Description

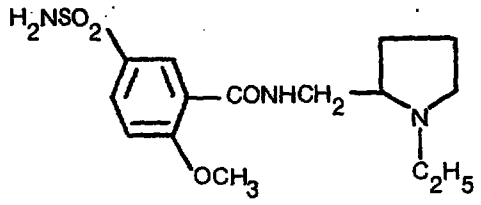
Field of the Invention

The present invention relates to novel, pharmacologically active derivatives of benzamide, intermediates and processes for their preparation, pharmaceutical compositions containing the benzamido-derivatives and to methods of their pharmacological use.

The object of the invention is to provide a benzamido-derivative useful in the treatment of emesis, psychosomatic diseases and psychiatric disorders.

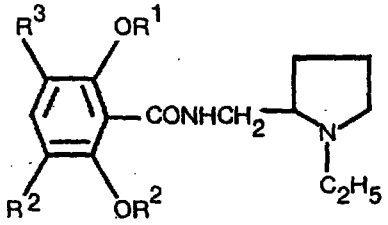
Prior Art

Sulpiride, (US patent 3,342,826) with the formula

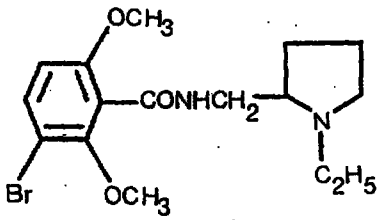


is a recently marketed antipsychotic agent. Sulpiride produces weak extrapyramidal side effects in humans and weak catalepsy in experimental animals.

In EP—A—4831 antipsychotic compounds of the formula



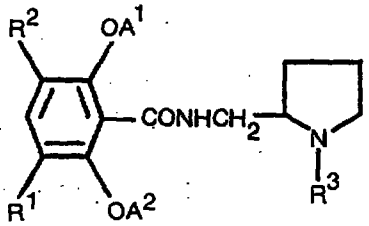
wherein R^1 is an alkyl group with 1—3 carbon atoms, R^2 and R^3 are the same or different and each is hydrogen, chlorine or bromine, are described. Among these compounds the compound of the formula



and with the designation FLA 731, is disclosed. The compounds of the EP—A—4831 have a less potent antipsychotic effect than the compounds of the present invention.

Disclosure of the Invention

The present invention relates to compounds of the formula



I

wherein R^1 and R^2 are the same or different and each represents a hydrogen atom, a halogen atom, a cyano group, a lower alkyl group or an acyl group, R^3 is a lower alkyl group; an alkenyl group; or a benzyl group optionally substituted with fluorine, chlorine, bromine, trifluoromethyl, lower alkyl or lower alkoxy, A^1 and A^2 are the same or different and each represents a hydrogen atom, a lower alkyl group, an acyl group, an alkoxycarbonyl group or a dialkylcarbamyl group, provided that when A^1 and A^2 are the same lower alkyl

group and R^3 is ethyl, R^1 or R^2 or both are selected among cyano, lower alkyl and acyl; or a physiologically acceptable salt or optical isomers thereof.

It has been found that such compounds have valuable therapeutical properties.

The invention thus provides compounds, and physiologically acceptable salts thereof, which compounds are useful in therapeutic treatment of emesis, of psychosomatic diseases such as gastric and duodenal ulcer, and of psychiatric disorders such as depression, anxiety and especially psychoses e.g. schizofrenia.

Halogen atoms in formula I comprises chlorine, bromine, iodine and fluorine atoms.

Lower alkyl groups in formula I are straight or branched alkyl groups with 1 to 5 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, s-butyl, isobutyl, t-butyl, pentyl, 2-methylbutyl and 2,2-dimethylpropyl.

Acyl groups in formula I are groups alkyl-CO— wherein the alkyl moiety is defined as lower alkyl above.

Alkenyl groups in formula I are straight or branched hydrocarbon chains with 2—5 carbon atoms and one, two or more double bonds, e.g. vinyl, allyl, isopropenyl, but-2-enyl, buta-1,3-dienyl and pent-2-enyl.

Lower alkoxy groups in formula I are groups alkyl-O— wherein the alkyl moiety is defined as lower alkyl above.

Alkoxycarbonyl groups in formula I are groups alkyl-O—CO— wherein the alkyl moiety is defined as lower alkyl above.

Dialkylcarbamyl groups in formula I are groups $(alkyl)_2$—N—CO— wherein the alkyl moiety is defined as lower alkyl above.

A first preferred sub-group of compounds of the invention is obtained when in formula I R^1 and R^2 are the same or different and each represents a hydrogen atom, a halogen atom, a cyano group, a lower alkyl group or an acyl group, R^3 is a lower alkyl group; an alkenyl group or an optionally substituted benzyl group and one of A^1 and A^2 is a lower alkyl group and the other is a hydrogen atom.

Within this first sub-group compounds of the formula I wherein R^1 is bromine or chlorine and R^2 is hydrogen or bromine, R^3 is ethyl and one of A^1 and A^2 is methyl or ethyl and the other is hydrogen, are preferred.

A second preferred sub-group of compounds of the invention is obtained when in formula I R^1 and R^2 are the same or different and each represents a hydrogen atom, a halogen atom, a cyano group, a lower alkyl group or an acyl group, R^3 is a lower alkyl group; an alkenyl group or an optionally substituted benzyl group and one of A^1 and A^2 is a lower alkyl group and the other is an acyl group, an alkoxy-carbonyl group or a dialkylcarbamyl group.

Within this second sub-group compounds of the formula I wherein R^1 is bromine, R^2 is hydrogen, R^3 is ethyl, A^1 is methyl and A^2 is acetyl, ethyloxycarbonyl or dimethylcarbamyl, are preferred.

A third preferred sub-group of compounds of the invention is obtained when in formula I R^1 and R^2 are the same or different and each represents a hydrogen atom, a halogen atom, a cyano group, a lower alkyl group or an acyl group, A^1 and A^2 are the same or different and each represents a hydrogen atom, a lower alkyl group, an acyl group, an alkoxycarbonyl group or a dialkylcarbamyl group and R^3 is a lower alkyl group other than ethyl or an alkenyl group or an optionally substituted benzyl group.

Within this third sub-group compounds of the formula I wherein R^1 is chlorine or bromine, R^2 is hydrogen, A^1 is methyl, A^2 is methyl and R^3 is methyl, n-propyl, allyl or benzyl, are preferred.

The new compounds of this invention may be used therapeutically as the racemic mixtures of (+)- and (−)-forms, which are obtained by synthesis. They may also be resolved into the corresponding enantiomers which, likewise, may be used in therapy. The (+)- and (−)-forms may also be obtained by the reaction of the corresponding enantiomeric 2-(aminomethyl)-1-alkyl/alkenylpyrrolidine with the benzoic acid moiety.

The compounds of this invention may be administered in the form of free bases or their salts with non-toxic acids. Some typical examples of these salts are the hydrobromide, hydrochloride, phosphate, sulphate, sulphonate, citrate, lactate, maleate, and tartrate.

Pharmaceutical preparations

In clinical practice the compounds of the present invention will normally be administered orally, rectally or by injection in the form of pharmaceutical preparations comprising the active ingredient either as a free base or as a pharmaceutically acceptable non-toxic, acid addition salt, e.g. the hydrochloride, hydrobromide, lactate, acetate, sulphate, sulphamate and the like in association with a pharmaceutically acceptable carrier. Accordingly, terms relating to the novel compounds of this invention whether generically or specifically are intended to include both the free amine base and the acid addition salts of the free base, unless the context in which such terms are used, e.g. in the specific examples would be inconsistent with the broad concept.

The carrier may be a solid, semisolid or liquid diluent or capsule. These pharmaceutical preparations constitute a further aspect of this invention. Usually the active substance will constitute between 0.1 and 99% by weight of the preparation, more specifically between 0.5 and 20% by weight for preparation intended for injection and between 2 and 50% by weight for preparations suitable for oral administration.

To produce pharmaceutical preparations containing a compound of the invention in the form of dosage units for oral application, the selected compound may be mixed with a solid pulverulent carrier, e.g.

lactose, saccharose, sorbitol, mannitol, starches such as potato starch, corn starch or amylopectin, cellulose derivatives, or gelatine, and a lubricant such as magnesium stearate, calcium stearate, polyethylene glycol waxes, and the like, and then compressed to form tablets. If coated tablets are required, the cores, prepared as described above, may be coated with a concentrated sugar solution which may contain, e.g. gum arabic, gelatine, talcum, titanium dioxide, and the like. Alternatively, the tablet can be coated with a lacquer dissolved in a readily volatile organic solvent or mixture of organic solvents. Dyestuffs may be added to these coatings in order to readily distinguish between tablets containing different active substances or different amounts of the active compound.

For the preparation of soft gelatine capsules (pearl-shaped close capsules) consisting of gelatine and for example, glycerol or similar closed capsules, the active substance may be admixed with a vegetable oil. Hard gelatine capsules may contain granulates of the active substance in combination with solid, pulverulent carriers such as lactose, saccharose, sorbitol, mannitol, starches (e.g. potato starch, corn starch or amylopectin), cellulose derivatives or gelatine.

Dosage units for rectal application can be prepared in the form of suppositories comprising the active substance in admixture with a neutral fatty base, or gelatine rectal capsules comprising the active substance in admixture with vegetable oil or paraffin oil.

Liquid preparations for oral application may be in the form of syrups or suspensions for example, solutions containing from about 0.2% to 20% by weight of the active substance herein described, the balance being sugar and a mixture of ethanol, water, glycerol, and propyleneglycol. Optionally such liquid preparations may contain colouring agents, flavouring agents, saccharine and carboxymethylcellulose as a thickening agent.

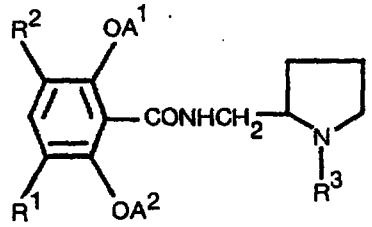
Solutions for parenteral applications by injection can be prepared in an aqueous solution of a water-soluble pharmaceutically acceptable salt of the active substance preferably in a concentration of from about 0.5% to about 10% by weight. These solutions may also contain stabilizing agents and/or buffering agents and may conveniently be provided in various dosage unit ampoules.

Suitable peroral daily doses of the compounds of the invention are 100—500 mg, preferably 200—300 mg.

Methods of preparation

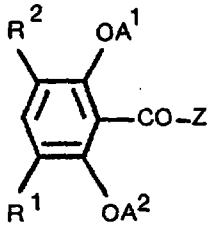
The compounds of the invention may be obtained by one of the following methods.

A. The compounds of the formula



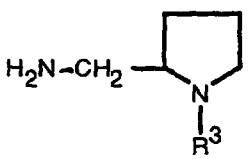
I

wherein R^1 and R^2 are the same or different and each represents a hydrogen atom, a halogen atom, a cyano group, a lower alkyl group or an acyl group, R^3 is a lower alkyl group; an alkenyl group; or a benzyl group optionally substituted with fluorine, chlorine, bromine, trifluoromethyl, lower alkyl or lower alkoxy, A^1 and A^2 are the same or different and each represents a hydrogen atom, a lower alkyl group, an acyl group, an alkoxycarbonyl group or a dialkylcarbamyl group, provided that when A^1 and A^2 are the same lower alkyl group and R^3 is ethyl, R^1 or R^2 or both are selected among cyano, lower alkyl and acyl can be obtained by reaction of a compound of the formula



II

wherein R^1, R^2, A^1 and A^2 have the definition given above and —CO—Z is a reactive group capable of reacting with an amino group under formation of an amide moiety with a compound of the formula



III

wherein R^3 has the definition given above, or a reactive derivative thereof.

The reaction is carried out in a suitable solvent, such as diethyl ether, acetone, methylethyl ketone, chloroform or toluene between 0°C and the boiling point of the reaction mixture. The resulting amine hydrochloride salt is readily recovered e.g. by filtration. Alternatively, the obtained salt is dissolved in water and converted to the free base using conventional techniques, such as the addition of sodium hydroxide solution.

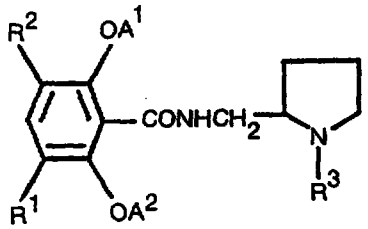
Z in the acylating group —CO—Z may be a halogen group, such as chlorine or bromine, a hydroxy group or an organic residue.

The organic residue comprises groups which can form reactive acid derivatives. These can be carboxylic acid esters, e.g. methyl, ethyl, propyl, butyric, isobutyric and pentyl esters or comparable reactive esters, e.g. cyanomethyl or methoxymethyl ester, N-hydroxyimido ester or substituted or unsubstituted aromatic esters; acid hydrazides; acid azides; symmetrical anhydrides; mixed anhydrides for instance formed with lower alkylhalogenformates; azolides, e.g. triazolide, tetrazolide or imidazolide; or acid isocyanates.

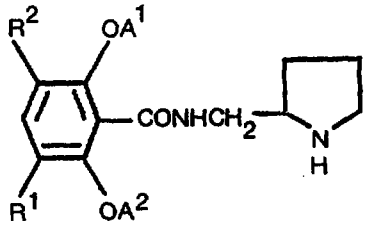
According to the invention the following compounds can be used as reactive derivatives of the amine III: Reaction products of the amine with phosphorus chloride, phosphorus oxychloride, dialkyl, diaryl or o-phenylenechlorophosphites or alkyl or aryldichlorophosphites, or an isothiocyanate of the amine. The mentioned reactive derivatives can be reacted with the acid in situ or after previous isolation.

It is also possible to react the free acid and the free amine in the presence of a condensating agent, e.g. silicon tetrachloride, diphosphoruspentoxide or carbodiimides such as dicyclohexylcarbodiimide, N,N'-carbonyldiimidazole, N,N'-thionyldiimidazole, and diethyldiazodicarboxylate.

B. The compounds of the formula



wherein R^1, R^2, R^3, A^1 and A^2 have the definition given above can be obtained by N-alkylation of a compound of the formula



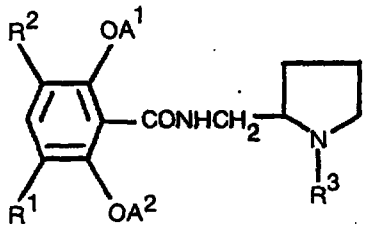
wherein R^1, R^2, A^1 and A^2 have the definition given above, with a compound of the formula

$$R^3—X$$

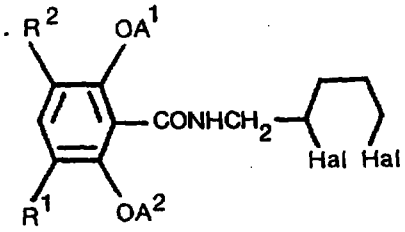
wherein R^3 has the definition given above and X is chlorine, bromine, sulphate, phosphate, benzenesulphonate or toluenesulphonate.

The reaction can be effected by treating the reactants at 50—100°C in a suitable solvent, e.g. acetone, alcohols, dimethylformamide (DMF), dimethylsulphoxide (DMSO) in the presence of a base, for example NaOH or K_2CO_3.

C. The compounds of the formula



wherein R^1, R^2, R^3, A^1 and A^2 have the definition given above can be obtained by reaction of a compound of the formula



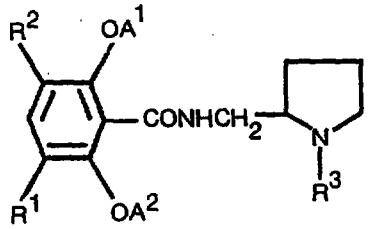
wherein R^1, R^2, A^1 and A^2 have the definition given above and Hal is Cl or Br with a compound of the formula

$$R^3—NH_2$$

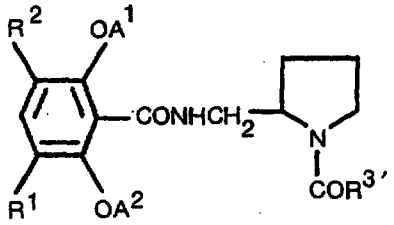
wherein R^3 has the definition given above.

The reaction is performed with the amine in excess, either without solvent or with a suitable solvent, such as lower alcohols, halogenated aliphatic hydrocarbons, DMF, DMSO at temperatures from 0°C to 100°C.

D. The compounds of the formula



wherein R^1, R^2, R^3, A^1 and A^2 have the definition given above can be obtained by reduction of a compound of the formula

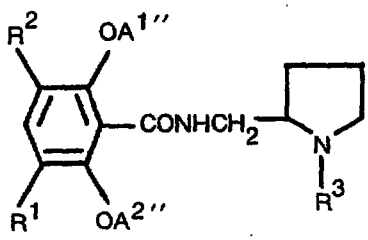


wherein R^1, R^2, A^1 and A^2 have the definition given above and $R^{3'}$ means the same as R^3 but for the content of carbon atoms, which is one less.

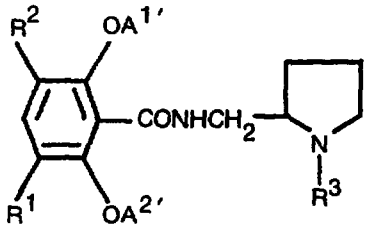
Suitable reducing agents working on the less sterically hindered amide group are a) $LiAlH_4$ and alkoxy complexes thereof; b) $NaBH_4$ with addition of transition metal salts, or $AlCl_3$ or BF_3 or $POCl_3$ or carboxylic acids such as CH_3COOH and CF_3COOH; c) B_2H_6.

The reaction is effected in alkyl ethers, such as diethylether, dimethoxyethane, diglyme, THF, dioxane, at temperatures from 0°C to reflux temperatures of the reaction mixtures.

E. The compounds of the formula



wherein R^1, R^2 and R^3 have the definition given above and $A^{1''}$ and/or $A^{2''}$ is a hydrogen atom and the other, when necessary, a lower alkyl group, can be obtained by dealkylation with a protonic acid or a Lewis acid of a compound of the formula



IV

wherein R^1, R^2 and R^3 have the definition given above and $A^{1'}$ and $A^{2'}$ are lower alkyl groups.

Suitable protonic acids are e.g. HBr and HI.

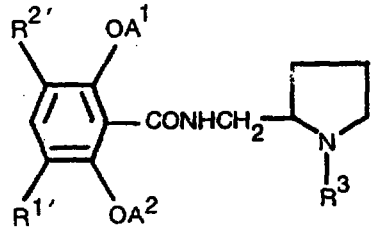
Suitable Lewis acids are e.g. BBr_3, BCl_3, BF_3, $AlCl_3$ and $AlBr_3$.

Via selective dealkylation one of $A^{1'}$ and $A^{2'}$ ($A^{1'}$ and $A^{2'}$ are alkyl) in formula IV can be transferred to a hydrogen atom. By the selective dealkylation an equivalent amount of dealkylating agent is used.

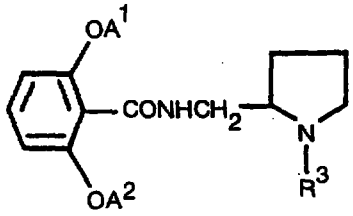
Otherwise both $A^{1'}$ and $A^{2'}$ ($A^{1'}$ and $A^{2'}$ are alkyl) in formula IV can be transferred in the same reaction step to hydrogen atoms. By this procedure an excess of dealkylating agent is used.

The reaction is performed between 0—20°C in a halogenated lower aliphatic hydrocarbon, for example methylene chloride or chloroform. In the case of hydrogen halides acetic acid is preferred as solvent and the reaction is performed at elevated temperatures.

F. The compounds of the formula



wherein R^3, A^1 and A^2 have the definition given above and $R^{1'}$ and/or $R^{2'}$ is a halogen atom, a lower alkyl group, an acyl group or a cyano group, and the other, when necessary, a hydrogen atom, can be obtained by halogenation with halogen or a halogen-dioxane complex, or reaction with an alkylhalide with Lewis acid catalysis or reaction with an acylhalide with Lewis acid catalysis or reaction with a cyanogen halide with Lewis acid catalysis, respectively, of a compound of the formula



wherein R^3, A^1 and A^2 have the definition given above.

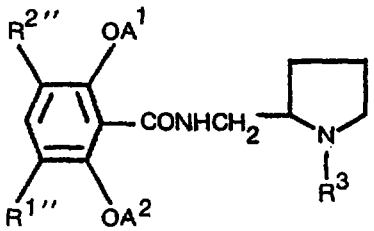
The introduction of a cyano group is accomplished by the action of trichloroacetonitrile or cyanogen halide in the presence of a Lewis acid.

Chlorination is effected by heating the starting compound with chlorine with or without Lewis acid catalysis or with HOCl, N-chloroamides in the presence of acid catalyst in suitable solvent e.g. chloroform, nitrobenzene.

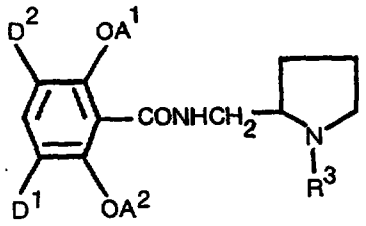
Bromination is carried out with Br_2 with or without Lewis acid catalysis or bromination in acetic acid in the presence of a base e.g. sodium acetate or by using bromine-dioxane complex. Other reagents can be used among them HOBr and N-bromoamides especially N-bromosuccinimide with acid catalysis.

Acylations, alkylations and introduction of a cyano group are performed by using well-known Friedel-Crafts procedures.

G. The compounds of the formula



wherein R^3, A^1 and A^2 have the definition given above and $R^{1''}$ and/or $R^{2''}$ is halogen or cyano and the other, when necessary, a hydrogen atom, can be obtained by the reaction in a first step with $NaNO_2$ and in a second step with cuprous halogenide or cuprous cyanide of a compound of the formula

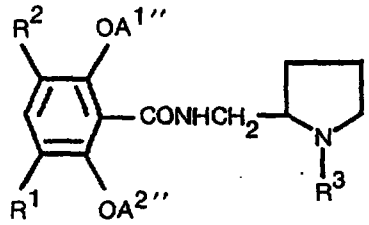


wherein R^3, A^1 and A^2 have the definition given above and D^1 and D^2 are the same or different and each represents a hydrogen atom or an amino group and at least one of D^1 and D^2 is an amino group.

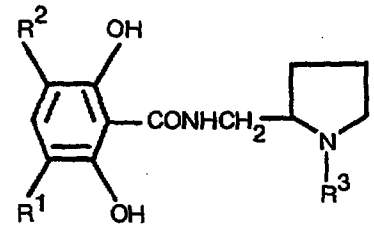
Diazotation is performed in water at 0°C with $NaNO_2$ in the presence of mineral acid. Compounds where $R^{1''}$ and $R^{2''}$ are Cl, Br or CN are performed by using a Sandmeyer reaction with CuBr, CuCl or CuCN. Compounds where $R^{1''}$ and/or $R^{2''}$ is fluorine are prepared by heating the corresponding diazoniumtetrafluoborate salt in a dry state (Schiemann reaction).

The introduction of a cyano group is accomplished as described in Method F.

H. The compounds of the formula



wherein R^1, R^2, R^3, $A^{1''}$ and $A^{2''}$ have the definition given above, can be obtained by reaction of a compound of the formula



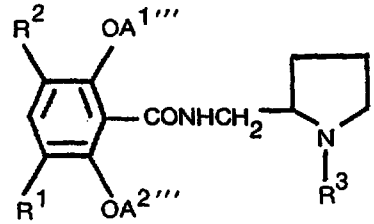
wherein R^1, R^2 and R^3 have the definition given above, with a compound of the formula

$$A^{1'}—B$$

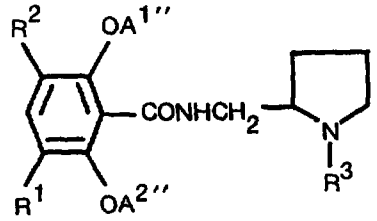
wherein $A^{1'}$ is a lower alkyl group and B is $—(SO_4)_{1/2}$, $—(PO_4)_{1/2}$ or halogen.

The reaction is effected selectively in a suitable solvent, e.g. acetone, DMF at elevated temperatures with one equivalent of alkylating agent in the presence of base, e.g. alkali metal carbonates or hydroxides.

I. The compounds of the formula



wherein R^1, R^2 and R^3 have the definition given above and $A^{1'''}$ and/or $A^{2'''}$ is an acyl group, an alkoxycarbonyl group or a dialkylcarbamyl group and the other, when necessary, a lower alkyl group, can be obtained by reaction of a compound of the formula



wherein R^1, R^2, R^3, $A^{1''}$ and $A^{2''}$ have the definition given above, with a compound of the formula

$$R—CO—Z'$$

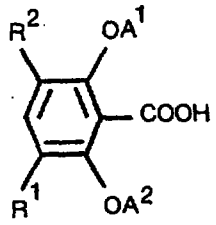
wherein R is an alkyl, alkoxy or dialkylamino group and Z' is Cl or Br.

The compounds wherein $A^{1''}$ and/or $A^{2''}$ are acyl are prepared by the reaction with the appropriate acid anhydride without solvent or in a suitable solvent such as benzene or chloroform with acid catalysis or by using a tertiary amine as solvent and/or catalyst.

The alkoxycarbonyl group and alkylcarbamyl group are introduced by the reaction of the corresponding halides in a suitable solvent in the presence of a tertiary amine.

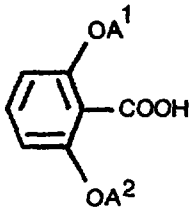
Intermediates

The compounds of the formula



wherein R^1 and R^2 are the same or different and each represents a hydrogen atom, a halogen atom, a cyano group, a lower alkyl group or an acyl group and A^1 and A^2 are the same or different and each represents a hydrogen atom, a lower alkyl group, an acyl group, an alkoxycarbonyl group or a dialkylcarbamyl group, provided that when both A^1 and A^2 are a lower alkyl group, R^1 and R^2 are selected among cyano, lower alkyl and acyl and also provided that when R^1/R^2 is H, Cl or Br and A^1/A^2 is H or CH_3 the substituent of R^1 is different from the substituent of R^2 *and* the substituent of A^1 is different from the substituent of A^2, are valuable intermediates for the preparation of the compounds of this invention by the process A.

The intermediate benzoic acids can be prepared by reacting a compound of the formula



as follows:

a) when R^1 and/or R^2 is Cl or Br: by chlorination or bromination for example as described under Method F above;

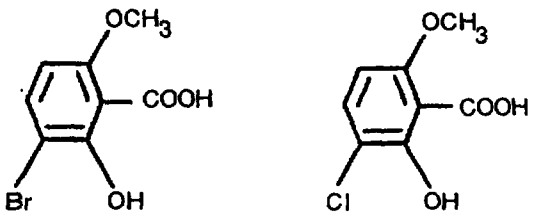
b) when R^1 and/or R^2 is F: by fluorination for example as described under Method G above;

c) when R^1 and/or R^2 is lower alkyl or acyl: by reacting with an alkylhalide or an acylhalide for example as described under Method F above;

d) when R^1 and/or R^2 is cyano: by reacting with a cyanogen halide or trichloroacetonitrile with Lewis acid catalysis as described under Method F above.

Any of free acids can be converted to a compound of the formula II by esterification with for instance an acylhalogenide, an acylanhydride, a halogen formic acid ester or a dialkylcarbamyl halide.

Particularly preferred intermediates are those with the formulas



Working examples

Example 1

N-Ethyl-2-(3-bromo-2,6-dihydroxybenzamidomethyl)-pyrrolidine

To 5.0 g (0.0118 mole) of N-ethyl-2-(3-bromo-2,6-dimethoxybenzamidomethyl)pyrrolidine in 125 ml of methylene chloride is added dropwise 7 ml (0.07 mole) of boron tribromide. The reaction mixture is left at room temperature for 9 days. It is then washed with 2M NH_3 and water, dried over Na_2SO_4 whereafter the solvent is evaporated. The residue is recrystallized from ethanol. Yield 0.3 g. M.p. 166—8°C.

Example 2

N-Ethyl-2-(3-bromo-2-hydroxy-6-methoxybenzamidomethyl)pyrrolidine

To 5.0 g (0.0118 mole) of N-ethyl-2-(3-bromo-2,6-dimethoxybenzamidomethyl)pyrrolidine hydrochloride in 125 ml of methylene chloride is added 1.3 ml (0.0135 mole) of boron tribromide. A white precipitate is obtained. The reaction mixture is left for 2 hours at room temperature while stirring. It is then washed with 2M NH_3 and with water and the organic phase is dried over Na_2SO_4. Evaporation resulted in 4.1 g of product, which was recrystallized from ethanol. Yield 2.0 g (48%). M.p. 68.8—69.4°C.

Example 3

(−)-N-Ethyl-2-(3-bromo-2-hydroxy-6-methoxybenzamidomethyl)pyrrolidine hydrochloride

10.0 g (0.025 ml) of (−)-N-ethyl-2-(3-bromo-2,6-dimethoxybenzamidomethyl)pyrrolidine is dissolved in 250 ml of methylene chloride. 2.6 ml (0.027 mol) of boron tribromide is added. The mixture is left over night at room temperature. It is then washed with 2N NH_3, dried over Na_2SO_4 and evaporated after addition of HCl-ether. The residue is dissolved in water and extracted with ether. The water phase is made alkaline with NH_3 and is extracted with chloroform. The chloroform phase is dried over Na_2SO_4 and evaporated. To the residue is added HCl-ether. The salt is filtered off, washed with ether and dried over P_2O_5. M.p.: sinterring at 100°C. Yield 6.6 g. Hygroscopic $[\alpha]_D^{20} = -45.5°$ (base).

Example 4

(−)-N-Ethyl-2-(3-chloro-2-hydroxy-6-methoxybenzamidomethyl)pyrrolidine hydrochloride

9.1 g (0.025 mole) of (−)-N-ethyl-2-(3-chloro-2,6-dimethoxybenzamidomethyl)pyrrolidine is dissolved in 250 ml of methylene chloride. 2.6 ml (0.027 mole) of boron tribromide is added. The mixture is left overnight at room temperature. It is then washed with 2 × 100 ml of 2N NH_3 and 100 ml of water, dried over Na_2SO_4 and evaporated. The residue is dissolved in diluted HCl and extracted with ether. The water phase is made alkaline with NH_3 and is extracted with chloroform. The extract is dried over Na_2SO_4 and evaporated. The residue is dissolved in ether and HCl-ether is added. The precipitate is filtered off and dried over P_2O_5. M.p. sinterring at 100°C. Yield 7.4 g $[\alpha]_D^{20} = -51.4°$ (2% ethanol; pH 10.3).

Example 5

N-Ethyl-2-(3-bromo-6-ethoxy-2-hydroxybenzamidomethyl)pyrrolidine

5.0 g (0.0115 mole) of N-ethyl-2-(3-bromo-2,6-diethoxybenzamidomethyl)pyrrolidine hydrochloride is dissolved in 125 ml of methylene chloride. 1.25 ml (0.013 mole) of boron tribromide is added. The mixture is left for two hours at room temperature. It is then washed with 2M NH_3 and with water. The organic phase is dried over Na_2SO_4 and evaporated. The oily base obtained crystallizes after treatment with petroleum ether. The precipitate is filtered off and is recrystallized from ethanol. M.p. 83—83.5°C. Yield 2.4 g (56%).

Example 6

(−)-N-Ethyl-2-(3-bromo-6-ethoxy-2-hydroxybenzamidomethyl)pyrrolidine

10.0 g (0.023 mole) of (−)-N-ethyl-2-(3-bromo-2,6-diethoxybenzamidomethyl)pyrrolidine is dissolved in 250 ml of methylene chloride. 2.4 ml (0.025 mole) of boron tribromide is added. The mixture is left over night at room temperature and is then washed with 2N NH_3. The extract is dried with Na_2SO_4 and evaporated. The oily residue crystallizes after a while. Petroleum ether is added to the product, which is then filtered off. Yield 7.0 g. M.p. 74—76°C. $[\alpha]_D^{20} = -66.7°$ (1% acetone).

Example 7

(−)-N-Ethyl-2-(3,5-dibromo-2-hydroxy-6-methoxybenzamidomethyl)pyrrolidine hydrochloride

44.0 g (10.1 mole) of (−)-2-(aminomethyl)-1-ethylpyrrolidine (−)ditartrate is dissolved in 200 ml of 20% NaOH. The mixture is then extracted with 2 × 100 ml of chloroform. The extract is dried with chloroform.

To. 34.0 g (0.1 mole) of 3,5-dibromo-2,6-dimethoxybenzoic acid 40 ml thionyl chloride and 300 ml of toluene are added. The mixture is heated while stirring on a steam bath for 30 minutes. Toluene and excess thionyl chloride are evaporated. To the residue is added the chloroform extract mentioned above. The mixture is heated for 10 minutes on a steam bath. The chloroform is then evaporated. The residue is dissolved in diluted HCl and the mixture is extracted with ether. The water phase is cooled and made alkaline with NaOH. The obtained precipitate is filtered off, dissolved in 500 ml of methanol, acidified with HCl-ether and evaporated. Yield 32.0 g (0.065 mole) of (−)-N-ethyl-2-(3,5-dibromo-2,6-dimethoxybenzamidomethyl)pyrrolidine hydrochloride. The product (0.065 mole) is dissolved in 500 ml of $CHCl_3$ and 6.3 ml (0.065 mole) of boron tribromide is added. The mixture is left over night at room temperature and is then washed with 2N NH_3 and water. The organic phase is dried with Na_2SO_4 and evaporated. The residue is dissolved in 400 ml of petroleum ether and the undissolved residue is filtered off. The ether is evaporated and the residue is dissolved in ether and acidified with HCl-ether. The precipitate is filtered off and dried over P_2O_5. Yield 27.3 g. M.p. sinterring after a while. $[\alpha]_D^{20} = -8.6°$ (2% H_2O).

Example 8

N-Ethyl-2-(2-acetoxy-3-bromo-6-methoxybenzamidomethyl)pyrrolidine

To a suspension of 2,6-dimethoxybenzoic acid (80 g, 0.44 mole) in 1.5 l of dry chloroform was added dropwise with stirring a solution of 70.4 g bromine in 100 ml of dry chloroform during 3 h at 0°C. The solution is allowed to reach room temperature slowly during 20 h. The solvent was evaporated *in vacuo* and the residual crystalline mass was recrystallized from methanol giving 3-bromo-2-hydroxy-6-methoxybenzoic acid. Yield 82 g (76%). M.p. 143—4°C.

3-Bromo-2-hydroxy-6-methoxybenzoic acid (24.6 g 0.1 mole) was dissolved in 50 ml of acetic anhydride. A few drops of conc. sulfuric acid was added and the mixture was heated at 60°C during 20 h. After cooling about 100 mg of sodium bicarbonate was added and then ice water. The solvents were evaporated under reduced pressure. The residue was crystallized from diisopropylether to give 34.5 g (85%) of the desired acetoxy acid. M.p. 146—7°C.

The preceeding acetoxy acid (5.8 g, 20 mmol) was dissolved in 30 ml of thionyl chloride. The solution was stirred at ambient temperature for 20 h. The solvent was evaporated and from the residue dry toluene was distilled twice. The resulting acid chloride (6 g) was used in the next step without further purification.

The crude acid chloride was dissolved in 50 ml of dry toluene and to this solution was added 1-ethyl-2-(aminomethyl)-pyrrolidine (2,6 g, 20 mmol) in 10 ml of dry toluene at room temperature. Stirring was continued over night. The precipitate was filtered off and washed with dry toluene and dried. The crude amine hydrochloride was recrystallized from acetone to give the desired amine salt as white crystals. Yield 7.2 g (83%). M.p. 156°C (dec.).

Example 9

N-Ethyl-2-(3-bromo-6-hydroxy-2-methoxybenzamidomethyl)pyrrolidine

To a solution of N-ethyl-2-(2,6-dimethoxybenzamidomethyl)pyrrolidine hydrochloride (23.0 g, 0.07 mole) in 300 ml of dry dichloromethane was added dropwise with stirring a solution of boron tribromide (17.5 g, 0.07 mole) in 25 ml of dry dichloromethane at 0°C. After the addition was completed the solution was allowed to reach room temperature over night. Water was added and pH adjusted to 7. The organic layer was washed with water and dried ($MgSO_4$). The solvent was evaporated *in vacuo* affording the title compound as a viscous oil (20 g) which was judged by TLC and GC analysis to be sufficiently pure for use in the next step without further purification.

A solution of bromine (4.3 g, 27 mmol) in 10 ml of glacial acetic acid was added dropwise with stirring to a solution of the preceding crude amide (7.5 g, 27 mmol) in 100 ml of glacial acetic acid at room temperature. Stirring was continued for 15 h. The solvent was evaporated *in vacuo* to give a viscous oil (8.5 g). The product was analyzed by GC (3% OV-17) and consisted of 10% of the title 2-methoxy-3-bromo-6-hydroxy substituted isomer and 90% of the 2-hydroxy-3-bromo-6-methoxy substituted isomer. The desired phenol-isomer was isolated using preparative HPLC (SiO_2, $CHCl_2$ + EtOH + conc. NH_3, 97 + 3 + 0.1). The solvent was evaporated *in vacuo* and the residual oil crystallized on standing. Yield 0.75 g. Recrystallization from n-hexane gave the pure title compound 0.6 g (6.5%). M.p. 62—3°C.

Example 10

(−)-N-n-propyl-2-(3-bromo-2,6-dimethoxybenzamidomethyl)pyrrolidine

The title compound was prepared from 3-bromo-2,6-dimethoxybenzoic acid *via* the acylchloride and (−)-1-*n*-propyl-2-(aminomethyl)pyrrolidine in the same manner as described in Example 8. Yield 79%. M.p. 103—104°C. $[\alpha]_D^{20} = -85.4°$ (c = 0.5; $CHCl_3$).

Example 11

(−)-N-Ethyl-2-(3,5-dichloro-6-hydroxy-2-methoxybenzamidomethyl) pyrrolidine

The title compound was prepared from (−)-N-ethyl-2-(3,5-dichloro-2,6-dimethoxybenzamidomethyl)

pyrrolidine by dealkylation in the same manner as described in Example 2. Yield 37%. M.p. 48—49°C (i-octane). $[\alpha]_D^{25} = -64°C$ (c = 1.26; $CHCl_3$).

Example 12

(−)-N-n-propyl-2-(3-bromo-2-hydroxy-6-methoxybenzamidomethyl) pyrrolidine hydrochloride

The title compound was prepared from (−)-N-n-propyl-2-(3-bromo-2,6-dimethoxybenzamidomethyl) pyrrolidine by dealkylation in the same manner as described in Example 2. Yield 48%. M.p. (HCl) 140—141°C (acetone).

$[\alpha]_D^{25} = -78°C$ [c = 0.80, EtOH) base.

Example 13

(−)-N-benzyl-2-(3-bromo-2-hydroxy-6-methoxybenzamidomethyl) pyrrolidine hydrochloride

The title compound was prepared from (−)-N-benzyl-2-(3-bromo-2,6-dimethoxybenzamidomethyl) pyrrolidine by dealkylation in the same manner as described in Example 2. Yield 55%. M.p. (HCl) 207—209°C (EtOH).

Example 14

(−)-N-n-propyl-2-(3-bromo-6-hydroxy-2-methoxybenzamidomethyl) pyrrolidine hydrochloride

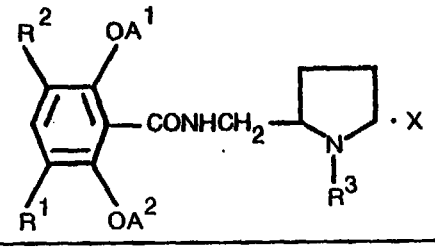
The title compound was prepared from (−)-N-n-propyl-2-(3-bromo-2,6-dimethoxybenzamidomethyl) pyrrolidine by dealkylation in the same manner as described in Example 2. Yield 55%. M.p. (HCl) 137—138°C (acetone).

$[\alpha]_D^{25} = -68°C$ (c = 0.12; MeOH).

In Table I are summarized physical data for the compounds prepared according to the description in the preceding examples.

NMR data for the compounds prepared according to the preceding examples were obtained. The NMR data were consistent with the assigned structures.

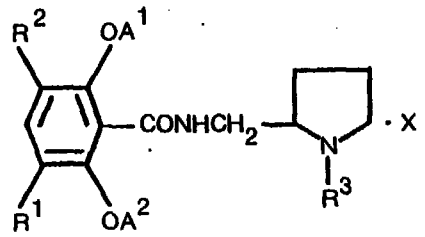
TABLE I



Compound prepared in Example	R^1	R^2	R^3	A^1	A^2	X	M.p. °C	$[\alpha]_D^{20°}$	Analysis: Calculated % / Found C	H	Br	Cl	N	O
1 rac	Br	H	C_2H_5	H	H	–	166–68		48.99 48.0	5.58 5.53			8.16 7.68	13.89 14.1
2 rac	Br	H	C_2H_5	CH_3	H	–	68–69		50.43 50.4	5.92 5.99	22.37 22.4		7.84 7.87	13.44 13.6
3 (–)	Br	H	C_2H_5	CH_3	H	HCl	sinters[1]	–45.5° (base)	45.76	5.63			7.12	12.19
4 (–)	Cl	H	C_2H_5	CH_3	H	HCl	sinters[1]	–51.4° (base)				10.15 10.1	8.02 7.70	
5 rac	Br	H	C_2H_5	C_2H_5	H	–	83–84		51.76 51.7	6.24 6.09	21.52 21.4		7.55 7.36	12.93 13.0
6 (–)	Br	H	C_2H_5	C_2H_5	H	–	74–76	–66.7°	51.76 51.7	6.24 6.02	21.52 21.9		7.55 7.31	12.93 13.1
7 (–)	Br	Br	C_2H_5	CH_3	H	HCl	sinters[1]	–8.6°	38.12 37.9	4.48 4.51			5.93 6.13	10.16 9.96
8 rac	Br	H	C_2H_5	CH_3	CH_3CO–	HCl	156 (dec)		46.86 47.1	5.55 5.70	18.34 18.3	8.13 8.12	6.43 6.23	

1/ Owing to hygroscopic properties the analytical values of this salt are unreliable. The absence of impurities was therefore examined by gas chromatography. The NMR of the compound was consistent with the proposed structure.

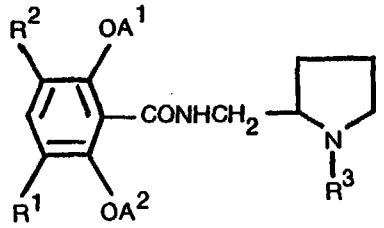
TABLE I (Continued)



Compound prepared in Example	R^1	R^2	R^3	A^1	A^2	X	M.p. °C	$[\alpha]_D^{20°}$	Analysis: Calculated % / Found C	H	Br	Cl	N	O
9 rac	Br	H	C_2H_5	H	CH_3	–	62–63		51.73 50.1	6.08 6.07	20.36 22.3		8.04 7.44	
10 (–)	Br	H	$CH_3(CH_2)_2$–	CH_3	CH_3	–	103–104	–85.4° (base)	52.99 53.2	6.54 6.67	20.74 21.3		7.27 7.18	
11 (–)	Cl	Cl	C_2H_5	H	CH_3	–	48–49	–64°	51.88 51.74	5.80 5.70		20.42 20.50	8.07 8.07	13.82 13.99
12 (–)	Br	H	$CH_3(CH_2)_2$–	CH_3	H	HCl	140–141	–78°	47.11 47.11	5.88 5.97	19.63 19.42	8.71 8.68	6.87 6.89	
13 (–)	Br	H	Ph–CH_2–	CH_3	H	HCl	207–209							
14 (–)	Br	H	$CH_3(CH_2)_2$–	H	CH_3	HCl	137–138	–68°	47.11 47.09	5.88 6.02	19.63 19.50	8.71 8.65	6.87 6.89	

The compounds in the table below have been prepared by method A or by method E (the compounds wherein $A^1 = H$)

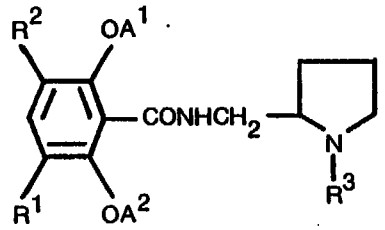
TABLE IA



Code	R^1	R^2	R^3	A^1	A^2	M.p. °C	$[\alpha]_D^{20}$	Analysis: Calculated % / Found C	H	Br	Cl	N	O
FLA 925	Br	H	$Ph-CH_2-$	CH_3	CH_3								
FLA 957(−)	C_2H_5	H	C_2H_5	CH_3	CH_3		−72°						
FLA 985	$CH_3(CH_2)_2$	H	C_2H_5	CH_3	CH_3	105–6							
FLB 130	Cl	C_2H_5	C_2H_5	CH_3	CH_3	103–4							
FLA 964	Br	C_2H_5	C_2H_5	CH_3	CH_3								
FLA 987	C_2H_5	C_2H_5	C_2H_5	CH_3	CH_3	83–4		69.04 68.96	9.12 9.19			7.92 8.04	

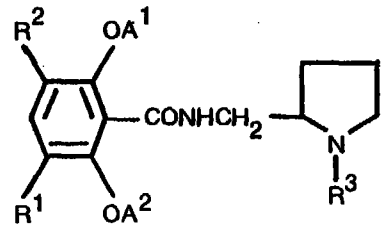
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TABLE IA (Continued)



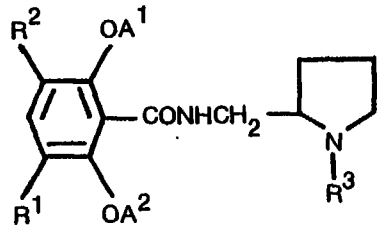
Code	R^1	R^2	R^3	A^1	A^2	M.p. °C	$[\alpha]_D^{20}$	Analysis: Calculated % / Found						
								C	H	Br	Cl	N	O	F
FLB 189	CH_3CO	H	C_2H_5	CH_3	CH_3									
FLB	$CH_3(CH_2)_2$	CH_3	C_2H_5	CH_3	CH_3									
FLB 168	$CH_3(CH_2)_2$	Cl	C_2H_5	CH_3	CH_3									
FLA 981(–)	H	H	C_2H_5	H	CH_3	141–2		55.64 55.92	7.74 7.24		10.95 10.93	8.65 8.60		
FLA 954(–)	H	F	C_2H_5	H	CH_3	154–5		54.14	6.66			8.42		5.71
FLA 961(–)	H	I	C_2H_5	H	CH_3	oil								
FLA 965(–)	H	C_2H_5	C_2H_5	H	CH_3	101–2	–72°	59.55	7.94		10.34	8.17		
FLA 986(–)	H	$CH_3(CH_2)$	C_2H_5	H	CH_3	170–1	–73°	60.58 60.56	8.19 8.21		9.93 9.74	7.85 7.77		

TABLE IA (Continued)



Code	R^1	R^2	R^3	A^1	A^2	M.p. °C	$[\alpha]_D^{20}$	Analysis: Calculated % / Found C	H	Br	Cl	N	O	F
FLA 968(−)	Br	Cl	C_2H_5	H	CH_3									
FLA 967(−)	Cl	Br	C_2H_5	H	CH_3									
FLA 950(−)	F	Br	C_2H_5	H	CH_3	136–7		43.74 43.82	5.10 5.20	19.44 19.53	8.62 8.63	6.80 6.78		4.61 4.70
FLA 988(−)	C_2H_5	C_2H_5	C_2H_5	H	CH_3	145–6		59.43 59.27	7.60 7.55			6.60 6.53		
FLA 966(−)	Br	C_2H_5	C_2H_5	H	CH_3									
FLA 974(−)	C_2H_5	Br	C_2H_5	H	CH_3	59–60								
FLB 110(−)	C_2H_5	H	C_2H_5	H	CH_3									
FLB 131(−)	Cl	C_2H_5	C_2H_5	H	CH_3	144–6		54.12 54.20	6.94 7.04		18.79 18.75	7.42 7.36		
FLB 132(−)	C_2H_5	Cl	C_2H_5	H	CH_3	170–1		54.12 54.35	6.94 6.94		18.79 18.85	7.42 7.30		

TABLE IA (Continued)



Code	R^1	R^2	R^3	A^1	A^2	M.p. °C	$[\alpha]_D^{20°}$	Analysis: Calculated % Found C	H	Br	Cl	N	O
	Br	H	C_2H_5	CH_3	C_2H_5OCO-								
	Br	H	C_2H_5	CH_3	$CH_3(CH_2)_8CO-$								

Example 15

The following examples illustrate the preparation of pharmaceutical compositions of the invention. The wording "active substance" denotes a compound according to the present invention or a salt thereof, and preferably the compound N-ethyl-2-(3-bromo-2-hydroxy-6-methoxy-benzamidomethyl)pyrrolidine or the 3-bromo-6-hydroxy-2-methoxy substituted isomer.

Formulation A. Soft gelatin capsules

500 g of active substance were mixed with 500 g of corn oil, whereupon the mixture was filled in soft gelatin capsules, each capsule containing 100 mg of the mixture (i.e. 50 mg of active substance).

Formulation B. Soft gelatin capsules

500 g of active substance were mixed with 750 g of pea nut oil, whereupon the mixture was filled in soft gelatin capsules, each capsule containing 125 mg of the mixture (i.e. 50 mg of active substance).

Formulation C. Tablets

50 kg of active substance were mixed with 20 kg of silicic acid of the trade mark Aerosil. 45 kg of potato starch and 50 kg of lactose were mixed therewith and the mixture was moistened with a starch paste prepared from 5 kg of potato starch and distilled water, whereupon the mixture was granulated through a sieve. The granulate was dried and sieved, whereupon 2 kg of magnesium stearate was mixed into it. Finally the mixture was pressed into tablets each weighing 172 mg.

Formulation D. Effervescing tablets

100 g of active substance, 140 g of finely divided citric acid, 100 g of finely divided sodium hydrogen carbonate, 3.5 g of magnesium stearate and flavouring agents (q.s.) were mixed and the mixture was pressed into tablets each containing 100 mg of active substance.

Formulation E. Sustained release tablet

200 g of active substance were melted together with 50 g of stearic acid and 50 g of carnauba wax. The mixture thus obtained was cooled and ground to a particle size of at most 1 mm in diameter. The mixture thus obtained was mixed with 5 g of magnesium stearate and pressed into tablets each weighing 305 mg. Each tablet thus contains 200 mg of active substance.

Formulation F. Injection solution

Active substance	3.000 mg
Sodium pyrosulfite	0.500 mg
Disodium edetate	0.100 mg
Sodium chloride	8.500 mg
Sterile water for inj.	ad 1.00 ml

Pharmacology

Introduction

A number of studies suggest that the antipsychotic action of neuroleptic drugs is in some way related to the decrease in catecholamine transmission in the brain caused by these drugs and more specifically due to central dopamine (DA) receptor blockade in cortical and subcortical brain regions. Most compounds with an antipsychotic action affect several DA systems in the brain. There is evidence that the antipsychotic action may be linked to blockade of DA receptors in the subcortical and cortical limbic structures (J. Pharm. Pharmacol. *25*, 346, 1973; Lancet, nov. *6* 1027, 1976) while the well-known extrapyramidal side effects produced by neuroleptic drugs are due to blockade of DA receptors in the nigroneostriatal DA system (Intern. J. Neurol. *6*, 27—45, 1967).

There are presently several techniques available to study DA receptor blockade in the brain in vivo. One method is based on the ability of antipsychotic drugs to block the behavioural effects induced by the DA agonist apomorphine in the rat. Several studies indicate an excellent correlation between the in vivo DA-receptor blockade as measured in the apomorphine test and therapeutic efficacy of different antipsychotic drugs. Apomorphine produces in rats and other species as characteristic syndrome consisting of repetitive movements (stereotypies) and hyperactivity which appear to be due to activation of postsynaptic DA receptors in the brain (J. Pharm. Pharmacol. *19*, 627, 1967; J. Neurol. Transm. *40*, 97—113, 1977). The stereotypies (chewing, licking, biting) appear mainly to be induced via activation of DA receptors linked to the neostriatal DA system (J. Psychiat. Res., *11*, 1, 1974) whereas the increased locomotion (hyperactivity) mainly appears to be due to activation of DA receptors in mesolimbic structures (nucleus olfactorium, nucleus accumbens) i.e. the mesolimbic DA-system. (J. Pharm. Pharmacol. *25*, 1003, 1973).

A number of studies have demonstrated that neuroleptics of different structural classes block the apomorphine stereotypies in the rat and that this blockade is well related to blockade of DA transmission measured by biochemical or neurophysiological techniques. Thus, the antiapomorphine effect correlates well with changes in DA turnover produced by neuroleptic drugs (Eur. J. Pharmacol., *11*, 303, 1970), DA receptor binding studies (Life Science, *17*, 993—1002, 1976) and most important with antipsychotic efficacy (Nature *263*, 388—341, 1976).

Methods

Male Sprague-Dawley rats (weighing 225—275 g) were used. The rats were observed in perspex cages (40 (L) × 25 (w) × 30 (h) cm) and the behaviour was scored 5, 20, 40, and 60 min. after apomorphine. The compounds were injected 60 min. prior to apomorphine hydrochloride (1 mg/kg) which was injected subcutaneously (s.c.) into the neck. This dose and form of administration was found to produce a very consistent response and very low variation in response strength. Further more, apomorphine given s.c. also produced a very consistent hyperactivity.

Directly after injection, the animals were placed in the cages, one in each cage. Scoring of the stereotypies were performed by two separate methods. The first scoring system was a modified version of the system introduced by Costall and Naylor (1973). The strength of the stereotype was scored on a 0—3 scale as follows:

Score	Description of stereotyped behaviour
0	No change in behaviour compared to saline controls or sedated
1	Discontinuous sniffing
2	Continuous sniffing
3	Continuous sniffing. Chewing, biting and licking.

In the second system the number of animals displaying hyperactivity caused by apomorphine were scored. Each group consisted of 6—8 animals. Saline controls were always run simultaneously. ED_{50}'s are in the first scoring system (0—3 scale), the doses which reduce the strength of the stereotypies by 50% over the observation period of 60 min. ED_{50}'s of the second scoring system are the doses which reduce the number of animals showing hyperactivity by 50% over the observation period of 60 min. The ED_{50} were calculated from log dose-response curves by the method of least squares from 4—6 dose levels with 6—8 animals per dose level.

Results

The results are presented in Table II. The compounds of the invention were compared with the prior art antipsychotic compounds sulpiride (Life Science, *17*, 1551—1556, 1975) and N-ethyl-2-(3-bromo-2,6-dimethoxybenzamidomethyl)pyrrolidine (racemic and levo-rotatory) designated FLA 731 and FLA 731 (−), resp. The tabulated results indicate that the compounds of the present invention are potent inhibitors of DA receptors in the brain. Due to their ability to antagonize both apomorphine stereotypies and hyperactivity they probably block DA receptors in both striatal and limbic areas (see Introduction). The compounds of the invention are clearly more potent than prior art compounds FLA 731 and FLA 731 (−) (racemic and levo-rotatory compounds compared separately) to inhibit apomorphine. Further, they are considerably more potent than the antipsychotic drug sulpiride. Since there is a highly significant correlation between the blockage of apomorphine and clinical antipsychotic efficacy (Nature, *263*, 338—341, 1976), it is very likely that the compounds of the present invention will show a highly potent antipsychotic action in man.

TABLE II

The ability to block apomorphine induced stereotypies and hyperactivity

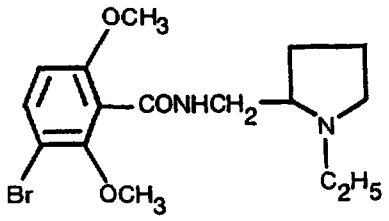
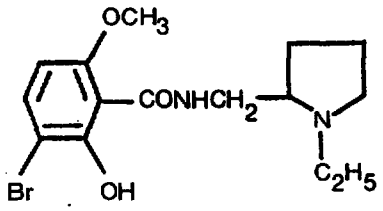
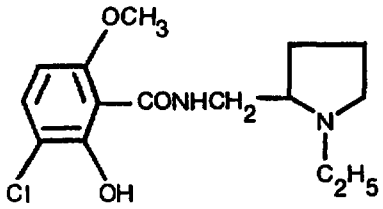
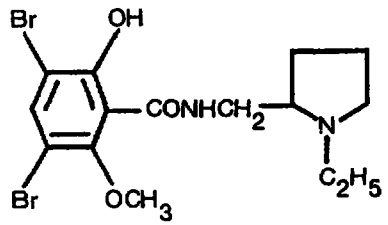
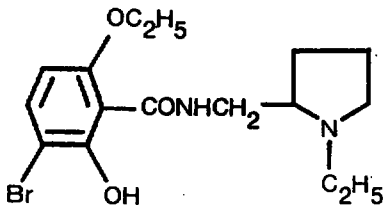
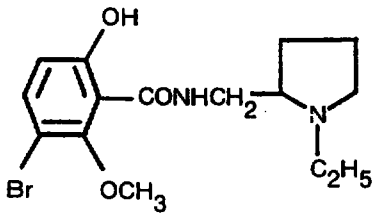
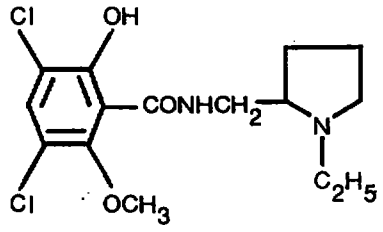
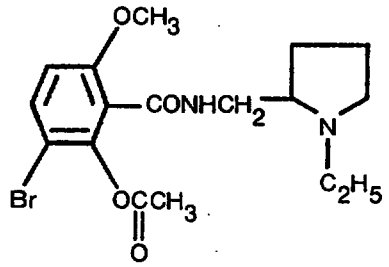
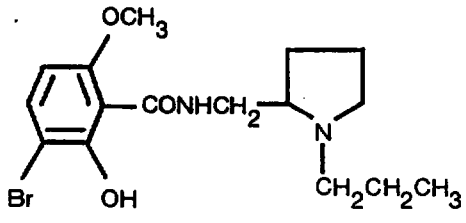
Compound	Structure	Block of apomorphine ED_{50}, µmol/kg i.p.	
		stereotypies	hyperactivity
Sulpiride		203	50
FLA 731		23	11
FLA 731 (–)		5.6	0.83
FLA 797		1.1	0.22
FLA 797 (–)		0.38	0.035
FLA 814		–	–
FLA 814 (–)		1.1	0.14
FLA 659		–	–
FLA 659 (–)		2.3	0.40

TABLE II (Continued)

Compound	Structure	Block of apomorphine ED_{50}, μmol/kg i.p. stereotypies	hyperactivity
FLA 901		3.4	1.1
FLA 908		10	1.1
FLA 870			
FLA 870 (–)		2.4	0.11
FLA 903		0.53	0.28
FLA 889			
FLA 889 (–)		0.75	0.27

The compounds of the invention were also compared to sulpiride in the same test system after oral administration. The results are tabulated below.

TABLE III
The potency to block apomorphine following oral administration to the rat

Compound acc. to Example no.	ED_{50}, µmol/kg p.o.	
	Stereotypies	Hyperactivity
797 (–)	22	3
814 (–)	25	4,4
901 (–)	34	3.0
659 (–)	12	3.2
Sulphiride	>586	>586

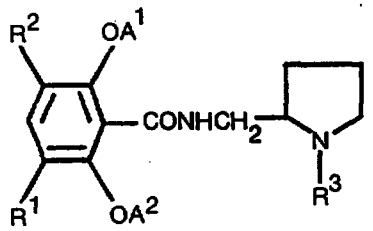
As can be seen sulpiride has lost all activity. This is in contrast to the tested compounds of the invention, which are still highly effective after oral administration to the rat.

Best mode for carrying out the invention

Among the compounds of the present invention according to formula I the levo-rotatory enantiomers of N-ethyl-2-(5-chloro-2-hydroxy-6-methoxybenzamidomethyl) pyrrolidine, N-ethyl-2-(3,5-dibromo-2-hydroxy-6-methoxybenzamidomethyl) pyrrolidine, N-ethyl-2-(3,5-diethyl-2-hydroxy-6-methoxybenzamidomethyl) pyrrolidine, N-ethyl-2-(3-bromo-2-hydroxy-6-methoxybenzamidomethyl) pyrrolidine and their use for the treatment of psychosis represent the best mode known at present.

Claims for the Contracting States: BE CH DE FR GB LI IT LU NL SE

1. A compound of the formula



I

wherein R^1 and R^2 are the same or different and each represents a hydrogen atom, a halogen atom, a cyano group, a straight or branched alkyl group with 1 to 5 carbon atoms or a group alkyl-CO—, wherein alkyl is as defined above, R^3 is a straight or branched alkyl group with 1 to 5 carbon atoms; alkenyl group with 2—5 carbon atoms or a benzyl group optionally substituted with fluorine, chlorine, bromine, trifluoromethyl, a straight or branched alkyl group with 1 to 5 carbon atoms or a group alkyl-O—, wherein alkyl is as defined above, A^1 and A^2 are the same or different and each represents a hydrogen atom, a straight or branched alkyl group with 1 to 5 carbon atoms, a group alkyl-CO—, wherein alkyl is as defined above, an alkoxycarbonyl group or a group $(alkyl)_2$-N—CO—, wherein alkyl is as defined above, provided that when A^1 and A^2 are the same alkyl group and R^3 is ethyl, R^1 or R^2 or both are selected among cyano, alkyl and alkyl-CO—; or a physiologically acceptable salt or an optical isomer thereof.

2. A compound according to claim 1 with the formula I wherein R^1, R^2 and R^3 have the meanings given in claim 1 and one of A^1 and A^2 is a straight or branched alkyl group with 1 to 5 carbon atoms and the other is a hydrogen atom.

3. A compound according to claim 1 with the formula I wherein R^1, R^2 and R^3 have the meanings given in claim 1 and one of A^1 and A^2 is a straight or branched alkyl group with 1 to 5 carbon atoms and the other is a group alkyl-CO, wherein alkyl is as defined above, an alkoxycarbonyl group or a group $(alkyl)_2$-N—CO—, wherein alkyl is as defined above.

4. A compound according to claim 1 with the formula I wherein R^1, R^2, A^1 and A^2 have the meanings given in claim 1, and R^3 is a straight or branched alkyl group with 1 to 5 carbon atoms other than ethyl; an alkenyl group; or a benzyl group optionally substituted with fluorine, chlorine, bromine, trifluoromethyl, a straight or branched alkyl group with 1 to 5 carbon atoms or a group alkyl-O—, wherein alkyl is as defined above.

The compounds of the invention were also compared to sulpiride in the same test system after oral administration. The results are tabulated below.

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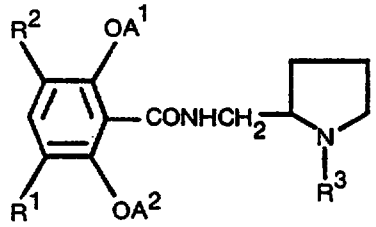
As can be seen sulpiride has lost all activity. This is in contrast to the tested compounds of the invention, which are still highly effective after oral administration to the rat.

Best mode for carrying out the invention

Among the compounds of the present invention according to formula I the levo-rotatory enantiomers of N-ethyl-2-(5-chloro-2-hydroxy-6-methoxybenzamidomethyl) pyrrolidine, N-ethyl-2-(3,5-dibromo-2-hydroxy-6-methoxybenzamidomethyl) pyrrolidine, N-ethyl-2-(3,5-diethyl-2-hydroxy-6-methoxybenzamidomethyl) pyrrolidine, N-ethyl-2-(3-bromo-2-hydroxy-6-methoxybenzamidomethyl) pyrrolidine and their use for the treatment of psychosis represent the best mode known at present.

Claims for the Contracting States: BE CH DE FR GB LI IT LU NL SE

1. A compound of the formula



I

wherein R^1 and R^2 are the same or different and each represents a hydrogen atom, a halogen atom, a cyano group, a straight or branched alkyl group with 1 to 5 carbon atoms or a group alkyl-CO—, wherein alkyl is as defined above, R^3 is a straight or branched alkyl group with 1 to 5 carbon atoms; alkenyl group with 2—5 carbon atoms or a benzyl group optionally substituted with fluorine, chlorine, bromine, trifluoromethyl, a straight or branched alkyl group with 1 to 5 carbon atoms or a group alkyl-O—, wherein alkyl is as defined above, A^1 and A^2 are the same or different and each represents a hydrogen atom, a straight or branched alkyl group with 1 to 5 carbon atoms, a group alkyl-CO—, wherein alkyl is as defined above, an alkoxycarbonyl group or a group $(alkyl)_2$-N—CO—, wherein alkyl is as defined above, provided that when A^1 and A^2 are the same alkyl group and R^3 is ethyl, R^1 or R^2 or both are selected among cyano, alkyl and alkyl-CO—; or a physiologically acceptable salt or an optical isomer thereof.

2. A compound according to claim 1 with the formula I wherein R^1, R^2 and R^3 have the meanings given in claim 1 and one of A^1 and A^2 is a straight or branched alkyl group with 1 to 5 carbon atoms and the other is a hydrogen atom.

3. A compound according to claim 1 with the formula I wherein R^1, R^2 and R^3 have the meanings given in claim 1 and one of A^1 and A^2 is a straight or branched alkyl group with 1 to 5 carbon atoms and the other is a group alkyl-CO, wherein alkyl is as defined above, an alkoxycarbonyl group or a group $(alkyl)_2$-N—CO—, wherein alkyl is as defined above.

4. A compound according to claim 1 with the formula I wherein R^1, R^2, A^1 and A^2 have the meanings given in claim 1, and R^3 is a straight or branched alkyl group with 1 to 5 carbon atoms other than ethyl; an alkenyl group; or a benzyl group optionally substituted with fluorine, chlorine, bromine, trifluoromethyl, a straight or branched alkyl group with 1 to 5 carbon atoms or a group alkyl-O—, wherein alkyl is as defined above.

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5. A compound according to claim 1; (−)-N-ethyl-2-(3-bromo-2-hydroxy-6-methoxybenzamidomethyl) pyrrolidine.

6. A compound according to claim 1; (−)-N-ethyl-2-(3,5-dibromo-2-hydroxy-6-methoxybenzamidomethyl) pyrrolidine.

7. A compound according to claim 1; (−)-N-ethyl-2-(5-chloro-2-hydroxy-6-methoxybenzamidomethyl) pyrrolidine.

8. A compound according to claim 1; (−)-N-ethyl-2-(3,5-diethyl-2-hydroxy-6-methoxybenzamidomethyl) pyrrolidine.

9. A compound according to claim 1; (−)-N-ethyl-2-(3,5-dichloro-6-hydroxy-2-methoxybenzamidomethyl) pyrrolidine.

10. A compound according to any of claims 1—9 in the form of an optical (−)-form isomer thereof.

11. A compound according to any of claims 1—10 in the form of a physiologically acceptable salt thereof.

12. A pharmaceutical preparation comprising as active ingredient a compound according to any of claims 1—11 or a physiologically acceptable salt or an optical isomer thereof.

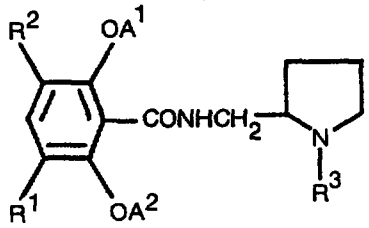
13. A pharmaceutical preparation according to claim 12 in dosage unit form.

14. A pharmaceutical preparation according to claims 12—13 comprising the active ingredient in association with a pharmaceutically acceptable carrier.

15. A compound according to any of claims 1—11 for use as a drug for the treatment of emesis, psychosomatic diseases or psychiatric diorders.

Claims for the Contracting State: AT

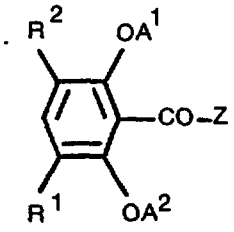
1. A process for the preparation of a compound of the formula



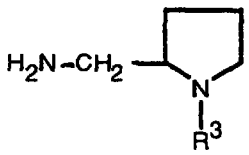
I

wherein R^1 and R^2 are the same or different and each represents a hydrogen atom, a halogen atom, a cyano group, a straight or branched alkyl group with 1 to 5 carbon atoms, or a group alkyl-CO—, wherein alkyl is as defined above, R^3 is a straight or branched alkyl group with 1 to 5 carbon atoms or alkenyl with 2—5 carbon atoms; an alkenyl group or a benzyl group optionally substituted with fluorine, chlorine, bromine, trifluoromethyl, a straight or branched alkyl group with 1 to 5 carbon atoms, or a group alkyl-O—, wherein alkyl is as defined above, A^1 and A^2 are the same or different and each represents a hydrogen atom, a straight or branched alkyl group with 1 to 5 carbon atoms, a group alkyl-CO—, wherein alkyl is as defined above, an alkoxycarbonyl group or a group $(alkyl)_2$-N—CO, wherein alkyl is as defined above, provided that when A^1 and A^2 are the same alkyl group and R^3 is ethyl, R^1 or R^2 or both are selected among cyano, alkyl and alkyl-CO—; or a physiologically acceptable salt or an optical isomer thereof, which process comprises

a) reaction of a compound of the formula



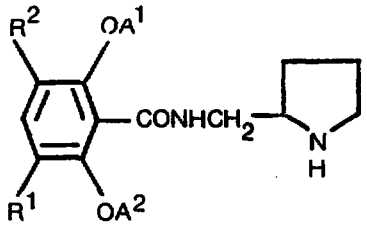
wherein R^1, R^2, A^1 and A^2 have the above given definition and —CO—Z is a reactive group capable of reacting with an amino group under formulation of an amide moiety, with a compound of the formula



wherein R^3 has the above given definition, to the formation of a compound of the formula I, or

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b) N-alkylation of a compound of the formula

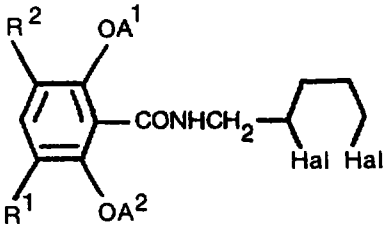


wherein R^1, R^2, A^1 and A^2 have the above given definition, with a compound of the formula

$$R^3—X$$

wherein R^3 has the above given definition and X is chlorine, bromine, sulphate, phosphate, benzenesulphonate or toluenesulphonate, to the formation of a compound of the formula I, or

c) reaction of a compound of the formula

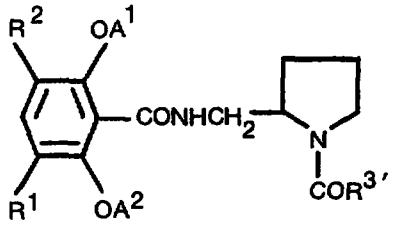


wherein R^1, R^2, A^1 and A^2 have the above given definition and Hal is Cl or Br, with a compound of the formula

$$R^3—NH_2$$

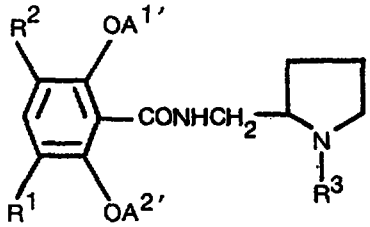
wherein R^3 has the above given definition to the formation of a compound of the formula I, or

d) reduction of a compound of the formula



wherein R^1, R^2, A^1 and A^2 have the above given definition and $R^{3'}$ means the same as R^3 but for the content of carbon atoms, which is one less, to the formation of a compound of the formula I, or

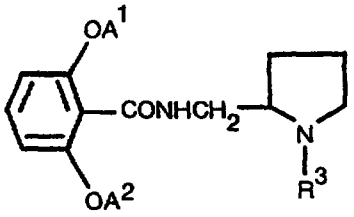
e) dealkylation of a compound of the formula



wherein R^1, R^2 and R^3 have the above given definition and $A^{1'}$ and $A^{2'}$ are straight or branched alkyl groups with 1 to 5 carbon atoms, with a protonic acid or a Lewis acid to the formation of a compound of the formula I wherein A^1 and/or A^2 is a hydrogen atom and the other, when necessary, a straight or branched alkyl group with 1 to 5 carbon atoms, or

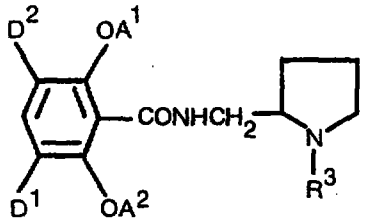
* C L M S *

f) reaction of a compound of the formula



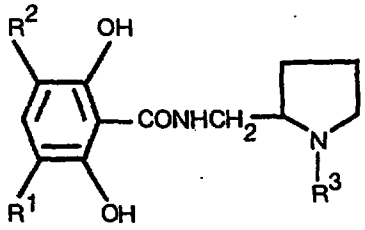
wherein R^3, A^1 and A^2 have the above given definition with halogen or a halogen-dioxane complex or with an acylhalide with Lewis acid catalysis or with an alkylhalide with Lewis acid catalysis; or with trichloroacetonitrile or a cyanogen halide with Lewis acid catalysis to the formation of a compound of the formula I wherein R^1 and/or R^2 is a halogen atom, a group alkyl-CO, wherein alkyl is as defined above or a straight or branched alkyl group with 1 to 5 carbon atoms, respectively, and the other, when necessary, a hydrogen atom, or

g) reaction of a compound of the formula



wherein A^1, A^2 and R^3 have the above given definition and D^1 and D^2 are the same or different and each represents a hydrogen atom or an amino group and at least one of D^1 and D^2 is an amino group, in a first step with $NaNO_2$ and in a second step with cuprous halogenide or cuprous cyanide to the formation of a compound of formula I wherein R^1 and/or R^2 is a halogen atom or a cyano group and the other, when necessary, a hydrogen atom, or

h) O-alkylation of a compound of the formula

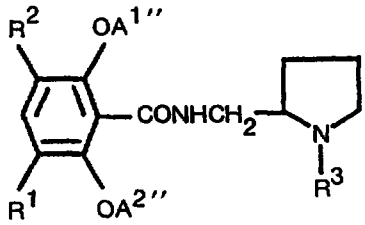


wherein R^1, R^2 and R^3 have the above given definition with a compound of the formula

$$A^{1'}—B$$

wherein $A^{1'}$ is a straight or branched alkyl group with 1 to 5 carbon atoms and B is $—(SO_4)_{1/2}$, $—(PO_4)_{1/3}$ or halogen to the formation of a compound of the formula I wherein A^1 and/or A^2 is a straight or branched alkyl group with 1 to 5 carbon atoms and the other, when necessary, a hydrogen atom, or

i) esterification of a compound of the formula



wherein R^1, R^2 and R^3 have the above given definition and $A^{1''}$ and/or $A^{2''}$ is hydrogen, and the other, when necessary, a straight or branched alkyl group with 1 to 5 carbon atoms, with a compound of the formula

$$R—CO—Z'$$

wherein R is an alkyl, alkoxy or dialkylamino group and Z' is Cl or Br, to the formation of a compound of the formula I wherein A^1 and/or A^2 is an acyl group, an alkoxycarbonyl group or a dialkylcarbamyl group, and the other, when necessary, an alkyl group, whereafter, if desired, the compound obtained by any of methods a)—i) is converted to a physiologically acceptable salt thereof and/or converted to a physiologically acceptable salt thereof and/or converted to a substantially pure optical isomer thereof.

2. A process according to claim 1 wherein a compound of the formula I is prepared, in which formula R^1, R^2 and R^3 have the meanings given in claim 1, and one of A^1 and A^2 is a straight or branched alkyl group with 1 to 5 carbon atoms and the other is a hydrogen atom.

3. A process according to claim 1 wherein a compound of the formula I is prepared, in which formula R^1, R^2 and R^3 have the meanings given in claim 1 and one of A^1 and A^2 is a straight or branched alkyl group with 1 to 5 carbon atoms and the other is a group alkyl-CO, wherein alkyl is as defined above, an alkoxycarbonyl group or a group $(alkyl)_2$-N—CO—, wherein alkyl is as defined above.

4. A process according to claim 1 wherein a compound of the formula I is prepared, in which formula R^1, R^2, A^1 and A^2 have the meanings given in claim 1, and R^3 is a straight or branched alkyl group with 1 to 5 carbon atoms other than ethyl; an alkenyl group; or a benzyl group optionally substituted with fluorine, chlorine, bromine, trifluoromethyl, a straight or branched alkyl group with 1 to 5 carbon atoms or a group alkyl-O—, wherein alkyl is as defined above.

5. A process according to claim 1 wherein (−)-N-ethyl-2-(3-bromo-2-hydroxy-6-methoxybenzamidomethyl) pyrrolidine is prepared.

6. A process according to claim 1 wherein (−)-N-ethyl-2-(3,5-dibromo-2-hydroxy-6-methoxybenzamidomethyl) pyrrolidine is prepared.

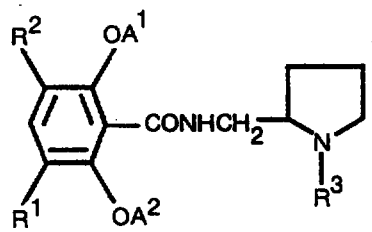
7. A process according to claim 1 wherein (−)-N-ethyl-2-(5-chloro-2-hydroxy-6-methoxybenzamidomethyl) pyrrolidine is prepared.

8. A process according to claim 1 wherein (−)-N-ethyl-2-(3,5-diethyl-2-hydroxy-6-methoxybenzamidomethyl) pyrrolidine is prepared.

9. A process according to claim 1 wherein (−)-N-ethyl-2-(3,5-dichloro-6-hydroxy-2-methoxybenzamidomethyl) pyrrolidine is prepared.

Patentansprüche für die Vertragsstaaten: BE CH DE FR GB IT LU NL SE

1. Verbindung der Formel



I

worin R^1 und R^2 gleich oder verschieden sind, und jedes ein Wasserstoffatom, ein Halogenatom, eine Cyanogruppe, eine gerade oder verzweigte Alkylgruppe mit 1 bis 5 Kohlenstoffatomen oder eine Alkyl-CO-Gruppe, worin Alkyl wie oben definiert ist, darstellt, R^3 eine gerade oder verzweigte Alkylgruppe mit 1 bis 5 Kohlenstoffatomen; eine Alkenylgruppe mit 2 bis 5 Kohlenstoffatomen oder eine gewünschtenfalls mit Fluor, Chlor, Brom, Trifluormethyl, einer geraden oder verzweigten Alkylgruppe mit 1 bis 5 Kohlenstoffatomen oder einer Alkyl-O-Gruppe, worin Alkyl wie oben definiert ist, substituierten Benzylgruppe, A^1 und A^2 gleich oder verschieden sind, und jedes ein Wasserstoffatom, eine gerade oder verzweigte Alkylgruppe mit 1 bis 5 Kohlenstoffatomen, eine Alkyl-CO-Gruppe, worin Alkyl wie oben definiert ist, eine Alkoxycarbonylgruppe oder eine $(Alkyl)_2$-N—CO-Gruppe, worin Alkyl wie oben definiert ist, darstellt, mit der Maßgabe daß, wenn A^1 und A^2 die gleiche Alkylgruppe sind, und R^3 Äthyl ist, R^1 oder R^2 oder beide ausgewählt sind aus Cyano, Alkyl und Alkyl-CO—; oder ein physiologisch akzeptables Salz oder ein optisches Isomeres davon.

2. Verbindung gemäß Anspruch 1 mit der Formel I, worin R^1, R^2 und R^3 die in Anspruch 1 angegebenen Bedeutungen haben, und jeweils eines von A^1 und A^2 eine gerade oder verzweigte Alkylgruppe mit 1 bis 5 Kohlenstoffatomen und das andere ein Wasserstoffatom darstellt.

3. Verbindung gemäß Anspruch 1 mit der Formel I, worin R^1, R^2 und R^3 die in Anspruch 1 angegebenen Bedeutungen haben, und jeweils eines von A^1 und A^2 eine gerade oder verzweigte Alkylgruppe mit 1 bis 5 Kohlenstoffatomen und das andere eine Alkyl-CO-Gruppe, worin Alkyl wie oben definiert ist, eine Alkoxycarbonylgruppe oder eine $(Alkyl)_2$-N—CO-Gruppe, worin Alkyl wie oben definiert ist, darstellt.

4. Verbindung gemäß Anspruch 1 mit der Formel I, worin R^1, R^2, A^1 und A^2 die in Anspruch 1 angegebenen Bedeutungen haben, und R^3 eine gerade oder verzweigte Alkylgruppe mit 1 bis 5 Kohlenstoffatomen, die nicht Äthyl ist; eine Alkenylgruppe; oder eine gewünschtenfalls mit Fluor, Chlor, Brom, Trifluormethyl, einer geraden oder verzweigten Alkylgruppe mit 1 bis 5 Kohlenstoffatomen oder einer Alkyl-O-Gruppe, worin Alkyl wie oben definiert ist, substituierte Benzylgruppe darstellt.

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5. Verbindung gemäß Anspruch 1; (−)-N-Äthyl-2-(3-brom-2-hydroxy-6-methoxybenzamidomethyl)-pyrrolidin.

6. Verbindung nach Anspruch 1; (−)-N-Äthyl-2-(3,5-dibrom-2-hydroxy-6-methoxybenzamidomethyl)-pyrrolidin.

7. Verbindung nach Anspruch 1; (−)-N-Äthyl-2-(5-chlor-2-hydroxy-6-methoxybenzamidomethyl)-pyrrolidin.

8. Verbindung nach Anspruch 1; (−)-N-Äthyl-2-(3,5-diäthyl-2-hydroxy-6-methoxybenzamidomethyl)-pyrrolidin.

9. Verbindung nach Anspruch 1; (−)-N-Äthyl-2-(3,5-dichlor-6-hydroxy-2-methoxybenzamidomethyl)-pyrrolidin.

10. Verbindung nach irgendeinem der Ansprüche 1 bis 9 in Form eines optischen (−)-Isomeren davon.

11. Verbindung nach irgendeinem der Ansprüche 1 bis 10 in Form eines physiologisch akzeptablen Salzes davon.

12. Pharmazeutische Präparation, dadurch gekennzeichnet, daß sie als aktives Ingrediens eine Verbindung nach irgendeinem der Ansprüche 1 bis 11 oder ein physiologisch akzeptables Salz oder ein optisches Isomeres davon umfaßt.

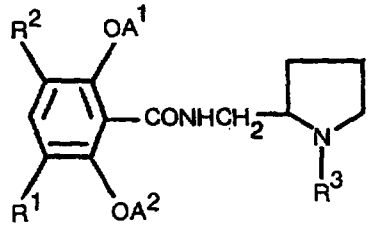
13. Pharmazeutische Präparation nach Anspruch 12 in Dosierungseinheitsform.

14. Pharmazeutische Präparation nach den Ansprüchen 12 bis 13, dadurch gekennzeichnet, daß sie das aktive Ingrediens zusammen mit einem pharmazeutisch akzeptablen Träger umfaßt.

15. Verbindung nach irgendeinem der Ansprüche 1 bis 11 zur Verwendung als ein Medikament zur Behandlung von Erbrechen, psychosomatischen Krankheiten oder psychiatrischen Störungen.

Patentansprüche für den Vertragsstaat: AT

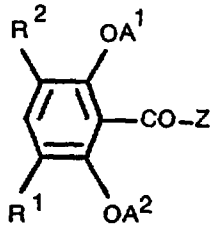
1. Verfahren zur Herstellung einer Verbindung der Formel



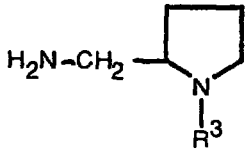
I

worin R^1 und R^2 gleich oder verschieden sind, und jedes ein Wasserstoffatom, ein Halogenatom, eine Cyanogruppe, eine gerade oder verzweigte Alkylgruppe mit 1 bis 5 Kohlenstoffatomen oder eine Alkyl-CO-Gruppe, worin Alkyl wie oben definiert ist, darstellt, R^3 eine gerade oder verzweigte Alkylgruppe mit 1 bis 5 Kohlenstoffatomen oder Alkenyl mit 2 bis 5 Kohlenstoffatomen; eine gewünschtenfalls mit Fluor, Chlor, Brom, Trifluormethyl, einer geraden oder verzweigten Alkylgruppe mit 1 bis 5 Kohlenstoffatomen oder einer Alkyl-O-Gruppe, worin Alkyl wie oben definiert ist, substituierten Alkenyl- oder Benzylgruppe, A^1 und A^2 gleich oder verschieden sind, und jedes ein Wasserstoffatom, eine gerade oder verzweigte Alkylgruppe mit 1 bis 5 Kohlenstoffatomen, eine Alkyl-CO-Gruppe, worin Alkyl wie oben definiert ist, eine Alkoxycarbonylgruppe oder eine $(Alkyl)_2$-N—CO-Gruppe, worin Alkyl wie oben definiert ist, darstellt, mit der Maßgabe daß, wenn A^1 und A^2 die gleiche Alkylgruppe sind, und R^3 Äthyl ist, R^1 oder R^2 oder beide ausgewählt sind aus Cyano, Alkyl und Alkyl-CO—; oder ein physiologisch akzeptables Salz oder ein optisches Isomeres davon, welches Verfahren dadurch gekennzeichnet ist, daß

a) eine Verbindung der Formel



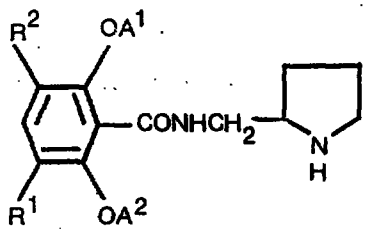
worin R^1, R^2, A^1 und A^2 die oben angegebene Bedeutung haben, und —CO—Z eine zur Reaktion mit einer Aminogruppe unter Bildung eines Amidteiles fähige reaktive Gruppe ist, mit einer Verbindung der Formel



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worin R^3 die oben angegebene Bedeutung hat, zur Bildung einer Verbindung der Formel I umgesetzt wird, oder

b) eine Verbindung der Formel

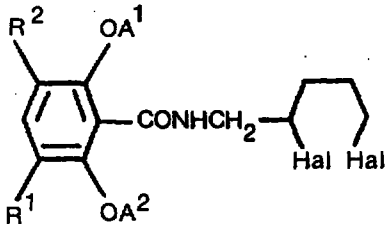


worin R^1, R^2, A^1 und A^2 die oben angegebene Bedeutung haben, mit einer Verbindung der Formel

$$R^3—X,$$

worin R^3 die oben angegebene Bedeutung hat und X Chlor, Brom, Sulfat, Phosphat, Benzolsulfonat oder Toluolsulfonat, zur Bildung einer Verbindung der Formel I N-alkyliert wird, oder

c) eine Verbindung der Formel

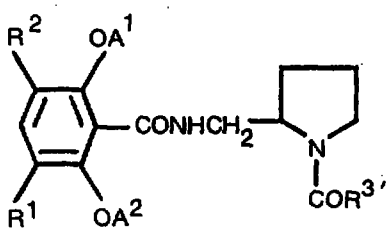


worin R^1, R^2, A^1 und A^2 die oben angegebene Bedeutung haben und Hal für Cl oder Br steht, mit einer Verbindung der Formel

$$R^3—NH_2,$$

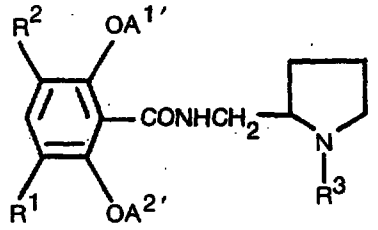
worin R^3 die oben angegebene Bedeutung hat, zur Bildung einer Verbindung der Formel I umgesetzt wird, oder

d) eine Verbindung der Formel



worin R^1, R^2, A^1 und A^2 die oben angegebene Bedeutung haben und $R^{3'}$ bis auf die Anzahl der Kohlenstoffatome welche um eines weniger ist, die gleiche Bedeutung wie R^3 hat, zur Bildung einer Verbindung der Formel I reduziert wird, oder

e) eine Verbindung der Formel

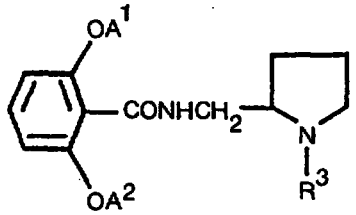


worin R^1, R^2 und R^3 die oben angegebene Bedeutung haben, und $A^{1'}$ und $A^{2'}$ gerade oder verzweigte Alkylgruppen mit 1 bis 5 Kohlenstoffatomen sind, mit einer protonenbildenden Säure oder einer Lewis-Säure

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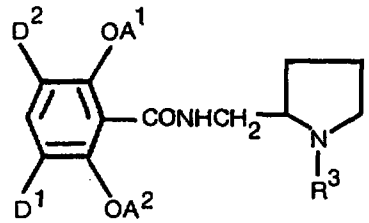
zur Bildung einer Verbindung der Formel I, worin A^1 und/oder A^2 ein Wasserstoffatom ist und das andere, nötigenfalls, eine gerade oder verzweigte Alkylgruppe mit 1 bis 5 Kohlenstoffatomen ist, dealkyliert wird, oder

f) eine Verbindung der Formel



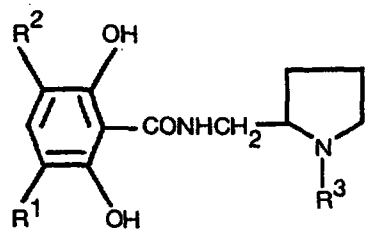
worin R^3, A^1 und A^2 die oben angegebene Bedeutung haben, mit Halogen oder einem Halogen-Dioxan-Komplex oder mit einem Acylhalogenid mit Lewis-Säure Katalyse oder mit einem Alkylhalogenid mit Lewis-Säure Katalyse; oder mit Trichloracetonitril oder einem Cyanhalogenid mit Lewis-Säure Katalyse zur Bildung einer Verbindung der Formel I, worin R^1 und/oder R^2 jeweils ein Halogenatom, eine Alkyl-CO-Gruppe, worin Alkyl wie oben definiert ist, oder eine gerade oder verzweigte Alkylgruppe mit 1 bis 5 Kohlenstoffatomen ist und das andere nötigenfalls ein Wasserstoffatom ist, umgesetzt wird, oder

g) eine Verbindung der Formel



worin A^1, A^2 und R^3 die oben angegebene Bedeutung haben und D^1 und D^2 gleich oder verschieden sind und jedes ein Wasserstoffatom oder eine Aminogruppe repräsentiert und wenigstens eines von D^1 und D^2 eine Aminogruppe ist, in einem ersten Schritt mit $NaNO_2$ und in einem zweiten Schritt mit Kupfer(I)halogenid oder Kupfer(I)cyanid zur Bildung einer Verbindung der Formel I, worin R^1 und/oder R^2 ein Halogenatom oder eine Cyanogruppe ist und das andere nötigenfalls ein Wasserstoffatom ist, umgesetzt wird, oder

h) eine Verbindung der Formel

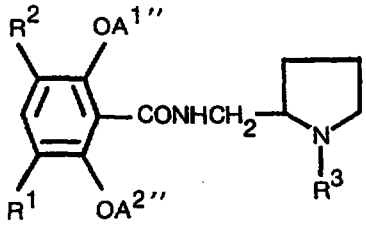


worin R^1, R^2 und R^3 die oben angegebene Bedeutung haben, mit einer Verbindung der Formel

$$A^{1'}—B,$$

worin $A^{1'}$ eine gerade oder verzweigte Alkylgruppe mit 1 bis 5 Kohlenstoffatomen ist, und B $—(SO_4)_{1/2}$, $—(PO_4)_{1/3}$ oder Halogen ist, zur Bildung einer Verbindung der Formel I, worin A^1 und/oder A^2 eine gerade oder verzweigte Alkylgruppe mit 1 bis 5 Kohlenstoffatomen ist, und das andere nötigenfalls ein Wasserstoffatom ist, O-alkyliert wird, oder

i) eine Verbindung der Formel



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worin R^1, R^2 und R^3 die oben angeführte Bedeutung haben, und $A^{1''}$ und/oder $A^{2''}$ Wasserstoff ist, und das andere nötigenfalls eine gerade oder verzweigte Alkylgruppe mit 1 bis 5 Kohlenstoffatomen ist, mit einer Verbindung der Formel

$$R—CO—Z',$$

worin R eine Alkyl, Alkoxy- oder Dialkylaminogruppe und Z' Cl oder Br ist, zur Bildung einer Verbindung der Formel I, worin A^1 und/oder A^2 eine Acylgruppe, eine Alkoxycarbonylgruppe oder eine Dialkylcarbamylgruppe ist, und das andere nötigenfalls eine Alkylgruppe ist, verestert wird, wonach gewünschtenfalls die mittels irgendeiner der Methoden a) bis i) erhaltene Verbindung in ein physiologisch akzeptables Salz davon übergeführt wird und/oder in ein im wesentlichen reines optisches Isomeres davon übergeführt wird.

2. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß eine Verbindung der Formel I hergestellt wird, in welcher Formel R^1, R^2 und R^3 die in Anspruch 1 angegebenen Bedeutungen haben, und eines von A^1 und A^2 eine gerade oder verzweigte Alkylgruppe mit 1 bis 5 Kohlenstoffatomen ist, und das andere ein Wasserstoffatom ist.

3. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß eine Verbindung der Formel I hergestellt wird, in welcher Formel R^1, R^2 und R^3 die in Anspruch 1 angegebenen Bedeutungen haben, und eines von A^1 und A^2 eine gerade oder verzweigte Alkylgruppe mit 1 bis 5 Kohlenstoffatomen ist, und das andere eine Alkyl-CO-Gruppe, worin Alkyl wie oben definiert ist, eine Alkoxycarbonylgruppe oder eine $(Alkyl)_2$-N—CO-Gruppe, worin Alkyl wie oben definiert ist, bedeutet.

4. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß eine Verbindung der Formel I hergestellt wird, in welcher Formel R^1, R^2, A^1, und A^2 die in Anspruch 1 angegebenen Bedeutungen haben, und R^3 eine gerade oder verzweigte Alkylgruppe mit 1 bis 5 Kohlenstoffatomen, die nicht Äthyl ist; eine Alkenylgruppe; oder eine gegebenenfalls mit Fluor, Chlor, Brom, Trifluormethyl, einer geraden oder verzweigten Alkylgruppe mit 1 bis 5 Kohlenstoffatomen oder einer Alkyl-O-Gruppe, worin Alkyl wie oben definiert ist, substituiert Benzylgruppe darstellt.

5. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß (−)-N-Äthyl-2-(3-brom-2-hydroxy-6-methoxybenzamidomethyl)-pyrrolidin hergestellt wird.

6. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß (−)-N-Äthyl-2-(3,5-dibrom-2-hydroxy-6-methoxybenzamidomethyl)-pyrrolidin hergestellt wird.

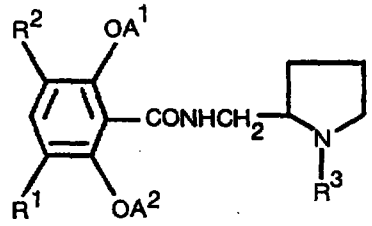
7. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß (−)-N-Äthyl-2-(5-chlor-2-hydroxy-6-methoxybenzamidomethyl)-pyrrolidin hergestellt wird.

8. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß (−)-N-Äthyl-2-(3,5-diäthyl-2-hydroxy-6-methoxybenzamidomethyl)-pyrrolidin hergestellt wird.

9. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß (−)-N-Äthyl-2-(3,5-dichlor-6-hydroxy-2-methoxybenzamidomethyl)-pyrrolidin hergestellt wird.

Revendications pour les Etats contractants: BE CH DE FR GB IT LU NL SE

1. Composé de formule:



I

dans laquelle R^1 et R^2 sont identiques ou différents et représentent chacun un atome d'hydrogène, un atome d'halogène, un groupe cyano, un groupe alkyle linéaire ou ramifié ayant 1 à 5 atomes de carbone ou un groupe alkyl-CO—, dans lequel alkyle est comme défini ci-dessus; R^3 représente un groupe alkyle linéaire ou ramifié ayant 1 à 5 atomes de carbone; un groupe alkényle ayant 2 à 5 atomes de carbone ou un groupe benzyle, éventuellement substitué par du fluor, du chlore, du brome, un groupe trifluorométhyle, un groupe alkyle linéaire ou ramifié ayant 1 à 5 atomes de carbone, ou un groupe alkyl-O, dans lequel alkyle est comme défini ci-dessus; A^1 et A^2 sont identiques ou différents et représentent chacun un atome d'hydrogène, un groupe alkyle linéaire ou ramifié ayant 1 à 5 atomes de carbone, un groupe alkyl-CO—, dans lequel alkyle est comme défini ci-dessus, un groupe alkoxy carbonyle ou un groupe $(alkyl)_2$—N—CO—, dans lequel alkyle est comme défini ci-dessus, à la condition que, lorsque A^1 et A^2 représentent le même groupe alkyle et que R^3 représente un groupe éthyle, R^1 ou R^2 ou les deux, soi(en)t choisi(s) parmi un groupe cyano, alkyle et alkyl-CO—; ou un sel physiologiquement acceptable ou un énantiomère de ce composé.

2. Composé selon la revendication 1, ayant la formule I dans laquelle R^1, R^2 und R^3 ont les sens indiqués à la revendication 1, et l'un des symboles A^1 et A^2 représente un groupe alkyle linéaire ou ramifié ayant 1 à 5 atomes de carbone, et l'autre représente un atome d'hydrogène.

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3. Composé selon la revendication 1, ayant la formule I dans laquelle R^1, R^2 und R^3 ont les sens indiqués à la revendication 1, et l'un des symboles A^1 et A^2 est un groupe alkyle linéaire ou ramifié ayant 1 à 5 atomes de carbone et l'autre est un groupe alkyl-CO—, dans lequel alkyle est comme défini ci-dessus, un groupe alkoxycarbonyle ou un groupe $(alkyl)_2$-N—CO—, où alkyle est comme défini ci-dessus.

4. Composé selon la revendication 1, ayant la formule I, dans laquelle R^1, R^2, A^1 et A^2 ont les sens indiqués à la revendication 1, et R^3 représente un groupe alkyle linéaire ou ramifié ayant 1 à 5 atomes de carbone autre qu'un groupe éthyle; un groupe alkényle; ou un groupe benzyle éventuellement substitué par du fluor, du chlore, du brome, un groupe trifluorométhyle, un groupe alkyle linéaire ou ramifié ayant 1 à 5 atomes de carbone ou un groupe alkyl-O—, dans lequel alkyle est comme défini ci-dessus.

5. Composé selon la revendication 1:1a(−)-N-éthyl-2-(3-bromo-2-hydroxy-6-méthoxybenzamidométhyl) pyrrolidine.

6. Composé selon la revendication 1:1a(−)-N-éthyl-2-((3,5-dibromo-2-hydroxy-6-méthoxybenzamidométhyl) pyrrolidine.

7. Composé selon la revendication 1:1a(−)-N-éthyl-2-(5-chloro-2-hydroxy-6-méthoxybenzamidométhyl)pyrrolidine.

8. Composé selon la revendication 1:1a(−)-N-éthyl-2-(3,5-diéthyl-2-hydroxy-6-méthoxybenzamidométhyl) pyrrolidine.

9. Composé selon laa revendication 1:1a(−)-N-éthyl-2-(3,5-dichloro-6-hydroxy-2-méthoxybenzamidométhyl) pyrrolidine.

10. Composé selon l'une quelconque des revendications 1 à 9, sous forme de l'énantiomère (−).

11. Composé selon l'une quelconque des revendications 1 à 10, sous forme d'un sel physiologiquement acceptable de ce composé.

12. Préparation pharmaceutique, comprenant à titre de principe actif un composé selon l'une quelconque des revendications 1 à 11, ou un sel physiologiquement acceptable, ou un énantiomère de ce composé.

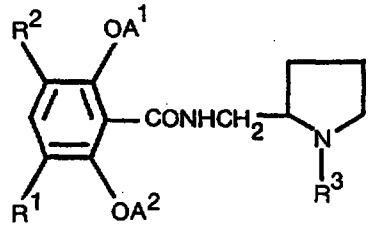
13. Préparation pharmaceutique selon la revendication 12, sous forme de dose unitaire.

14. Préparation pharmaceutique selon les revendications 12—13, comprenant le principe actifen association avec un support pharmaceutiquement acceptable.

15. Composé selon l'une quelconque des revendications 1 à 11, destiné à servir de médicament pour le traitement des vomissements, des maladies psychosomatiques ou des troubles psychiatriques.

Revendications pour l'Etat contractant: AT

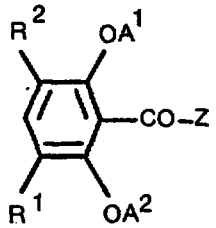
1. Procéde de préparation d'un composé de formule:



I

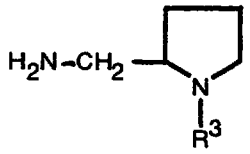
dans laquelle R^1 et R^2 sont identiques ou différents et représentent chacun un atome d'hydrogène, un atome d'halogène, un groupe cyano, un groupe alkyle linéaire ou ramifié ayant 1 à 5 atomes de carbone, ou un groupe alkyl—CO—, dans lequel alkyle est comme défini ci-dessus; R^3 représente un groupe alkyle linéaire ou ramifié ayant 1 à 5 atomes de carbone ou alkényle ayant 2 à 5 atomes de carbone; ou un groupe benzyle éventuellement substitué par du fluor, du chlore, du brome, un groupe trifluorométhyle, un groupe alkyle linéaire ou ramifié ayant 1 à 5 atomes de carbone ou un groupe alkyl—O—, dans lequel alkyle est comme défini ci-dessus; A^1 et A^2 sont identiques ou différents et représentent chacun un atome d'hydrogène, un groupe alkyle linéaire ou ramifié ayant 1 à 5 atomes de carbone, un groupe alkyl—CO—, dans lequel alkyle est comme défini ci-dessus, un groupe alkoxycarbonyle ou un groupe $(alkyl)_2$—N—CO, dans lequel alkyle est comme défini ci-dessus, à la condition que, lorsque les symboles A^1 et A^2 représentent le même groupe alkyle et que R^3 représente un groupe éthyle, R^1 ou R^2, ou les deux, soi(en)t choisi(s) parmi un groupe cyano, alkyle et alkyl-CO, ou d'un sel physiologiquement acceptable ou d'un énantiomère de ce composé, ce procédé comprenant:

a) la réaction d'un composé de formule:



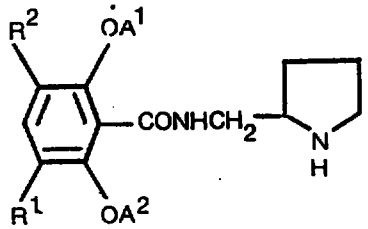
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dans laquelle R^1, R^2, A^1 et A^2 ont la définition donnée ci-dessus; et —CO—Z représente un groupe capable de réagir avec un groupe amino avec formation d'une fonction amide, avec un composé de formule:



dans laquelle R^3 a la définition donnée ci-dessus pour former un composé de formule 1, ou

b) la N-alkylation d'un composé de formule:

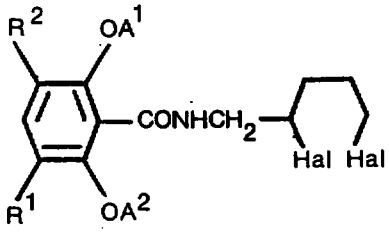


dans laquelle R^1, R^2, A^1 et A^2 ont les définitions données ci-dessus avec un composé de formule:

$$R^3—X$$

dans laquelle R^3 a la définition donnée ci-dessus et X représente un atome de chlore ou de brome ou un groupe sulfate, phosphate, benzène sulfonate ou toluène sulfonate pour former un composé de formule 1, ou

c) la réaction d'un composé de formule:

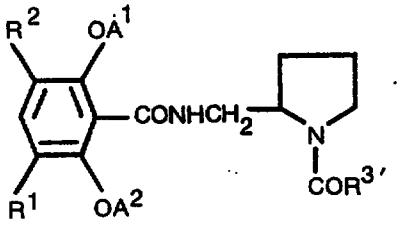


dans laquelle R^1, R^2, A^1 et A^2 ont la définition donnée ci-dessus, et Hal représente Cl ou Br avec un composé de formule:

$$R^3—NH_2$$

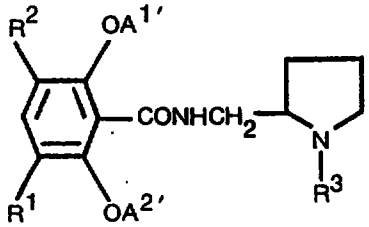
dans laquelle R^3 a la définition donnée ci-dessus pour former un composé de formule I, ou

d) la réduction d'un composé de formule:



dans laquelle R^1, R^2, A^1 et A^2 ont la définition donnée ci-dessus, et $R^{3'}$ a le même sens que R^3 sauf pour la teneur en atomes de carbone, qui est inférieure d'une unité, pour former un composé de formule I, ou

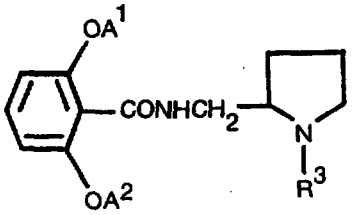
e) la désalkylation d'un composé de formule:



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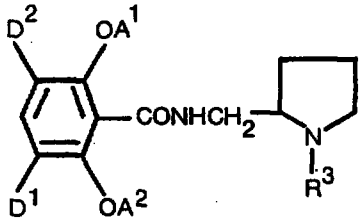
dans laquelle R^1, R^2 et R^3 ont la définition donnée ci-dessus et A^1 et $A^{2'}$ représentent des groupes alkyles linéaires ou ramifiés ayant 1 à 5 atomes de carbone, avec un acide protonique ou un acide de Lewis pour former un composé de formule I dans laquelle A^1 et/ou A^2 représentent un atome d'hydrogène et l'autre, quand cela est nécessaire, représente un groupe alkyle linéaire ou ramifié ayant 1 à 5 atomes de carbone, ou

f) la réaction d'un composé de formule:



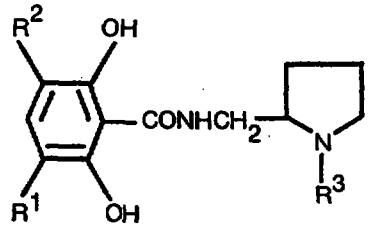
dans laquelle R^3, A^1 et A^2 ont la définition donnée ci-dessus, avec un halogène ou un complexe halogène-dioxanne ou avec un halogénure d'acide avec catalyse par un acide de Lewis ou avec un halogénure d'alkyle avec catalyse par un acide de Lewis; ou avec du trichloracétonitrile ou un halogénure de cyanogène avec catalyse par un acide de Lewis, pour former un composé de formule I dans laquelle R^1 et/ou R^2 représentent un atome d'halogène, un groupe alkyle-CO—, où l'alkyle est comme défini ci-dessus, ou est un groupe alkyle linéaire ou ramifié ayant 1 à 5 atomes de carbone, respectivement, et l'autre, quand cela est nécessaire, représente un atome d'hydrogène, ou

g) la réaction d'un composé de formule:



dans laquelle A^1, A^2 et R^3 ont la définition donnée ci-dessus et D^1 et D^2 sont identiques ou différents et représentent chacun un atome d'hydrogène ou un groupe amino, et au moins l'un des symboles D^1 et D^2 représente un groupe amino, dans une première étape avec $NaNO_2$ et dans une seconde étape avec un halogénure cuivreux ou du cyanure cuivreux pour former un composé de formule I dans laquelle R^1 et/ou R^2 représente(nt) un atome d'halogène ou un groupe cyano et l'autre, si cela est nécessaire, un atome d'hydrogène, ou

h) la O-alkylation d'un composé de formule:



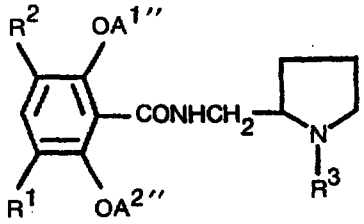
dans laquelle R^1, R^2 et R^3 ont la définition donnée ci-dessus avec un composé de formule:

$$A^{1'}—B$$

dans laquelle $A^{1'}$ représente un groupe alkyle linéaire ou ramifié ayant 1 à 5 atomes de carbone, et B représente $—(SO_4)_{1/2}$, $—(PO_4)_{1/3}$ ou un atome d'halogène, pour former un composé de formule I dans laquelle A^1 et/ou A^2 est un groupe alkyle linéaire ou ramifié ayant 1 à 5 atomes de carbone, et l'autre, si cela est nécessaire, est un atome d'hydrogène, ou

i) l'estérification d'un composé de formule:

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dans lequel R^1, R^2 et R^3 ont la définition donnée ci-dessus, et $A^{1''}$ et/ou $A^{2''}$ représente(nt) un atome d'hydrogène, et l'autre, quand cela est nécessaire, représente un groupe alkyle linéaire ou ramifié ayant 1 à 5 atomes de carbone, avec un composé de formule:

$$R—CO—Z'$$

dans laquelle R est un groupe alkyle, alkoxy ou dialkylamino et Z' représente Cl ou Br, pour former un composé de formule I dans laquelle A^1 et/ou A^2 représentent un groupe acyle, un groupe alkoxycarbonyle ou un groupe dialkylcarbamyle, et l'autre, quand cela est nécessaire, représente un groupe alkyle, puis, si on le désire, on transforme le composé obtenu par l'un quelconque des procédés a) à i) en un sel physiologiquement acceptable et/ou on isole en un énantiomère pratiquement pur de ce composé.

2. Procéde selon la revendication 1, par lequel on prépare un composé de formule I, dans laquelle R^1, R^2 et R^3 ont les significations indiquées à la revendication 1, et l'un des symboles A^1 et A^2 représente un groupe alkyle linéaire ou ramifié ayant 1 à 5 atomes de carbone et l'autre représente un atome d'hydrogène.

3. Procédé selon la revendication 1, par lequel on prépare un composé de formule I, dans laquelle R^1, R^2 et R^3 ont les significations indiquées à la revendication 1, et l'un des symboles A^1 et A^2 représente un groupe alkyle linéaire ou ramifié ayant 1 à 5 atomes de carbone et l'autre représente un groupe alkyl—CO, dans lequel l'alkyle est comme défini ci-dessus, un groupe alkoxycarbonyle ou un groupe $(alkyl)_2$—N—CO—, où alkyle est comme défini ci-dessus.

4. Procédé selon la revendication 1, par lequel on prépare un composé de formule I, dans laquelle R^1, R^2; A^1 et A^2 ont les significations indiquées à la revendication 1, et R^3 représente un groupe alkyle linéaire ou ramifié ayant 1 à 5 atomes de carbone, autre qu'un groupe éthyle, un groupe alkényle; ou un groupe benzyle éventuellement substitué par du fluor, du chlore, du brome, un groupe trifluorométhyle, un groupe alkyle linéaire ou ramifié ayant 1 à 5 atomes de carbone ou un groupe alkyl—O—, dans lequel alkyle est comme défini ci-dessus.

5. Procédé selon la revendication 1, par lequel on prépare la (−)-N-éthyl-2-(3-bromo-2-hydroxy-6-méthoxybenzamidométhyl)pyrrolidine.

6. Procédé selon la revendication 1, par lequel on prépare la (−)-N-éthyl-2-(3,5-dibromo-2-hydroxy-6-méthoxybenzamidométhyl) pyrrolidine.

7. Procédé selon la revendication 1, par lequel on prépare la (−)-N-éthyl-2-(5-chloro-2-hydroxy-6-méthoxybenzamidométhyl) pyrrolidine.

8. Procédé selon la revendication 1, par lequel on prépare la (−)-N-éthyl-2-(3,5-diéthyl-2-hydroxy-6-méthoxybenzamidométhyl) pyrrolidine.

9. Procédé selon la revendication 1, par lequel on prépare la (−)-N-éthyl-2-(3,5-dichloro-6-hydroxy-2-méthoxybenzamidométhyl) pyrrolidine.

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