another salt and/or, if desired, separating a resulting mixture of isomers or racemates into the individual isomers or racemates and/or, if desired,

resolving racemates obtained into the optical antipodes.

A reactive esterified hydroxy group in the starting materials of the above-described processes is hydroxy esterified by a strong acid, especially by an inorganic acid, such as a hydrohalic acid, especially hydrochloric, hydrobromic or hydriodic acid, or sulfuric acid, or by a strong organic acid, especially sulfonic acid, such as an aliphatic or aromatic sulfonic acid, for example methanesulfonic acid, 4-methylphenylsulfonic acid or 4-bromophenylsulfonic acid.

In starting compounds and intermediates which are converted to the compounds of the invention in a manner described herein, functional groups present, such as formyl, carboxy, amino and hydroxy groups, may be protected by conventional protecting groups that are known in preparative organic chemistry. Protected formyl, carboxy, amino and hydroxy groups are those that can be converted under mild conditions into free formyl, carboxy, amino and hydroxy groups without the molecular framework being destroyed or other undesired side reactions taking place. The need and choice of protecting groups for a particular reaction is known to those skilled in the art and depends on the group to be protected (carbonyl group, carboxy group, amino group etc.), the structure and stability of the molecule of which the substituent is a part, and the reaction conditions.

Known protecting groups that meet these conditions and their introduction and removal are described, for example, in J.F.W. McOmie, "Protective Groups in Organic Chemistry",. Plenum Press, London/New York 1973, T.W. Greene, "Protective Groups in Organic Synthesis", Wiley, New York 1981, and also in "The Peptides", Vol. I,

Schroeder and Luebke, Academic Press, London/New York 1965, as well as in Houben-Weyl, "Methoden der Organischen Chemie", Vol. 15/1, Georg Thieme Verlag, Stuttgart, 1974.

The preparation of compounds of the invention according to process a) involving the N-alkylation of an amine of formula III with a compound of formula IV is carried out according to known methods, usually in an inert solvent or a mixture of inert solvents and, if necessary, with cooling or heating, for example in a temperature range of from approximately -20°C to approximately 150°C, and/or in an inert gas atmosphere.

The reaction is carried out advantageously in the presence of a base, such as an inorganic base, for example an alkali metal or alkaline earth metal carbonate, hydride or hydroxide, or in the presence of an organic base, such as a tertiary amine, such as triethylamine or pyridine.

The preparation of compounds of the invention according to process a) involving the condensation of an amine of formula III with an aldehyde of formula V by reductive N-alkylation is carried out in a manner known per se, e.g. with catalytic hydrogenation using catalytically activated hydrogen, for which noble metal catalysts that comprise platinum, palladium or nickel are used, or with chemical reducing agents, such as compounds or complexes of light metal hydrides, advantageously an alkali metal cyanoborohydride such as sodium cyanoborohydride. When using an alkali metal cyanoborohydride the reaction is preferably carried out in the presence of an inert solvent, e.g. methanol or acetonitrile, advantageously in the presence of an acid, e.g. hydrochloric acid or acetic acid.

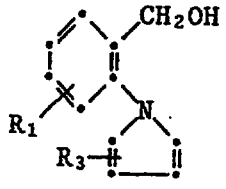
Process variant a) is preferred for the preparation of the compounds of the invention of formula I wherein an amide functional grouping is present.

The preparation of the compounds of the invention of formula I according to process b) is carried out in a manner known per se using suitable reducing agents, especially hydride reducing agents, such as complex metal hydrides, e.g. lithium aluminium hydride, or boro-hydrides, which are normally used in an inert solvent, such as tetrahydrofuran or diethyl ether, the preparation advantageously being carried out in a temperature ranging from room temperature to near the boiling point of the solvent.

The starting compounds of formula III are known, or can be prepared according to known methods.

The starting compounds of formula IV and V are prepared according to known methods.

An ester of the appropriately substituted anthranilic acid is heated with a 2,5-di-lower alkoxytetrahydrofuran, e.g. in acetic acid, and condensed to yield the o-(1-pyrrolyl)-benzoic acid ester, e.g. a lower alkyl ester, which is subsequently reduced, e.g. with lithium aluminium hydride in an inert solvent, to the correspondingly substituted o-(1-pyrrolyl)-benzyl alcohol of formula VII.

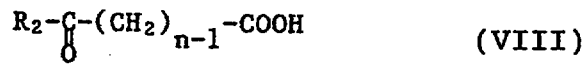


(VII)

wherein R_1 and R_3 are as defined for formula I.

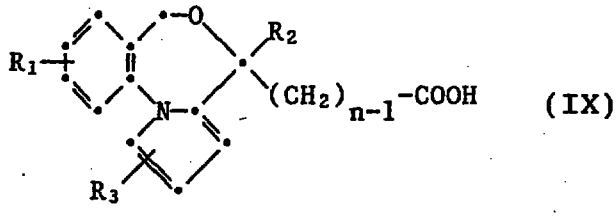
Condensation of a compound of formula VII with a compound

of the formula VIII



(VIII)

wherein n and R_2 are as defined for formula I, or an ester thereof, e.g. a lower alkyl ester, advantageously in the presence of a strong base, e.g. butyl lithium or lithium diisopropylamide, or in the presence of an acid, e.g. hydrobromic acid, yields a compound of formula IX



(IX)

or an ester thereof, e.g. a lower alkyl ester, wherein n, R_1, R_2 and R_3 are as defined for formula I.

The starting compounds of formula V are obtained by the reduction of an ester of a compound of formula IX with a selective chemical reducing agent, e.g. diisobutyl aluminium hydride.

The starting compounds of formula IV wherein X is hydroxy are obtained by reduction of a compound of formula IX with a reducing agent that is suitable for the reduction of a carboxylic acid or of an ester of the corresponding alcohol, e.g. diborane, sodium bis-(2-methoxyethoxy)-aluminium hydride or lithium aluminium hydride.

The starting compounds of formula IV wherein X represents hydroxy can be converted in a manner known per se into the corresponding compounds of formula IV wherein X represents esterified hydroxy. For example the compounds of formula IV wherein X represents halogen, such as chlorine or bromine, can be obtained by treating with conventional agents, such as thionyl chloride or phos-

phorus oxychloride.

The starting compounds of formula VI are prepared in a manner known per se by condensation of a carboxylic acid of a compound of formula IX or a reactive functional derivative thereof with an amine corresponding to the group R_4 in formula I, namely a compound of the formula R_4-H wherein R_4 is as defined above and H is attached to the nitrogen atom of the amino group R_4.

A reactive functional derivative of a carboxylic acid of formula IX above represents e.g. an acyl halide, such as an acid chloride, an anhydride of such an acid, a mixed anhydride e.g. derived from a lower alkyl halocarbonate, such as ethyl chloroformate, a reactive ester, e.g. a lower alkyl ester such as an ethyl or methyl ester or an optionally substituted phenyl ester, or an amide, e.g. derived from imidazole (prepared from N,N-carbonyl-diimidazole).

The condensation of an amine of formula III (R_4-H) that may be present in protected form with a compound of formula IX in the form of a free carboxylic acid is carried out advantageously in the presence of a condensing agent, such as dicyclohexylcarbodiimide or 1,1-diimidazolylcarbonyl (carbonyldiimidazole) in an inert solvent, such as methylene chloride or tetrahydrofuran, at a temperature near the boiling point of the solvent.

The condensation of a compound of formula III with a compound of formula IX which is in the form of a reactive derivative of the carboxylic acid, e.g. in the form of an acid halide, advantageously an acid chloride, or a mixed anhydride, is carried out in an inert solvnet, such as toluene or methylene chloride, advantageously in the presence of a base, e.g. an inorganic base, such as

potassium carbonate, or an organic base, such as triethylamine or pyridine, at a temperature ranging from about 0° to 100°, preferably at room temperature.

The resulting compounds of the invention of formula I can be converted into other compounds of the invention of formula I in a manner known per se.

For example, compounds of formula I wherein R_1 represents lower alkoxy can be converted into compounds of formula I wherein R_1 represents hydroxy in a manner known per se, e.g. with a mineral acid, such as hydriodic acid or, advantageously for compounds wherein R_1 is methoxy, with boron tribromide in methylene chloride or with sodium or lithium diphenyl phosphide in tetrahydrofuran.

The above-mentioned reactions are carried out according to methods known per se, in the presence or absence of diluents, preferably those that are inert to the reagents and are solvents thereof, of catalysts, condensing agents or other mentioned agents, and/or in an inert atmosphere, with cooling, at room temperature or at elevated temperature, preferably at the boiling point of the solvent used, at normal or elevated pressure.

The invention further includes any variant of the present process in which an intermediate obtainable at any stage thereof is used as starting material and the remaining process steps are carried out, or the process is discontinued at any stage, or in which a starting material is fomred under the reaction conditions, or in which a starting material is used in the form of a salt or in the form of pure isomers.

There are advantageously used in the process of the present invention those starting materials that lead to

the formation of those compounds indicated at the beginning as being especially valuable.

Finally, the compounds of the invention are obtained either in free form, or in the form of their salts whenever a compound is suitable for salt formation. A resulting free base can be converted into the corresponding acid addition salt, preferably with the use of such acids or anion exchange preparations that yield pharmaceutically acceptable salts. A resulting salt can be converted into the corresponding free base, for example, with the use of a stronger base, such as a metal or ammonium hydroxide, or a basic salt, e.g. an alkali metal hydroxide or carbonate, or a cation exchange preparation. The acid addition salts are formed preferably with those of the above-described inorganic or organic acids that yield pharmaceutically acceptable salts. These or other salts, for example picrates, can also be used for purification of the bases obtained. The bases are converted into their salts, the salts are separated and the free compounds are freed from the salts.

In view of the close relationship between the novel compounds in free form and in the form of salts, throughout this specification any reference to the free compounds or their salts is to be understood as including the corresponding salts or free compounds respectively, as appropriate and expedient.

The compounds, including their salts, may also be obtained in the form of their hydrates, or include other solvents used for the crystallization.

The present invention additionally relates to compounds of formula I and their therapeutically acceptable, non-

toxic acid addition salts for use as medicaments, and especially for use in the preparation of pharmaceutical compositions, especially compositions that can be used for the treatment of mammals, especially as gastrointestinal active ingredients, such as gastrointestinal antisecretory agents for the treatment of gastrointestinal secretory disorders, such as diarrhoea, ulcers, inflammatory bowel diseases and dehydration.

The present invention also relates to the use of the compounds of the invention of formula I for the preparation of pharmaceutical compositions, especially gastrointestinal antisecretory compositions, and more particularly anti-diarrhoeal pharmaceutical compositions, that have calmodulin inhibitory activity.

The compositions according to the invention are those suitable for enteral, such as oral or rectal, and parenteral administration to mammals, including man. The pharmaceutical compositions of the invention comprise at least one compound of formula I, or a therapeutically acceptable salt thereof, as active ingredient, alone or in combination with one or more therapeutically acceptable carriers.

The pharmacologically usable compounds of the present invention can be used for the manufacture of pharmaceutical compositions comprising an effective amount of the active ingredient in conjunction or admixture with carriers that are suitable for either enteral or parenteral administration. Preferred are tablets and gelatin capsules comprising the active ingredient together with a) diluents, e.g. lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine; b) lubricants, e.g. silica, talcum, stearic acid or salts thereof, e.g. magnesium or calcium stearate, and/or polyethylene

glycol; for tablets also c) binders, e.g. magnesium aluminium silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone; if desired, d) disintegrants, e.g. starches, agar, alginic acid or a salt thereof, e.g. sodium alginate, and/or effervescent mixtures; or e) adsorbents, colorants, flavours and sweeteners. Injectable compositions are preferably aqueous isotonic solutions or suspensions, and suppositories are advantageously prepared from fatty emulsions or suspensions. The pharmacological compositions may be sterilized and/or contain adjuvants, such as preserving, stabilizing, wetting and/or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers. The pharmaceutical compositions which, if desired, may also contain other pharmacologically valuable substances, are prepared in a manner known per se, e.g. by conventional mixing, granulating or confectioning methods, and contain from about 0.1 to about 75 %, preferably from about 1 to about 50 %, of the active ingredient.

The pharmacologically active compounds of the invention can furthermore be used for the manufacture of pharmaceutical compositions that comprise an effective amount of the active ingredient together or in admixture with carriers that are suitable for transdermal application. Preferably used for this formulation are applications in the form of bandages comprising a backing member, a reservoir containing the active ingredient, optionally with carriers, otpionally a controllable membrane to deliver the active ingredient to the skin at a controlled rate over a predetermined period of time, and means to secure the device to the skin.

More specifically, the present invention relates to methods of treating disorders in mammals that are

responsive to calmodulin inhibition, particularly gastrointestinal secretory disorders, such as diarrhoea, ulcers, inflammatory bowel diseases and dehydration, using an effective amount of a compound of formula I of the invention or a therapeutically acceptable salt thereof as active ingredient, preferably in the form of the above-described pharmaceutical compositions. The dosage of active compound administered is dependent on the species of warm-blooded animal, the body weight, age and individual condition, and on the form of administration. A unit dosage for a mammal of about 50 to 70 kg may comprise between about 5 and 100 mg of the active ingredient.

The following Examples are intended to illustrate the invention. Temperatures are given in degrees Celsius. If not mentioned otherwise, all evaporations are performed under reduced pressure, preferably between about 15 and 100 mm Hg (≙ 2 to 13.3 KPa). The structure of final products, intermediates and starting materials is confirmed by analytical methods, e.g. microanalysis and spectroscopic characteristics (e.g. IR, NMR).

Example 1:

1,3-Dihydro-1-{1-[(4-methyl-4H,6H-pyrrolo[1,2-a][4,1]-benzoxazepin-4-yl)-methyl]-4-piperidinyl}-2H-benzimidazol-2-one (1:1) maleate

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700 mg of lithium aluminium hydride are added to a suspension of 3.0 g of 1,3-dihydro-1-{1-[(4-methyl-4H,6H-pyrrolo[1,2-a][4,1]benzoxazepin-4-yl)-carbonyl]-4-piperidinyl}-2H-benzimidazol-2-one in 120 ml of tetrahydrofuran. The reaction mixture is stirred at reflux for 6 hours and then at room temperature for 18 hours. The reaction mixture is diluted with 150 ml of ether and the excess lithium aluminium hydride is eliminated in the manner described below. The solid is removed by filtra-

tion. The organic phase is washed with 150 ml of sodium hydroxide solution and then 150 ml of brine. The organic extracts are then dried over magnesium sulfate, filtered and the solvent removed in vacuo to yield 1,3-dihydro-1-{1-[(4-methyl-4H,6H-pyrrolo[1,2-a][4,1]benzoxazepin-4-yl)-methyl]-4-piperidinyl}-2H-benzimidazol-2-one, m.p. 199-201°C, a compound of formula II wherein R_1 and R_5 = H, and R_2 = CH_3 and n = 1.

The compound obtained is then converted into its maleate salt by combining the free base and a molar equivalent amount of maleic acid in acetone. The 1:1 maleate salt crystallizes out and has a melting point of 183-185°.

The 1:1 fumarate salt is prepared in a similar manner and has a melting point of 125-127°.

The starting material is prepared as follows:

A mixture of 500 g of methyl anthranilate and 438 g of 2,5-dimethoxytetrahydrofuran in 670 ml of glacial acetic acid is boiled under reflux for 1 1/2 hours. The acetic acid is then evaporated off in vacuo and the residue is distilled to yield methyl 2-(1H-pyrrol-1-yl)-benzoate, b.p. 109°/0.1 mmHg.

A solution of 428 g of methyl 2-(1H-pyrrol-1-yl)benzoate in 1.5 l of ether is added dropwise over a period of 4 hours to a suspension of 117 g of lithium aluminium hydride in 2 l of anhydrous ether (under an inert atmosphere). The reaction mixture is boiled under reflux for an additional 4 hours and then cooled to room temperature.

After cooling in an ice-bath, the excess lithium aluminium hydride is destroyed by the dropwise addition of

117 ml of water over a period of 1 hour, followed by the dropwise addition of 117 ml of 15 % sodium hydroxide and the subsequent addition over a 30 minute period of 351 ml of water. The solid residue is separated by filtration, the ether layer is then dried over magnesium sulfate and the solvent is removed in vacuo to yield 2-(pyrrol-1-yl)-benzyl alcohol which is then purified by distillation in vacuo; b.p. 110-114°/0.1 mmHg.

183 ml of a 2.4 molar solution of n-butyl lithium is added in such an amount to a solution of 34.6 g of 2-(pyrrol-1-yl)-benzyl alcohol in 300 ml of anhydrous tetrahydrofuran and 32 ml of tetramethylethylene diamine (TMEDA) that the internal temperature of the reaction falls below 30°C. On completion of the addition, the reaction mixture is stirred at room temperature for 3 hours. The reaction mixture is then cooled to -70° by means of a dry-ice/acetone bath, and 24 ml of ethyl pyruvate are added to the mixture over a period of 1 minute. The reaction is heated to room temperature and stirred overnight (18 hours).

The reaction mixture is then poured into an ice-water/-ether mixture, the organic phase is removed and dried over magnesium sulfate and the solvent is evaporated in vacuo to yield ethyl 4-methyl-4H,6H-pyrrolo[1,2-a]-[4,1]benzoxazepine-4-carboxylate, m.p. 94-96°, which may be recrystallized from a mixture of ether/hexane (1:1).

A mixture of 41 g thereof, 180 ml of 3N sodium hydroxide and 150 ml of ethanol is boiled under reflux for 6 hours. The ethanol is then removed by evaporation in vacuo and the aqueous solution is acidified to pH 5 with 6N HCl. The resulting product, 4-methyl-4H,6H-pyrrolo[1,2-a][4,1]benzoxazepine-4-carboxylic acid, m.p. 182-183°, is filtered off and may be recrystallized from aqueous

ethanol. To a solution of 7.5 g thereof, in 300 ml of tetrahydrofuran, there are added 5 g of 1,1-carbonyl-diimidazole and the resulting mixture is stirred at room temperature for 1 hour. 5 g of 1,3-dihydro-1-(4-piperidyl)-2H-benzimidazol-2-one are added, and the reaction mixture is boiled under reflux for 48 hours. After cooling to room temperature, the reaction mixture is poured into 150 ml of ice-water and extracted in 150 ml of methylene chloride. The organic extract is washed successively with 150 ml of sodium carbonate solution, 150 ml of water and 150 ml of dilute hydrochloric acid, then dried over magnesium sulfate and filtered, and the solvent is evaporated off in vacuo to yield 1,3-dihydro-1-{1-[(4-methyl-4H,6H-pyrrolo[1,2-a][4,1]benzoxazepin-4-yl)-carbonyl]-4-piperidinyl}-2H-benzimidazol-2-one, m.p. 208-210°.

Example 2:

1,3,4,5-Tetrahydro-1-{1-[(4-methyl-4H,6H-pyrrolo[1,2-a][4,1]benzoxazepin-4-yl)-methyl]-piperidinyl}-2H-imidazol-2-one

3.6 ml of 5.5N methanolic HCl and 3.4 g of 1,3,4,5-tetrahydro-1-(4-piperidinyl)-2H-imidazol-2-one followed by 900 mg of sodium cyanoborohydride are added to a solution of 4.5 g of 4-formyl-4-methyl-4H,6H-pyrrolo[1,2-a][4,1]benzoxazepine in 50 ml of methanol. The reaction mixture is stirred at room temperature for 8 days. 2 ml of conc. HCl are added to the reaction mixture and the solvent is removed by evaporation in vacuo. The residue is dissolved in 150 ml of water and washed with 150 ml of 1:1 ethyl acetate/ether mixture. The aqueous phase is separated off, rendered basic with sodium hydroxide solution to pH 9 and extracted with 2 x 150 ml of ethyl acetate. The combined ethyl acetate extract is dried over anhydrous $MgSO_4$, filtered, and the solvent is removed by evaporation in vacuo to yield 1,3,4,5-tetra-

hydro-1-{1-[(4-methyl-4H,6H-pyrrolo[1,2-a][4,1]benz-oxazepin-4-yl)-methyl]-4-piperidinyl}-2H-imidazol-2-one which is characterised as its maleate salt, m.p., 197-199°.

The starting material is prepared as follows:

A solution of 7.0 g of methyl 4-methyl-4H,6H-pyrrolo[1,2-a][4,1]benzoxazepine-4-carboxylate (for preparation see Example 1) in 200 ml of methylene chloride is cooled to -65° and 65 ml of 1.0 m diisobutylaluminium hydride in methylene chloride are added dropwise over a 30 minute period. On completion of the addition, the reaction mixture is stirred for 30 minutes at -60° and then quenched with methanol. Water is then added and the cooling bath is removed. The reaction mixture is stirred for 15 minutes in order to reach room temperature. Solid material is removed by filtration, the methylene chloride solution is then dried over anhydrous $MgSO_4$, and the solvent is evaporated off <u>in vacuo</u> to yield an oily residue which on recrystallisation from ether yields 4-formyl-4-methyl-4H,6H-pyrrolo[1,2-a][4,1]benzoxazepine, m.p. 83-85°.

<u>Example 3:</u> The following compounds are prepared essentially according to procedures described in the previous Examples:

a) 8-[(4-methyl-4H,6H-pyrrolo[1,2-a][4,1]benzoxazepin-4-yl)-methyl]-1-phenyl-1,3,8-triazaspiro[4,5]decan-4-one; IR : 1680, 1555, 745, 715 cm^{-1};

b) 1-[(4-methyl-4H,6H-pyrrolo[1,2-a][4,1]benzoxazepin-4-yl)-methyl]-4-hydroxy-4-phenylpiperidine 1:1 maleate, m.p. 175-177°;

c) 1-[(4-methyl-4H,6H-pyrrolo[1,2-a][4,1]benzoxazepin-4-yl)-methyl]-4-hydroxy-4-(p-chlorophenyl)-piperidine;

d) 1-[(4-methyl-4H,6H-pyrrolo[1,2-a][4,1]benzoxazepin-4-yl)-methyl]-4-phenylpiperazine dihydrochloride, m.p. 155-157°;

e) 1-[(4-methyl-4H,6H-pyrrolo[1,2-a][4,1]benzoxazepin-4-yl)-methyl]-4-phenylpiperidine 1:1 maleate, m.p. 129-131°;

f) 1-[(4-methyl-4H,6H-pyrrolo[1,2-a][4,1]benzoxazepin-4-yl)-methyl]-4-methylpiperazine 1:1 maleate, m.p. 128-130°;

g) 1,3-dihydro-1-{1-[(8-chloro-4-methyl-4H,6H-pyrrolo-[1,2-a][4,1]benzoxazepin-4-yl)-methyl]-4-piperidinyl}-2H-benzimidazol-2-one.

Example 4:

A) Preparation of 10,000 tablets each comprising 10 mg of the active ingredient:

Formulation:

1,3-dihydro-1-{1-[(4-methyl-4H,6H-pyrrolo[1,2-a][4,1]benzoxazepin-4-yl)-methyl]-4-piperidinyl}-2H-benzimidazol-2-one 1:1 maleate	100.00 g
lactose	2,400.00 g
cornstarch	125.00 g
polyethylene glycol 6000	150.00 g
magnesium stearate	40.00 g
purified water	q.s.

Procedure:

All the powders are passed through a sieve with a mesh size of 0.6 mm. Then the active ingredient, lactose,

magnesium stearate and half of the starch are mixed in a suitable mixer. The other half of the starch is suspended in 65 ml of water and the suspension is added to a boiling solution of the polyethylene glycol in 260 ml of water. The paste obtained is added to the powders, and the mixture is granulated, if necessary with the addition of a further amount of water. The granulate is dried overnight at 35°, forced through a sieve with a mesh size of 1.2 mm and compressed into tablets.

B) Preparation of 10,000 capsules each containing 10 mg of the active ingredient:

Formulation:

1,3-dihydro-1-{1-[(4-methyl-4H,6H-pyrrolo[1,2-a][4,1]benzoxazepin-4-yl)-methyl]-4-piperidinyl}-2H-benzimidazol-2-one 1:1 maleate	10.00 g
lactose	207.00 g
modified starch	80.00 g
magnesium stearate	3.00 g

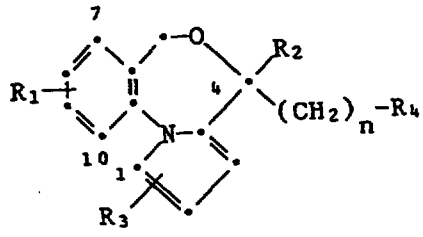
Procedure:

All the powders are passed through a sieve with a mesh size of 0.6 mm. Then the active ingredient is homogenised in a suitable mixer first with the magnesium stearate, then with the lactose and starch. No. 2 capsules are filled with 300 mg of said mixture each, using a capsule-filling machine.

Tablets or capsules containing about 5-100 mg of other compounds of the invention, e.g. those illustrated in the other Examples, are prepared in an analogous manner to the foregoing procedures.

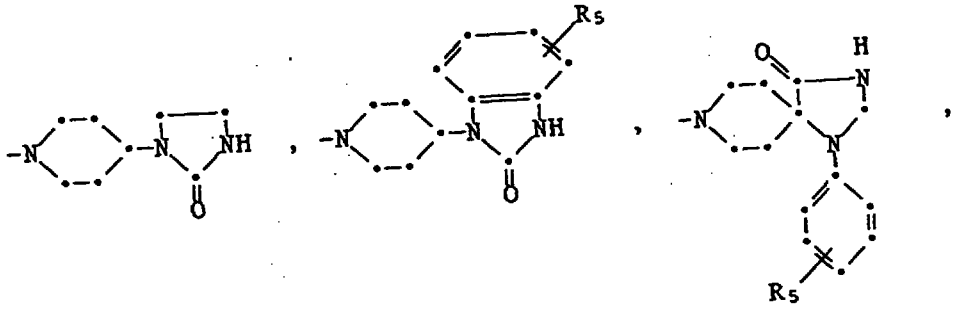
Patent Claims for all designated Contracting States apart from AT, ES and GR

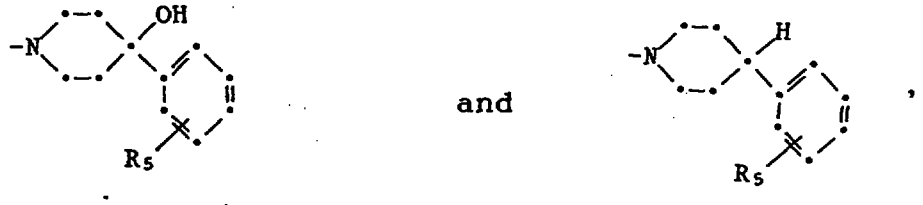
1. Compounds of the general formula I



(I)

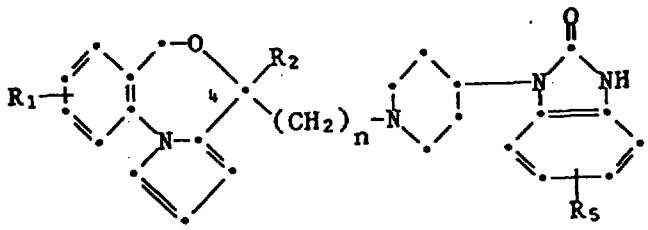
wherein n represents the integer 1 or 2; R_1 represents hydrogen, lower alkyl, halogen, trifluoromethyl, hydroxy or lower alkoxy; R_2 represents hydrogen or lower alkyl; R_3 represents hydrogen, lower alkyl or halogen; R_4 represents N-lower alkylpiperazino, N-phenylpiperazino that is unsubstituted or substituted in the phenyl moiety by halogen or by lower alkyl, or piperidino or substituted piperidino selected from





in which R_5 represents hydrogen, halogen or lower alkyl: and salts thereof, the radicals designated "lower" having a maximum of 7 carbon atoms.

2. Compounds of formula II



(II)

wherein R_1 represents hydrogen, lower alkyl, halogen, trifluoromethyl, hydroxy or lower alkoxy; R_2 represents hydrogen or lower alkyl; n represents the integer 1 or 2; and R_5 represents hydrogen, halogen or lower alkyl; and pharmaceutically acceptable salts thereof, the radicals designated "lower" having a maximum of 7 carbon atoms.

3. Compounds of formula II shown in claim 2, wherein n represents the integer 1 or 2; R_2 represents straight-chain lower alkyl having from 1 to 4 carbon atoms; R_1 and R_5 represent hydrogen or halogen, and pharmaceutically acceptable salts thereof.

4. Compounds of formula II shown in claim 2, wherein R_1 and R_5 represent hydrogen; R_2 represents methyl; and n represents 1; and pharmaceutically acceptable salts thereof.

5. 1,3-Dihydro-1-{1-[(4-methyl-4H,6H-pyrrolo[1,2-a]-[4,1]benzoxazepin-4-yl)-methyl]-4-piperidinyl}-2H-benzimidazol-2-one and pharmaceutically acceptable salts thereof.

6. Pharmaceutical compositions containing compounds of claims 1 to 5 in combination with a pharmaceutical carrier.

7. The compounds mentioned in claims 1 to 5 for use in a method for the therapeutic treatment of the human or animal body.

8. The compounds mentioned in claims 1 to 5 for use as antidiarrhoeal agents.

9. The compounds mentioned in claims 1 to 5 for use as gastrointestinal secretion inhibitors.

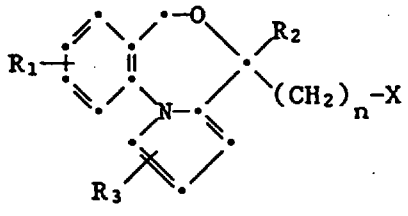
10. The use of the compounds mentioned in claims 1 to 5 for the manufacture of pharmaceutical compositions.

11. A process for the preparation of the compounds of formula I mentioned in claim 1, and salts thereof, comprising:

a) condensing an amine of formula III

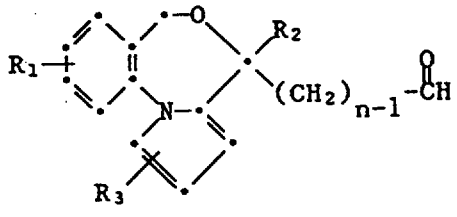
$$R_4\text{-}H \qquad \text{(III)},$$

wherein R_4 is as defined in claim 1 and H is attached to the nitrogen atom of the group R_4, with a compound of formula IV



(IV),

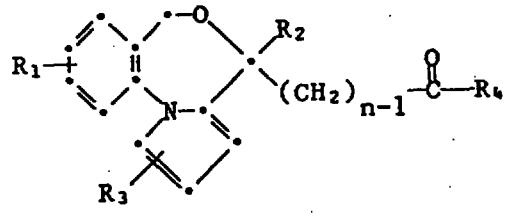
wherein n, R_1, R_2 and R_3 are as defined for formula I and X represents reactive esterified hydroxy; or with a compound of formula V



(V),

wherein n, R_1, R_2 and R_3 are as defined for formula I in claim 1, under conditions of reductive amination; or

b) reducing a compound of formula VI

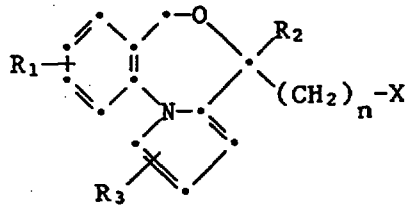


(VI),

wherein R_1, R_2, R_3, R_4 and n are as defined for formula I in claim 1; and, if desired, in all of these processes temporarily protecting an interfering reactive group, and isolating the resulting compound of formula I; and, if desired, converting a resulting compound of formula I into another compound of formula I of the invention and/or, if desired, converting a resulting compound of formula I into a salt or a resulting salt into the free compound or into another salt and/or, if desired, separating a resulting mixture of isomers or racemates into the individual isomers or racemates and/or, if desired, resolving racemates obtained into the optical antipodes.

12. The compounds obtainable in accordance with the process of claim 11.

13. Compounds of the general formula IV

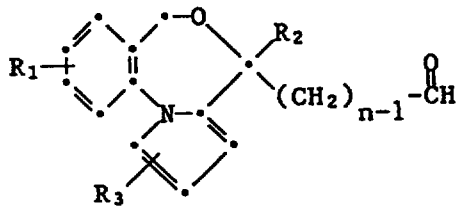


(IV)

wherein n represents the integer 1 or 2; R_1 represents hydrogen, lower alkyl, halogen, trifluoromethyl, hydroxy or lower alkoxy; R_2 represents hydrogen or lower alkyl; R_3 represents hydrogen, lower alkyl or halogen; and X represents hydroxy, the radicals designated "lower"

having a maximum of 7 carbon atoms.

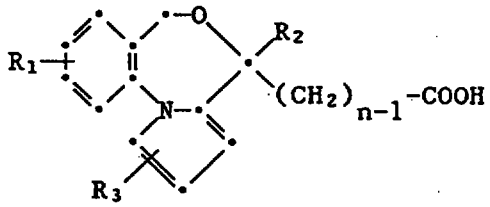
14. Compounds of the general formula V



(V)

wherein n represents the integer 1 or 2; R_1 represents hydrogen, lower alkyl, halogen, trifluoromethyl, hydroxy or lower alkoxy; R_2 represents hydrogen or lower alkyl; and R_3 represents hydrogen, lower alkyl or halogen, the radicals designated "lower" having a maximum of 7 carbon atoms.

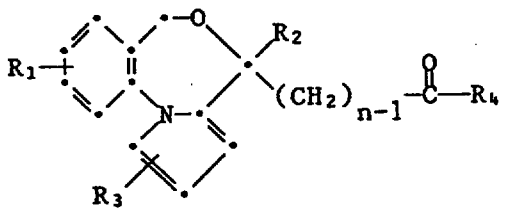
15. Compounds of the general formula IX



(IX)

wherein n represents the integer 1 or 2; R_1 represents hydrogen, lower alkyl, halogen, trifluoromethyl, hydroxy or lower alkoxy; R_2 represents hydrogen or lower alkyl; and R_3 represents hydrogen, lower alkyl or halogen, the radicals designated "lower" having a maximum of 7 carbon atoms.

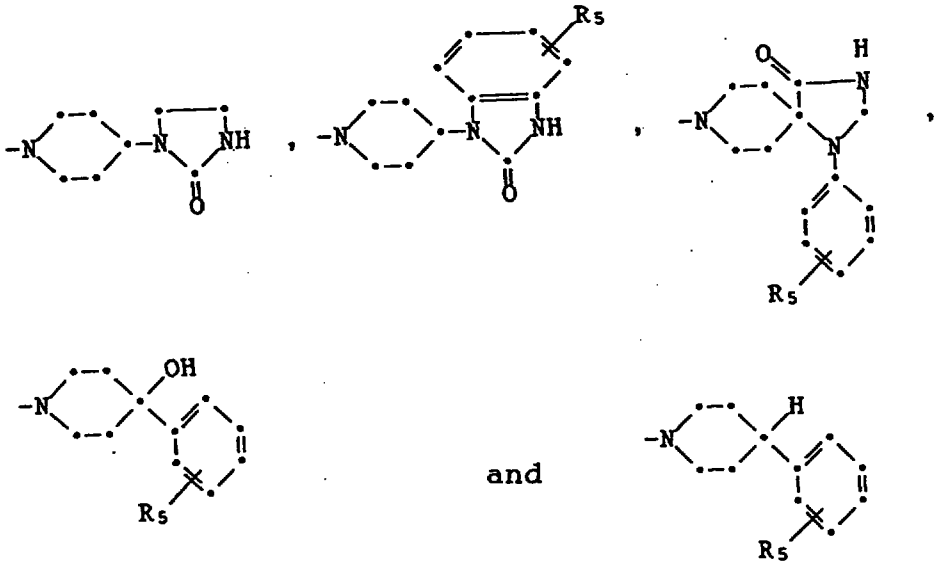
16. Compounds of the general formula VI



(VI)

wherein n represents the integer 1 or 2; R_1 represents

hydrogen, lower alkyl, halogen, trifluoromethyl, hydroxy or lower alkoxy; R_2 represents hydrogen or lower alkyl; R_3 represents hydrogen, lower alkyl or halogen; R_4 represents N-lower alkylpiperazino, N-phenylpiperazino that is unsubstituted or substituted in the phenyl moiety by halogen or by lower alkyl, or piperidino or substituted piperidino selected from

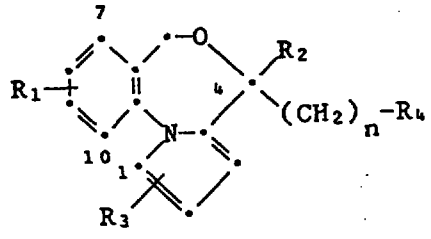


and

in which R_5 represents hydrogen, halogen or lower alkyl, the radicals designated "lower" having a maximum of 7 carbon atoms.

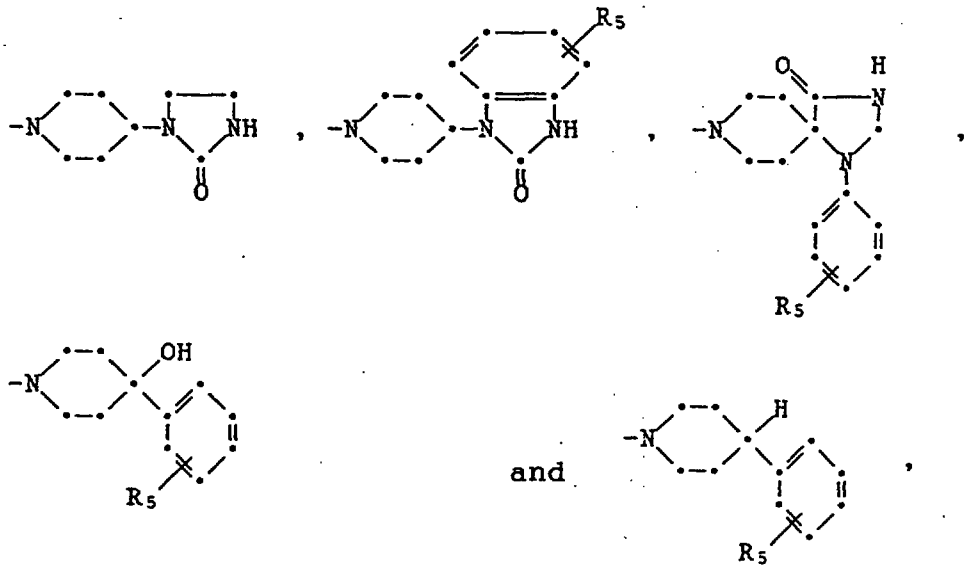
Patent Claims for the Contracting States AT, ES and GR

1. A process for the preparation of compounds of the general formula I



(I)

wherein n represents the integer 1 or 2; R_1 represents hydrogen, lower alkyl, halogen, trifluoromethyl, hydroxy or lower alkoxy; R_2 represents hydrogen or lower alkyl; R_3 represents hydrogen, lower alkyl or halogen; R_4 represents N-lower alkylpiperazino, N-phenylpiperazino that is unsubstituted or substituted in the phenyl moiety by halogen or by lower alkyl, or piperidino or substituted piperidino selected from



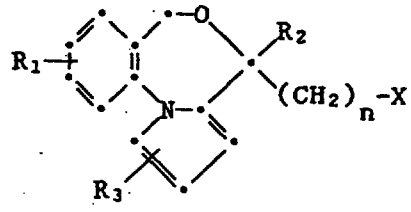
and

in which R_5 represents hydrogen, halogen or lower alkyl; and salts thereof, the radicals designated "lower" having a maximum of 7 carbon atoms, comprising:

a) condensing an amine of formula III

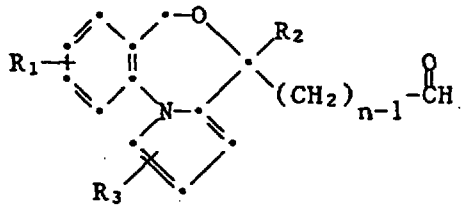
R_4-H (III),

wherein R_4 is as defined above and H is attached to the nitrogen atom of the group R_4, with a compound of formula IV



(IV),

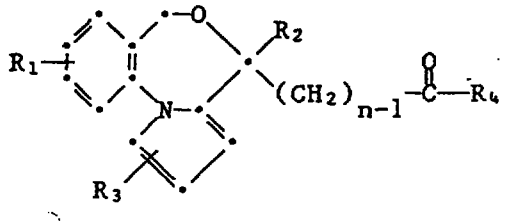
wherein n, R_1, R_2 and R_3 are as defined for formula I and X represents reactive esterified hydroxy; or with a compound of formula V



(V),

wherein n, R_1, R_2 and R_3 are as defined for formula I, under conditions of reductive amination; or

b) reducing a compound of formula VI

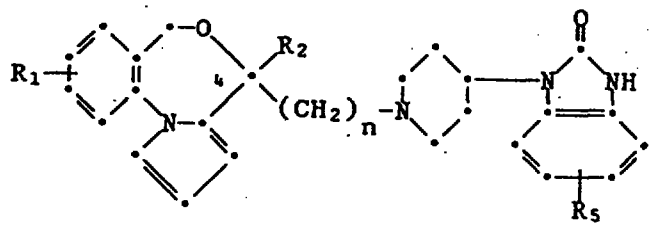


(VI),

wherein R_1, R_2, R_3, R_4 and n are as defined for formula I, and, if desired, in all of these processes temporarily protecting an interfering reactive group, and isolating the resulting compound of formula I; and, if desired, converting a resulting compound of formula I into another compound of formula I of the invention and/or, if desired, converting a resulting compound of formula I into a salt or a resulting salt into the free compound or

into another salt and/or, if desired, separating a resulting mixture of isomers or racemates into the individual isomers or racemates and/or, if desired, resolving racemates obtained into the optical antipodes.

2. A process according to claim 1 for the preparation of compounds of formula II



(II)

wherein R_1 represents hydrogen, lower alkyl, halogen, trifluoromethyl, hydroxy or lower alkoxy; R_2 represents hydrogen or lower alkyl; n represents the integer 1 or 2; and R_5 represents hydrogen, halogen or lower alkyl; and pharmaceutically acceptable salts thereof, the radicals designated "lower" having a maximum of 7 carbon atoms.

3. A process according to claim 1 for the preparation of compounds of formula II shown in claim 2, wherein n represents the integer 1 or 2; R_2 represents straight-chain lower alkyl having from 1 to 4 carbon atoms; R_1 and R_5 represent hydrogen or halogen, and pharmaceutically acceptable salts thereof.

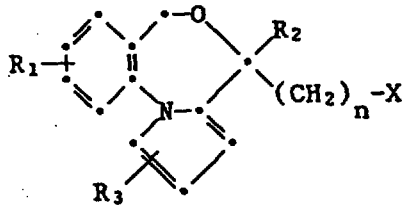
4. A process according to claim 1 for the preparation of compounds of formula II shown in claim 2, wherein R_1 and R_5 represent hydrogen; R_2 represents methyl; and n represents 1; and pharmaceutically acceptable salts thereof.

5. A process according to claim 1 for the preparation of 1,3-dihydro-1-{1-[(4-methyl-4H,6H-pyrrolo[1,2-a][4,1]-benzoxazepin-4-yl)-methyl]-4-piperidinyl}-2H-benz-

imidazol-2-one and pharmaceutically acceptable salts thereof.

6. A process for the manufacture of a pharmaceutical composition, which comprises processing an active ingredient of the invention according to any one of claims 1 to 5 with a pharmaceutical carrier.

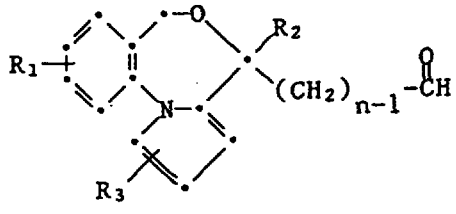
7. The use of compounds of the general formula IV



(IV)

wherein n represents the integer 1 or 2; R_1 represents hydrogen, lower alkyl, halogen, trifluoromethyl, hydroxy or lower alkoxy; R_2 represents hydrogen or lower alkyl; R_3 represents hydrogen, lower alkyl or halogen; and X represents hydroxy, the radicals designated "lower" having a maximum of 7 carbon atoms, for the preparation of compounds of the general formula I according to claim 1.

8. The use of compounds of the general formula V

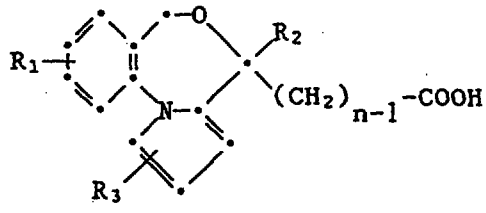


(V)

wherein n represents the integer 1 or 2; R_1 represents hydrogen, lower alkyl, halogen, trifluoromethyl, hydroxy or lower alkoxy; R_2 represents hydrogen or lower alkyl; and R_3 represents hydrogen, lower alkyl or halogen, the radicals designated "lower" having a maximum of 7 carbon

atoms, for the preparation of compounds of the general formula I according to claim 1.

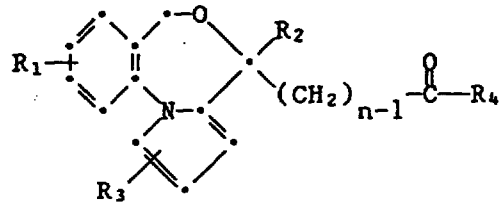
9. The use of compounds of the general formula IX



(IX)

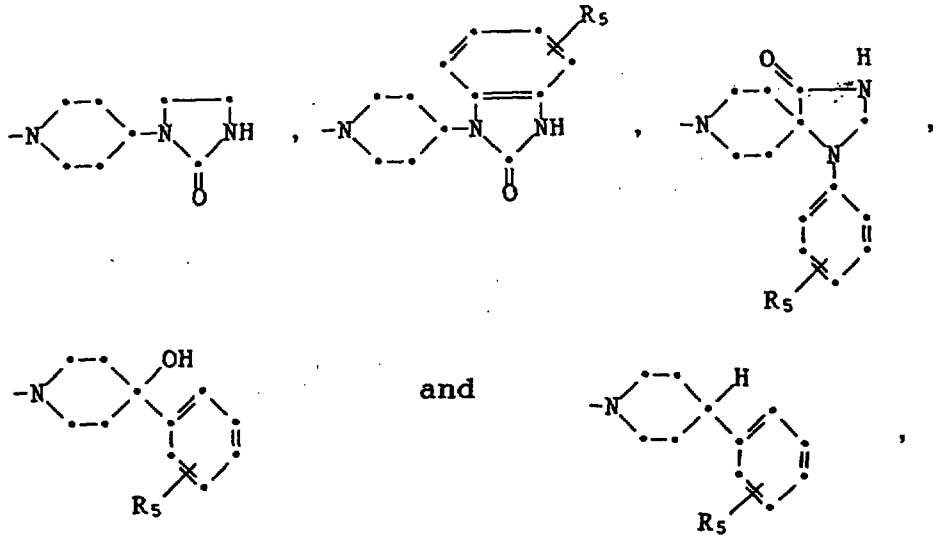
wherein n represents the integer 1 or 2; R_1 represents hydrogen, lower alkyl, halogen, trifluoromethyl, hydroxy or lower alkoxy; R_2 represents hydrogen or lower alkyl; and R_3 represents hydrogen, lower alkyl or halogen, the radicals designated "lower" having a maximum of 7 carbon atoms, for the preparation of compounds of the general formula I according to claim 1.

10. The use of compounds of the general formula VI



(VI)

wherein n represents the integer 1 or ; R_1 represents hydrogen, lower alkyl, halogen, trifluoromethyl, hydroxy or lower alkoxy; R_2 represents hydrogen or lower alkyl; R_3 represents hydrogen, lower alkyl or halogen; R_4 represents N-lower alkylpiperazino, N-phenylpiperazino that is unsubstituted or substituted in the phenyl moiety by halogen or by lower alkyl, or piperidino or substituted piperidino selected from



and

in which R_5 represents hydrogen, halogen or lower alkyl, the radicals designated "lower" having a maximum of 7 carbon atoms, for the preparation of compounds of formula I according to claim 1.