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(19)

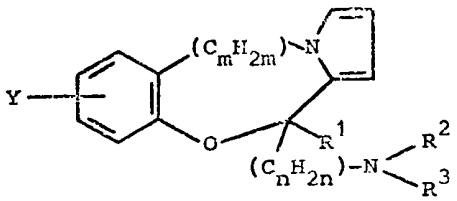
(54) AMINOALKYLPYRROLOBENZOXAZALKANES

(71) We, HOECHST AKTIENGESELLSCHAFT, a body corporate organised according to the laws of the Federal Republic of Germany, of 6230 Frankfurt/Main 80, Postfach 80 03 20, Federal Republic of Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to aminoalkylpyrrolobenzoxazalkanes.

The compounds herein disclosed have a new tricyclic ring structure and display significant pharmacological activity as analgesics, anticonvulsants and tranquilizers.

The present invention provides a compound of the general formula



A

wherein

Y represents a hydrogen or halogen atom or a lower alkoxy, lower alkyl, trifluoromethyl, nitro or unsubstituted or substituted amino group;

R^1 represents a hydrogen atom or a lower alkyl group;

R^2 represents a hydrogen atom or an alkyl group having from 1 to 5 carbon atoms, a phenyl group, a cycloalkyl group having from 3 to 6 carbon atoms, a phenalkyl group having up to 9 carbon atoms, a cycloalkylalkyl group having from 3 to 6 carbon atoms in the ring and up to 4 carbon atoms in the alkyl moiety, with usually a total of from 4 to 7 carbon atoms, all these groups represented by R^2 being unsubstituted or substituted, or R^2 represents a radical of the general formula —COR^4, wherein R^4 represents a hydrogen atom, a lower alkyl group, a phenyl, benzyl or phenethyl group, a cycloalkyl group having from 3 to 6 carbon atoms, a cycloalkylalkyl group having from 3 to 6 carbon atoms in the ring and up to 3 carbon atoms in the alkyl moiety, with usually a total of from 4 to 6 carbon atoms, or a phenoxy or lower alkoxy group; and the group represented by R^4 may be unsubstituted or substituted;

R^3 represents an alkyl group having from 1 to 5 carbon atoms, a phenyl group, a cycloalkyl group having from 3 to 6 carbon atoms, a phenylalkyl group having up to 9 carbon atoms, (provided that the NR^2R^3 group does not contain two phenalkyl groups with branched alkyl moieties), a cycloalkylalkyl group having from 3 to 6 carbon atoms in the ring and up to 4 carbon atoms in the alkyl moiety, with usually a total of from 4 to 7 carbon atoms; and the group represented by R^3 may be unsubstituted or substituted;

m is the integer 1 or 2, and
n is the integer 1, 2 or 3.

In one embodiment the (C_mH_{2m}) and (C_nH_{2n}) groups are straight chain, i.e. $(CH_2)_m$ and/or $(CH_2)_n$. Alternatively one or both of these may be branched chain alkylene groups.

The present invention also provides an acid addition salt, especially a physiologically tolerable acid addition salt, of a compound of the general formula A.

A halogen atom represented by Y may be a chlorine, iodine, fluorine or bromine atom, and an amino group represented by Y may be unsubstituted or substituted, for example by one or more lower alkyl groups, but is preferably unsubstituted; other groups represented by R^2, R^3 and R^4 may also be unsubstituted or substituted, for example alkyl-substituted, additionally to the carbon atoms already specified in the group, e.g. phenyl, cycloalkyl and cycloalkylalkyl groups and, especially, phenalkyl groups, more especially R^4 phenalkyl groups, may be substituted; there should especially be mentioned phenyl groups and moieties substituted by one of the groups or atoms listed for Y.

It will be understood that, unless stated to the contrary, an alkyl group or moiety may be a straight or branched chain hydrocarbon; preferably a phenalkyl group represented by R^2, R^4 or R^3 contains a straight-chain alkyl moiety and has the formula $C_6H_5(CH_2)_n$ where n is 1 or 2, or, in the case of R^2 and R^3, 3.

When used herein in connection with alkyl and alkoxy groups, the term "lower" is used to denote groups having from 1 to 4 carbon atoms.

There should especially be mentioned compounds in which Y represents a hydrogen or halogen atom, for example a chlorine atom, especially such compounds in which R^1 represents a hydrogen, methyl, ethyl or propyl group, R^2 represents a hydrogen atom or a lower alkyl group, and R^3 represents a lower alkyl, phenyl, phenalkyl or cycloalkyl group and also compounds in which n represents 1.

Preferred embodiments of the invention are those compounds wherein m is 1. Also preferred are those compounds in which R^1 represents a hydrogen atom.

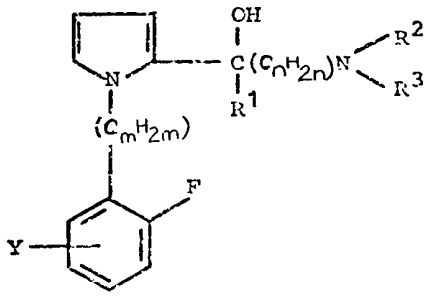
Acids useful for preparing the acid addition salts of the invention are inorganic acids, for example hydrochloric, hydrobromic, sulphuric, nitric, phosphoric and perchloric acids, as well as organic acids, for example tartaric, citric, acetic, succinic, maleic, fumaric and oxalic acids.

Some examples of compounds of the invention are:

TABLE 1

4-(ethylaminomethyl)-4H,10H-pyrrolo[2,1-c][1,4]benzoxazepine;
4-(dimethylaminomethyl)-4H,10H-pyrrolo[2,1-c][1,4]benzoxazepine;
4-(methylaminomethyl)-4H,10H-pyrrolo[2,1-c][1,4]benzoxazepine;
4-(diethylaminomethyl)-4H,10H-pyrrolo[2,1-c][1,4]benzoxazepine hydrochloride;
4-(cyclohexylaminomethyl)4H,10H-pyrrolo[2,1-c][1,4]benzoxazepine;
6-methoxy-4-(diethylaminomethyl)-4H,10H-pyrrolo[2,1-c]-[1,4]benzoxazepine;
7-ethyl-4-(isopropylaminomethyl)-4H,10H-pyrrolo[2,1-c][1,4]benzoxazepine;
10,11-dihydro-6-methyl-4-(dimethylaminoethyl)-4H-pyrrolo[2,1-c][1,4]-benzoxazocine;
4-butyl-4-(diethylaminopropyl)-4H,10H-pyrrolo[2,1-c][1,4]benzoxazepine;
4-(diphenylaminoethyl)-4H,10H-pyrrolo[2,1-c][1,4]benzoxazepine;
4-(dimethylaminopropyl)-9-trifluoromethyl-4H,10H-pyrrolo[2,1-c][1,4]-benzoxazepine;
10,11-dihydro-4-ethyl-4-(isopropylaminopropyl)-4H-pyrrolo[2,1-c]-[1,4]benzoxazocine;
4-(dimethylaminoethyl)-6-nitro-4H,10H-pyrrolo[2,1-c][1,4]benzoxazepine;
7-amino-4-(cyclopropylmethylaminomethyl)-4H,10H-pyrrolo[2,1-c]-[1,4]benzoxazepine; and
4-benzylaminopropyl)-4H,10H-pyrrolo[2,1-c][1,4]benzoxazepine.

The present invention also provides a process for the preparation of a compound of the general formula A or an acid addition salt thereof, which comprises cyclising a compound of the general formula



B

in which Y, R^1, R^2, R^3, m and n have the meanings given above but R^2 is not a group of the formula COR^4 and, if desired,

i) a) reacting a compound of the general formula A in which R^2 represents an alkyl, phenyl, cycloalkyl, phenalkyl or cycloalkylalkyl group as specified above with an alkyl or aryl chloroformate to give a compound of the general formula A in which $R^2=COR^4$ where R^4 represents an alkoxy or phenoxy group as specified above, and, optionally,

b) hydrolysing this compound to give one of the general formula A in which R^2 represents a hydrogen atom, or

ii) a) reacting a compound of the general formula A in which R^2 represents a hydrogen atom with a compound of the general formula R^4COX wherein R^4 represents a hydrogen atom or, preferably, has one of the other meanings given for formula A, especially an alkyl, phenyl, benzyl, phenethyl, cycloalkyl or cycloalkylalkyl group, X represents a bromine, fluorine or chlorine atom, to give an amide compound of the general formula A in which $R^2=COR^4$, and, optionally,

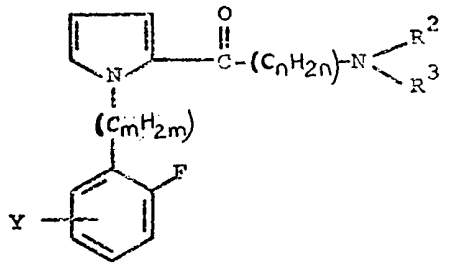
b) reducing this amide compound of the general formula A to give another compound of the general formula A in which R^2 represents an alkyl, phenalkyl or cycloalkylalkyl group as specified above.

The present invention further provides a process for the preparation of a compound of the general formula A in which $R^2 \neq COR^4$, or an acid addition salt thereof, from another compound of the general formula A in which $R^2=COR^4$, by steps ib) or iib) above.

In the starting material of the general formula B, preferably R^2 represents a hydrogen atom, an alkyl, phenyl, cycloalkyl, phenalkyl or cycloalkylalkyl group but is generally only hydrogen if n=1 and especially if n=1 and R^1=hydrogen.

The starting material B may be prepared from

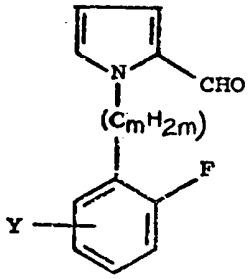
1) a compound of the general formula



C

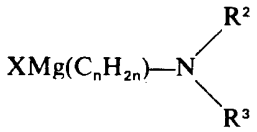
in which Y, R^2, R^3, m and n have the meanings given above, but R^2 is not a group of the formula COR^4, by reduction to form a compound of the general formula B in which R^1 represents a hydrogen atom or by reaction with a Grignard reagent and hydrolysis to form a compound of the general formula B in which R^1 represents an alkyl group, or from

2) a compound of the general formula



D

in which Y and m have the meanings given above, by reaction with a compound of the general formula

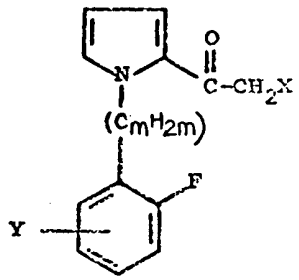


in which X represents a fluorine, chlorine or bromine atom and R^2, R^3 and n have the meanings given above but R^2 is not COR^4, and hydrolysing to form a compound of the general formula B in which R^1 represents a hydrogen atom.

In these methods, preferably R^2 represents a hydrogen atom, an alkyl, phenyl, cycloalkyl, phenalkyl or cycloalkylalkyl group, but is generally only hydrogen if n=1 and especially if n=1 and R^1=hydrogen. In method 2) above, generally n=2 or 3, preferably 3.

The compound of the general formula C may be prepared from

I) a compound of the general formula



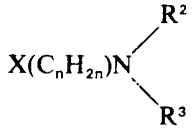
E

in which X represents a fluorine, chlorine or bromine atom and Y and m have the meanings given above, by reaction with an amine of the general formula HNR^2R^3 in which R^2 and R^3 have the meanings given above but $R^2 \neq COR^4$ to form a compound of the general formula C in which n=1, or

II) a compound of the general formula D by the steps

a) reaction with 1,3-propanedithiol to give the corresponding dithiane,

b) reaction of the dithiane with a compound of the general formula

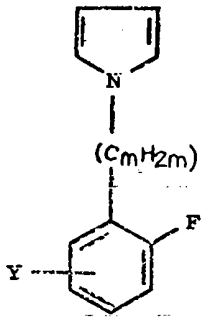


in which R^2 has the meaning give above but is not COR^4 to form the corresponding pyrrylaminodithiane, and

c) conversion of the pyrrylaminodithiane to the corresponding pyrrylpiperazinoketone.

In method II, step b), above, R^2 preferably represents an alkyl, phenyl, cycloalkyl, phenylalkyl or cycloalkylalkyl group and not a hydrogen atom, and n represents 2 or 3.

Compounds of the general formulae D and E may be prepared from a compound of the general formula



by methods known *per se*.

It should be understood that in the processes described above, a salt of a specified compound may be used where appropriate.

Several examples of preparation are outlined below and illustrated in the attached flow sheet with reference to compounds in which (C_nH_{2n}) and (C_mH_{2m}) are straight chain groups; when mentioned below or in the flow sheet, n, m, R^1, R^2, R^3 and Y are, with the exceptions noted, as defined earlier (and $R^2 \neq COR^4$), X represents chlorine or bromine and R^4 is as defined in Method G.

METHOD A

1. An orthofluorophenylalkylamine (I) is reacted with 2,5-dimethoxytetrahydrofuran to produce an orthofluorophenylalkyl pyrrole (II).

Compounds of formula (I) wherein m is 1 can be obtained by brominating a 2-fluorotoluene to produce a 2-fluorobenzylbromide; reacting the 2-fluorobenzylbromide with potassium phthalimide by a Gabriel's synthesis to form a corresponding N-benzyl-phthalimide and cleaving the phthalimide by thermal addition of hydrazine to form a 2-fluorobenzylamine of formula (I).

Compounds of formula (I) wherein m is 2 can be obtained by chlorinating a 2-fluorotoluene to produce a 2-fluorobenzyl-chloride, reacting the benzyl chloride with sodium cyanide to form a corresponding benzyl cyanide and reducing the cyano radical with diborane to produce a 2-fluorophenethylamine of formula (I).

2. The orthofluorophenylalkylpyrrole II is allowed to react with a halogenated acetonitrile such as chloroacetonitrile, optionally in the presence of an organic solvent which is inert under the reaction conditions and at a cooled temperature, preferably 0—5°C, and the reaction solution is saturated with hydrogen chloride gas to form the corresponding ketimine. The ketimine is subjected to hydrolysis to form the corresponding haloketone (III). A preferred organic solvent for carrying out the reaction is ether.

3. A pyrrylaminoketone (IV) is prepared by the reaction of the haloketone (III) with a mono or disubstituted amine according to the method described by Teotino *et al.* in U.S. Patent No. 3,706,750.

4. The pyrrylaminoketone (IV) is reduced to its corresponding pyrrylaminoethanol (V) by a method known in the art such as the method described by Teotino *et al.* in U.S. Patent 3,539,589. A preferred method utilises sodium borohydride as the reducing agent and carries out the reduction in isopropyl alcohol at a temperature of from ambient to the reflux point of the reaction solution.

5. Cyclising the pyrrylaminoethanol (V) produces a tricyclic compound of the present invention (VI) wherein R^1 is hydrogen and n is 1. A preferred method utilised sodium hydride in the presence of an organic solvent, e.g. dry benzene or dimethylformamide.

METHOD B

1. A pyrrylaminoketone (IV) is reacted with a Grignard reagent of the formula R^1MgX under conditions known to the art and the reaction mixture is hydrolysed with ice-water to give a corresponding pyrrylaminoalkanol (VII) wherein R^1 is alkyl. Preferred Grignard conditions utilise refluxing ether as the reaction medium.

2. The pyrrylaminoalkanol (VII) is treated by the procedure described above in Method A, step 5, to produce the corresponding tricyclic compound of the present invention (VI) wherein R^1 is alkyl and n is 1.

METHOD C

1. An aldehyde (VIII) is prepared from the orthofluorophenylalkylpyrrole by a

method known in the art. One such method is the Vilsmeier-Haack Reaction described in Berichte *60*, 119 (1927).

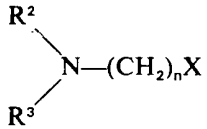
2. The aldehyde (VIII) is reacted with a Grignard reagent of the formula $(R^2)(R^3)N(CH_2)_3MgX$ wherein R^2 is not hydrogen and is preferably alkyl, $C_6H_5(CH_2)_n$, cycloalkyl or cycloalkylalkyl, by a method known in the art to produce the corresponding pyrrylaminobutanol (IX). A preferred method carries out the reaction in a combined solvent of ether and benzene at a temperature of 45°C.

3. The pyrrylaminobutanol (IX) is treated by the procedure described above in Method A, step 5, to produce the corresponding tricyclic compound of the present invention (VI), wherein R^2 is not hydrogen and n is 3. This method may also be used for n=2.

METHOD D

1. An aldehyde (VIII), optionally in an organic solvent, e.g. chloroform, is reacted with 1,3-propanedithiol, preferably at about ambient temperature, to produce a dithiane (X). The yield and purity of the dithiane is enhanced by addition of hydrogen chloride gas to the reaction mixture at −15°C.

2. The dithiane, preferably dissolved in an organic solvent, e.g. tetrahydrofuran, and cooled to about between −80 and −20°C is reacted with n-butyl lithium. The reaction mixture is maintained in the range of from −80 to −20°C and a di-substituted aminoalkyl halide of the formula



wherein R^2 is not hydrogen and is preferably alkyl, cycloalkyl, $C_6H_5(CH_2)_{n'}$ (n'=1, 2 or 3) or cycloalkylalkyl and n is 2 or 3 is added and the reaction mixture is allowed to react in the range of from −20°C to ambient temperature to produce a pyrrylaminodithiane (XI).

3. The pyrrylaminodithiane (XI) is converted, preferably with mercuric chloride and acetonitrile in the presence of an acid scavenger, e.g. calcium carbonate, and water to the corresponding pyrrylpiperazinoketone (XII).

4. The pyrrylaminoketone (XII) is reduced by the procedure described above in method A, step 4 to a pyrrylaminoalkanol (XIII) wherein R^2 is not hydrogen and n is 2 or 3 which in turn is treated by the procedure described above in Method A, step 5 to produce the corresponding tricyclic compound of the present invention (VI) wherein R^2 is not hydrogen, preferably alkyl and n is 2 to 3.

METHOD E

1. A pyrrylaminoketone (XII) is treated by the procedure described above in Method B, step 1 to a corresponding pyrrylaminoalkanol (XIV) wherein R^1 is alkyl, $R^2 \neq H$, and is preferably alkyl, cycloalkyl, $C_6H_5(CH_2)_{n'}$ (n'=1, 2 or 3) or cycloalkylalkyl.

2. The pyrrylaminoalkanol (XIV) is treated by the procedure described above in Method A, step 5 to produce the corresponding tricyclic compound of the present invention (VI) wherein R^1 is alkyl, $R^2 \neq H$ and n is 2 or 3.

METHOD F

1. A tricyclic compound of the invention wherein R^2 is not hydrogen can be reacted in a known manner with a substituted chloroformate to produce the corresponding phenoxy or alkoxy-carbonyl compound (XV), a novel intermediate of the present invention wherein Z is phenyl or alkyl. One such method utilises benzene as a solvent and carries out the reaction at ambient temperature. An acid scavenger, e.g. sodium bicarbonate, can be optionally added to the reaction mixture to remove any hydrogen chloride.

2. The carbonyl compound (XV) is hydrolysed, preferably with a strong mineral base, e.g. potassium hydroxide, in a solvent, e.g. n-propanol, to produce a monosubstituted amino compound of the invention (XVI).

METHOD G

1. A tricyclic compound of the invention (VI or XVI), wherein R^2 is hydrogen can be treated with a carbonyl halide of the formula R^4-COX wherein R^4 is

unsubstituted or substituted alkyl, phenyl, phenylalkyl, cycloalkyl or cycloalkylalkyl and X is bromine, fluorine, or chlorine, to produce the corresponding N-carbonylamino compound (XVII), of the present invention.

2. The above N-carbonylamino compound (XVII) can be reduced in a known manner with a reagent, e.g. lithium aluminium hydride, to give the corresponding tricyclic compound of the invention (XVIII) wherein R^2 is unsubstituted or substituted alkyl, phenylalkyl or cycloalkylalkyl.

The above methods may also be carried out where appropriate with compounds in which $(CH_2)_m$ and/or $(CH_2)_n$ groups are replaced by branched chain groups.

Compounds of the present invention are useful as analgesic agents due to their ability to alleviate pain in mammals. The analgesic acitivity of compounds of this invention is demonstrated in the phenyl-2-quinone-induced writhing assay in mice, a standard assay for analgesia [Proc. Soc. Exptl. Biol. Med., *95*, 729 (1957)]. Thus, for instance, an approximately 50% inhibition of writhing is effected by 0.78 mg/kg subcutaneous dose of 4 - (ethylaminomethyl) - 4H,10H - pyrrolo[2,1-c][1,4]benzoxazepine. Similarly effective are oral doses of about 3.2 mg/kg, 8.0 mg/kg, and less than 10.0 mg/kg of 4-(dimethylaminomethyl) - 4H,10H - pyrrolo[2,1-c][1,4]benzoxazepine, 4 - (methylaminomethyl) - 4H,10H - pyrrolo[2,1-c][1,4]benzoxazepine and 4 - (diethylaminomethyl) - 4H,10H - pyrrolo[2,1-c][1,4]benzoxazepine hydrochloride, respectively. For comparison, aspirin and propoxyphene hydrochloride, known analgesic agents, effect a 34% and 50% inhibition of writhing with doses of 60 mg/kg and 28 mg/kg, respectively. Thus a tricyclic compound of this invention is useful for the alleviation of pain in mammals and may be administered in an amount ranging from 0.1 to 100 mg/kg of body weight per day.

Compounds of the present invention are also useful as tranquilizers due to their depressant action on the central nervous system of mammals. This activity is demonstrated in the mouse observation procedure, a standard assay for CNS depressants [Psychlopharmacologia, *9*, 259 (1966)]. We have found that the minimum effective dose (MED) at which 4 - (ethylaminomethyl) - 4H,10H - pyrrolo[2,1-c][1,4]benzoxazepine and 4 - (diethylaminomethyl) - 4H,10H - pyrrolo[2,1-c][1,4]benzoxazepine hydrochloride display significant effects on behaviour and reflex depression together with muscle relaxation is 10 mg/kg. Thus a compound of the present invention is useful as a tranquilizer in mammals and may be administered in an amount ranging from 0.1 to 100 mg/kg of body weight per day.

Compounds of the present invention are furthermore useful as anti-convulsant agents for mammals, as determined by the method of Woodbury, L.A. and Davenport, V.D., in Arch. Int. Pharmacodynam, Vol. *92*, (1952) at pages 97—107. For example, intraperitoneal doses of 25 mg/kg of 4 - (ethylaminomethyl) - 4H,10H - pyrrolo[2,1-c][1,4]benzoxazepine, 18 mg/kg of 4 - (diethylaminomethyl) - 4H,10H - pyrrolo[2,1-c][1,4]benzoxazepine hydrochloride and 36 mg/kg 4 - (methylaminomethyl) - 4H,10H - pyrrolo[2,1-c][1,4] - benzoxazepine produce a 67%, 50% and 50% protection from the effect of supra maximal electro shock, respectively. Thus a compound of the invention may be used for the treatment of convulsion in mammals; the compound may be administered in an amount ranging from 0.1 to 100 mg/kg of body weight per day.

The present invention provides a pharmaceutical preparation which comprises a compound of the general formula A, or a physiologically tolerable acid addition salt thereof, in admixture or conjunction with a pharmaceutically suitable carrier.

A compound of the invention may be administered to a patient by any one of various methods, for example, orally, e.g. by capsule or suspension, and in some cases intravenously in the form of a sterile solution. A free base final product, while effective itself, may also be formulated and administered in the form of a physiologically tolerable addition salt, for example for purposes of stability, convenience of crystallisation or increased solubility.

A compound of the present invention may be orally administered, for example, with an inert diluent or with an edible carrier, or may be enclosed in a gelatin capsule, or they may be compressed into a tablet. For the purpose of oral therapeutic administration, the active compound of the invention may be incorporated with one or more excipient and used, for example, in the form of a tablet, troche, capsule, elixir, suspension, syrup, wafer or chewing gum. These preparations advantageously should contain at least 0.5% of active compound, but may be varied depending upon the particular form and may conveniently be from

4% to about 70% of the weight of the unit. The amount of active compound in such a preparation is such that a suitable dosage will be obtained. Preferably an oral dosage unit form contains from 1.0—300 mg of active compound.

A tablet, pill, capsule or troche, for example, may also contain one or more of the following ingredients: a binder, e.g. microcrystalline cellulose, gum tragacanth or gelatin; an excipient, e.g. starch or lactose; a disintegrating agent, e.g. alginic acid, Primogel or corn starch; a lubricant, e.g. magnesium stearate or Sterotex; a glidant, e.g. colloidal silicon dioxide; a sweetening agent, e.g. sucrose or saccharin; and a flavouring agent, e.g. peppermint, methyl salicylate, or orange flavouring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such, for example, as a fatty oil. Other dosage unit forms may contain other materials which modify the physical form of the dosage unit, for example, as coatings. Thus, tablets or pills may be coated with sugar, shellac, or other enteric coating agents. A syrup may contain, in addition to the active compounds, sucrose as a sweetening agent, and certain preservatives, dyes and colourings, and flavours. Materials used in preparing these various pharmaceutical preparations should be pharmaceutically pure and non-toxic in the amounts used.

For the purpose of parenteral therapeutical administration, an active compound of the invention may be incorporated into a solution or suspension. Such preparations advantageously should contain at least 0.1% of active compound, but may be varied, for example in the range of from 0.5 to 30% of the weight thereof. The amount of active compound in such a preparation is such that a suitable dosage will be obtained. Preferably a parenteral dosage unit contains from 0.5 to 100 mg of active compound.

A solution or suspension may also include one or more of the following components: a sterile diluent, e.g. water for injection, saline solution, fixed oil, polyethylene glycol, glycerine, propylene glycol or other synthetic solvent; antibacterial agents, e.g. benzyl alcohol or methyl parabens; antioxidant, e.g. ascorbic acid or sodium bisulphite; chelating agent, e.g. ethylenediaminetetraacetic acid; buffer, e.g. acetate, citrate or phosphate, and agent for the adjustment of tonicity, e.g. sodium chloride or dextrose. The parenteral preparation can be enclosed in an ampoule, disposable syringe or multiple-dose vial made of glass or plastics.

The present invention is further illustrated by the following Examples.

Example 1

a. A solution of 40 g of 1-(*o*-fluorobenzyl)pyrrole and 17.2 g of chloroacetonitrile in 200 ml of anhydrous ether at a temperature between 0 and −5°C is saturated with hydrogen chloride gas and then the solution is stirred until a heavy white cake forms. This cake is broken up and permitted to sit for one hour at ambient temperature. The white solid is filtered, washed with ether and dried and then hydrolyzed in water and extracted with ether. Concentration of the ether extracts leaves white crystals, mp 76—78°C, of 2-chloro-acetyl-1-(*o*-fluorobenzyl)pyrrole. The analogous treatment of *o*-fluorophenethylpyrrole produces 2-chloroacetyl-1-(*o*-fluorophenethyl)pyrrole.

b. Ethylamine is bubbled into a solution of 57.3 g of 2-chloroacetyl-1-(*o*-fluorobenzyl)pyrrole and 23.0 g of triethylamine in 400 ml of methanol over a 7 hour span. The methanol is evaporated off leaving an orange semi-solid which is washed with water and extracted with ether. The combined ether extracts are washed with water, dried and the ether removed leaving an orange oil which is treated with ethereal hydrogen chloride to produce a crystalline hydrochloride salt. The salt is recrystallized from an ethyl acetate-methanol mixture leaving white crystals, mp 178—179°C, of 1 - (*o* - fluorobenzyl) - 2 - [(ethylamino)acetyl]pyrrole hydrochloride. The analogous treatment of 2 - chloroacetyl - 1 - (*o* - fluorophenethyl)pyrrole produces 1 - (*o* - fluorophenethyl) - 2 - [(ethylamino) - acetyl]pyrrole hydrochloride.

c. A solution of 31.6 g of 1 - (*o* - fluorobenzyl) - 2 - [(ethylamino)acetyl]pyrrole, free base of step b, in 200 ml of isopropyl alcohol at ambient temperature is added dropwise to a suspension of 9.2 g of sodium borohydride in 200 ml of isopropyl alcohol at ambient temperature. After total addition the mixture is refluxed for 24 hours and the isopropyl alcohol removed in vacuo leaving a semi-solid. The semi-solid is treated with water for thirty minutes and the product extracted with ether and the ether extract is dried and concentrated leaving a crystalline solid which is recrystallised from a hexane-acetone mixture to give white crystals, mp 108—110°C, of 1 - [1 - (*o* -

fluorobenzyl) - 2 - pyrryl] - 2 - (ethylamino)ethanol. The analogous reduction and treatment of the free base of 1 - (*o* - fluorophenethyl) - 2 - (ethylamino)acetylpyrrole hydrochloride produces 1 - [1 - (*o* - fluorophenethyl) - 2 - pyrryl] - 2 - (ethylamino)ethanol.

d. A mixture of 14.5 g of 1 - [1 - (*o* - fluorobenzyl) - 2 - pyrryl] - 2 - (ethylamino)ethanol and 2.7 g of 57% sodium hydride in 200 ml of dimethylformamide under nitrogen at 70°C is stirred for 6 hours. The resulting dark brown solution is poured into 2.5 l of ice-water and treated with 5 ml of ammonium chloride solution. This mixture is allowed to stand for 20 hours and the resulting precipitate is filtered and recrystallized four times from hexane to give the solid, mp 60—61.5°C, of 4 - (ethylaminomethyl) - 4H,10H - pyrrolo[2,1-c][1,4]benzoxazepine.

Analysis:

Calculated for $C_{15}H_{18}N_2O$:	74.35% C;	7.49% H;	11.56% N
Found:	74.21% C;	7.54% H;	11.55% N

The condensation and treatment of 1 - [1 - (*o* - fluorophenethyl) - 2 - pyrryl] - 2 - (ethylamino)ethanol in analogous fashion produces 10,11 - dihydro - 4 - (ethylaminomethyl) - 4H - pyrrolo[2,1-c][1,4]benzoxazocine.

Example 2

a. Methylamine is bubbled into a solution of 22.7 g of 2-chloroacetyl-1-(*o*-fluorobenzyl)pyrrole, Example 1a, and 9.1 g of triethylamine in 140 ml of methanol over an 8 hour span. The solution is refluxed until the reaction ceases and then stirred at ambient temperature for 14 hours. The methanol is evaporated off leaving an orange semi-solid which is treated with water and extracted with methylene chloride. The extract is dried and the solvent removed leaving an orange oil which is acidified with ethereal hydrogen chloride to produce a crystalline hydrochloride salt. The salt is recrystallized from an ethyl acetate-methanol mixture to give light tan coloured crystals, mp 185—186°C, of 1 - (*o* - fluorobenzyl) - 2 - [(2 - methylamino)acetyl]pyrrole hydrochloride.

b. A solution of 6.4 g of 1 - (*o* - fluorobenzyl) - 2 - [(2 - methylamino)acetyl]pyrrole, free base of a, in 70 ml of isopropyl alcohol is added dropwise to a suspension of 2.0 g of sodium borohydride in 70 ml of isopropyl alcohol at ambient temperature. The resulting mixture is refluxed for 24 hours, the isopropyl alcohol removed in vacuo leaving a semi-solid. The semi-solid is treated with water for thirty minutes and extracted with ether. The ether extract is dried and the ether removed leaving a crystalline solid which is recrystallized from an hexane-acetone mixture to give 1 - [1 - (*o* - fluorobenzyl) - 2 - pyrryl] - 2 - (methylamino)ethanol.

c. 0.74 g of 57% sodium hydride is added portionwise at ambient temperature to a stirred solution under nitrogen of 3.1 g of 1 - [1 - (*o* - fluorobenzyl - 2 - pyrryl] - 2 - (methylamino)ethanol in 40 ml of dimethylformamide. The reaction mixture is heated slowly with stirring until the temperature is 70°C and then stirring at this temperature is continued for 5 hours. The mixture is allowed to cool to ambient temperature and is poured into ice-water to give a crystalline product after stirring and rubbing. The product is filtered, washed with water, chromatographed on silica and eluted with chloroform and then a chloroform-ethanol mixture to yield crystals. The crystals were combined and recrystallized from hexane to give white crystals, mp 78—79°C, of 4 - (methylaminomethyl) - 4H,10H - pyrrolo[2,1-c][1,4]benzoxazepine.

Analysis:

Calculated for $C_{14}H_{16}N_2O$:	73.66% C;	7.07% H;	12.27% N
Found:	73.84% C;	7.12% H;	12.32% N

Example 3

a. Dimethylamine is bubbled into a solution of 2-chloroacetyl-1-(*o*-fluorobenzyl)pyrrole, Example 1a, and 10.1 g of triethylamine in 100 ml of methanol at ambient temperature over an 8 hour span. The reaction solution is stirred for 14 hours. The solvent is removed leaving an orange semi-solid which is treated with water and extracted into methylene chloride. The extract is dried and the solvent removed leaving an orange oil. The oil is acidified with ethereal-hydrogen chloride to effect a crystalline hydrochloride salt which is recrystallized from an ethyl acetate-methanol mixture to yield white crystals, mp 194—195°C, of 1 - (*o* - fluorobenzyl) - 2 - (dimethylaminoacetyl)pyrrole hydrochloride.

b. The reduction and treatment of 1 - (*o* - fluoro - benzyl) - 2 - (dimethylaminoacetyl)pyrrole, free base of a, by the procedure of Example 2b produces 1 - [1 - (*o* - fluorobenzyl) - 2 - pyrryl] - 2 - (dimethylamino)ethanol as an oil. The oil is distilled to give the product as a colorless oil, bp 146°C/0.3 mm.

c. A solution of 9.6 g of 1 - [1 - (*o* - fluorobenzyl) - 2 - pyrryl] - 2 - (dimethylamino)ethanol in 60 ml of dimethylformamide is added portionwise under nitrogen to a stirred suspension of 1.84 g of 57% sodium hydride in dimethylformamide. The reaction is maintained at ambient temperature for 30 minutes and then is slowly raised to 70°C with stirring and stirring is continued at this elevated temperature for 4 hours. The mixture is permitted to cool to ambient temperature and then poured into ice-water. Upon rubbing the aqueous mixture crystals appear which are filtered off, washed with water, dried and recrystallized from petroleum ether to leave a white solid, mp 59—60.5°, 4 - (dimethylaminomethyl) - 4H,10H - pyrrolo[2,1-c][1,4]benzoxazepine.

Analysis:

Calculated for $C_{15}H_{18}N_2O$:	74.35% C;	7.49% H;	11.56% N
Found:	74.18% C;	7.65% H;	11.49% N

Example 4

a. A mixture of 18.9 g of 2-chloroacetyl - 1 - (*o* - fluorobenzyl)pyrrole, Example 1a, and 22.0 g of diethylamine in 65 ml of methanol is stirred at ambient temperature for 24 hours. The methanol is removed in vacuo leaving a dark semi-solid which is acidified in dilute hydrochloric acid and washed with ether. The aqueous phase is basified with a saturated sodium carbonate solution and extracted with ether. The ether extract is washed with a saturated sodium chloride solution, treated with charcoal and dried. The ether is removed leaving a reddish oil which upon distillation leaves a light yellow oil, bp 140°C/0.05 mm, 2 - (diethylaminoacetyl) - 1 - (*o* - fluorobenzyl)pyrrole.

b. A solution of 23.0 g of 2 - (diethylaminoacetyl) - 1 - (*o* - fluorobenzyl)pyrrole in 75 ml of isopropyl alcohol is added portionwise to a stirred suspension of 6.04 g of sodium borohydride in isopropyl alcohol at ambient temperature. After complete addition the reaction mixture is refluxed for 14 hours. The isopropyl alcohol is removed in vacuo leaving an orange semi-solid which is treated consecutively with water, a saturated sodium chloride solution and charcoal, and dried. The ether is removed leaving a yellow oil which is distilled (170°C/0.45 mm) to give a light yellow oil which upon standing in the cold solidifies to a light yellow solid, mp 28—29.5°C, 2 - (diethylamino) - 1 - [1 - (*o* - fluorobenzyl) - 2 - pyrryl]ethanol.

c. A solution of 7.26 g of 2 - (diethylamino) - 1 - [1 - (*o* - fluorobenzyl) - 2 - pyrryl]ethanol in 15 ml of dimethylformamide is added portionwise at ambient temperature under nitrogen to a suspension of 1.16 g of 57% sodium hydride in 25 ml of dimethylformamide. After complete addition the reaction mixture is permitted to sit for 1 hour at ambient temperature and then at 70°C for 5 additional hours. The mixture is cooled to ambient temperature and poured over ice. The resulting aqueous mixture is extracted with benzene, the benzene extract washed consecutively with water and a saturated sodium chloride solution and dried. The benzene solution is treated with charcoal, filtered and the benzene removed leaving a pale yellow oil which is dissolved in ether and cooled. The addition of ethereal-hydrogen chloride with stirring to the cool solution yields a salt as a white solid which is filtered off and washed twice by stirring in acetone to give a pale yellow solid, mp 159—160°C, 4 - (diethylaminomethyl) - 4H,10H - pyrrolo[2,1-c][1,4]benzoxazepine.

Analysis:

Calculated for $C_{17}H_{22}N_2O$. HCl:	66.53% C;	7.57% H;	9.13% N
Found:	66.58% C;	7.56% H;	9.20% N

Example 5

a. A mixture of 20.0 g of 2-chloroacetyl-1-(*o*-fluorobenzyl)pyrrole, Example 1a, 7.0 g of cyclopropylamine and 12.0 g of triethylamine in 150 ml of methanol is stirred for 4 hours at 50°C and then at ambient temperature for 20 additional hours. The methanol is removed leaving an orange semi-solid which is treated with water and then extracted into ether. The ether extract is washed with water, dried and filtered and the ether removed leaving an orange oil. The oil is converted to a hydrochloride salt which is recrystallized from an ethyl acetate-methanol mixture

to yield a solid product, mp 185—187°C, 2 - [(cyclopropylamino)acetyl] - 1 - (*o* - fluorobenzyl)pyrrole hydrochloride.

b. A solution of 8.0 g of 2 - (2 - cyclopropylamino) - acetyl - 1 - (*o* - fluorobenzyl)pyrrole, free base of a, in 100 ml of isopropyl alcohol is added to a suspension of 2.2 g sodium borohydride in 100 ml of isopropanol. The reaction mixture is refluxed at 85°C for 4 hours, allowed to cool to ambient temperature and 50 ml of methanol introduced. The solvent is removed leaving a yellow semi-solid which is treated with water and then extracted into ether. The ether extract is washed with water, dried and filtered and the solvent removed leaving a pure yellow oil, 2 - (cyclopropylamino) - 1 - [1 - (*o* - fluorobenzyl) - 2 - pyrryl]ethanol. Infrared and nuclear magnetic resonance spectra confirm this structure.

c. A solution of 6.5 g of 2 - (cyclopropylamino) - 1 - [1 - (*o* - fluorobenzyl) - 2 - pyrryl]ethanol in 100 ml of benzene is added to a suspension of 50% sodium hydride in 50 ml of benzene. The mixture is heated to reflux, then 25 ml of dimethylformamide added and the temperature is maintained at 85°C for 5 hours. The reaction mixture is permitted to cool to ambient temperature and poured into 500 ml water. The aqueous mixture is stirred for 10 minutes and then extracted with ether. The combined organic extracts are washed with water, dried and filtered and the solvent removed leaving a dark oil. The oil is dissolved in ether and converted to its oxalate salt which is recrystallized from a methanol-ether mixture to provide the solid product, mp 150°C dec., 4 - (cyclopropylaminomethyl) - 4H,10H - pyrrolo[2,1-c][1,4]benzoxazepine oxalate.

Analysis:

Calculated for $C_{16}H_{18}N_2O \cdot (CO_2H)_2$:	62.78% C;	5.85% H; 8.13 N
Found:	62.64% C;	6.00 H; 8.08% N.

Example 6

a. A mixture of 19.0 g of 2 - chloroacetyl - 1 - (*o* - fluorobenzyl)pyrrole, Example 1a, 7.05 g of n-propylamine and 12.0 g of triethylamine in 150 ml of methanol is stirred at ambient temperature for 20 hours and at 60°C for 4 additional hours. The mixture is allowed to cool and the solvent removed leaving a brown oil which is treated with water and extracted into ether. The ether extract is washed with water, dried and filtered and the solvent removed again leaving a brown oil. The oil is converted to a hydrochloride salt which is recrystallized from an ethyl acetate-methanol mixture to yield a salt, mp 135—137°C, 1 - (*o* - fluorobenzyl) - 2 - [(n - propylamino)acetyl]pyrrole hydrochloride.

b. The reduction and treatment of 1 - (*o* - fluorobenzyl) - 2 - [(2 - propylamino)acetyl]pyrrole, free base of a, by the procedure of Example 5b produces a pure brown oil, 1 - [1 - (*o* - fluorobenzyl) - 2 - pyrryl] - 2 - (propylamino)ethanol. Infrared and nuclear magnetic resonance spectra confirm this structure.

c. The condensation and treatment of 1 - [1 - (*o* - fluorobenzyl) - 2 - pyrryl] - 2 - (propylamino)ethanol by the procedure of Example 5c produces the oxalate salt, mp 170°C dec., of 4 - (propylaminomethyl) - 4H,10H - pyrrolo[2,1-c][1,4]benzoxazepine.

Analysis:

Calculated for $C_{16}H_{20}N_2O \cdot (CO_2H)_2$:	62.42% C;	6.40% H; 8.09% N
Found: H;	62.24% C;	6.65% H; 7.92% N

Example 7

a. A mixture of 16.0 g of 2 - chloroacetyl - 1 - (*o* - fluorobenzyl)pyrrole, Example 1a, 8.3 g of di-sec-butylamine and 20.0 g of potassium carbonate in 250 ml xylene is stirred at 120°C for 72 hours. The mixture is cooled, washed with water, dried and filtered and the xylene is evaporated leaving a brown oil. The oil is dissolved in ether and extracted into a 2N hydrogen chloride solution. The aqueous acidic solution is basified with a sodium carbonate solution and extracted with ether. The ether solution is washed, dried and filtered and the ether removed leaving a brown oil, 1 - (*o* - fluorobenzyl) - 2[(di-sec-butylamino)acetyl] - pyrrole. Infrared and nuclear magnetic resonance spectra confirm this structure.

b. The above acetyl compound is added to a suspension of 1.33 g of sodium borohydride in 200 ml of isopropyl alcohol. The reaction mixture is refluxed for 20 hours, allowed to cool to ambient temperature and the solvent removed leaving a white semi-solid which is treated with water and extracted into ether. The ether extract is washed with water, dried and filtered and the solvent removed leaving 1 -

[1 - (*o* - fluorobenzyl) - 2 - pyrryl] - 2 - (di-sec-butylamino)ethanol as a brown oil. Infrared and nuclear magnetic resonance spectra confirm this structure.

c. A solution of 7.0 g of 1-[1-(*o*-fluorobenzyl)2-pyrryl]-2-(disec-butylamino)ethanol in 100 ml of benzene is added to a suspension of 50% sodium hydride in 50 ml of benzene. The mixture is heated to reflux, 30 ml of dimethylformamide is added and refluxing continued for 4 hours. The reaction mixture is allowed to cool, poured into water and the two phase mixture is stirred for 15 minutes and extracted with ether. The combined organic extracts are washed with water, dried and filtered and the solvent removed leaving a brown oil. The oil is dissolved in ether and converted to its hydrochloride salt which is recrystallized from an ethyl acetate-methanol mixture to yield the solid product, mp 130°C dec., 4 - (di - sec - butylaminomethyl)4H,10H - pyrrolo[2,1 - c][1,4]benzoxazepine · hydrochloride.

Analysis:

Calculated for $C_{21}H_{30}N_2O$. HCl:	69.49% C;	8.61% H;	7.72% N
Found:	69.28% C;	8.62% H;	7.67% N

Example 8

a. A mixture of 12.0 g of 2-chloroacetyl-1-(*o*-fluorobenzyl)pyrrole, Example 1a, 9.0 g of aniline, and 9.0 g of triethylamine in 100 ml of n-butanol is stirred at 120°C for 24 hours. The mixture is allowed to cool to ambient temperature and the n-butanol removed leaving a brown oil. The oil is treated with water and extracted with ether. The combined ether extracts are washed with water, dried and filtered. Any residual unreacted aniline is selectively precipitated as the oxalate salt. The ether solution is evaporated leaving a yellow solid which is recrystallized from petroleum ether to give the product, mp 74—75°C, 2 - (2 - anilinoacetyl) - 1 - (*o* - fluorobenzyl)pyrrole.

b. The reduction and treatment of 2-(2-anilinoacetyl)-1-(*o*-fluorobenzyl)pyrrole by the procedure of Example 5b produces 2-anilino-1-[1-(*o*-fluorobenzyl)-2-pyrryl]ethanol as a brown oil. Infrared and nuclear magnetic resonance spectra confirm this structure.

c. The condensation and treatment of 2-anilino-1-[1(o-fluorobenzyl)-2-pyrryl]ethanol by the procedure of Example 5c produces a brown oil which is converted to a hydrochloride salt and recrystallized from a methanol-ether mixture to give the solid, mp 140°C, dec., 4-anilino-methyl-4H,10H-pyrrolo[2,1-c][1,4]benzoxazepine · hydrochloride.

Analysis:

Calculated for $C_{19}H_{18}N_2O$. HCl:	69.82% C;	5.86% H;	8.57% N
Found:	69.56% C;	5.90% H;	8.52% N

Example 9

a. A solution of (4-chloro-2-fluorobenzyl)pyrrole and chloroacetonitrile in ether is treated by the procedure described in Example 1a to produce 2-chloroacetyl-1-(4-chloro-2-fluorobenzyl)pyrrole.

b. A mixture of 14.3 g of 2-chloroacetyl-1-(4-chloro-2-fluorobenzyl)pyrrole, 3.65 g of diethylamine and 5.05 g of triethylamine in 75 ml of methanol is stirred at ambient temperature for 14 hours. To this mixture is added another 3.65 g of diethylamine and 5.05 g of triethylamine and the mixture is stirred at reflux for 3 hours. An additional 1.5 g of diethylamine is added and stirring and refluxing is continued for 2 hours. After the mixture is allowed to cool the methanol is removed leaving an orange semi-solid which is treated with water and extracted into ether. The ether extract is dried and the ether evaporated in vacuo leaving an orange oil. The oil is dissolved in ether, the ether solution is filtered and then acidified with ethereal hydrogen chloride to give a salt as a crystalline precipitate. The salt is recrystallized from an ethyl acetate-methanol mixture to produce white crystals, mp 165—166°C, of 1-(4-chloro-2-fluorobenzyl)-2-[(diethylamino)acetyl]pyrrole.

c. The reduction and treatment of 1-(4-chloro-2-fluorobenzyl)-2-[(2-diethylamino)acetyl]pyrrole by the procedure described in Example 5b produces a yellow oil, 1-[1-(4-chloro-2-fluorobenzyl)-2-pyrryl]-2-(diethylamino)-ethanol. Infrared and nuclear magnetic resonance spectra confirm this structure.

d. A solution of 7.6 g of 1-[1-(4-chloro-2-fluorobenzyl)-2-pyrryl]-2-(diethylamino)ethanol in 100 ml of benzene is added dropwise to a suspension of 50% sodium hydride in 50 ml benzene. After complete addition the mixture is heated to reflux, 30 ml of dimethylformamide is added and refluxing continued for 4 hours. The reaction mixture is allowed to cool and then poured into 1 l. of water and

stirred for 10 minutes. This mixture is extracted with ether and the combined organic extracts are washed with water, dried, treated with charcoal, filtered and the solvent removed leaving a brown oil. The oil is dissolved in ether and converted to its hydrogen chloride salt which is recrystallized from an ethyl acetate-methanol mixture (9:1) to yield the salt, mp 125°C dec., 7-chloro-4-(diethylaminomethyl)-4H,10H-pyrrolo[2,1-c][1,4]-benzoxazepine hydrochloride.

Analysis:

Calculated for $C_{17}H_{21}ClN_2O$. HCl:	59.82% C;	6.50% H;	8.21% N
Found:	60.29% C;	6.85% H;	8.31% N

Example 10

a. A solution of 11.0 g of 1 - (*o* - fluorobenzyl) - 2 - (dimethylaminoacetyl)pyrrole, free base of Example 3a, in ether is added dropwise to a stirring solution of n-propylmagnesium bromide which is prepared from 1.67 g of magnesium turnings and 8.4 g of n-propylbromide. The mixture is refluxed for 4 hours, allowed to cool, hydrolyzed with ice-water and treated with concentrated ammonium chloride solution to dissolve the magnesium hydroxide precipitate. The organic phase is separated and the aqueous phase extracted with ether and the organic phases are combined, washed with a 5% sodium bicarbonate solution and water and dried. Removal of the ether leaves a crude yellow oil which is distilled at 133—137°C/0.08 mm gives a light yellow oil, 1 - (dimethylamino) - 2 - [1 - (*o* - fluorobenzyl) - 2 - pyrryl] - 2 - hydroxypentane.

b. 1.4 g of 57% sodium hydride is added portionwise to a stirred solution of 7.1 g of 1 - (dimethylamino) - 2 - [1 - (*o* - fluorobenzyl) - 2 - pyrryl] - 2 - hydroxypentane in 70 ml of dimethylformamide at ambient temperature. The reaction mixture is carefully heated with stirring to 70°C over a 1 hour span and stirring is then maintained at this temperature for an additional 5 hours. The mixture is allowed to cool and poured into ice-water to give an oily product which is extracted into ether. The ether extract is washed with water, dried and the ether removed leaving an oil. The oil is dissolved in ether and the oxalate salt prepared. The salt is recrystallized from an ethyl acetate-methanol mixture to yield greyish crystals, mp 135—136°C, of 4 - (n - propyl) - 4 - (dimethylaminomethyl) - 4H,10H - pyrrolo[2,1-c][1,4] - benzoxazepine · oxalate.

Analysis:

Calculated for $C_{18}H_{20}N_2O$. $(CO_2H)_2$:	64.15% C;	7.00% H;	7.48% N
Found:	64.03% C;	7.06% H;	7.47% N

Example 11

a. A solution of 16.0 g of 1 - (*o* - fluorobenzyl) - 2 - (dimethylaminoacetyl)pyrrole, free base of Example 3a, in 60 ml of ether is treated with a solution of methylmagnesium iodide, prepared from 2.7 g of magnesium turnings and 15.3 g of methyl iodide, in 40 ml of ether according to the procedure described in Example 9a to produce a crude yellow oil, 1 - (dimethylamino) - 2 - [1 - (*o* - fluorobenzyl) - 2 - pyrryl] - 2 - hydroxypropane. Distillation at 130—138°C/0.1 mm gives the product as a faintly yellow oil.

b. 1.95 g of 57% sodium hydride is added portionwise to a solution of 8.3 g of 1 - dimethylamino - 2 - [1 - (*o* - fluorobenzyl) - 2 - pyrryl] - 2 - hydroxypropane in 80 ml of dimethylformamide at ambient temperature. The mixture is carefully heated with stirring to 70°C over a 1 hour span and stirring is continued at this temperature for an additional 5 hours. The mixture is allowed to cool and poured into ice-water giving an oil product which is extracted into ether. The ether extract is washed with water and dried and the solvent removed leaving a crude oil. The oil is purified by column chromatography (silica gel, eluted with ether), dissolved in ether and ethereal malonic acid is added to produce an amorphous malonate salt. This salt is washed well with ether and by the addition of an aqueous sodium carbonate solution the free base is recovered as an oil. The base is dissolved in ether and the oxalate salt prepared which is recrystallized from an ethyl acetate-methanol mixture to afford cream coloured crystals, mp 141—142.5°C, of 4 - methyl - 4 - (dimethylaminomethyl) - 4H,10H - pyrrolo[2,1-c][1,4]benzoxazepine . oxalate.

Analysis:

Calculated for $C_{18}H_{20}N_2O$. $(CO_2H)_2$:	62.42% C;	6.40% N;	8.09% N
Found:	62.19% C;	6.52% N;	8.00% N

Example 12

a. In a 500 ml three neck round bottom flask 8 g of dimethylformamide is cooled to 5°C and 16.9 g of phosphorous oxychloride is added dropwise with stirring while maintaining the temperature below 20°C. After total addition the mixture is stirred at ambient temperature for 15 minutes, 25 ml of ethylene dichloride introduced and the solution cooled to 5°C. The temperature of the solution is maintained at this low temperature with stirring during the addition of a solution of 17.5 g of 1-(*o*-fluorobenzyl)pyrrole, Example 1a, in 25 ml of ethylene dichloride. The reaction solution is stirred at this temperature for 30 minutes at ambient temperature for an additional 30 minutes and then refluxed under nitrogen for 5 hours. The mixture is allowed to cool to ambient temperature and a solution of 75 g of sodium acetate . trihydrate in 120 ml of water is added. The two phase mixture is stirred vigorously at ambient temperature for 15 minutes and then refluxed for 30 minutes. After the reaction mixture cools to ambient temperature the ethylene dichloride layer is removed and the aqueous phase is extracted with ether. The combined organic extracts are washed twice with a saturated sodium carbonate solution and once with a saturated sodium chloride solution and dried. Removal of the solvent leaves a light yellow oil which solidifies upon standing to a pale yellow solid which is recrystallized from an ether-hexane mixture to give nearly white crystals, mp 39—41°C, of 1 - (*o* - fluorobenzyl)pyrrole - 2 - carboxaldehyde.

b. To 2.4 g of magnesium turnings in 100 ml ether is added 1 ml dibromoethane and a crystal of iodine. When the reaction starts a solution of 12.1 g of dimethylaminopropyl chloride in 100 ml of ether is added under vigorous reflux over a 15 minute span. After total addition 100 ml of benzene is added and the mixture is refluxed at 45°C for 1 hour. The mixture is allowed to cool and a solution of 10.0 g of 1 - (*o* - fluorobenzyl)pyrrole - 2 - carboxaldehyde in 50 ml of ether is added and the mixture is stirred at 45°C for 20 hours. The reaction is allowed to cool, poured into 1 l. of ammonium chloride solution, stirred for 30 minutes and extracted with chloroform. The chloroform extract is washed well with water, dried and filtered and the solvent removed leaving a tan solid which is recrystallised from ether to leave the solid, mp 99—101°C, 1 - [1 - (*o* - fluorobenzyl) - 2 - pyrryl] - 4 - (dimethylamino)butanol.

c. A solution of 10.4 g of 1 - [1 - (*o* - fluorobenzyl) - 2 - pyrryl] - 4 - (dimethylamino)butanol in 100 ml of benzene is treated with a suspension of 2.2 g of 50% sodium hydride in 50 ml of benzene according to the procedure described in Example 8d to produce a brown oil. The oil is dissolved in ether and converted to its oxalate salt which is recrystallized from a methanol-ether mixture to afford the compound, mp 155°C dec., 4 - (dimethylaminopropyl) - 4H,10H - pyrrolo[2,1-c][1,4]benzoxazepine . oxalate.

Analysis:

Calculated for $C_{17}H_{22}N_2O \cdot (CO_2H)_2$:	63.32% C;	6.71% H;	7.77% N
Found:	63.18% C;	6.90% H;	7.93% N

Example 13

To a cooled solution of 2.8 g of 4 - propylamino - methyl - 4H,10H - pyrrolo[2,1-c][1,4]benoxazepine, Example 6c, and 3 ml of triethylamine in 50 ml of chloroform is added a solution of 2.3 g of phenylacetyl chloride in 25 ml of chloroform. The reaction mixture is stirred at ambient temperature for 24 hours, and the mixture is washed, dried and filtered. The solvent is evaporated off leaving a brown oil which is dissolved in 50 ml of tetrahydrofuran and this solution added to a refluxing solution of 1.0 g of lithium aluminum hydride in 100 ml of tetrahydrofuran. The mixture is refluxed at 65°C for 20 hours, cooled treated with 30 ml of a saturated ammonium chloride solution, filtered and diluted with ether. The combined organic layers are washed with water, dried and filtered and the solvent removed leaving a brown oil. The oil is dissolved in ether and converted to an oxalate salt which is recrystallized from a methanol-ether mixture to give the product, mp 125°C, dec., 4 - (N - phenethyl - N - propylaminoethyl) - 4H,10H - pyrrolo[2,1-c][1,4]benzoxazepine . oxalate.

Analysis:

Calculated for $C_{24}H_{28}N_2O \cdot (CO_2H)_2$:	69.31% C;	6.71% H;	6.22% N
Found:	68.73% C;	6.99% H;	6.37% N

Example 14

a. A solution of 25.0 g of 1 - (*o* - fluorobenzyl) - pyrrole - 2 - carboxaldehyde,

Example 12a, and 13.5 g of 1,3-propanedithiol in 200 ml of chloroform is stirred at ambient temperature for 1 hour and the mixture is cooled to −15°C. Hydrogen chloride gas is bubbled into the mixture over a 10 minute span and after stirring the reaction mixture for 20 hours at ambient temperature the mixture is washed successively with water; 10% potassium hydroxide solution, and water and dried. After filtering the solvent is evaporated leaving a yellow solid which is recrystallized twice from hexane to give an off-white solid, mp 105—106°C, 2 - [1-(*o* - fluorobenzyl) - 2 - pyrryl] - 1,3 - dithiane.

b. To a solution of 25.0 g of 2 - [1 - (*o* - fluorobenzyl) - 2 - pyrryl] - 1,3 - dithiane in 150 ml tetrahydrofuran at −60°C is added portionwise a solution of 50 ml of n-butyl lithium in hexane over a 30 minute span. After stirring at −20°C for 1 hour, the mixture is cooled to −60°C, and 12.4 g of dimethylaminoethyl chloride is added portionwise over a five minute span. The reaction mixture is stirred at −20°C for six hours and allowed to stand for 14 hours at 5°C and then stirred at ambient temperature for 4 additional hours. The mixture is filtered and the solvent evaporated off leaving a dark oil, which is converted to an oxalate salt. The salt is reconverted to the free base, purified on a silica gel column and eluted with chloroform to give the base as a solid which is recrystallised from hexane to give the solid, mp ~55°C, 2 - (2 - dimethylaminoethyl) - 2 - [1 - (*o* - fluorobenzyl) - 2 - pyrryl] - 1,3 - dithiane. Infrared and nuclear magnetic resonance spectra confirm this structure.

c. To a solution of 28.1 g of mercuric chloride and 10.3 g of calcium carbonate in 150 ml of aqueous 80% acetonitrile is added under nitrogen a solution of 17.0 g of 2 - (2 - dimethylaminoethyl) - 2 - [1 - (*o* - fluorobenzyl) - 2 - pyrryl] - 1,3 - dithiane in 100 ml of aqueous 80% acetonitrile. The reaction mixture is stirred at reflux for 4 hours, the mixture is permitted to cool and filtered through celite. The filter cake is washed with a hexane-dichloromethane mixture and the wash solution is washed successively with a 5M aqueous ammonium acetate solution and water, dried and filtered. The solvents are evaporated off leaving a dark oil which solidifies upon trituration with n-hexane to give the solid product 2 - (3 - dimethylaminopropionyl) - 1 - (*o* - fluorobenzyl)pyrrole.

d. The reduction of 2 - (3 - dimethylaminopropionyl) - 1 - (*o* - fluorobenzyl)pyrrole by the procedure described in Example 1c produces a 1 - [1 - (*o* - fluorobenzyl) - 2 - pyrryl] - 2 - (3 - dimethylamino) - 1 - propanol.

e. The condensation and treatment of 1 - [1 - (*o* - fluorobenzyl) - 2 - pyrryl] - 2 - (3 - dimethylamino) - 1 - propanol by the procedure described in Example 1d produces 4 - (dimethylaminoethyl) - 4H,10H - pyrrolo[2,1-c][1,4]benzoxazepine.

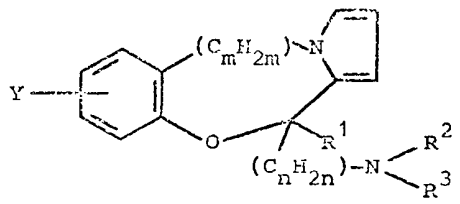
Example 15

a. To a solution of 4 - (diethylaminomethyl) - 4H,10H - pyrrolo[2,1-c][1,4]benzoxazepine and sodium bicarbonate in benzene at ambient temperature is added portionwise phenylchloroformate. The reaction mixture is allowed to stand for five hours and the benzene removed leaving 4 - [(N - ethyl - N - phenoxycarbonyl)aminomethyl] - 4H,10H - pyrrolo[2,1-c][1,4]benzoxazepine.

b. To a solution of 4 - [(N - ethyl - N - phenoxycarbonyl - aminomethyl] - 4H,10H - pyrrolo[2,1-c][1,4]benzoxapine in n-propanol is added potassium hydroxide solution and the reaction mixture allowed to stand for 5 hours. The mixture is washed and dried and the solvent removed leaving 4 - (ethylamino - methyl) - 4H,10H - pyrrolo[2,1-c][1,4]benzoxazepine.

WHAT WE CLAIM IS:—

1. A compound of the general formula



A

wherein

Y represents a hydrogen or halogen atom or a lower alkoxy, lower alkyl, trifluoromethyl, nitro or unsubstituted or substituted amino group;

R^1 represents a hydrogen atom or a lower alkyl group;

R^2 represents a hydrogen atom or an alkyl group having from 1 to 5 carbon atoms, a phenyl group, a cycloalkyl group having from 3 to 6 carbon atoms, a phenalkyl group having up to 3 carbon atoms in the alkyl moiety, a cycloalkylalkyl group having from 3 to 6 carbon atoms in the ring and up to 4 carbon atoms in the alkyl moiety, all these groups represented by R^2 being unsubstituted or substituted, or R^2 represents a radical of the general formula —COR^4, wherein R^4 represents a hydrogen atom or a lower alkyl group, a phenyl, benzyl or phenethyl group or a cycloalkyl group having from 3 to 6 carbon atoms, a cycloalkylalkyl group having from 3 to 6 carbon atoms in the ring and up to 3 carbon atoms in the alkyl moiety, or a phenoxy or lower alkoxy group and the group represented by R^4 may be unsubstituted or substituted;

R^3 represents an alkyl group having from 1 to 5 carbon atoms, a phenyl group, a cycloalkyl group having from 3 to 6 carbon atoms, a phenalkyl group having up to 3 carbon atoms in the alkyl moiety (provided that the group NR^2R^3 does not contain two phenalkyl groups with branched chain alkyl moieties) or a cycloalkylalkyl group having from 3 to 6 carbon atoms in the ring and up to 4 carbon atoms in the alkyl moiety, and the group represented by R^3 may be unsubstituted or substituted;

m is 1 or 2, and

n is 1, 2 or 3.

2. A compound as claimed in claim 1, wherein R^2 represents a hydrogen atom or an alkyl, phenyl or cycloalkyl group or a phenalkyl group of the formula $C_6H_5(CH_2)_{n'}$— or a cycloalkylalkyl group having from 4 to 7 carbon atoms and R^3 represents an alkyl, phenyl or cycloalkyl group or a phenalkyl group of the formula $C_6H_5(CH_2)_{n''}$— or a cycloalkylalkyl group having from 4 to 7 carbon atoms, wherein n' and n'', which may be the same or different, each is 1, 2 or 3.

3. A compound as claimed in claim 1 or claim 2, wherein Y represents a hydrogen or halogen atom.

4. A compound as claimed in claim 3, wherein R^1 represents a hydrogen atom or a methyl, ethyl or propyl group; R^2 represents a hydrogen atom or a lower alkyl group; R^3 represents a lower alkyl group, a phenyl group, a phenalkyl group of the formula $C_6H_5(CH_2)_{n'}$— or a cycloalkyl group and n' is 1, 2 or 3.

5. A compound as claimed in claim 4, wherein Y represents a hydrogen or chlorine atom.

6. A compound as claimed in claim 5, wherein n is 1.

7. A compound as claimed in claim 5, wherein n is 2.

8. A compound as claimed in claim 5, wherein n is 3.

9. A compound as claimed in claim 3, wherein R^2 represents a group of the formula COR^4 and R^3 represents a lower alkyl group or a phenyl or cycloalkyl group.

10. A compound as claimed in claim 9, wherein n is 1.

11. A compound as claimed in any one of claims 1 to 10, wherein m is 1.

12. A compound as claimed in any one of claims 1 to 10, wherein m is 2.

13. A compound as claimed in claim 1 or claim 2, wherein R^1 represents a hydrogen atom and n is 1.

14. A compound as claimed in any one of claims 1 to 5, 7 to 9 and 12, wherein C_nH_{2n} and C_mH_{2m} are each straight chain groups.

15. 4-(ethylaminomethyl)-4H,10H-pyrrolo[2,1-c][1,4]benzoxazepine.

16. 4-(Methylaminoethyl)-4H,10H-pyrrolo[2,1-c][1,4]benzoxazepine.

17. 4-(Cyclopropylaminomethyl)-4H,10H-pyrrolo[2,1-c][1,4]benzoxazepine.

18. 4-(Dimethylaminomethyl)-4H,10H-pyrrolo[2,1-c][1,4]benzoxazepine.

19. 4-(Diethylaminomethyl)-4H,10H-pyrrolo[2,1-c][1,4]benzoxazepine.

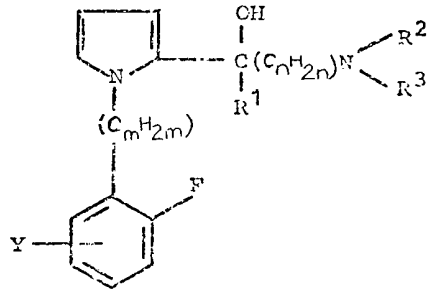
20. A compound as claimed in claim 1, which is listed in any one of Examples 1 to 15 or in Table 1 herein.

21. An acid addition salt of a compound as claimed in any one of claims 1 to 20.

22. A physiologically tolerable acid addition salt of a compound as claimed in any one of claims 1 to 20.

23. A process for the preparation of a compound as claimed in claim 1 or an acid addition salt thereof, which comprises

I) cyclising a compound of the general formula



B

in which Y, R^1, R^2, R^3, m and n have the meanings given in claim 1 but R^2 is not a group of the formula COR^4 and, if desired,

i) a) reacting a compound of the general formula A in which R^2 represents an alkyl, phenyl, cycloalkyl, phenalkyl or cycloalkylalkyl group as specified in claim 1 with an alkyl or aryl chloroformate to give a compound of the general formula A in which $R^2=COR^4$ where R^4 represents an alkoxy or phenoxy group as specified in claim 1, and, optionally,

b) hydrolysing this compound to give one of the general formula A in which R^2 represents a hydrogen atom, or

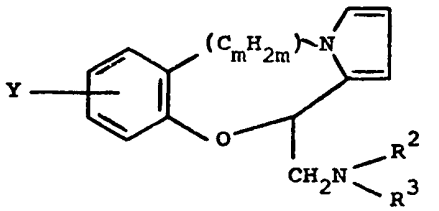
ii)a) reacting a compound of the general formula A in which R^2 represents a hydrogen atom with a compound of the general formula R^4COX wherein R^4 represents a hydrogen atom, or a lower alkyl, lower alkoxy, phenoxy, phenyl, benzyl, phenethyl, cycloalkyl or cycloalkylalkyl group as specified in claim 1, X represents a bromine, fluorine or chlorine atom, to give an amide compound of the general formula A in which $R^2=COR^4$, and, optionally,

b) reducing this amide compound of the general formula A to give another compound of the general formula A in which R^2 represents an alkyl, phenalkyl or cycloalkylalkyl group, or as specified in claim 1,

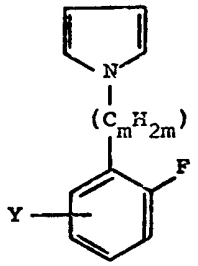
II) i) hydrolysing a compound of the general formula A in which R^2 represents a group of the formula COR^4 wherein R^4 represents an alkoxy or phenoxy group as specified in claim 1, to give a compound of the general formula A in which R^2 represents a hydrogen atom, or

ii) reducing a compound of the general formula A in which R^2 represents a group of the formula COR^4 and R^4 represents a hydrogen atom or a lower alkyl, lower alkoxy, phenoxy phenyl, benzyl, phenethyl, cycloalkyl or cycloalkylalkyl group as specified in claim 1, to give a compound of the general formula A in which R^2 represents an alkyl, phenalkyl or cycloalkylalkyl group as specified in claim 1.

24. A process for the preparation of an aminoalkylpyrrolobenzoxazalkane of the general formula

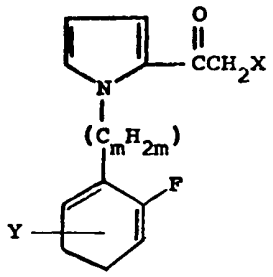


wherein Y, R^2, R^3 and m are as defined in claim 1 and $R^2 \neq COR^4$, which comprises reacting a compound of the general formula



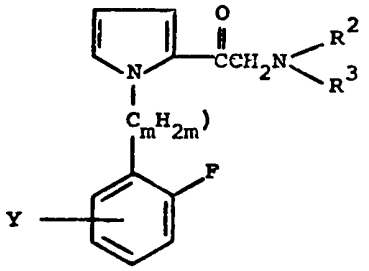
II'

with a halogenated acetonitrile and introducing hydrogen chloride gas into the reaction solution forming a ketimine; hydrolysing this ketimine to produce a haloketone of the general formula



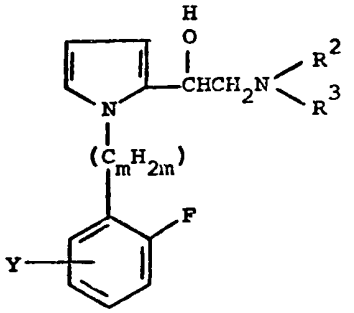
III'

wherein X represents chlorine or bromine; reacting this haloketone with an amine of the general formula $H_2NR^2R^3$ wherein R^2 does not represent a group of formula COR^4, to produce a pyrrylamino ketone of the formula



IV'

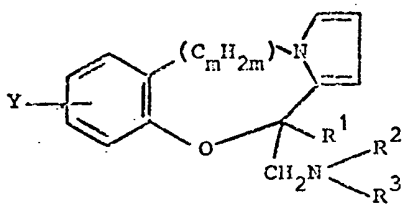
reducing the pyrrylamino ketone to a pyrrylamino ethanol of the general formula



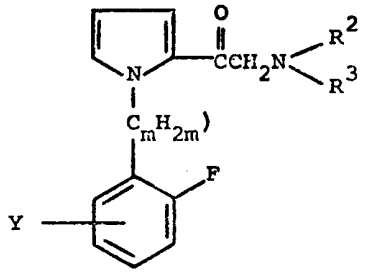
V'

and cyclising this pyrrylamino ethanol to form the aminoalkyl-pyrolobenzoxazalkene.

25. A process for the preparation of an aminoalkylpyrrolobenzoxazalkane of the general formula

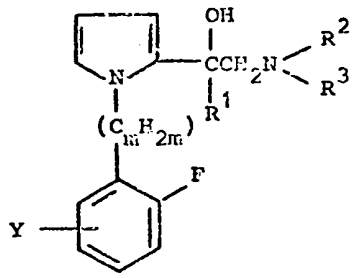


wherein Y, R^2, R^3 and m are as defined in claim 1, $R^2 \neq COR^4$ and R^1 represents lower alkyl which comprises reacting a pyrrylaminoketone of the general formula



IV'

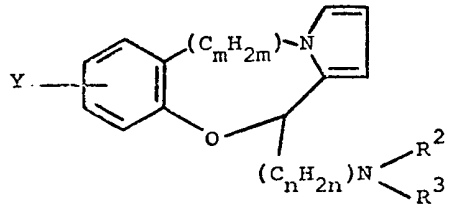
in which R^2 does not represent a group of the formula COR^4, with a Grignard reagent of the general formula R^1MgX wherein X represents bromine or chlorine; hydrolysing the reaction mixture to form a pyrrylamino alkanol of the general formula



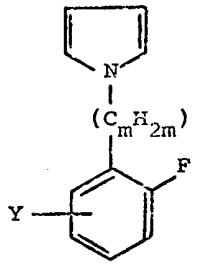
VII'

and cyclising this pyrrylamino alkanol to form the aminoalkylpyrrolobenzoxazalkane.

26. A process for the preparation of an aminoalkylpyrrolobenzoxazalkane of the formula

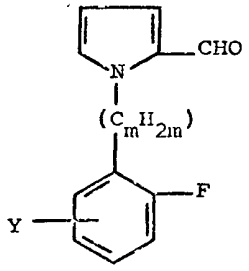


wherein Y, R^3 and m are as defined in claim 1, R^2 is as defined in claim 1 but does not represent hydrogen or COR^4 and n is the integer 2 or 3 which comprises formylating an ortho-fluorophenylalkylpyrrole of the general formula



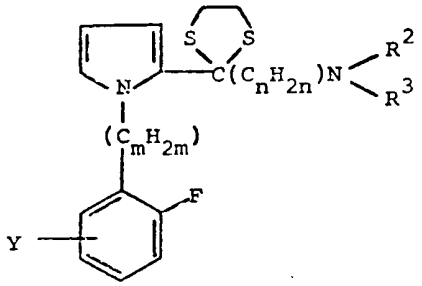
II'

to form an aldehyde of the general formula



VIII'

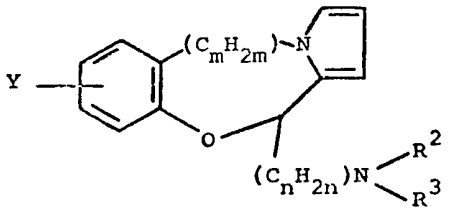
reacting this aldehyde with a Grignard reagent of the general formula $R^2R^3N(C_nH_{2n})MgX$ wherein n=2 or 3 and X represents bromine or chlorine to form a pyrrylamino butanol of the general formula



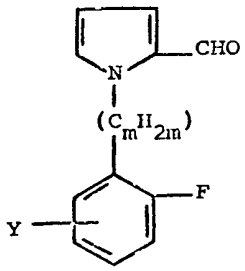
XI'

and cyclising this pyrrylamino butanol to form the aminoalkyl-pyrrolobenzoxazalkane.

27. A process for the preparation of an aminoalkyl pyrrolobenzoxazalkane of the formula

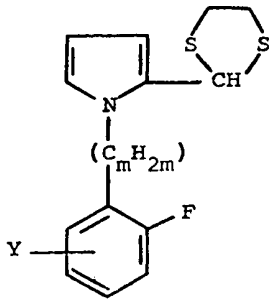


wherein Y, R^3 and m are as defined in claim 1; R^2 is as defined in claim 1 but does not represent hydrogen or COR^4 and n is 2 or 3 which comprises reacting an aldehyde of the general formula



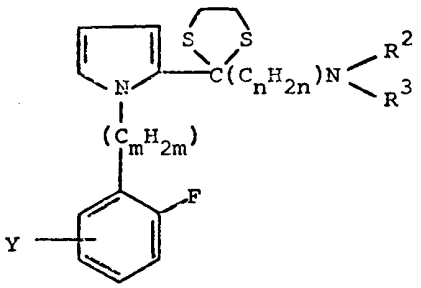
VIII'

with 1,3-propanedithiol to form a dithiane of the general formula



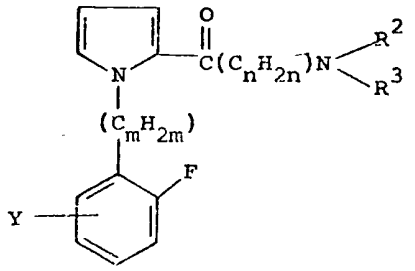
X'

converting this dithiane to a pyrrylaminodithiane of the general formula



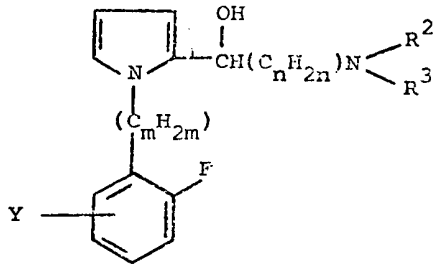
XI'

by reacting the dithiane with n-butyl lithium and with a dialkylaminoalkyl halide of the general formula $R^2R^3N(C_nH_{2n})X$ wherein X represents bromine or chlorine to form the pyrrylaminodithiane; converting this pyrrylaminodithiane to a pyrrylaminoketone of the general formula



XII'

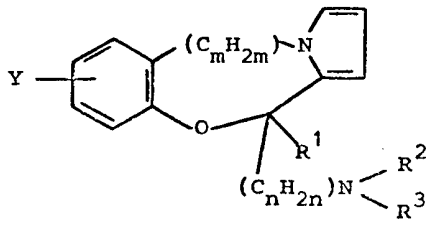
reducing this pyrrylamino ketone to a pyrrylamino alkanol of the general formula



XIII'

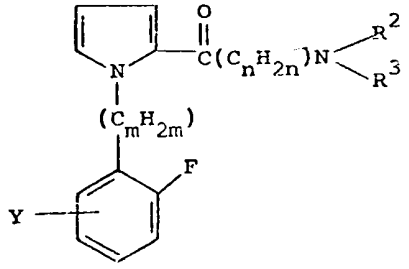
and cyclising this pyrrylamino alkanol to form the aminoalkylpyrrolobenzoxazalkane.

28. A process for the preparation of an aminoalkylpyrrolobenzoxazalkane of the general formula



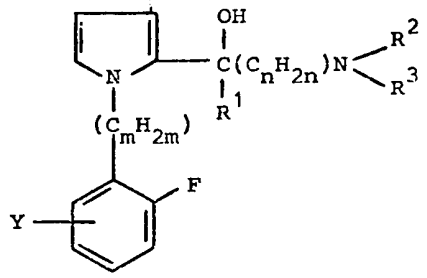
VI'

wherein Y, R^3 and m are as defined in claim 1, n=2 or 3, R^1 represents a lower alkyl group, R^2 is as defined in claim 1 but does not represent hydrogen or COR^4, which comprises reacting a pyrrylamino ketone of the formula



XII'

with a Grignard reagent of the general formula R^1MgX; hydrolysing the reaction mixture to form a pyrrylamino alkanol of the general formula



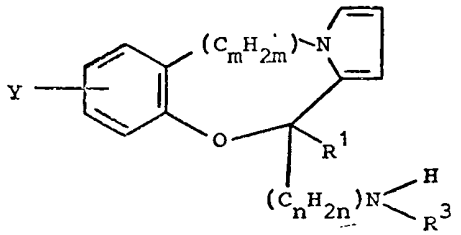
XIV'

and cyclising this pyrrylamino alkanol to form the aminoalkylpyrrolobenzoxazalkane.

29. A process as claimed in any one of claims 23 to 28, wherein the cyclisation is carried out in the presence of a base.

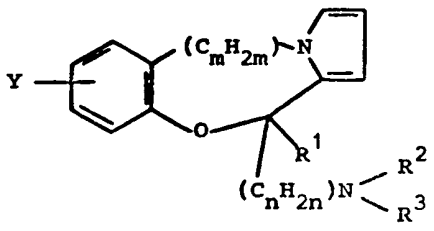
30. A process as claimed in claim 29, wherein the base is sodium hydride.

31. A process for the preparation of a mono-substituted aminoalkylpyrrolobenzoxazalkane of the general formula



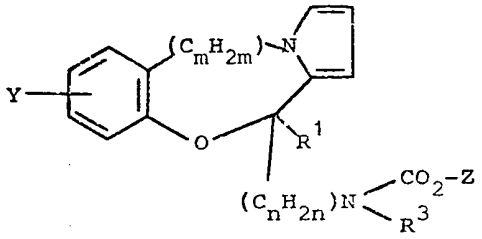
XVI'

wherein Y, R^1, R^3, m and n are as defined in claim 1, which comprises reacting a compound of the general formula



VI'

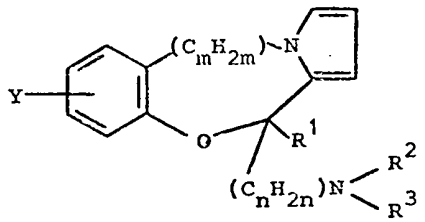
wherein R^2 does not represent hydrogen or a group of the formula COR^4 with a phenylchloroformate or an alkylchloroformate to form a phenoxy- or alkoxycarbonyl compound of the general formula



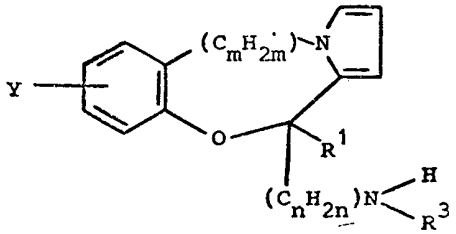
XV'

wherein Z represents phenyl or lower alkyl and hydrolysing this phenoxy or alkoxy carbonyl compound to form the mono-substituted aminoalkyl-pyrrolobenzoxazalkane.

32. A process for the preparation of an aminoalkylpyrrolobenzoxazalkane of the general formula

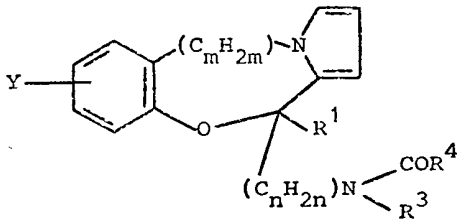


wherein Y, R^1, R^3, m and n are as defined in claim 1 and R^2 represents an unsubstituted or substituted alkyl, phenylalkyl or cycloalkylalkyl group, which comprises reacting a mono-substituted aminoalkylpyrrolobenzoxazalkane of the general formula



XVI'

with a carbonyl halide of the general formula R^4COX wherein R^4 represents a straight or branched chain alkyl group having from 1 to 4 carbon atoms, a phenyl, benzyl or phenethyl group or a cycloalkylalkyl group having from 3 to 6 carbon atoms in the cycloalkyl moiety and 1 to 3 carbon atoms in the alkyl moiety, or a cycloalkyl group having from 3 to 6 carbon atoms, and R^4 is unsubstituted or substituted, and X represents bromine, fluorine or chlorine, to form a N-carbonylamino compound of the general formula



XVII'

and reducing this N-carbonylamino compound to the aminoalkyl-pyrrolobenzoxazalkane.

33. A process as claimed in claim 23, carried out substantially as described in any one of the Examples 1 to 15 herein.

34. A compound as claimed in claim 1, whenever prepared by a process as claimed in any one of claims 23 to 33.

35. An acid addition salt of a compound claimed in claim 1, whenever prepared by a process as claimed in any one of claims 23 to 33.

36. A physiologically tolerable acid addition salt of a compound claimed in claim 1, whenever prepared by a process as claimed in any one of claims 23 to 33.

37. A pharmaceutical preparation which comprises a compound as claimed in any one of claims 1 to 20, 22, 34 and 36, in admixture or conjunction with a pharmaceutically suitable carrier.

38. A pharmaceutical preparation as claimed in claim 37, which is in dosage unit form.

39. A pharmaceutical preparation as claimed in claim 37 or claim 38, which is in a form suitable for oral administration.

40. A pharmaceutical preparation as claimed in claim 39, which contains from 1 to 300 mg of active ingredient per dosage unit.

41. A pharmaceutical preparation as claimed in claim 37 or claim 38, which is in a form suitable for parenteral administration.

42. A pharmaceutical preparation as claimed in claim 41, which contains from 0.5 to 100 mg of active ingredient per dosage unit.

43. A pharmaceutical preparation as claimed in any one of claims 37 to 42, wherein R^2 represents a hydrogen atom or an alkyl, phenyl, cycloalkyl, phenalkyl or cycloalkylalkyl group.

44. A process for the manufacture of a pharmaceutical preparation, which comprises bringing a compound as claimed in any one of claims 1 to 20, 22, 34 and 36, in admixture or conjunction with a pharmaceutically suitable carrier and/or a stabiliser into a form suitable for therapeutic use.

45. A method of treating pain in a non-human animal, which comprises administering to the animal a compound as claimed in any one of claims 1 to 20, 22, 34 and 36 or a pharmaceutical preparation as claimed in any one of claims 37 to 44.

46. A method of depressing the central nervous system in a non-human animal, which comprises administering to the animal a compound as claimed in any one of claims 1 to 20, 22, 34 and 36 or a pharmaceutical preparation as claimed in any one of claims 37 to 44.

47. A method of treating convulsions in a non-human animal, which comprises administering to the animal a compound as claimed in any one of claims 1 to 20, 22, 34 and 36 or a pharmaceutical preparation as claimed in any one of claims 37 to 44.

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