Description

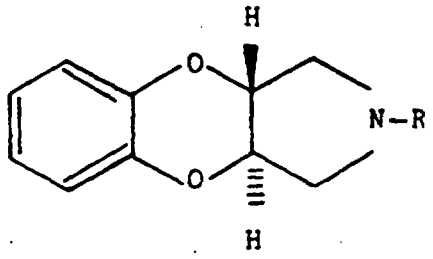
This invention relates to heterocyclic amino compounds. More specifically this invention relates to benzodioxinopyrrole derivatives, to processes for the preparation thereof, to pharmaceutical preparations contining them, and to their use in medicine.

The alpha (α)-adrenoreceptors of the sympathetic nervous system are classified pharmacologically into two sub-groups, namely α_1 and α_2. The α_2- type are situated predominantly on the presynaptic terminals of noradrenergic neurones and are activated by the released neurotransmitter. Such activation results in a diminished release of noradrenaline on subsequent stimulation of the neurones, the α_2-adrenoreceptors thus forming part of an autoinhibitory feedback mechanism for regulating the synaptic concentration of the neurotransmitter. A selective α_2-adrenoreceptor antagoninist would be expected to produce an increase in the synaptic concentrations of noradrenaline by blocking the autoinhibitory feedback mechanism and would thus be of potential value in human medicine for the treatment of disorders such as depression which are associated with a deficiency of noradrenaline at postsynaptic adrenoreceptors.

α_2-Adrenoreceptors also occur at non-neuronal sites such as on blood-platelets, in pancreatic islet cells, on adipocytes and in the proximal tubules of the kidney. Activation of α_2-adrenoreceptors at these sites leads to platlet aggregation, inhibition of insulin release, inhibition of lipolysis and retention of sodium respectively.

A selective α_2-adrenoreceptor antagonist thus has a potential therapeutic use as an antidepressant either alone or in a complementary combination with an established antidepressant, and in either treating or preventing conditions such as migraine, thrombosis, diabetes, obesity, hypertension, constipation, paralytic ileus and senile dementia

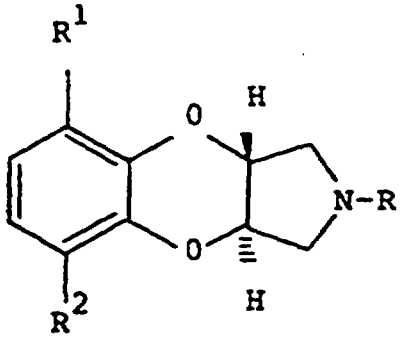
French Patent Application FR—A—2534921 (filed 25th October 1983, published 27th April 1984) describes compounds of the formula:



(wherein R is H, C_{1-6} alkyl optionally substituted by C_{3-7}-cycloalkyl, C_{3-6} alkenyl or alkynyl, C_{3-7} cycloalkyl, aralkyl or —CHO) and physiologically acceptable salts thereof, which have selective α_2-adrenoreceptor antagonist action.

We have now found that the compounds of formula (I) below and their physiologically acceptable salts nave a selective α_2-adrenoreceptor antagonist action.

The invention thus provides compounds of general formula (I)



wherein

R is a hydrogen atom or a group selected from C_{1-6} alkyl (optionally substituted by C_{3-7} cycloalkyl), C_{3-6} alkenyl, C_{3-6} alkynyl, C_{3-7} cycloalkyl, aralkyl (in which the alkyl moiety contains 1—5 carbon atoms) and —CHO;

R^1 is a halogen atom or a group selected from C_{1-4} alkyl, C_{1-4} alkoxy, hydroxyl, cyano, nitro and $-NR^3R^4$ where R^3 and R^4 is each a hydrogen atom or a C_{1-4} alkyl group; and

R^2 is a hydrogen atom, a halogen atom or is a group as defined above for R^1;

and the physiologically acceptable salts and hydrates thereof.

In general formula (I), the alkyl, alkenyl and alkynyl groups represented by R, R^1 and R^2 may be straight or branched chain groups.

When R contains a —C=C— or —C≡C— linkage this is not directly attached to the nitrogen atom. When R is alkyl it may be, for example, methyl, ethyl or propyl, methyl being preferred. When R is an alkyl group substituted by a C_{3-7} cycloalkyl group it may be, for example, cyclopronyl C_{1-3} alkyl such as

cyclopropylmethyl. When R is alkenyl it may be, for example, allyl and when R is alkynyl it may be, for example, propynyl. When R is cycloalkyl it may be, for example, cyclopropyl. When R is an aralkyl group it may be, for example phenC_{1-5}alkyl, such as benzyl.

The halogen atoms represented by R^1 and R^2 may be fluorine, chlorine, bromne or iodine atoms. Examples of alkyl and alkoxy groups represented by R^1 and R^2 are methyl, ethyl, methoxy and ethoxy groups. The group $—NR^3R^4$ may be, for example, an amino, methylamino, ethylamino, dimethylamino or diethylamino group.

Suitable physiologically acceptable salts are the acid addition salts formed with inorganic acids, for example hydrochlorides, hydrobromides, phosphates and sulphates, and with organic acids, for example citrates, tartrates, acetates, maleates and succinates. The hydrochlorides are particularly useful.

It will be appreciated that each compound of general formula (I) is a *trans* isomer and exists as two enantiomers. The structural formulae herein are to be understood to depict either enantiomer of each compound as well as mixtures of the enantiomers, including racemates, even though the precise structure as set out only relates to one enantiomer.

A preferred group of compounds of general formula (I) is that wherein R is a hydrogen atom. Another preferred group of compounds of general formula (I) is that wherein R is a C_{1-3} alkyl group, particularly a methyl or ethyl group.

In a further preferred group of compounds of formula (I) R^1 is a halogen atom or a C_{1-4} alkyl or C_{1-4} alkoxy group, in particular a chlorine or fluorine atom or a methyl or methoxy group.

A further preferred group of compounds of formula (I) is that in which R^2 is a hydrogen or fluorine atom, particularly a hydrogen atom.

Particularly important compounds of formula (I) are those in which, R is a hydrogen atom or a methyl or ethyl group, particularly a hydrogen atom; R^1 is a chlorine or fluorine atom or a methyl or metnoxy group, particularly a chlorine or fluorine atom and especially a flourine atom; and R^2 is a hydrogen or fluorine atom, especially a hydrogen atom.

Important compounds are (±)-*trans*-2,3,3a,9a-tetrahydro-5-methyl-1H-[1,4]benzodioxino[2,3-c]pyrrole, and its 3aS- and 3aR-isomers; (±)-*trans*-5-chloro-2,3,3a,9a-tetrahydro-1H-[1,4]baenzodioxino[2,3-c]-pyrrole, and its 3aS- and 3aR-isomers) (±)-*trans*-5,8-difluoro-2,3,3a,9a-tetrahydro-1H-[1,4]benzodioxino[2,3-c]pyrrole and its 3aS- and 3aR-isomers; and their physiologically acceptable salts and hydrates, particularly the hydrochlorides.

Particularly important compounds, by virtue of their especially useful biological profiles, are (±)-*trans*-5-fluoro-2,3,3a,9a-tetrahydro-1H-[1,4]benzodioxino[2,3-c]pyrrole and its 3aS- and 3aR-isomers and their physiologically acceptable salts and hydrates, particularly the hydrochlorides.

The compounds of the invention have selective α_2-adrenoreceptor antagnostic action. The test for determining the α_2-adrenoreceptor antagonist action is based on the ability to prevent the action of the selective α_2-adrenoreceptor agonist such as clonidine or 5-bromo-N-(4,5-dihydro-1H-imidazol-2-yl)-6-quinoxalinamine, [R—(R*R*)]-2,3-dihydroxybutanedioate (UK 14304—18) on the rat field stimulated vas deferens preparation.

Clonidine and UK 14304—18 inhibit the twitch response of the rat isolated vas deferens to low frequency motor nerve stimulation. This inhibition is a consequence of activation of presynaptic adrenoreceptors of the α_2-type. Antagonism of the effect of clonidine or UK 14304—18 is quantified by measuring the parallel shift to the right of the inhibitory α_2-adrenoreceptor agonist log $_{10}$ (concentration)/ response curve in the presence of increasing concentrations of the antagonist. Potency and competitiveness of antagonism are determined by the method of Arunlakshana & Schild (Br.J.Pharmac. 1959, *14* 48—58).

The α-adrenoreceptor-type selectivity of the compounds of general formula (I) is similarly assessed by measuring the ability to produce a parallel shift to the right of the $\log_{10}$ (concentration)/response cure for the α_1-adrenoreceptor agonist phenylephrine. The α_1-adrenoreceptor-mediated responses of phenylephrine measured were contractions of the rat isolated anococcygeus muscle (Leighton, Butz & Parameter, Eur.J.Phamac., 1979, *58* 27—38).

The compounds of the invention are thus of interest in the treatment or prevention of migraine, thrombosis, diabetes, obesity, hypertension, constipation, paralytic ileus and senile dementia, and in particular for the treatment of depression.

According to a further aspect, the invention provides compounds of general formula (I) and their physiologically acceptable salts for use in the therapy or prophylaxis of migraine, thrombosis, diabetes, obesity, hypertension, constipation, paralytic ileus and senile dementia and in particular depression. The compounds of the invention may be used either alone or with an additional active ingredient. Thus, for example, in the treatment of depression, the compound of the invention may be used alone, or may be co-administered with an established antidepressant (e.g. desmethylimipramine, imipramine or amitriptyline) either in a single formulation or in separate formulations. The established antidepressant can be used in accordance with conventional practice.

The compounds according to the invention may be formulated in a conventional manner, optionally together with one or more other active ingredients, for administration by any convenient route for example for oral, rectal, intravenous or intramuscular administration. Oral administration is preferred.

Thus according to another aspect, the invention provides a pharmaceutical composition comprising a

compound of general formula (I) and/or a physiologically acceptable salt thereof together with a physiologically acceptable carrier or excipient. The composition may optionally contain an additional active ingredient, for example an antidepressant such as desmethylimipramine, imipramine or amitriptyline.

For oral administration, the pharmaceutical composition may take the form of, for example, tablets, capsules, powders, solutions, syrups or suspensions prepared by conventional means with physiologically acceptable excipients.

Compositions for rectal administration may be in the form of suppositories using a conventional suppository excipient.

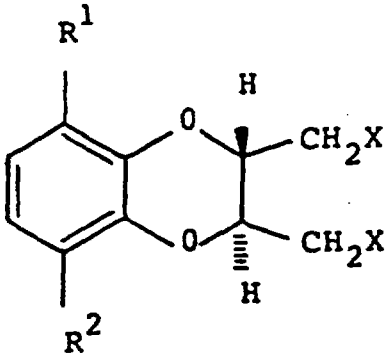
The compounds may be formulated for intravenous or intramuscular administration in dry form for reconstitution before use, or as a sterile solution or suspension.

A proposed daily dose for administration to man is 0.01 to 10mg/kg, for example 0.05 to 3mg/kg, which may be conveniently administered in 1 to 3 doses per day. The precise dose administered will of coure depend on the age and condition of the patient. The daily dosage may conveniently be administered in the form of dosage units, each unit containing for example 0.01 to 3 mg/kg of active ingredient.

The compounds according to the invention may be prepared by a number of processes. In the following description the groups R, R^1 and R^2 are as previously defined for general formula (I) except where otherwise indicated.

It will be appreciated that certain of the reactions described below are capable of affecting other groups in the starting material (e.g. nitro, cyano) which are desired in the end product; care must therefore be taken in accordance with conventional practice, either to use reaction conditions under which such groups remain substantially inert, or to perform the reaction as part of a sequence which avoids its use when such groups are present in the starting material.

According to a first example (A), a compound of general formula (I) may be prepared by amination of a compound of general formula (II).



(where X is a leaving group such as a halogen atom, (e.e. chlorine, bromine or iodine), or a hydrocarbylsulphonyloxy group (e.g. methylsulphonyloxy)] with ammonia, aqueous ammonia or an amine of formula RNH_2 where R is as previously defined except that R is not a hydrogen atom or the group —CHO.

In a particular embodiment of this process, following the amination reaction, the resulting compound of general formula (I) or a salt thereof, may be converted into another compound of general formula (I). Thus, for example, when R is arylmethyl, the amination reaction may optionally be followed by removal of the arylmethyl group to yield a compound of formula (I) where R is a hydrogen atom.

The amination reaction is conveniently effected at an elevated temperature e.g. under refux or in a sealed tube at e.g. 110°C, preferably in the presence of a suitable base e.g. sodium hydride or an alkali metal hydroxide such as sodium hydroxide, or in the presence of an excess of the amine RNH_2 optionally in the presence of a solvent such as a chlorinated hydrocarbon e.g. chloroform or an ether e.g. dioxan, or an alcohol eg ethanol. Optional removal of an arylmethyl group may be carried out, for example, by hydrogenolysis or, where appropriate, under acidic conditions, as described below.

According to another example (B), a compound of general formula (I) where R represents a hydrogen atom may be prepared by deprotection of a corresponding compound where R represents a protecting group. Suitable protecting groups include, for example, arylmethyl and acyl groups. Conventional deprotection procedures may be used. For example, where appropriate an arylmethyl group (e.g. benzyl) may be removed by hydrogenolysis using, for example, hydrogen in the presence of a catalyst, such as platinum or palladium on a support (e.g. charcoal), in a solvent such as an alcohol e.g. methanol. Alternatively, where appropriate, an arylmethyl group (e.g. trityl or bis (4-methoxyphenyl) methyl) may be removed under acidic conditions, using for example an acid such as trifluoroacetic acid, formic acid, hydrochloric acid or hydrobromic acid. Acyl groups may be removed by hydrolysis using an acid such as a mineral acid or a base such as an alkali metal hydroxide as appropriate. The protected starting materials for this process may be prepared using standard methods for the protection of amines, for example as described by McOmie (see above).

According to a further example (C), a compound of general formula (I) where R represents an alkyl group may be prepared by reduction of the corresponding compound in which R is an acyl group using a reducing agent such a lithium aluminium hydride or diborane in a suitable solvent such as ether or tetrahydrofuran at an elevated temperature e.g. reflux. Suitable acyl groups are, for example, formyl, acetyl, or carbonyoxyalkyl e.g. carbonyloxymethyl. The intermediate starting materials for this reaction may be prepared by acylation using conventional methods, for example by reaction of the compound of formula (I) in which R represents a hydrogen atom, with an acid chloride, acid anhydride, or ester.

Compounds of formula (I) in which R_1 and/or R_2 is cyano may be prepared by heating the corresponding carboxamide with a dehydrating agent such as phosphorus pentoxide (P_2O_5). The carboxamide may be prepared by methods analogous to those described herein for the preparation of a compound of formula (I).

The product of any of the processes (A), (B) and (C) described above may be subjected to one or two further reactions comprising:

(D)(i) converting the resulting compound of general formula (I) or a salt thereof into another compound of general formula (I); and/or

(D)(ii) converting a compound of general formula (I) or a salt thereof into a physiologically acceptable salt thereof.

Thus, it is also possible to prepare a compound of general formula (I) by a process comprising interconversion of another compound of general formula (I).

For example, a compound of general formula (I) in which R is a hydrogen atom may be converted by alkylation to a compound of general formula (I) in which R is an alkyl, substituted alkyl, alkenyl, alkynyl or aralkyl group. Conventional alkylation procedures may be used, for example reductive alkylation using an appropriate aldehyde with a complex metal hydride such as sodium or potassium borohydride or sodium cyanoborohydride in a suitable solvent such as an alcohol e.g. methanol. Methylation may be achieved using a formic acid/formaldehye reaent system. Alternatively, the alkylation may be performed with an alkylating agent RX (where R is an alkyl, substituted alkyl, alkenyl, alkynyl or aralkyl group and X is a leaving group such as a halogen atom e.g. chlorine or bromine, or a hydrocarbylsulphonyloxy group e.g. *p*-toluenesulphonyloxy) preferably in the presence of a base, such as potassium carbonate, optionally in a solvent such as an alcohol, e.g. ethanol.

Another example of this embodiment is the preparation of a compound of general formula (I) where R is a group —CHO, which may be prepared by formylation of a corresponding compound of formula (I) in which R is a hydrogen atom using an appropriate formylating agent such as a formyl ester, e.g. an alkyl formate such as methyl formate.

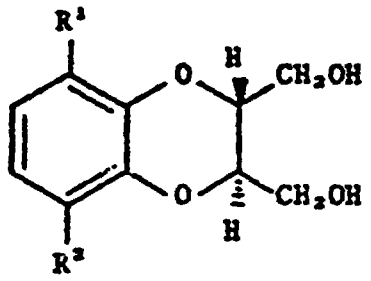
In a further example, a compound of formula (I) in which R^1 and/or R^2 is an amino group may be prepared by reduction of a corresponding compound of formula (I) in which R^1 and/or R^2 is a nitro group. Suitable reducing agents include lithium aluminium hydride, in a solvent such as ether or tetrahydrofuran at elevated temperature, or hydrogen in the presence of a catalyst such as platinum or palladium on a support (e.g. charcoal) in a solvent such as an alcohol e.g. methanol.

In yet another example, a compound of formula (I) in which R^1 and/or R^2 is hydroxyl may be prepared by O-dealkylation of a corresponding compound of formula (I) in which R^1 and/or R^2 is an alkoxy group. For example, O-demethylation may be effected using an appropriate thiol e.g. methyl, ethyl or propyl mercaptan in the presence of a strong alkali metal base such as sodium hydride. The reaction is conveniently carried out in a refluxing solvent (e.g. dimethylacetamide, dimethylsulphoxide or dimethylformamide). Alternatively, the O-dealkylation reaction may be carried out using a Lewis acid such as boron tribromide or boron trichloride in a halohydrocarbon solvent (e.g. dichloromethane) or using pyridinium hydrochloride or hydrobromide as a melt, or aqueous hydrogen bromide.

Physiologically acceptable salts of the compounds of general formula (I) may be prepared by reacting the free base of formula (I) or a salt thereof with an appropriate acid, such as hydrogen chloride in the presence of a suitable solvent e.g. ethyl acetate, ether or CH_2Cl_2 or hydrochloric acid in a solvent such as methanol, to obtain the desired physiologicaly acceptable salt.

It may be desirable to protect various reactive substituents in the starting materials for a particular reaction or sequence of reactions and subsequently to remove the protecting group after completion of the reaction or sequence. Such protection and subsequent deprotection may be particularly pertinent when R_1 and/or when R_2 is a hydroxy or amino substituent. Conventional protection and deprotection procedures can be employed cf. "Protective Groups in Organic Chemistry" Ed. by J. F. W. McOmie (Plenum Press, 1973). Thus. for example, a primary amine may be protected by formation of a phthalimide group which may subsequently be cleaved by treatment with a hydrazine, e.g. hydrazine hydrate or a primary amine, for example methylamine, and a phenolic hydroxyl group may be protected as an ether e.g. a 2-tetrahydropyranyl or methyl ether, which may subsequently be cleaved by a Lewis acid such as boron tribromide or aqueous hydrogen bromide.

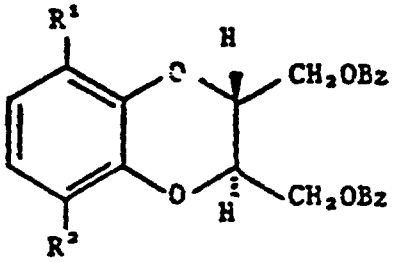
The intermediate compounds of general formula (II) may be prepared by reaction of a corresponding diol of formula (III)



(III)

with a halide of formula X_1A (where X_1 is a hydrocarbylsulphonyl group e.g. methylsulphonyl and A is a halogen atom e.g. a chlorine atom) in the presence of a base e.g. triethylamine in a solvent such as dichloromethane; or with a halogenating agent such as thionyl chloride, phosphorous tribromide or hydrogen iodide.

A diol (III) may be prepared by reduction of a corresponding dibenzyl ether of formula (IV):

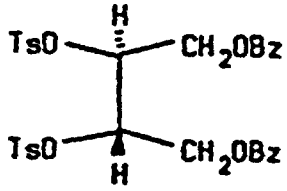


(IV)

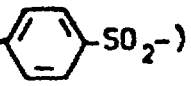
(where Bz represents benzyl) using hydrogen and palladium on charcoal with a solvent e.g. ethanol.

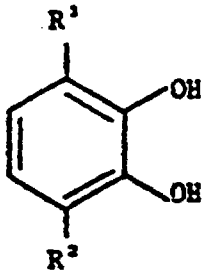
Alternatively, an ether of formula (IV) may be treated with a Lewis acid, such as aluminium chloride, in a solvent such as toluene to yield a diol of formula (III).

A compound of formula (IV) may be prepared by heating the bistosylate (V):



(V)

(where Ts represents ) with a catechol of formula (VI)

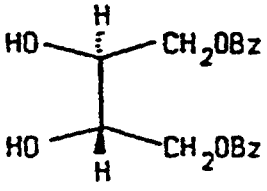


(VI)

in acetonitrile or dimethylformamide containing cesium fluoride or cesium carbonate.

The intermediates of formula (VI) are known compounds and may be prepared by standard methods of benzene ring substitution (cf. for example Barton, Linnell & Senior, Quat.J.Pharmacy & Pharmac., 1945, *18* 41—47 and Ladd & Weinstock. J.Or.Chem. 1981, *46*, 203—206).

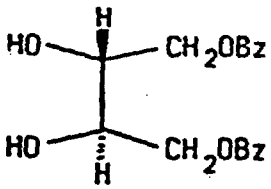
The bis-tosylate of formula (V) may be prepared by reaction of the known dibenzyl threitol of formula (VII)



(VII)

with 4-toluenesulphonyl chloride in pyridine.

To obtain a specific enantiomer of formula (I), a diol of formu a (III) having the required chirality should be used in the above processes. The entantiomeric diol starting material can be prepared from the appropriate dibenzyl threitol of formula (VII) or (VIII)



(VIII)

as described above.

A specific enantiomer of general formula (I) may also be prepared by resolution of a mixture of enantiomers of formula (I) by conventional methods, e.g. by salt formation with an optically active acid followed by separation of the resulting diastereoisomeric salts, e.g. by fractional crystallisation. Alternatively, resolution may be effected at any suitable intermediate stage.

The following examples illustrate the invention. All temperatures are in °C. In the following, ER represents ether, IMS represents industrial methylated spirits, MeOH represents methanol, EtOH represents ethanol and "light petroleum" refers to the fraction boiling at 60—80°. "Dried" refers to drying over magnesium sulphate unless otherwise stated.

Intermediate 1

(±)-(trans)-5-Fluoro-2,3-dihydro-2,3-bis[(phenylmethoxy)methyl]-1,4-benzodioxin

A mixture of 3-fluorobenzene-1,2-diol (5.12g) and (R*,R*)-(±)-1,4-bis (phenylmethoxy)-2,3-butanedioi, bis(4-methylbenzenesulphonate) (24.4 g) was stirrred with dimethylformamide (D.M.F.) (160 ml) under a nitrogen stream for 45 min. Anhydrous cesium carbonate (13.0g) was added and the mixture was heated to 150° under reflux for 18 hours. The dark brown mixture was cooled to 30° and diluted with di-isopropyl ether (370 ml) and water (320 ml). The layers were separated and the aqueous layer was re-extracted with di-isopropyl ether (150 ml then 100 ml). The extracts were sequentially washed with M hydrochloric acid (300 ml), 30% aqueous sodium chloride (100 ml) and were combined and evaporated *in vacuo* to a dark brown oil (12.6 g) which was dissolved in light petroleum-dichloromethane (3:1) (40 ml) and chromatographed over Sorbsil (126 g) using light petroleum-dichloromethane mixtures of gradually increasing polarity. Combination of appropriate fractions and evaporation of the solvents gave the *title compound* as a yellow oil (7.0 g), NMR τ ($CDCl_3$) 2.6—2.8 (10H, m, Ph), 3.18—3.38 (3H, m, 6—H, 7—H, 8—H), 5.32—5.58 (4H, m, CH_2 Ph), 5.64 (2H, m, 2—H, 3—H), 6.06—6.32 (4H, m, CH_2O).

Intermediates 2—8 (shown in Table 1) were prepared in a similar manner from the appropriate catechol and (R*,R*)-(±)-1,4-bis(phenylmethoxy)-2,3-butanediol, bis(4-methylbenzenesulphonate).

TABLE 1

R^1	R^2	Reaction Solvent	NMR τ ($CDCl_3$)						
			Ph	Ph CH_2	OCH_2	2-H,3-H	Aromatic	Me	OMe
CH_3 (2)	H	CH_3CN	2.68	5.41	6.21	5.6-5.8	3.29	7.78	-
CH_3O (3)	H	CH_3CN	2.7	5.2-5.8	5.8-6.5	5.2-5.8	3.0-3.6	-	6.13
Cl (4)	H	CH_3CN	2.66	5.3-5.55	6.0-6.3	5.55-5.7	3.0-3.3	-	-
NO_2 (5)	H	D.M.F.	2.6-2.8	5.3-5.54	6.05-6.27	5.6	2.51,2.85 3.12	-	-
CH_3 (6)	CH_3	CH_3CN	2.6-2.8	5.38-5.44	6.1-6.3	5.67	3.39	7.82	-
Cl (7)	Cl	CH_3CN	2.73	5.43	6.18	5.6	3.17	-	-
F (8)	F	D.M.F.	2.5-2.8	5.37,5.48	6.1,6.2	5.58	3.39	-	-

Intermediate 9

(±)-(trans)-5-Chloro-2,3-dihydro-1,4-benzodioxin-2,3-dimethanol

A solution of (trans)-(±)-5-chloro-2,3-bis[(phenylmethoxy)methyl]-2,3-dihydro-1,4-benzodioxin (2.2 g) in trifluoroacetic acid (T.F.A.) (50 mls) was hydrogenated over 10% palladium on carbon (0.22 g). The solid was filtered off, washed with chloroform and the solution was evaporated to dryness to give the *diol* as a colourless liquid 1.2 g, NMR τ ($CDCl_3$) 2.9—3.3 (3H, m, aromatic), 7.72 (2H, s, OH), 5.7—6.2 (6H, m, 2—H, 3—H, CH_2O).

Intermediate 11—15 (shown in Table 2) were prepared in a similar manner

Intermediate 11 from Intermediate 2
Intermediate 12 from Intermediate 3
Intermediate 13 from Intermediate 6
Intermediate 14 from Intermediate 7
Intermediate 15 from Intermediate 8

Intermediate 10

(±)-(trans)-5-Fluoro-2,3-dihydro-1,4-benzodioxin-2,3-dimethanol

Intermediate 1 (7.0 g) was dissolved in a mixture of toluene (70 ml) and anisole (7.8 ml) and the solution was stirred and cooled to −5° under a gentle stream of nitrogen. Anhydrous aluminium chloride (2.4 g) was

added and the temperature was maintained at 0—5° for 20 min. More anhydrous aluminium chloride (2.4 g) was added and after 20 min. at 0—5° the mixture was allowed to warm to 20° with continued stirring. After 20 min. at 20°, it was cooled back to 0°, water (25 ml) was added and after 5 min. stirring at 20°, the mixture was diluted with ethyl acetate (75 ml) and the layers were separated. The aqueous (lower) layer was re-extracted with ethyl acetate (2 × 50 ml) and the organic solutions were washed with 30% aqueous sodium chloride (25 ml) and were combined and concentrated *in vacuo* to 36 g, giving a thick slurry of slightly purple crystals. After 30 min. at 20°, the crystals were harvested, washed with toluene (10 ml), light petroleum (20 ml) and di-isopropyl ether (20 ml) and dried to give the *title compound* (2.93 g) m.p. 122—124°. Concentration of the mother liquor gave a crude second crop of *title compound* (0.32 g) which after chromatographic purification afforded a further quantity of pure *title compound* (0.24 g) m.p. 121—123°. NMR τ (DMSO-d_6) 3.1—3.3 (3H, m, aromatic), 4.85—5.0 (2H, m, OH) 5.8—5.9 (2H, m, 2—H, 3H) 6.1—6.4 (4H, m, CH_2O).

Intermediate 16 (shown in table 2) was prepared in a similar manner from intermediate 5.

TABLE 2

R^1	R^2	Reaction Solvent	NMR (τ)						M.pt
			Solvent	Aromatic	CH_2OH	2-H,3-H	OH	Me	
CH_3 (11)	H	EtOH	$CDCl_3$	3.3	5.8-6.1	5.8-6.1	7.59	7.8	-
CH_3O (12)	H	EtOH	compound unstable, used without characterisation						
CH_3 (13)	CH_3	MeOH	DMSO-d_6	3.42	6.3	5.9	5.04	7.89	77-9°
Cl (14)	Cl	TFA	DMSO-d_6	3.02	6.0-6.4	5.75	4.8-5.5	-	172-5°
F (15)	F	EtOH	DMSO-d_6	3.2	6.08-6.32	5.8	4.89	-	128-130°
NO_2 (16)	H	Toluene	used without characterisation						

Intermediate 17

(±)-(trans)-5-Fluoro-2,3-dihydro-1,4-benzodioxin-2,3-dimethanol, bis methanesulphonate

A solution of Intermediate 10 (3.10 g) in dichloromethane (30 ml) and triethylamine (6.4 ml) was stirred for 10 min. with ice-bath cooling. A solution of methanesulphonyl chloride (3.2 ml) in dichloromethane (10 ml) was added during 10 min. and the resultant suspension was stirred for 30 min. Water (25 ml) was added and the mixture was stirred for 20 min, the layers were then separated and the aqueous layer was re-extracted with dichloromethane (25 ml). The organic solutions were washed with water (25 ml), and were combined and evaporated to an oil which was chromatographed over Sorbsil (40 g), eluting with 9:1

dichloro methane-ethyl acetate. Appropriate fractions were combined and evaporated to a pale yellow oil (5.9 g) which crystallised slowly from ethyl acetate — di-isopropyl ether to afford the *title compound* as prisms (4.15 g) m.p. 65.5—67.5°. NMR τ ($CDCl_3$) 3.1—3.35 (3H, m, aromatic), 5.3—5.5 (4H, m, CH_2O) 5.5—5.65 (2H, m, 2—H, 3—H) 6.89, 6.91 (6H, singlets, CH_3SO_3).

Intermediates 18—24 (shown in Table 3) were prepared in a similar manner

Intermediate 18 from Intermediate 11
Intermediate 19 from Intermediate 12
Intermediate 20 from Intermediate 9
Intermediate 21 from Intermediate 16
Intermediate 22 from Intermediate 13
Intermediate 23 from Intermediate 14
Intermediate 24 from Intermediate 15

TABLE 3

R^1	R^2	NMR τ							M.pt
		Solvent	Aromatic	CH_2O	2-H,3-H	$MeSO_3$	Me	OMe	
CH_3 (18)	H	DMSO-d_6	3.19	5.2-5.7	5.2-5.7	6.69	7.8	-	-
CH_3O (19)	H	$CDCl_3$	3.0-3.6	5.3-5.7	5.3-5.7	6.82	-	6.1	-
Cl (20)	H	$CDCl_3$	2.92-3.2	5.3-5.5	5.5-5.7	6.87,6.91	-	-	-
NO_2 (21)	H	DMSO-d_6	2.35, 2.58, 2.87	5.1-5.6	5.1-5.6	6.7	-	-	140-1°
CH_3 (22)	CH_3	$CDCl_3$	3.34	5.46	5.6	6.93	7.85	-	121-3°
Cl (23)	Cl	$CDCl_3$ + DMSO-d_6	3.1	5.3-5.5	5.3-5.5	6.81	-	-	142-4°
F (24)	F	$CDCl_3$	3.33	5.38	5.54	6.89	-	-	106-7°

Example 1

(±)-(trans)-5-Fluoro-2,3,3a,9a-tetrahydro-2-(phenylmethyl)-1H-[1,4] benzodioxino[2,3-c]pyrrole

A homogenised mixture of phenylmethanamine (8 ml) and Intermediate 17 (5.3 g) was heated to 130° for 15 min. then cooled to 25°. The partly crystalline mixture was partitioned between di-isopropyl ether (80 ml) and water (80 ml). The aqueous layer was re-extracted with di-isopropyl ether (100 ml) and the organic solutions were sequentially washed with 2.5% aqueous acetic acid (2 × 50ml) and 15% aqueous sodium chloride (100 ml) containing sodium hydrogen carbonate (5 g). They were then combined and evaporated *in vacuo* to an orange-brown oil (3.8 g) which crystallised spontaneously. This was recrystallised from di-isopropyl ether — light petroleum (1:1) to give pink crystals of the *title compound* as two crops; (1) 1.5 g m.p. 79—81° and (2) 1.4 g m.p. 79.5—81°. Chromatography of the mother liquor gave a third crop (0.6 g). A recrystallised sample, m.p. 80—81° had the following analysis:

Found: C, 71.7; H, 5.65; N, 4.95; F, 6.8

$C_{17}H_{16}FNO_2$ requires: C, 71.6; H, 5.65; N, 4.9; F, 6.65%

NMR τ ($CDCl_3$) 2.6—2.8 (5H, broad singlet, Ph), 3.1—3.35 (3H, m, aromatics), 5.6—5.8 (2H, m, 3a—H, 9a—H), 6.09 and 6.19 (2H, ABq, Ph CH_2), 6.65—6.85 and 6.9—7.1 (4H, multiplets, 1—H_2, 3—H_2).

The compounds of Examples 2—7 were prepared in a similar manner to the compound of Example 1.

Example 2 from Intermediate 18
Example 3 from Intermediate 19
Example 4 from Intermediate 20
Example 5 from Intermediate 22
Example 6 from Intermediate 23
Example 7 from Intermediate 24

TABLE A

R^1	R^2	Salt or free base	NMR τ									M.pt
			Solvent	Aromatic	Ph	Ph $\underline{CH_2}$	3a-H, 9a-H	1-H_2, 3-H_2	NH^+	Me	OMe	
CH_3 (2)	H	HCl	TFA	3.17	2.47	5.34	5.2-6.7	5.2-6.7	0.75	7.79	-	-
CH_3O (3)	H	HCl	TFA	2.7-3.4	2.43	5.31	5.2-5.7	5.7-6.7	0.75	-	6.0	-
Cl (4)	H	HCl	TFA	2.8-3.2	2.3-2.6	5.2,5.5	5.4-6.1 6.3-6.5	5.4-6.1 6.3-6.5	-	-	-	215-222°
CH_3 (5)	CH_3	Free base	$CDCl_3$	3.36	2.6-2.8	6.07, 6.19	5.78	6.73, 7.02	-	7.83	-	83°
Cl (6)	Cl	HCl	TFA	2.94	2.39	5.0-6.6			-	-	-	250-257°
F (7)	F	Free base	$CDCl_3$	3.34	2.5-2.8	6.07, 6.17	5.67	6.69, 6.96	-	-	-	86°

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Example 8

(±)-(trans)-5-Fluoro-2,3,3a,9a-tetrahydro-1H-[1,4]benzodioxino[2,3-c] pyrrole hydrochloride

A solution of the compound of Example 1 (2.3 g) in IMS (110 ml) was stirred under hydrogen a *ca.* 25° with 5% palladium on charcoal (1.15 g) until uptake ceased (270 ml). The catalyst was filtered off using a kieselguhr pad, the filter was washed through with IMS (3 × 20 ml) and the combined filtrates were evaporated *in vacuo* to a pale pink oil (1.6 g). This was re-dissolved in IMS (10 ml hydrochloric acid (1 ml) was added. After 30 min. at 20°, the resultant white crystals were harvested, washed with IMS (3 ml), 1:1 IMS -di-isopropyl ether (4 ml) and di-isopropyl ether (2 × 5 ml) to afford the *title compound* as a hemihydrate, (1.09 g) m.p. *ca.* 245° (sublimes above 210°) NMR τ (DMSO-d_6) −0.25 (2H, broad s, NH_2^+), 2.9—3.2 (3H, m, 6H—, 7—H and 8—H), 5.4—5.65 (2H, m, 3a—H, 9a—H), 6.0—6.3, 6.6—6.8 (4H, ABq, 1—H_2, 3—H_2).

The compounds of Examples 9—14 were prepared in a similar manner to the compound of Example 8 from the compounds of Examples 2—7.

Table 5

R^1	R^2	NMR τ							M.pt
		Solvent	Aromatic	3a-H, 9a-H	1-H_2, 3-H_2	NH_2^+	Me	OMe	
CH_3 (9)	H	DMSO-d_6	3.22	5.5, 5.9	6.1-6.4, 6.6-7.0	0.0	7.87	-	258-264°
CH_3O (10)	H	TFA	2.8-3.4	5.3, 5.6	5.6-6.6	1.86	-	5.97	241-244°
Cl (11)	H	DMSO-d_6	2.81,2.9, 3.1	5.4-5.65	6.0-6.3, 6.5-6.8	-0.19	-	-	275-277°
CH_3 (12)	CH_3	DMSO-d_6	3.24	5.66	6.1-6.25, 6.5-6.8	-0.1	7.83	-	250°
Cl (13)	Cl	DMSO-d_6	2.77	5.42	6.09,6.62	-0.19	-	-	270° (dec.)
F (14)	F	DMSO-d_6	3.01	5.45	6.13,6.65	-0.36	-	-	77-9°

Example 9

(±)-(trans)-2,3,3a,9a-Tetrahydro-5-methyl-1H-[1,4]benzodioxino[2,3-c] pyrrole hydrochloride.

Example 10

(±)-(trans)-2,3,3a,9a-Tetrahydro-5-methoxy-1H-[1,4]benzodioxino[2,3-c] pyrrole hydrochloride.

Example 11

(±)-(trans)-5-Chloro-2,3,3a,9a-tetrahydro-1H-[1,4]benzodioxino[2,3-c] pyrrole hydrochloride.

Example 12

(±)-(trans)-2,3,3a,9a-Tetrahydro-5,8-dimethyl-1H-[1,4]benzodioxino[2,3-c] pyrrole hydrochloride.

Example 13

(±)-(trans)-5,8-Dichloro-2,3,3a,9a-tetrahydro-1H-[1,4]benzodioxino[2,3-c] pyrrole hydrochloride.

Example 14

(±)-(trans)-5,8-Difluoro-2,3,3a,9a-tetrahydro-1H-[1,4]benzodioxino[2,3-c] pyrrole hydrochloride.

Example 15

(±)-(trans)-2,3,3a,9a-Tetrahydro-5-nitro-1H-[1,4]-benzodioxino[2,3-c] pyrrole hydrochloride.

(a) (±)-(trans)-2-[bis(4-methoxyphenyl)methyl]-2,3,3a,9a-Tetrahydro-5-nitro-1H-[1,4]benzodioxino[2,3-c]pyrrole

A solution of Intermediate 21 (2.0 g) and [bis(4-methoxyphenyl)] methanamine (3.7 g) in 1,4-dioxan (10 ml) was heated at *ca.* 90° for 65 hr. under nitrogen. The mixture, which had partially crystallised, was cooled to 25° and diluted with ethyl acetate (30 ml). The crystals were filtered off and washed with ethyl acetate (3 × 10 ml). The combined filtrates were washed with 3% aqueous sodium chloride (60 ml) containing glacial acetic acid (2 ml), then with saturated aqueous sodium bicarbonate (50 ml). The washes were re-extracted with ethyl acetate (25 ml). The combined extracts were evaporated to a pale yellow oil (4.6 g). This was chromatographed over Sorbsil (30 g) eluting with di-isopropyl ether, then ethyl acetate to give impure *title compound* (2.1 g). This was rechromatographed over Sorbsil (40 g) eluting with 5:1 di-isopropyl ether-dichloromethane to give pure *title compound*, crystallised from di-isopropyl ether as two crops (1.23 g; m.p. 139—140.5° and 0.47 g; m.p. 136—139°).

(b) (±)-(trans)-2,3,3a,9a-Tetrahydro-5-nitro-1H-[1,4]benzodioxino[2,3-c] pyrrole hydrochloride

A solution of (±)-(trans)-2-[bis(4-methoxyphenyl)methyl]-2,3,3a,9a-tetrahydro-5-nitro-1H-[1,4]benzodioxino[2,3-c]pyrrole (1.12 g) in formic acid (10 ml) was heated under reflux with 10M hydrochloric acid (0.5 ml), water (1 ml) and chloroform (5 ml) for 70 minutes. The maroon mixture was cooled and partitioned between chloroform (20 ml) and water (10 ml). The chloroform layer was re-extracted with water (10 ml) and the aqueous solutions were sequentially washed with chloroform (20 ml), combined and evaporated to *ca.* 2 ml, when crystals formed. These were triturated with warm propan-1-ol (5 ml), cooled to 20° for 1 hour and harvested to give a first crop of the *title compond* (0.58 g). Concentration of the mother liquor gave a small second crop (0.03 g). Recrystallisation of the first crop from slightly aqueous propan-1-ol gave purer *title compund* (0.54 g) m.p. *c.a.* 280° (dec.).

Example 16

(±)-(trans)-2,3,3a,9a-Tetrahydro-2-(phenylmethyl)-1H-[1,4]benzodioxino [2,3-c]pyrrole-5-carbonitrile

(a) (±)-(trans)-2,3-Dihydro-2,3-bis[(phenylmethoxy)methyl]-1,4-benzodioxin- 5-carboxylic acid, benzenemethanamine (salt) (Compound A)

A mixture of methyl 2,3-dihydroxybenzoate (30 g), cesium carbonate (58.1 g) and (R*,R*)-(±)-1,4-bis(phenylmethoxy)-2,3-butanediol, bis(4-methylbenzenesulphonate) (106.3 g) in acetonitrile (1400 ml) was stirred and heated under reflux for 5 days, during the first 2 hours of which *ca.* 80 ml acetonitrile was removed to effect azeotropic drying. The solid was filtered off from the cooled mixture and the filtrate was evaporate to dryness and the residue was suspended in diethyl ether and water added. A dark, sticky residue was discarded and the aqueous layer was back extracted with ether. The combined ether layers were extracted with cold 2M sodium hydroxide solution, and brine, dried over magnesium sulphate and the solvent was evaporated. The resulting oil (65.3 g) was heated at reflux in water (300 ml) containing potassium hydroxide (30 g) for 2 hours, cooled and diluted with dichloromethane. The organic layer was washed with 2M hydrochloric acid, 30% brine dried over magnesium sulphate and evaporated to an oil (61 g) which was taken up in diethyl ether (*ca.* 150 ml). To this stirred solution was added benzylamine (7.5 ml) and after overnight chilling the precipitated solid was collected, washed with ether and dried to give the *title compound* as an off-white solid 38.2 g, NMR τ (DMSO-d_6) 2.0—3.4 (21H, m, aromatic, and NH_3^+), 5.2— 6.6 (12H, multiplets, benzyl CH_2, 2—H, 3—H, and CH_2O).

(b) (±)-(trans)-2,3-Dihydro-2,3-bis(hydroxymethyl)-1,4-benzodioxin-5-carboxlyic acid (Compound (B)

A solution of Compound A (36.93 g) in ether (500 ml) was extracted twice with 2M hydrochloric acid (400 ml, 100 ml) and the aqueous layers back extracted with ether (50 ml). The combined ether layers were washed with 30% sodium chloride solution and the solvent removed to afford an oil (32 g) which was taken up in IMS (350 ml). This solution was hydrogenated at 45° in the presence of 5% palladium on carbon (16 g) until uptake was completed. The catalyst was removed by filtration, washed with IMS and the filtrate was evaporated to dryness. The product was crystallised from ethyl acetate to give the *title compund* as a white solid 14.5 g (two crops) m.pt.123—5°

(c) (±)-(trans)-2,3-Dihydro-2,3-bis[[(methylsulphonyl)oxy]methyl]-1,4-benzo dioxin-5-carboxylic acid, anhydride (Compound C)

Triethylamine (34.8 ml) was added to a stirred, chilled solution of Compound B (17.04 g) in methylene chloride (300 ml). At 0 to −5° a solution of methanesulphonyl chloride (13 ml) in methylene chloride (50 ml) was added over approx. 5 minutes. After 1 hour, when the temperature had risen to ambient, water was added and the layers were separated. The organic layer was washed twice with 2M hydrochloric acid solution and the aqueous layers back extracted with methylene chloride. Th combined organic extracts were washed with brine, dried over magenesium sulphate, stirred with decolourising charcoal (1 g) and evaporated to dryness to give the *title compound* as a white foam. 24.1 g, NMR τ ($CDCl_3$) 2.40, 2.82 and 3.05 (3H, multiplets, aromatic), 5.1 to 5.9 (6H, br, 2—H, 3—H and CH_2O), 6.92 and 6.96 (each 3H, s, CH_3SO_3).

(d) (±)-(trans)-2,3-Dihydro-2,3-bis[[(methylsulphonyl)oxy]methyl]-1,4-benzo dioxin-5-carboxamide (Compound D)

A solution of Compound C (18.0 g) in ethyl acetate (150 ml) was stirred at room temperature and ammonia solution (SG, 0.88; 4.5 ml) was added. After 10 minutes water (150 ml) was let in and the layers were separated. The aqueous layer was back extracted with ethyl acetate and the combined organic layers were washed with aqueous sodium bicarbonate solution, dried over magnesium sulphate and evaporated to a semi-solid residue. Crystallisation from ethyl acetate (*ca.* 50 ml) gave the *title compound* as buff coloured dense solid 7.12 g m.pt 144—146°.

(e) (±)-(trans)-2,3,3a,9a-Tetrahydro-2-(phenylmethyl)-1H-[1,4]benzodioxino [2,3-c]pyrrole-5-carboxamide (Compound E)

A solution of Compound D (6.76 g) in benzylamine (10 ml) was heated to 120° for 10 minutes. The warm (85°) solution was poured into stirred, distilled water (300 ml) at room temperature. An oil deposited which quickly solidified. After 1 hour's brisk stirring, the buff coloured particulate solid was collected, washed with water and dried to give the *title compound* 5.03 g, m.pt 155—165°.

(f) (±)-(trans)-2,3,3a,9a-tetrahydro-2-(phenylmethyl)-1H-[1,4]benzodioxino [2,3-c]pyrrole-5-carbonitrile

An intimate mixture of Compound E (1.24 g) and phosphorus pentoxide (0.6 g) was heated to 165°. Two further aliquots of phosphorus pentoxide (0.6 g each) were added at 10 minute intervals, mixing well in, while maintaining the temperature in the range 165° to 180°. Ten minutes after the final addition the solid mass was triturated with aqueous potassium hydroxide, ethyl acetate mixture and stirred well until free of solid. Evaporation of the organic layer gave a brown oil which was chromatographed on silica gel (50 g). Elution with ethyl acetate-petrol b.pt. 60°—80° (1:1) gve an oil (0.8 g) which solidified on trituration, with petrol, b.pt. 60°—80°. The product was collected, washed with petrol and dried to give the *title compound* as a buff coloured solid (0.57 g) m.pt. 101—103°, NMR τ ($CDCl_3$) 2.74 (5H, s, Ph), 2.5—3.4 (3H, m, aromatic), 5.4—6.1 (2H, m, 3a—H, 9a—H), 6.18 (2H, s, CH_2 Ph), 6.5—7.4 (4H, m, 1—H_2, 3—H_2).

Example 17

(±)-(trans)-2,3,3a,9a-tetrahydro-1H-[1,4]benzodioxino[2,3-c]pyrrole-5-carbonitrile, hydrochloride

A solution of (±)-(trans)-2,3,3a,9a-tetrahydro-2-phenylmethyl-1H-[1,4]-benzodioxino[2,3-c]pyrrole-5-carbonitrile (0.55 g) in IMS (30 ml) was hydrogenated over 10% palladium on charcoal (0.2 g). When uptake had ceased the catalyst was filtered off, washed with IMS and the filtrate was concentrated to *ca.* 20 ml volume. Conc. hydrochloric acid (5 drops) was added and a solid crystallised. After ageing 1 hour in the cold the product was collected, washed with IMS and dried to give the *title compound* as a white solid 0.25 mg m.pt. 249°—254°, NMR τ (DMSO-d_6) 2.53 (1H, dd, J8 and 2, 6—H), 2.60 (1H, dd, J8 and 2, 8—H), 2.84 (1H, t, J8, 7—H), 5.44 (2H, m, 3a—H, 9a—H), 6.0—6.3 and 6.4—7.0 (4H, multiplets, 1—H_2, 3—H_2).

Example 18

(±)-(trans)-2,3,3a,9a-Tetrahydro-1H-[1,4]benzodioxino[2,3-c]pyrrole-5-ol hydrochloride

A solution of (±)-(trans)-2,3,3a,9a-tetrahydro-5-methoxy-1H-[1,4]benzodioxino[2,3-c]pyrrole (0.11 g) in 48% hydrobromic acid (5 mls) was heated at 100° for 4.5 hours. The resulting solution was evaporated to dryness, sodium carbonate solution was added, the mixture was saturated with salt and extracted with ethyl acetate for 20 hours in a continuous extraction apparatus. The organic solution was evaporated to dryness and the crude product was purified by preparative TLC on silica gel. The required component was eluted with hot methanol, the solvent was evaporated and the residue was dissolved in 2M hydrochloric acid. Evaporation of the solvent and crystallisation of the resulting solid from 2M hydrochloric acid gave the *title compound* (35 mg). NMR τ (DMSO-d_6) −0.22 (2H, s, NH_2^+), 0.46 (1H, s, OH), 3.26 (1H, t, J8 Hz, 7H), 3.41 (1H, dd, J8, 2Hz, 8H), 3.51 (1H, dd, J8, 2Hz, 6H), 5.5—5.58 (2H, m, 3a—H, 9a—H), 6.1—6.3, 6.6—6.8 (4H, multiplets, 1—H_2, 3—H_2).

Example 19

(±)-(trans)-5-Fluoro-2,3,3a,9a-tetrahydro-2-methyl-1H-[1,4]benzodioxino [2,3,c]pyrrole hydrochloride

A solution of (±)-(trans)-5-fluoro-2,3,3a,9a-tetrahydro-1H-[1,4]benzodioxino[2,3-c]pyrrole hydrochloride in water (10 ml) was basified with 50% sodium hydroxide and extracted with ethyl acetate (1 × 20 ml, 1 × 10 ml and 1 × 5 ml). The combined extracts were evaporated *in vacuo* to an oil, redissolved in dichloromethane (25 ml) and decanted to remove some solid material. Evaporation of the solvent *in vacuo* gave a solid (0.52 g) m.pt. 92°, which was heated to 2 hours on a steam bath with a mixture of water (5 ml),

98% formic acid (0.5 ml), and 40% formaldehyde solution (1.12 ml). The clear soluton was diluted with water (20 ml), basified with 50% sodium hydroxide and extracted with dichloromethane (3 x 10ml). The combined extracts were evaporated to give the free base of the title compound as a solid (0.55 g), m.pt. 78—9°. The free base was dissolved in hot IMS (10 ml) and concentrated hydrochloric acid (0.3 ml) was added and the solution was evaporated to leave a solid. The solid was redissolved in IMS (10 ml) and the solvent evaporated *in vacuo* to give a solid (0.65 g) m.pt. 263—5° (dec.). Recrystallisation from IMS/ether gave the *title compound*, m.p. 260—2° (dec.) NMR τ (DMSO—d_6) 2.94—3.18 (3H, m, aromatic), 5.41 (2H, br, 3a—H, 9a—H), 5.9—6.6 (4H, multiplets, 1—H_2, 3—H_2), 7.02 (3H, s, NCH_3).

Pharmaceutical Examples

In the following examples, 'Active Ingredient' refers to (±)-*(trans)*-5-fluoro-2,3,3a,9a-tetrahydro-1H-[1,4]-benzodioxino[2,3-c]pyrrole hydrochloride. Other compounds of the invention may be formulated in similar fashion.

1. Oral Capsule

	per capsule
Active Ingredient	50 mg
Magnesium stearate	0.5 mg
Anhydrous lactose	50 mg

Blend the active ingredient with the lactose and magnesium stearate. Fill the blend into appropriate size hard gelatin capsules (lock fitting type) on an automatic capsule filling machine).

2. Oral Syrup

	per 5 ml dose
Active Ingredient	50 mg
Sodium citrate	25 mg
Citric acid	to pH 4.5
Sunset yellow FCF (Dye)	0.25 mg
Methyl hydroxybenzoate sodium	5.0 mg
Propyl hydroxybenzoate sodium	2.0 mg
Liquid orange flavour	qS
Sucrose	3.25 g
Purified water	to 5.0 ml

Dissolve the sucrose in a minimum quantity of water. Add a concentrated solution of sodium citrate with stirring and adjust the pH to 4.5 with citric acid. With continued stirring, add a 10% aqueous solution of the active ingredient, followed by a solution of the dye, a solution of the hydroxybenzoates and lastly the flavour. Adjust almost to volume with water and stir. Check the pH and adjust to 4.5 with citric acid if necessary. Make up to volume with water.

3. Oral Tablet

	per tablet
Active Ingredient	50 mg
Polyvinylpyrrolidone	4.0 mg
Sodium starch glycollate	10.0 mg
Magnesium stearate	2.0 mg
Lactose to tablet core weight to	200 mg

Blend the active ingredient with the lactose. Add a sufficient quantity of polyvinylpyrrolidone solution to produce a damp mass suitable for granulation. Prepare the granules and dry using a tray or fluid bed dryer. Pass through a sieve, blend with the remaining ingredients and compress into 8 mm diameter tablets on a tablet machine.

Film coat the tablet cores with hydroxypropyl methyl cellulose or similar film forming material, using either an aqueous or non-aqueous solvent system. A plasticizer and suitable colour may be included in the film coating solution.

Activity

The selective α_2-adrenoreceptor antagonist action of the product of Examples 2, 4, 5a, 5c and 7 was demonstrated using the following tests:

(1) α_2-adrenoreceptor antagonist action

Compounds were tested for their ability to prevent the action of the selective α_2-adrenoreceptor agonist clonidine on the rat field stimulated vas deferens preparation. Antagonism of the effect of clonidine was quantified by measuring the parallel shift to the right of the inhibitory clonidine $\log_{10}$ (concentration)/response curve in the presence of increasing concentrations of the test compound.

(2) α_1-Adrenoreceptor antagonist action

Compounds were tested for their ability to prevent the action of α_1-adrenoreceptor agonist phenylephrine in the rat isolated anococcygens muscle (Leighton, Butz & Parmeter, Eur. J. Pharmac., 1979, *58* 27—38). Antagonism of the effect of phenylephrine was quantified by measuring the parallel shift to the right of the phenylephrine $\log_{10}$-(concentration)/response curve in the presence of increasing concentrations of the test compound.

In (1) and (2) potency and competitiveness of antagonism were determined by the method of Arunlakshana & Schild (Br. J. Pharmac. 1959, *14* 48—58).

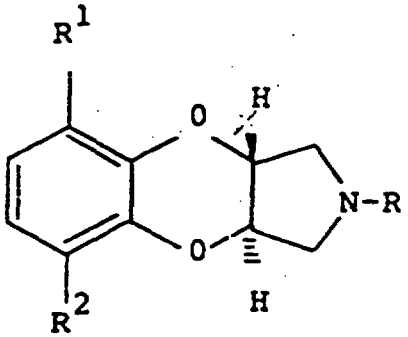
In these tests, the K_B values of the products of Examples 8, 9, 11 and 14 at α_1-adrenoreceptors were less than 0.1 µM and at α_1-adrenoreceptors were greater than 10 µM (K_B is defined as the concentration of the test compound required to shift the $\log_{10}$ (concentration)/response curve of an agonist to the right by a factor of 2).

Toxicity

The compounds of the invention are in general non-toxic at therapeutically useful doses. Thus, the compounds of the examples showed no adverse effects when tested in mice at concentrations up to 50 mg/kg orally.

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

1. A compound of general formula (I):



wherein

R is a hydrogen atom or a group selected from C_{1-6} alkyl (optionally substituted by C_{3-7} cycloalkyl), C_{3-6} alkenyl, C_{3-6} alkynyl, C_{3-7} cycloalkyl, aralkyl (in which the alkyl moiety contains 1—5 carbon atoms) and —CHO, with the proviso that when R contains a —C=C— or —C≡C— linkage this is not directly attached to the nitrogen atom;

R^1 is a halogen atom or a group selected from C_{1-4} alkyl, C_{1-4} alkoxy, hydroxyl, cyano, nitro and $-NR^3R^4$ where R^3 and R^4 is each a hydrogen atom or a C_{1-4} alkyl group; and

R^2 is a hydrogen atom, a halogen atom or is a group as defined above for R^1;

and the physiologically acceptable salts and hydrates thereof.

2. A compound according to claim 1, wherein, in the general formula (I), R is a hydrogen atom.

3. A compound according to claim 1, wherein, in the general formula (I), R is a C_{1-3} alkyl group.

4. A compound according to claim 1, wherein, in the general formula (I), R^1 is a halogen atom or a C_{1-4} alkyl or C_{1-4} alkoxy group.

Blend the active ingredient with the lactose. Add a sufficient quantity of polyvinylpyrrolidone solution to produce a damp mass suitable for granulation. Prepare the granules and dry using a tray or fluid bed dryer. Pass through a sieve, blend with the remaining ingredients and compress into 8 mm diameter tablets on a tablet machine.

Film coat the tablet cores with hydroxypropyl methyl cellulose or similar film forming material, using either an aqueous or non-aqueous solvent system. A plasticizer and suitable colour may be included in the film coating solution.

Activity

The selective α_2-adrenoreceptor antagonist action of the product of Examples 2, 4, 5a, 5c and 7 was demonstrated using the following tests:

(1) α_2-adrenoreceptor antagonist action

Compounds were tested for their ability to prevent the action of the selective α_2-adrenoreceptor agonist clonidine on the rat field stimulated vas deferens preparation. Antagonism of the effect of clonidine was quantified by measuring the parallel shift to the right of the inhibitory clonidine $\log_{10}$ (concentration)/response curve in the presence of increasing concentrations of the test compound.

(2) α_1-Adrenoreceptor antagonist action

Compounds were tested for their ability to prevent the action of α_1-adrenoreceptor agonist phenylephrine in the rat isolated anococcygens muscle (Leighton, Butz & Parmeter, Eur. J. Pharmac., 1979, *58* 27—38). Antagonism of the effect of phenylephrine was quantified by measuring the parallel shift to the right of the phenylephrine $\log_{10}$-(concentration)/response curve in the presence of increasing concentrations of the test compound.

In (1) and (2) potency and competitiveness of antagonism were determined by the method of Arunlakshana & Schild (Br. J. Pharmac. 1959, *14* 48—58).

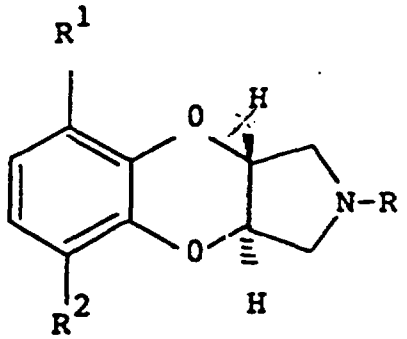
In these tests, the K_B values of the products of Examples 8, 9, 11 and 14 at α_1-adrenoreceptors were less than 0.1 µM and at α_1-adrenoreceptors were greater than 10 µM (K_B is defined as the concentration of the test compound required to shift the $\log_{10}$ (concentration)/response curve of an agonist to the right by a factor of 2).

Toxicity

The compounds of the invention are in general non-toxic at therapeutically useful doses. Thus, the compounds of the examples showed no adverse effects when tested in mice at concentrations up to 50 mg/kg orally.

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

1. A compound of general formula (I):



wherein

R is a hydrogen atom or a group selected from C_{1-6} alkyl (optionally substituted by C_{3-7} cycloalkyl), C_{3-6} alkenyl, C_{3-6} alkynyl, C_{3-7} cycloalkyl, aralkyl (in which the alkyl moiety contains 1—5 carbon atoms) and —CHO, with the proviso that when R contains a —C=C— or —C=C— linkage this is not directly attached to the nitrogen atom;

R^1 is a halogen atom or a group selected from C_{1-4} alkyl, C_{1-4} alkoxy, hydroxyl, cyano, nitro and $-NR^3R^4$ where R^3 and R^4 is each a hydrogen atom or a C_{1-4} alkyl group; and

R^2 is a hydrogen atom, a halogen atom or is a group as defined above for R^1;

and the physiologically acceptable salts and hydrates thereof.

2. A compound according to claim 1, wherein, in the general formula (I), R is a hydrogen atom.

3. A compound according to claim 1, wherein, in the general formula (I), R is a C_{1-3} alkyl group.

4. A compound according to claim 1, wherein, in the general formula (I), R^1 is a halogen atom or a C_{1-4} alkyl or C_{1-4} alkoxy group.

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5. A compound according to claim 1, wherein, in the general formula (I), R^2 is a hydrogen or fluorine atom.

6. A compound according to claim 1, wherein, in the general formula (I), R^1 is a halogen atom, a C_{1-4} alkyl group or a hydroxyl group; and R^2 is a hydrogen atom, a halogen atom, a C_{1-4} alkyl group or a hydroxyl group.

7. A compound according to claim 1, wherein, in the general formula (I), R is a hydrogen atom or a methyl or ethyl group; R^1 is a chlorine or fluorine atom or a methyl or methoxy group; and R^2 is a hydrogen or fluorine atome.

8. A compound selected from (±)-*(trans)*-2,3,3a,9a-tetrahydro-5-methyl-1H-[1,4]benzodioxino[2,3-c]pyrrole, and its 3aS- and 3aR-isomers); (±)-*trans*-5-chloro-2,3,3a,9a-tetrahydro-1H-[1,4]benzodioxino[2,3-c]-pyrrole, and its 3aS- and 3aR-isomers; (±)-*trans*-5,8-difluoro-2,3,3a,9a-tetrahydro-1H-[1,4]benzodioxino[2,3-c]pyrrole and its 3aS- and 3aR-isomers; and their physiologically acceptable salts.

9. A compound selected from (±)-*trans*-5-fluoro-2,3,3a,9a-tetrahydro-1H-[1,4]benzodioxino[2,3-c]pyrrole and its 3aS- and 3aR-isomers and their physiologically acceptable salts.

10. (±)-*trans*-5-Fluoro-2,3,3a,9a-tetrahydro-1H-[1,4]benzodioxino[2,3-c]pyrrole hydrochloride and its 3aS- and 3aR-isomers.

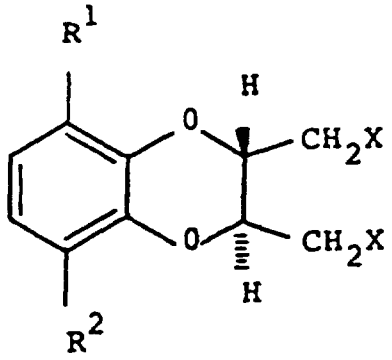
11. A pharmaceutical composition comprising a compound of general formula (I) and/or a physiologically acceptable salt thereof according to any of claims 1 to 10 together with a physiologically acceptable carrier or excipient.

12. A pharmaceutical composition according to claim 11 which also comprises an established antidepressant.

13. A compound of general formula (I) or a physiologically acceptable salt thereof according to any of claims 1 to 10 for use in the therapy or prophylaxis of depression, migraine, thrombosis, diabetes, obesity, hypertension, constipation, paralytic ileus or senile dementia.

14. A process for the preparation of a compound of general formula (I) as defined in claim 1 or a physiologically acceptable salt thereof which comprises:

(A) aminating a compound of general formula (II):



where R^1 and R^2 are as defined for general formula (I) and X is a leaving group with ammonia, aqueous ammonia or an amine of formula RNH_2 where R is as defined for general formula (I) except that R is not a hydrogen atom or the group —CHO; or

(B) in order to prepare a compound of general formula (I) where R represents a hydrogen atom, deprotecting a corresponding compound where R represents a protecting group; or

(C) in order to prepare a compound of general formula (I) where R represents an alkyl group, reducing the corresponding compound where R represents an acyl group; and, if desired, subjecting the compound thus obtained to one or two further reactions comprising:

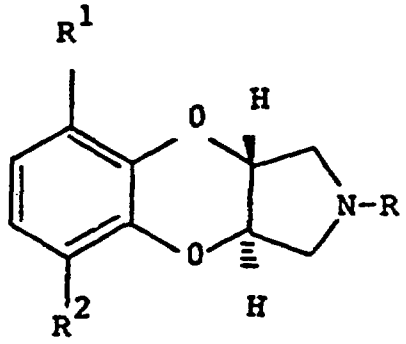
(D)(i) converting the resulting compound of general formula (I) or a salt thereof into another compound of general formula (I) and/or

(D)(ii) converting a compound of general formula (I) or a salt thereof into a physiologically acceptable salt thereof.

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Claims for the Contracting State: AT

1. A process for the preparation of a compound of general formula (I):



wherein

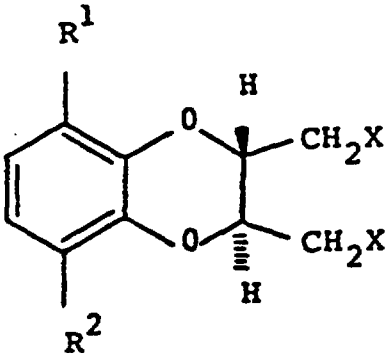
R is a hydrogen atom or a group selected from C_{1-6} alkyl (optionally substituted by C_{3-7} cycloalkyl), C_{3-6} alkenyl, C_{3-6} alkynyl, C_{3-7} cycloalkyl, aralkyl (in which the alkyl moiety contains 1—5 carbon atoms) and —CHO, with the proviso that when R contains a —C=C— or —C≡C— linkage this is not directly attached to the nitrogen atom;

R^1 is a halogen atom or a group selected from C_{1-4} alkyl, C_{1-4} alkoxy, hydroxyl, cyano, nitro and $-NR^3R^4$ where R^3 and R^4 is each a hydrogen atom or a C_{1-4} alkyl group; and

R^2 is a hydrogen atom, a halogen atom or is a group as defined above for R^1;

or a physiologically acceptable salt thereof which comprises:

(A) aminating a compound of general formula (II):



where R^1 and R^2 are as defined for general formula (I) and X is a leaving group

with ammonia, aqueous ammonia or an amine of formula RNH_2 where R is as defined for general formula (I) except that R is not a hydrogen atom or the group —CHO; or

(B) in order to prepare a compound of general formula (I) where R represents a hydrogen atom, deprotecting a corresponding compound where R represents a protecting group; or

(C) in order to prepare a compound of general formula (I) where R represents an alkyl group, reducing the corresponding compound where R represents an acyl group; and, if desired, subjecting the compound thus obtained to one or more further reactions comprising:

(D)(i) converting the resulting compound of general formula (I) or a salt thereof into another compound of general formula (I) and/or

(D)(ii) converting a compound of general formula (I) or a salt thereof into a physiologically acceptable salt thereof.

2. A process according to claim 1, wherein, in the general formula (I), R is a hydrogen atom.

3. A process according to claim 1, wherein, in the general formula (I), R is a C_{1-3} alkyl group.

4. A process according to claim 1, wherein, in the general formula (I), R^1 is a halogen atom of a C_{1-4} alkyl or C_{1-4} alkoxy group.

5. A process according to claim 1, wherein, in the general formula (I), R^2 is a hydrogen of fluorine atom.

6. A process according to claim 1, wherein, in the general formula (I), R^1 is a halogen atom, a C_{1-4} alkyl group or a hydroxyl group; and R^2 is a hydrogen atom, a halogen atom, a C_{1-4} alkyl group or a hydroxyl group.

7. A process according to claim 1, wherein, in the general formula (I), R is a hydrogen atom or a methyl or ethyl group; R^1 is a chlorine of fluorine atom or a methyl or methoxy group; and R^2 is a hydrogen of fluorine atom.

8. A process according to claim 1, wherein, the product is selected from (±)-(*trans*)-2,3,3a,9a-tetrahydro-5-methyl-1H-[1,4]benzodioxino[2,3-c]pyrrole, and its 3aS- and 3aR-isomers); (±)-*trans*-5-chloro-

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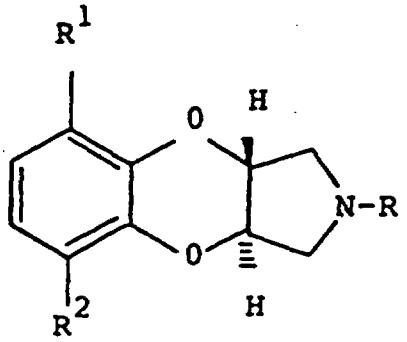
2,3,3a,9a-tetrahydro-1H-[1,4]benzodioxino[2,3-c]-pyrrole, and its 3aS- and 3aR-isomers; (±)-*trans*-5,8-difluoro-2,3,3a,9a-tetrahydro-1H-[1,4-benzodioxino[2,3-c]pyrrole and its 3aS- and 3aR-isomers; and their physiologically acceptable salts.

9. A process according to claim 1, wherein, the product is selected from (±)-*trans*-5-fluoro-2,3,3a,9a-tetrahydro-1H-[1,4]benzodioxino[2,3-c]pyrrole and its 3aS- and 3aR-isomers and their physiologically acceptable salts.

10. A process according to claim 1, wherein the product is (±)-*trans*-5-fluoro-2,3,3a,9a-tetrahydro-1H-[1,4]benzodioxino[2,3-c]pyrrole hydrochloride and its 3aS- and 3aR-isomers.

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

1. Verbindung der allgemeinen Formel (I):



worin

R ein Wasserstoffatom ode eine Gruppe, ausgewählt unter C_{1-6}-Alkyl (gegebenenfalls substituiert durch C_{3-7}-Cycloalkyl), C_{3-6}-Alkenyl, C_{3-6}-Alkinyl, C_{3-7}-Cycloalkyl, Aralkyl (worin der Alkyl-Moleküteil 1 bis 5 Kohlenstoffatome enthält) und —CHO, bedeutet, mit der Maßgabe, daß, wenn R eine —C=C— oder —C≡C— Bindung enthält, diese nicht direkt an das Stickstoffatom gebunden ist;

R^1 ein Halogenatom oder eine Gruppe, ausgewählt unter C_{1-4}-Alky, C_{1-4}-Alkoxy, Hydroxyl, Cyano, Nitro und $—NR^3R^4$, worin R^3 und R^4 je ein Wasserstoffatom oder eine C_{1-4}-Alkyl-gruppe bedeuten, bedeutet; und

R^2 ein Wasserstoffatom, ein Halogenatom oder eine Gruppe, wie sie oben für R^1 definiert wurde, bedeutet, und ihre physiologisch annehmbaren Salze.

2. Verbindung nach Anspruch 1, dadurch gekennzeichnet, daß in der allgemeinen Formel (I) R ein Wasserstoffatom bedeutet.

3. Verbindung nach Anspruch 1, dadurch gekennzeichnet, daß in der allgemeinen Formel (I) R eine C_{1-3}-Alkylgruppe bedeutet.

4. Verbindung nach Anspruch 1, dadurch gekennzeichnet, daß in der allgemeinen Formel (I) R^1 ein Halogenatom oder eine C_{1-4}-Alkyl- oder C_{1-4}-Alkoxygruppe bedeutet.

5. Verbindung nach Anspruch 1, dadurch gekennzeichnet, daß in der allgemeinen Formel (I) R^2 ein Wasserstoff- oder Fluoratom bedeutet.

6. Verbindung nach Anspruch 1, dadurch gekennzeichnet, daß in der allgemeinen Formel (I) R^1 ein Halogenatom, eine C_{1-4}-Alkylgruppe oder eine Hydroxylgruppe [illegible] und R^2 ein Wasserstoffatom, ein Halogenatom, eine C_{1-4}-Alkylgruppe oder eine Hydroxylgruppe bedeutet.

7. Verbindung nach Anspruch 1, dadurch gekennzeichnet, daß in der allgemeinen Formel (I) R ein Wasserstoffatom oder eine Methyl- oder Ethylgruppe bedeutet; R^1 ein Chlor- oder Fluoratom oder eine Methyl- oder Methoxygruppe bedeutet; ud R^2 ein Wasserstoff- oder Fluoratom bedeutet.

8. Verbindung, ausgewählt unter (±)-trans-2,3,3a,9a-Tetrahydro-5-methyl-1H-[1,4]benzodioxino[2,3-c]pyrrol und ihren 3aS- und 3aR-Isomeren; (±)-trans-5-Chlor-2,3,3a,9a-Tetrahydro-1H-[1,4]benzodioxino[2,3-c]pyrrol und ihren 3aS- und 3aR-Isomeren; (±)-trans-5,8-Difluor-2,3,3a,9a-Tetrahydro-1H-[1,4]benzodioxino[2,3-c]pyrrol und ihren 3aS- und 3aR-Isomeren, und ihre physiologisch annehmbaren Salze.

9. Verbindung, ausgewählt unter (±)-trans-5-Fluor-2,3,3a,9a-tetrahydro-1H-[1,4]benzodioxino[2,3-c]pyrrol und ihren 3aS- und 3aR-Isomeren, und ihre physiologisch annehmbaren Salze.

10. (±)-trans-5-Fluor-2,3,3a,9a-tetrahydro-1H-[1,4]benzodioxino[2,3-c]pyrrol-hydrochlorid und ihre 3aS- und 3aR-Isomeren.

11. Pharmazeutische Zubereitung, dadurch gekennzeichnet, daß sie eine Verbindung der allgemeinen Formel (I) und/oder eines ihrer physiologisch annehmbaren Salze nach einem der Ansprüche 1 bis 10 zusammen mit einem physiologisch annehmbaren Träger oder Verdünnungsmittel enthält.

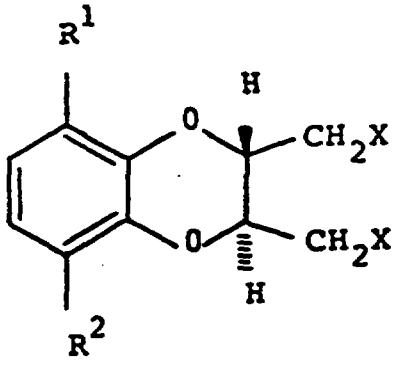
12. Pharmazeutische Zubereitung nach Anspruch 11, dadurch gekennzeichnet, daß sie ebenfalls ein anerkanntes Anti-Depressionsmittel enthält.

13. Verbindung der allgemeinen Formel (I) oder ihr physiologisch annehmbares Salz nach einem der Ansprüche 1 bis 10 für die Verwendung in der Therapie oder Prophylaxe von Depression, Migräne, Thrombose, Diabetes, Fettsucht, Bluthochdruck, Obstipation, paralytischem Darmverschluß oder seniler Dementia.

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14. Verfahren zur Herstellung einer Verbinding der allgemeinen Formel (I) nach Anspruch 1 oder ihres physiologisch annehmbaren Salzes, dadurch gekennzeichnet, daß

(A) eine Verbindung der allgemeinen Formel (II):



worin R^1 und R^2 die für die allgemeine Formel (I) gegebene Definition besitzn und X eine abspaltbare Gruppe bedeutet, mit Ammoniak, wäßrigem Ammoniak oder einem Amin der Formel RNH_2, worin R die für die allgemeine Formel (I) gegebene Bedeutung besitzt, ausgenommen, daß R nicht ein Wasserstoffatom oder die Gruppe —CHO bedeutet, aminiert wird; oder

(B) zur Herstellung einer Verbindung der allgemeinen Formel (I), worin R ein Wasserstoffatom bedeutet, bei der entsprechenden Verbindung, worin R eine Schutzgruppe bedeutet, die Schutzgruppe abgespalten wird; oder

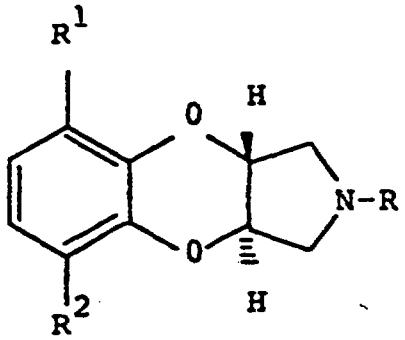
(C) zur Herstellung einer Verbindung der allgemeinen Formel (I), worin R eine Alkylgruppe bedeutet, die entsprechende Verbindung, worin R eine Acylgruppe bedeutet, reduziert wird und gegebenenfalls die so erhaltene Verbindung einer oder zwei der weiteren Reaktionen:

(D) (i) Umwandlung der entstehenden Verbindung der allgemeinen Formel (I) oder ihres Salzes in eine andere Verbindung der allgemeinen Formel (I) und/oder

(D) (ii) Umwandlung einer Verbindung der allgemeinen Formel (I) oder ihres Salzes in eines ihrer physiologisch annehmbaren Salze unterworfen wird.

Patentansprüche für den Vertragsstaat: AT

1. Verfahen zur Herstellung einer Verbindung der allgemeinen Formel (I):



worin

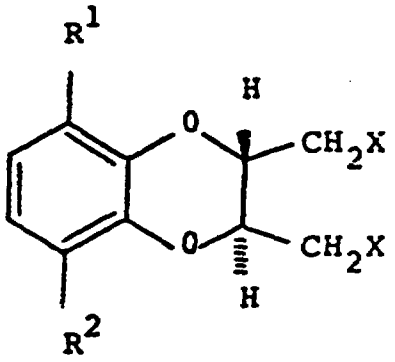
R ein Wasserstoffatom ode eine Gruppe, ausgewählt unter C_{1-6}-Alkyl (gegebenenfalls substituiert durch C_{3-7}-Cycloalkyl), C_{3-6}-Alkenyl, C_{3-6}-Alkinyl, C_{3-7}-Cycloalkyl, Aralkyl (worin der Alkyl-Moleküteil 1 bis 5 Kohlenstoffatome enthält) und —CHO, bedeutet, mit der Maßgabe, daß, wenn R eine —C=C— oder —C≡C— Bindung enthält, diese nicht direkt an das Stickstoffatom gebunden ist;

R^1 ein Halogenatom oder eine Gruppe, ausgewählt unter C_{1-4}-Alky, C_{1-4}-Alkoxy, Hydroxyl, Cyano, Nitro und $-NR^3R^4$, worin R^3 und R^4 je ein Wasserstoffatom oder eine C_{1-4}-Alkyl-gruppe bedeuten, bedeutet; und

R^2 ein Wasserstoffatom, ein Halogenatom oder eine Gruppe, wie sie oben für R^1 definiert wurde, bedeutet, oder eines ihrer physiologisch annehmbaren Salze, dadurch gekennzeichnet, daß

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(A) eine Verbindung der allgemeinen Formel (II):



worin R^1 und R^2 die für die allgemeine Formel (I) gegebene Definition besitzen und X eine abspaltbare Gruppe bedeutet, mit Ammoniak, wäßrigem Ammoniak oder einem Amin der Formel RNH_2, worin R die für die allgemeine Formel (I) gegebene Bedeutung besitzt, ausgenommen, daß R nicht ein Wasserstoffatom oder die Gruppe —CHO bedeutet, aminiert wird; oder

(B) zur Herstellung einer Verbindung der allgemeinen Formel (I), worin R ein Wasserstoffatom bedeutet, bei der entsprechenden Verbindung, worin R eine Schutzgruppe bedeutet, die Schutzgruppe abgespalten wird; oder

(C) zur Herstellung einer Verbindung der allgemeinen Formel (I), worin R eine Alkylgruppe bedeutet, die entsprechende Verbindung, worin R eine Acylgruppe bedeutet, reduziert wird und gegebenenfalls die so erhaltene Verbindung einer oder zwei der weiteren Reaktionen:

(D) (i) Umwandlung der entstehenden Verbindung der allgemeinen Formel (I) oder ihres Salzes in eine andere Verbindung der allgemeinen Formel (I) und/oder

(D) (ii) Umwandlung einer Verbindung der allgemeinen Formel (I) oder ihres Salzes in eines ihrer physiologisch annehmbaren Salze unterworfen wird.

2. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß in der allgemeinen Formel (I) R ein Wasserstoffatom bedeutet.

3. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß in der allgemeinen Formel (I) R eine C_{1-3}-Alkylgruppe bedeutet.

4. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß in der allgemeinen Formel (I) R^1 ein Halgenatom oder eine C_{1-4}-Alkyl- oder C_{1-4}-Alkoxygruppe bedeutet.

5. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß in der allgemeinen Formel (I) R^2 ein Wasserstoff- oder Fuoratom bedeutet.

6. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß in der allgemeinen Formel (I) R^1 ein Halogenatom, eine C_{1-4}-Alkylgruppe oder eine Hydroxylgruppe bedeutet und R^2 ein Wasserstoffatom, ein Halogenatom, eine C_{1-4}-Alkylgruppe oder eine Hydroxylgruppe bedeutet.

7. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß in der allgemeinen Formel (I) R ein Wasserstoffatom oder eine Methyl- oder Ethylgruppe bedeutet; R^1 ein Chlor- oder Fluoratom oder eine Methyl- oder Methoxygruppe bedeutet; und R^2 ein Wasserstoff- oder Fluoratom bedeutet.

8. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß das Produkt ausgewählt wird unter (±)-trans-2,3,3a,9a-Tetrahydro-5-methyl-1H-[1,4]-benzodioxino[2,3-c]pyrrol und ihren 3aS- und 3aR-Isomeren; (±)-trans-5-Chlor-2,3,3a,9a-tetrahydro-1H-[1,4]benzodioxino[2,3-c]pyrrol und ihren 3aS- und 3aR-Isomeren; (±)-trans-5,8-Difluor-2,3,3a,9a-Tetrahydro-1H-[1,4]benzodioxino[2,3-c]pyrrol und ihren 3aS- und 3aR-Isomeren, und ihre physiologisch annehmbaren Salzen.

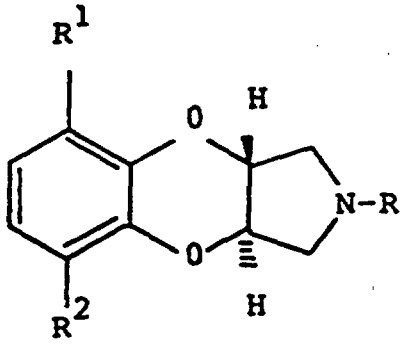
9. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß das Produkt ausgewählt wird unter (±)-trans-5-Fluor-2,3,3a,9a-tetrahydro-1H-[1,4]benzodioxino[2,3-c)pyrrol und ihren 3aS- und 3aR-Isomeren und ihren physiologisch annehmbaren Salzen.

10. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß das Produkt (±)-trans-5-Fluor-2,3,3a,9a-tetrahydro-1H-[1,4]benzodioxino[2,3-c]pyrrol-hydrochlorid und ihre seine 3aS- und 3aR-Isomeren ist.

* C L M S *

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

1. Composé de formule générale (I)



dans laquelle

R est un atome d'hydrogène ou un groupe choisi parmi les groupes alkyle en C_2—C_6 (eventuellement substitués par un groupe cycloalkyle en C_3—C_7), alcényle en C_3—C_6, alcynyle en C_3—C_6, cycloalkyle en C_3—C_7, arylalkyle (où le groupement alkyle contient 1—5 atomes de carbone) et —CHO, à condition que, lorsque R contient une liaison —C=C— ou —C≡C—, celle-ci ne soit pas fixée directement à l'atome d'azote;

R^1 et un atome d'halogène ou un gruppe choisi parmi les groupes alkyle en C_1—C_4, alcoxy en C_1—C_4, hydroxyle, cyano, nitro et —NR^3R^4, où R^4, où R^3 et R^4 sont chacun un atome d'hydrogène ou un groupe alkyle en C_1—C_4; et

R^2 est un atome d'hdrogène, un atome d'halogène ou est un groupe tel que défini ci-dessus pour R^1; et ses sels physiologiquement acceptables.

2. Composé selon la revendication 1, dans lequel, dans la formule générale (I), R est un atome d'hydrogène.

3. Composé selon la revendication 1, dans lequel, dans la formule générale (I), R est un groupe alkyle en C_1—C_3.

4. Composé selon la revendication 1, dans lequel, dans la formule générale (I), R^1 est un atome d'halogène ou un groupe alkyle en C_1—C_4 ou alcoxy en C_1—C_4.

5. Composé selon la revendication 1, dans lequel, dans la formule générale (I), R^2 est un atome d'hydrogène ou un atome de fluor.

6. Composé selon la revendication 1, dans lequel, dans la formule générale (I), R^1 est un atome d'halogène, un groupe alkyle en C_1—C_4 ou un groupe hydroxyle; et R^2 est un atome d'hydrogène, un atome d'halogène, un groupe alkyle en C_1—C_4 ou un groupe hydroxyle.

7. Composé selon la revendication 1, dans lequel, dans la formule générale (I), R est un atome d'hydrogène ou un groupe méthyle ou éthyle; R^1 est un atome de chlore ou de fluor ou un groupe méthyle ou méthoxy; et R^2 est un atome d'hydrogène ou de fluor.

8. Composé choisi parmi le (±)-trans-2,3,3a,9a-tétrahydro-5-méthyl-1H-[1,4]benzodioxino[2,3-c]pyrrole, et ses isomères 3aS et 3aR; le (±)-trans-5-chloro-2,3,3a,9a-tétrahydro-1H-(1,4]benzodioxino[2,3-c]pyrrole, et ses isomères 3aS et 3aR; le (±)-trans-5,8-difluoro-2,3,3a,9a-tétrahydro-1,H-[1,4]-benzodioxino[2,3-c]pyrrole, et ses isomères 3aS et 3aR; et leurs sels physiologiquement acceptables.

9. Composé choisi parmi le (±)-trans-5-fluoro-2,3,3a,9a-tétrahydro-1H[1,4]benzodioxino[2,3-c]pyrrole, et ses isomères 3aS et 3aR et leurs sels physiologiquement acceptables.

10. Chorhydrate de (±)-trans-5-fluoro-2,3,3a,9a-tétrahydro-1H-[1,4]benzodioxino[2,3-c]pyrrole, et ses isomères 3aS et 3aR.

11. Composition pharmaceutique comprenant un composé de formule générale (I) et/ou un de ses sels physiologiquement acceptables selon l'une quelconque des revendications 1 à 10, ansi qu'un véhicule ou excipient physiologiquement acceptable.

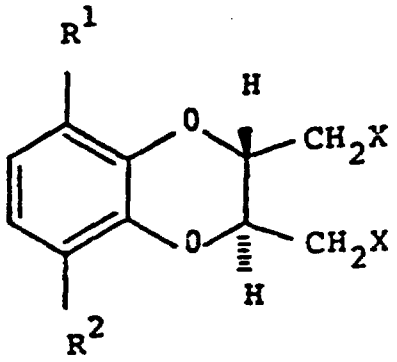
12. Composition pharmaceutique selon la revendication 11, qui comprend aussi un antidépresseur classique.

13. Composé de formule générale (I) ou sel physiologiquement acceptable de celui-ci selon l'une quelconque des revendications 1 à 10, utilisable dans le traitement ou la prophylaxie de la dépression, de la migraine, de la thrombose, du diabète, de l'obésité, de l'hypertension, de la constipation, de l'iléus paralytique ou de la démence sénile.

14. Procédé de préparation d'un composé de formule générale (I) selon la revendication 1 ou d'un de ses sels physiologiquement acceptables, qui comprend:

* C L M S *

(A) l'amination d'un composé de formule générale (II):



dans laquelle R^1 et R^2 sont tels que définis pour la formule générale (I) et X est un groupe partant, avec de l'ammoniac, de l'ammoniaque aqueux ou une amine de formule RNH_2, dans laquelle R est tel que défini pour la formule générale (I), sauf que R n'est pas un atome de hydrogène ni le groupe —CHO; ou

(B) pour préparer un composé de formule générale (I), dans laquelle R représente un atome d'hydrogène, la déprotection d'un composé correspondant dans lequel R représente un groupe protecteur; ou

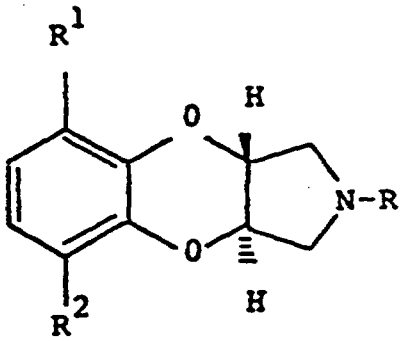
(C) pour préparer un composé de formule générale (I), dans laquelle R représente un group alkyle, la réduction du composé correspondant dans lequel R représente un groupe acyle; et, éventuellement, une ou deux autres réactions du composé ainsi obtenu comprenant:

(D) (i) la transformation du composé résultant de formule générale (I) ou d'un de ses sels en un autre composé de formule générale (I) et/ou

(D) (ii) la transformation d'un composé de formule générale (I) ou d'un de ses sels en un autre sel physiologiquement acceptable.

Revendications pour l'Etat contractant: AT

1. Procédé de préparation d'un composé de formule générale (I):



dans laquelle

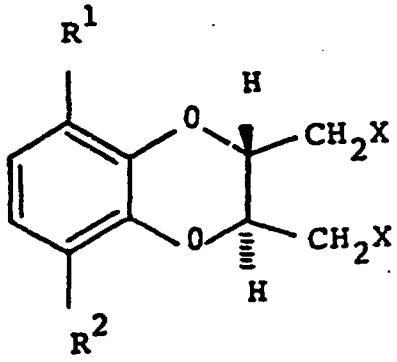
R est un atome d'hydrogène ou un groupe choisi parmi les groupes alkyle en C_2—C_6 (éventuellement substitués par un groupe cycloalkyle en C_3—C_7), alcényle en C_3—C_6, alcynyle en C_3—C_6, cycloalkyle en C_3—C_7, arylalkyle (où le groupement alkyle contient 1—5 atomes de carbone) et —CHO, à condition que, lorsque R contient une liaison —C=C— ou —C≡C—, celle-ci ne soit pas fixée directement à l'atome d'azote;

R^1 et un atome d'halogène ou un gruppe choisi parmi les groupes alkyle en C_1—C_4, alcoxy en C_1—C_4, hydroxyle, cyano, nitro et —NR^3R^4, où R^4, où R^3 et R^4 sont chacun un atome d'hydrogène ou un groupe alkyle en C_1—C_4; et

R^2 est un atome d'hydrogène, un atome d'halogène ou est un groupe tel que défini ci-dessus pour R^1; et ses sels physiologiquement acceptables, qui comprend:

* C L M S *

(A) l'amination d'un composé de formule générale (II):



dans laquelle R^1 et R^2 sont tels que définis pour la formule générale (I) et X est un groupe partant, avec de l'ammoniac, de l'ammoniaque aqueux ou une amine de formule RNH_2, dans laquelle R est tel que défini pour la formule générale (I), sauf que R n'est pas un atome de hydrogène ni le groupe —CHO; ou

(B) pour préparer un composé de formule générale (I), dans laquelle R représente un atome d'hydrogène, la déprotection d'un composé correspondant dans lequel R représente un groupe protecteur ou

(C) pour préparer un composé de formule générale (I), dans laquelle R représente un group alkyle, la réduction du composé correspondant dans lequel R représente un groupe acyle; et, éventuellement, une ou deux autres réactions du composé ainsi obtenu comprenant:

(D) (i) la transformation du composé résultant de formule générale (I) ou d'un de ses sels en un autre composé de formule générale (I) et/ou

(D) (ii) la transformation d'un composé de formule générale (I) ou d'un de ses sels en un autre sel physiogiquement acceptable.

2. Procédé selon la revendication 1, dans lequel, dans la formule générale (I), R et un atome d'hydrogène.

3. Procédé selon la revendication 1, dans lequel, dans la formule générale (I), R est un groupe alkyle en C_1—C_3.

4. Procédé selon la revendication 1, dans lequel, dans la formule générale (I), R^1 est un atome d'halogène ou un groupe alkyle en C_1—C_4 ou alcoxy en C_1—C_4.

5. Procédé selon la revendication 1, dans lequel, dans la formule générale (I), R^2 est un atome d'hydrogène ou un atome de fluor.

6. Procédé selon la revendication 1, dans lequel, dans la formule générale (I), R^1 est un atome d'halogène, un groupe alkyle en C_1—C_4 ou un groupe hydroxyle; et R^2 est un atome d'hydrogène, un atome d'halogène, un groupe alkyle en C_1—C_4 ou un groupe hydroxyle.

7. Procédé selon la revendication 1, dans lequel, dans la formule générale (I), R est un atome d'hydrogène ou un groupe méthyle ou éthyle; R^1 est un atome de chlore ou de fluor ou un groupe méthyle ou méthoxy; et R^2 est un atome d'hydrogène ou de fluor.

8. Procédé selon la revendication 1, dans lequel le produit est choisi parmi le (±)-trans-2,3,3a,9a-tétrahydro-5-méthyl-1H-[1,4]benzodioxino[2,3-c]pyrrole, et ses isomères 3aS et 3aR; le (±)-trans-5-chloro-2,3,3a,9a-tétrahydro-1H-[1,4]benzodioxino[2,3-c]pyrrole, et ses isomères 3aS et 3aR; le (±)-trans-5,8-difluoro-2,3,3a,9a-tétrahydro-1H-[1,4]-benzodioxino[2,3-c]pyrrole, et ses isomères 3aS et 3aR; et leurs sels physiologiquement acceptables.

9. Procédé selon la revendication 1, dans lequel le produit est choisi parmi le (±)-trans-5-fluoro-2,3,3a,9a-tétrahydro-1H[1,4]benzodioxino[2,3-c]pyrrole, et ses isomères 3aS et 3aR et leurs sels physiologiquement acceptables.

10. Procédé selon la revendication 1, dans lequel le produit est le chlorhydrate de (±)-trans--5-fluoro-2,3,3a,9a-tétrahydro-1H-[1,4]benzodioxino[2,3-c]pyrrole, et ses isomères 3aS et 3aR.

* C L M S *