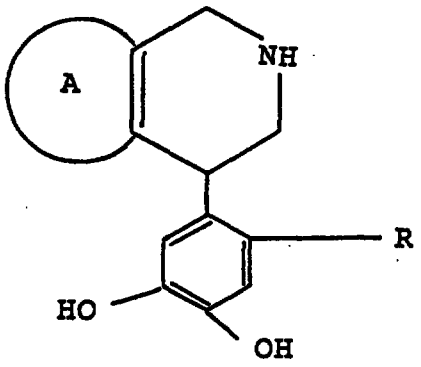
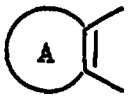
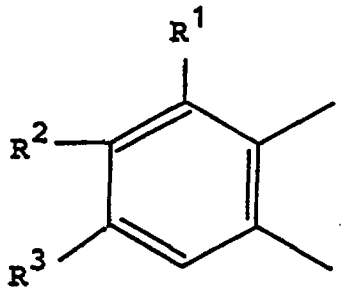
Description

This invention provides amino-substituted tetrahydroisoquinoline derivatives (I) and salts thereof



(I)

wherein  is



R^1 is hydrogen, lower alkyl, hydroxyl, halogen, amino, or lower acylamino;
R^2 is hydrogen, lower alkyl, hydroxyl, amino, or lower alkylsulfonylamino;
R^3 is hydrogen, lower alkyl, or hydroxyl; and
R is hydrogen or halogen;
with the proviso that when R^1 is other than lower alkyl, R^2, R^3 and R are not all hydrogens.

The above definitions apply throughout this specification. These compounds act directly upon dopamine receptor present in renal vascular tracts, and are useful as nephrovascular dilators.

The kidney is an important organ which participates in maintaining homeostasis of the circulatory system. If blood circulation insufficiency occurs in this organ, renal functions decrease to disrupt homeostasis of the circulatory system, thus inducing, maintaining or aggravating diseases of circulatory organs, such as hypertension and cardiac insufficiency.

Vasodilators and diuretics have been used for the treatment of these diseases, but no known vasodilator particularly dilates renal vascular tracts. It is also known that conventional diuretics tend to upset the balance among electrolytes. Dopamine shows diuretic and nephrovascular dilating effects, but it has unfavorable (vasoconstricting and heart-rate increasing) effects, it cannot be orally administered, and its effect is not well maintained. Thus, there is no drug presently available which is suited for clinical use.

We have tried to develop new compounds which act directly upon dopamine receptor in renal vascular tracts, can be orally administered, and maintain their effect over long periods.

EP 0040956 discloses 8-substituted 4-(3,4-dihydroxyphenyl)-1,2,3,4-tetrahydroisoquinolines and their renal vasodilating activity. The substituted tetrahydroisoquinolines of the present invention are structurally distinct from the known compounds.

This invention provides compounds (I) and salts thereof, a process for preparing them and nephrovascular dilators containing them as active ingredient.

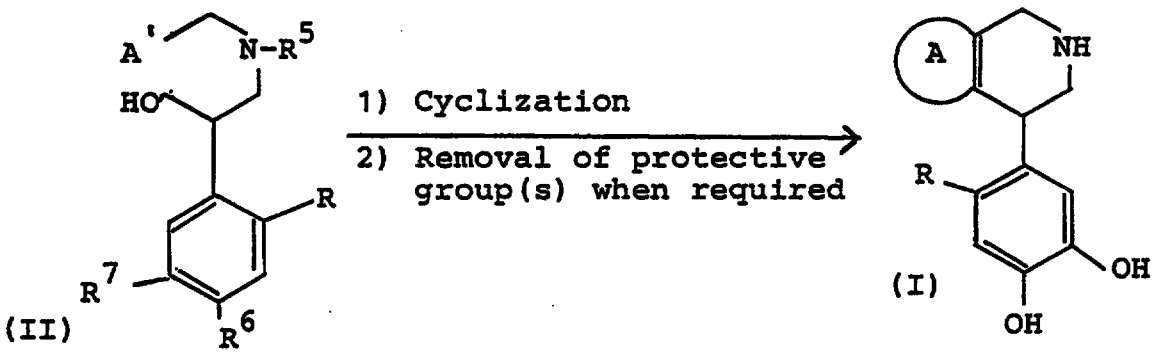
Compounds (I) form salts; pharmacologically acceptable salts include inorganic salts such as hydrochlorides, hydrobromides, sulfates, phosphates and nitrates, and organic salts such as maleates, fumarates, benzoates, ascorbates, methanesulfonates and tartrates.

In the definitions of the formula (I) compounds, "lower alkyl" means C_1 to C_5 straight or branched chain alkyl, examples being methyl, ethyl, propyl, iso-propyl, butyl, iso-butyl, sec-butyl, pentyl, etc. "Lower acyl"

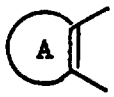
means C_1 to C_6 straight or branched chain acyl, examples being formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, iso-valeryl, pivaloyl, hexanoyl, etc. Examples of "halogen" are fluorine, chlorine, bromine and iodine. The compounds of this invention have an asymmetric carbon atom at the 4-position of the tetrahydroisoquinoline ring, and sometimes in lower alkyl and/or lower acyl group(s), and all optical isomers based on any asymmetric carbon, individually and in all combinations thereof, are included in this invention.

Compounds (I) of this invention may be prepared by the methods described below.

Method 1



(wherein R^6 and R^7 are hydroxyl groups which may optionally be protected; R^5 is hydrogen atom or a protective group for the nitrogen atom; and A' is a monovalent version of



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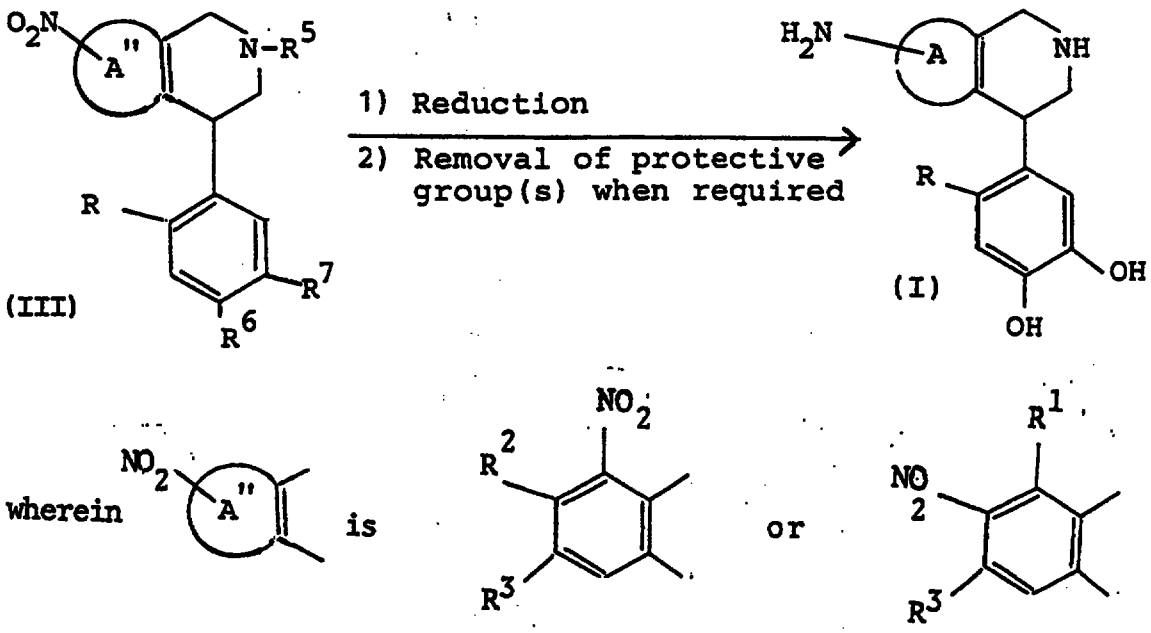
This method comprises cyclization of compound (II), followed by removal of protective group(s) when required. Examples of protective groups for hydroxyls in the starting materials (II) are linear and branched lower alkyls such as methyl, ethyl, isopropyl and tert-butyl, and aralkyls such as benzyl, benzhydryl and phenethyl. Suitable protective groups for the nitrogen atom(s) include the latter lower alkyls and aralkyls, tri-(lower)alkylsilyl groups such as trimethylsilyl and substituted and unsubstituted acyl groups such as formyl, acetyl, propionyl, trifluoroacetyl, tert-butoxycarbonyl, methoxyacetyl, methoxypropionyl and benzyloxycarbonyl.

Compounds (I) can be prepared by subjecting compound (II) to intramolecular cyclization by the action of cyclizing agent capable of forming carbonium ion from the alcoholic hydroxyl in compound (II), such as hydrochloric acid, sulfuric acid, sulfuric acid in trifluoroacetic acid, polyphosphoric acid, esters of polyphosphoric acid, methanesulfonic acid in dichloromethane, hydrogen bromide, and Lewis acids (e.g., boron trifluoride, aluminum chloride and stannic chloride).

There is no specific limitation upon the reaction temperature; the reaction can be performed under ice cooling or under reflux, with the reaction time being set in each case depending on other factors.

When the reaction products contain protective groups, these may be removed by catalytic reduction (e.g. catalytic hydrogenation) or by treatment with boron tribromide, hydrobromic acid, aluminum chloride, trimethylsilyl iodide or hydroiodic acid. The protective group on the nitrogen atom may be removed simultaneously with protective groups on hydroxyl groups, or in a separate step (for example, by treatment with cyanogen bromide, hydrochloric acid or ammonia water, hydrogenation in the presence of a catalyst, or other suitable methods).

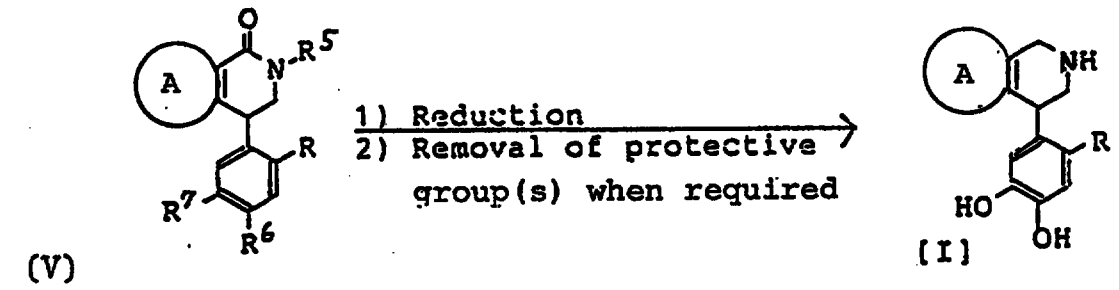
Method 2



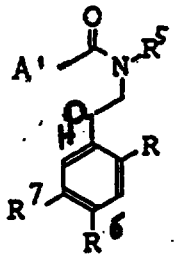
Compounds (I) can be prepared by reduction of nitro compound (III), followed by removal of protective groups(s) when required.

This reduction may be effected by the use of a sulfur compound, such as sodium sulfate, sodium hydrosulfide, sodium dithionite or ammonium sulfide; by catalytic reduction in the presence of platinum, platinum black, palladium-carbon (Pt-C) or Raney nickel, or by reduction using a metal hydride such as lithium aluminum hydride. Any solvents inert to the reaction may be used, including alcohols such as methanol, ethanol and isopropanol, tetrahydrofuran, diethyl ether, dioxane, benzene and toluene. The reaction is carried out at a temperature set depending on the type of reducing agent used (under ice cooling or at elevated temperatures). Protective groups of the nitrogen atom and hydroxyl groups can be simultaneously removed in this reducing step if the reaction is conducted under appropriate conditions.

Method 3



Compounds (I) can be prepared by reduction of carbonyl compound (V), followed by removal of the protective groups(s) when required. The carbonyl compounds (V) used in this reaction may be obtained by subjecting alcohol (IV)



(IV)

to intramolecular cyclization by the action of a cyclizing agent, such as those listed in Method 1.

Carbonyl compound (V) thus obtained is treated with a reducing agent, such as borane, diborane, lithium aluminum hydride, sodium borohydride plus propionic acid, aluminum hydride diisobutyl or aluminum hydride bis(2-methoxyethoxy)sodium, and protective group(s) are removed as required, giving compound (I). Any solvents inert to the reaction may be used, for example, tetrahydrofuran, diethyl ether, benzene or dioxane. The reaction is carried out at a temperature set depending on the type of reducing agent used (under ice cooling or at elevated temperatures). Protective groups can be removed as in Method 1.

Compounds (I) can be isolated and purified in the form of free amine or salt thereof by commonly employed techniques, for example, extraction, crystallization, recrystallization and various types of chromatography.

Compounds of this invention are efficiently absorbed when administered orally and are effective for treating diseases of circulatory organs, such as renal insufficiency, cardiac insufficiency and hypertension. In the treatment of hypertension, in particular, these compounds may provide an etiologically effective medicine unlike conventional symptomatic drugs.

Compounds of this invention dilate nephrovascular tracts, and this action is exerted through dopamine receptor. The compounds also dilate vascular tracts of other organs, and act directly upon renal tubules, thus showing a diuretic effect. In addition, these compounds may be effective for the prevention of oliguria during and after operation and for the treatment of visceral hyperfunction, edemas, arterioscrelosis and blood coagulation.

These pharmacological effects were confirmed by the test described below.

Male and female mongrel dogs weighing 11 to 16 Kg were anesthetised with pentobarbital (30 mg/Kg i.v.), and artificial respiration was started by means of a cannula inserted into the trachea of each dog. Throughout the test, pentobarbital was continuously administered (3 to 5 mg/Kg/hr) into the vein of the right forelimb to maintain a constant anesthetic condition. A cannula for drug administration was inserted into the vein of the right thigh. The systemic blood pressure was measured by means of a pressure transducer, with a cannula inserted into the artery of the right thigh. The heart rate was measured using a cardiotachometer driven by pulse waveform.

Incision was made from the flank to the posterior wall of the peritoneum to expose the kidney, a probe was set to the renal artery, and the rate of renal blood flow was measured with an electromagnetic blood flowmeter. After setting the probe, an injection needle for drug administration connected to a polyethylene tube was inserted at the origin of the renal artery.

Each of the compound tested was quickly injected in the form of a 0.2 ml solution, followed by continuous injection of physiological saline (0.5 ml/min) to ensure its rapid spreading in the renal artery.

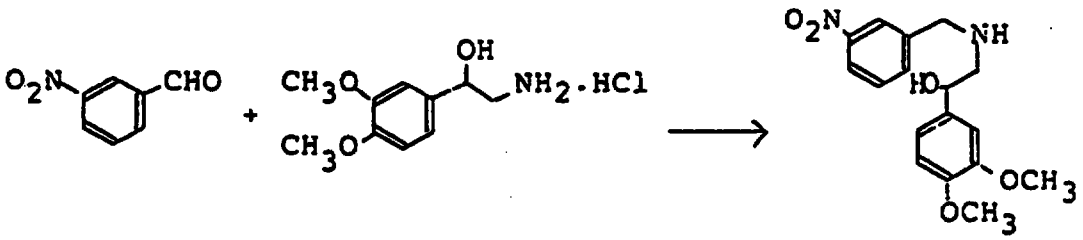
All the test values are expressed as percentage change in the rate of blood flow, with the value immediately before administration taken as 100%.

Administration of the compounds of this invention into the renal artery of dogs put under anesthesia at doses of 0.3 to 100 μg showed increases in the rate of blood flow proportional to the amounts administered, with an increase of about 35% being observed at the highest dose. some compounds at doses of 0.3-30μg showed increases with an increase of about 40% being observed at the highest dose (30μg).

Preparations containing, as active ingredient, at least one of the compounds of this invention may be manufactured in the form of tablets, powder, beadlets, granules, capsules, pills, injections, suppositories, ointment or poultices by using carriers, excipients and other commonly employed additives, and are orally (including sublingually) or parenterally administered.

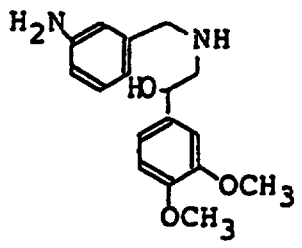
The suitable daily dose of the compounds of this invention should be determined according to physical condition, body weight, age, sex and other factors of particular patients, but is normally 50 to 1000 mg for adults (given all at one time or subdivided into several doses).

Reference Example 1



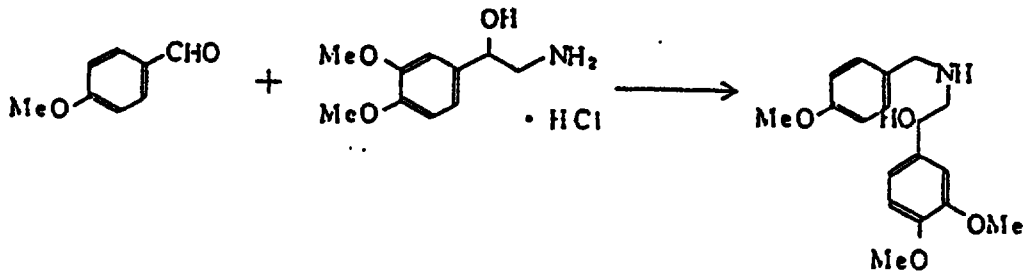
m-Nitrobenzaldehyde (1.8 g) was added to a suspension of α-(aminomethyl)-3,4-dimethoxybenzyl alcohol hydrochloride in 25 ml methanol, triethylamine (2.8 ml) was further added dropwise at room temperature with stirring, and the resulting solution was heated under reflux for 30 minutes. After cooling, sodium borohydride (1.45 g) was added in small portions with stirring under ice cooling, and the mixture was stirred at room temperature for one hour and concentrated. The residue was treated with chloroform and water, and the chloroform layer was collected, washed with water and dried over anhydrous sodium sulfate. The solvent was distilled off, and the residue was recrystallized from ether/n-hexane, affording 3.3 g of pure α-[(3-nitrobenzylamino)methyl]-3,4-dimethoxybenzyl alcohol, m.p. 105-107 °C.

Reference Example 2



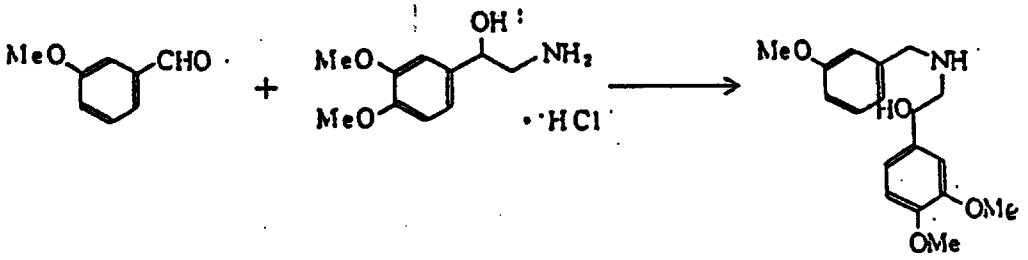
To a solution of 3.3 g α-[(3-nitrobenzylamino)methyl]-3,4-dimethoxybenzyl alcohol obtained in Reference Example 1 in 50 ml methanol, was added 0.6 g Raney nickel, and the mixture was subjected to hydrogenation at room temperature. After confirming complete absorption of hydrogen gas, the reaction mixture was filtered, the filtrate was concentrated, and the residue was recrystallized from ethyl acetate.

Reference Example 3



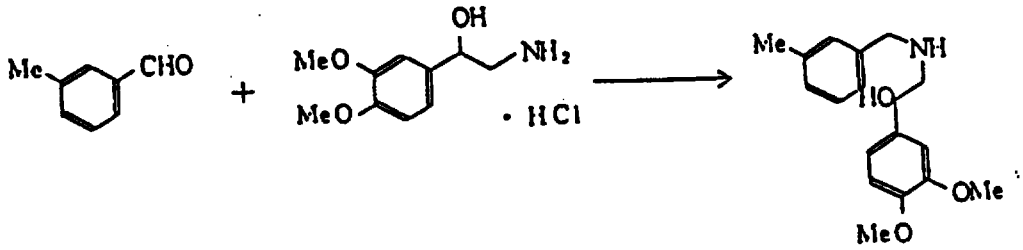
α-[[(4-methoxybenzyl)amino]methyl]-3,4-dimethoxybenzyl alcohol (m.p. 110-112 °C)

Reference Example 4



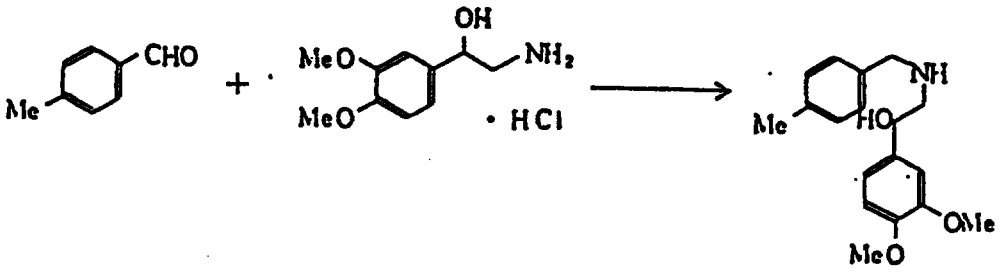
α-[[(3-methoxybenzyl)amino]methyl]-3,4-dimethoxybenzyl alcohol (m.p. 115-116°C)

Reference Example 5



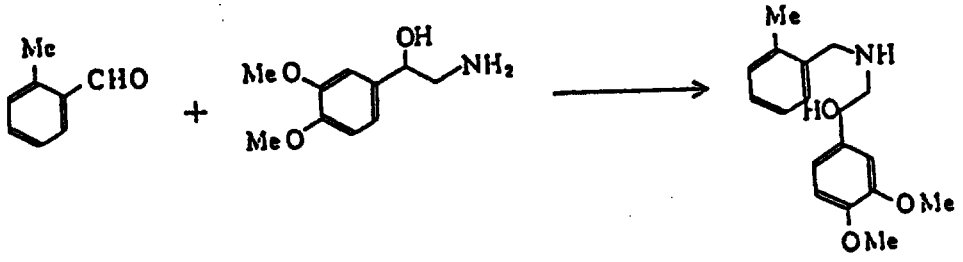
α-[[(3-methylbenzyl)amino]methyl]-3,4-dimethoxybenzyl alcohol.

Reference Example 6



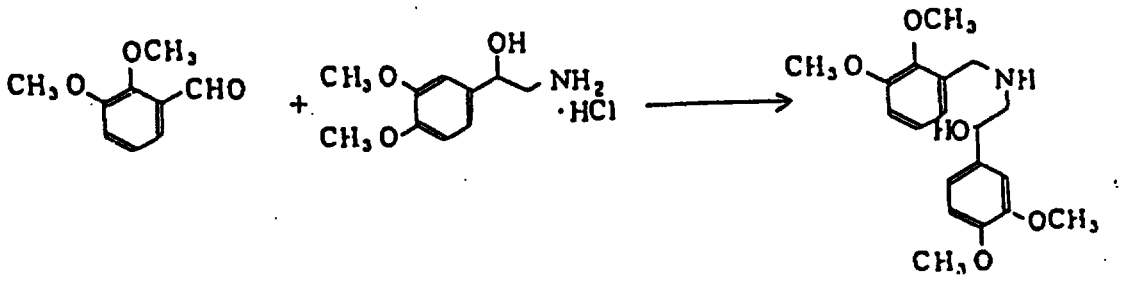
α-[[(4-methylbenzyl)amino]methyl]-3,4-dimethoxybenzyl alcohol.

Reference Example 7



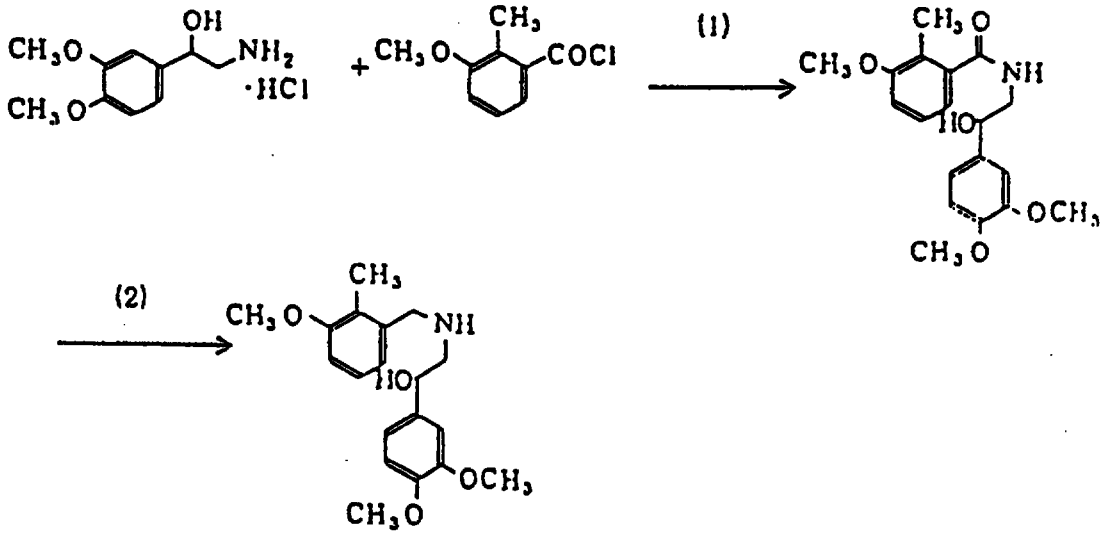
α-[[(2-methylbenzyl)amino]methyl]-3,4-dimethoxybenzylalcohol (m.p. 103-104°C)

Reference Example 8



1.0 g of α-(aminomethyl)-3,4-dimethoxybenzyl alcohol hydrochloride was suspended in 5 ml of methanol, and after adding thereto 0.85 g of 2,3-dimethoxybenzaldehyde, 0.63 ml of triethylamine was added dropwise to the mixture while stirring at room temperature. The mixture was heated under reflux for 30 minutes, and 0.24 g of sodium boron hydride was added slowly to the mixture while stirring under ice cooling. After the foaming stopped, the mixture was concentrated. The residue was subjected to a separating procedure with chloroform and water, the chloroform layer was collected, washed with water, and dried over anhydrous sodium sulfate. The solvent was distilled off, and the residue was recrystallized from ethyl acetate-n-hexane, giving 1.07 g of α-[[(2,3-dimethoxybenzyl)amino]methyl]-3,4-dimethoxybenzyl alcohol, m.p. 96-97 °C.

Reference Example 9

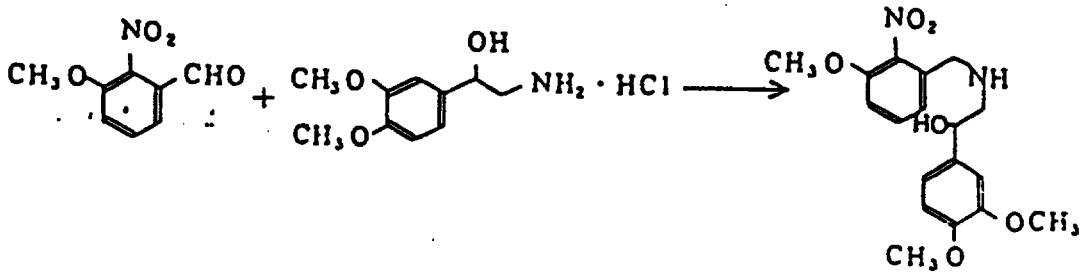


(1) To 1.56 g of 3-methoxy-2-methylbenzoic acid was added 2.03 g of thionyl chloride, and the mixture was heated under reflux for 30 minutes. The reaction solution was concentrated, and subjected to azeotropic distillation with toluene 2 times. The residue was dissolved in 8 ml of toluene, and the solution was added dropwise to a mixture of 2.0 g of α-(aminomethyl)-3,4-dimethoxybenzyl alcohol hydrochloride and 1.53 ml of pyridine and20 ml of isopropyl alcohol under ice cooling while stirring. The mixture returned to room temperature, and after 30 minutes, the reaction solution was concentrated. The residue was dissolved in ethyl acetate, washed with 1N aqueous HCl, saturated aqueous $NaHCO_3$ solution, and water, successively, and dried over anhydrous sodium sulfate. The solvent was distilled off, and the residue was recrystallized from ethyl acetate-n-hexane, giving 2.41 g of α-[N-(3-methoxy-4-methylbenzoyl)amidomethyl]-3,4-dimethoxybenzyl alcohol, m.p. 106-109 °C.

(2) 1.02 g of α-[N--(3-methoxy-4-methylbenzoyl)amidomethyl]-3,4-dimethoxybenzyl alcohol was dissolved in 10 ml of tetrahydrofuran, and 1M borane-tetrahydrofuran solution (10.8 ml) was added dropwise to the mixture under an argon gas stream under ice cooling. The mixture was heated under reflux for 2.5 hours, and after ice cooling, 0.44 ml of methanol was added dropwise, and the mixture was heated under reflux

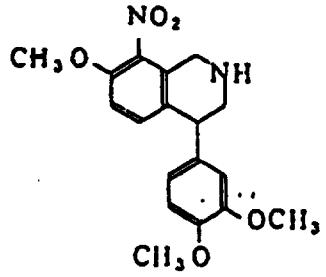
for 30 minutes. The mixture was cooled with ice, and after adding thereto 0.9 ml of conc. hydrochloric acid, the mixture was heated under reflux for 30 minutes, and concentrated. The residue was dissolved in water, washed with ether twice, and basified, and extracted with chloroform twice. The chloroform layers were collected, washed with water, and dried over anhydrous sodium sulfate. The solvent was distilled off, and the residue was recrystallized from chloroform-n-hexane, giving 560 mg of α-[[(3-methoxy-2-methylbenzyl)amino]methyl]-3,4-dimethoxybenzyl alcohol, m.p. 135-136 °C.

Reference Example 10



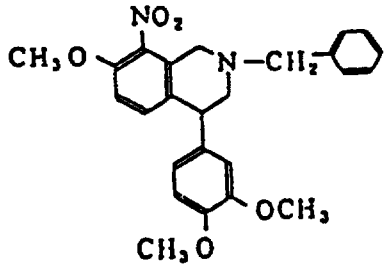
α-[[(3-methoxy-2-nitrobenzyl)amino]methyl]-3,4-dimethoxybenzyl alcohol (m.p. 92-94 °C)

Reference Example 11



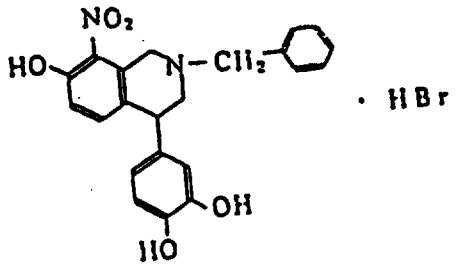
4-(3,4-dimethoxyphenyl)-7-methoxy-8-nitro-1,2,3,4-tetrahydroisoquinoline.

Reference Example 12



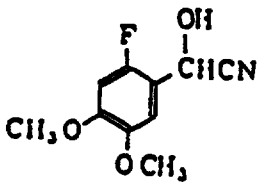
2-Benzyl-4-(3,4-dimethoxyphenyl)-7-methoxy-8-nitro-1,2,3,4-tetrahydroisoquinoline (m.p. 118-119 °C)

Reference Example 13



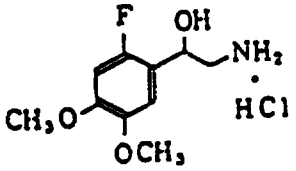
2-Benzyl-4-(3,4-dihydroxyphenyl)-7-hydroxy-8-nitro-1,2, 3,4-tetrahydroisoquinoline hydrobromide (m.p. above 180 °C (decomposition))

Reference Example 14



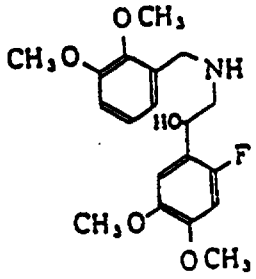
α-(cyano)-6-fluoro-3,4-dimethoxybenzyl alcohol.

Reference Example 15



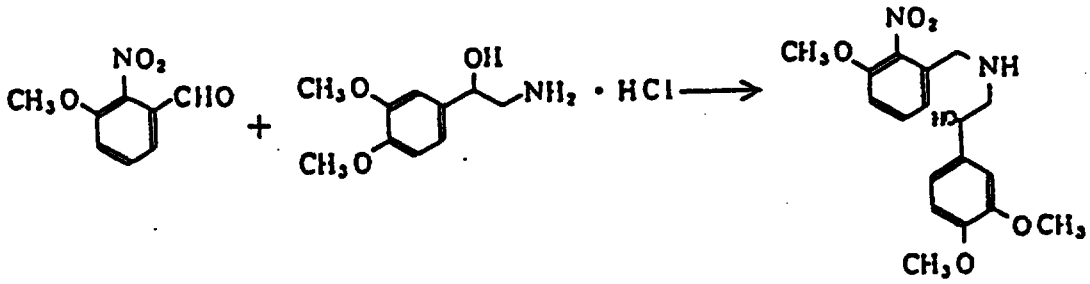
α-(aminomethyl)-6-fluoro-3,4-dimethoxybenzyl alcohol hydrochloride (m.p. 223-226 °C)

Reference Example 16



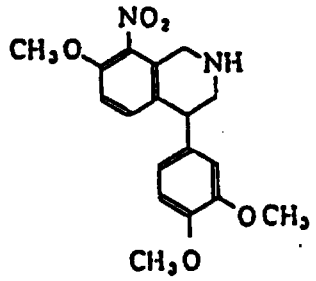
α-[[(2,3-dimethoxybenzylamino]methyl]-6-fluoro-3,4-dimethoxybenzyl alcohol (m.p. 110-112 °C)

Reference Example 17



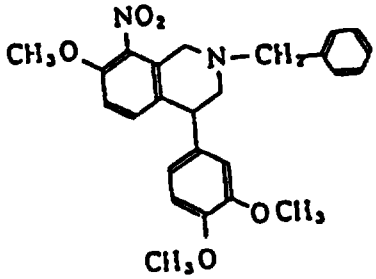
α-[[(3-methoxy-2-nitrobenzyl)amino]methyl]-3,4-dimethoxybenzyl alcohol (m.p. 92-94 °C)

Reference Example 18



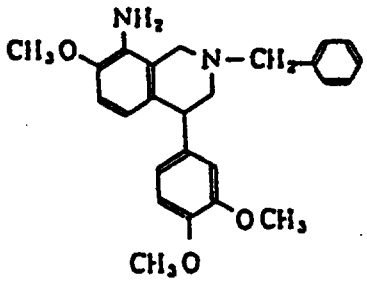
4-(3,4-dimethoxyphenyl)-7-methoxy-8-nitro-1,2,3,4-tetrahydroisoquinoline.

Reference Example 19



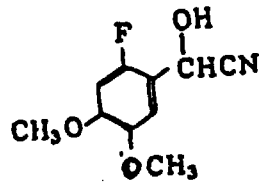
2-benzyl-4-(3,4-dimethoxyphenyl)-7-methoxy-8-nitro-1,2,3,4-tetrahydroisoquinoline (m.p. 118-119 °C)

Reference Example 20



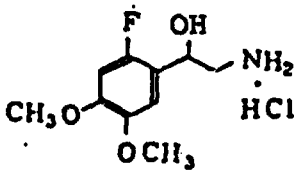
8-amino-2-benzyl-7-methoxy -4-(3,4-dimethoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (m.p. 142-143 °C)

Reference Example 21



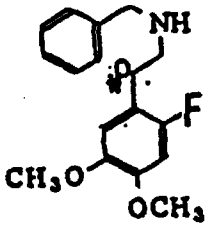
α-(cyano)-6-fluoro-3,4-dimethoxybenzyl alcohol (m.p. 112-114°C)

Reference Example 22



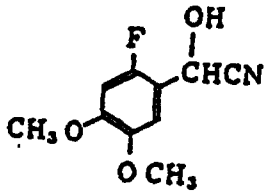
α-(aminomethyl)-6-fluoro-3,4-dimethoxybenzyl alcohol hydrochloride (m.p. 223-226°C)

Reference Example 23



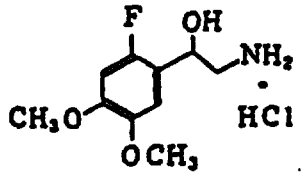
α-[(benzylamino)methyl]-6-fluoro-3,4-dimethoxybenzyl alcohol (m.p. 80-82.5°C)

Reference Example 24



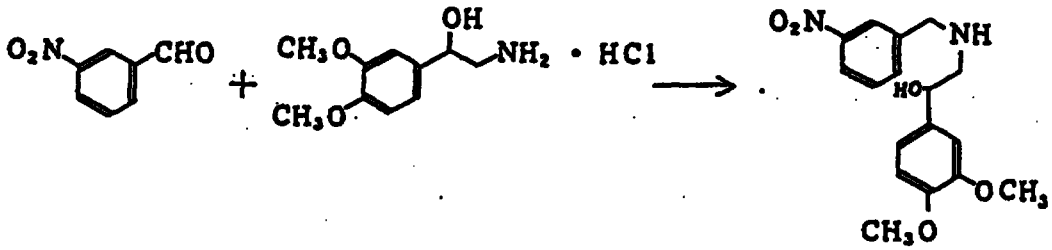
α-(cyano)-6-fluoro-3,4-dimethoxybenzyl alcohol (m.p. 112-114°C)

Reference Example 25



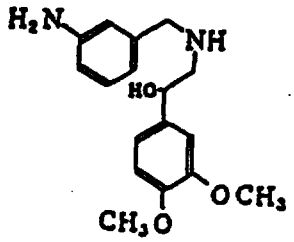
α-(aminomethyl)-6-fluoro-3,4-dimethoxybenzyl alcohol (m.p. 223-226 °C)

Reference Example 26



α-[(3-nitrobenzylamino)methyl]-3,4-dimethoxybenzyl alcohol (m.p. 105-107 °C)

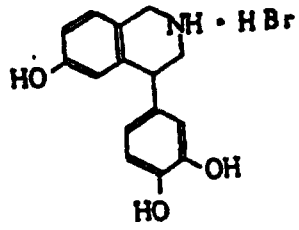
Reference Example 27



α-[(3-aminobenzylamino)methyl]-3,4-dimethoxybenzyl alcohol (m.p. 84-86 °C)

The above Reference Example compounds were prepared in conventional ways and are convertible to compounds according to the invention as previously described.

Example 1



(1) α-[[(4-methoxybenzyl)amino]methyl]-3,4-dimethoxybenzyl alcohol (950 mg) was dissolved in 7.2 ml of trifluoroacetic acid, and after adding thereto 0.22 ml of conc. sulfuric acid under ice cooling, the reaction

was allowed to react for 45 minutes. The reaction solution was concentrated, and subjected to azeotropic distillation with toluene 2 times. After adding chloroform, the mixture was basified by addition of 28% aqueous ammonia under ice cooling.

The chloroform layer was collected , washed with water, and dried over anhydrous sodium sulfate. The solvent was distilled off, and the residue obtained was subjected to silica gel column chromatography-(chloroform-methanol-28% aqueous ammonia = 15:1:0.1), giving 790 mg of 6-methoxy-4-(3,4-dimethoxyphenyl)-1,2,3,4-tetrahydroisoquinoline as an oily material.

(2) To 790 mg of 6-methoxy-4-(3,4-dimethoxyphenyl)-1,2, 3,4-tetrahydroisoquinoline was added 16 ml of 48% hydrobromic acid, and the mixture was heated under reflux for 3 hours under an argon stream. The reaction solution was cooled, and precipitates which separated out were collected by filtration, giving 630 mg of 6-hydroxy-4-(3,4-dihydroxyphenyl)-1,2,3,4-tetrahydroisoquinoline hydrobromide.

Elemental analysis (as $C_{15}H_{16}NO_3Br$)

	C(%)	H(%)	N(%)	Br(%)
Calcd.	53.27	4.77	4.14	23.63
Found	53.16	4.70	4.16	23.35

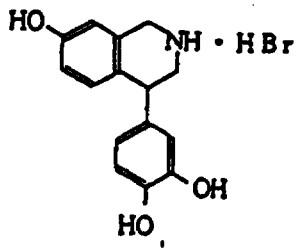
Melting Point: above 250 °C

Mass spectrum (FAB) 258 (M^+ + 1)

NMR spectrum (d_6-DMSO, internal standard TMS)

δ (ppm) 3.24 (1H, d), 3.49 (1H, dd), 6.23 (1H, d), 6.59 (1H, s) 6.74 (1H, s), 6.76 (1H, d) 7.40 (1H, d)

Example 2



(1) 17.5 ml of α-[[(3-methoxybenzyl)amino]methyl]-3,4-dimethoxybenzyl alcohol was dissolved in 17.5 ml of trifluoroacetic acid, and after adding thereto 0.54 ml of conc. sulfuric acid under ice cooling, the reaction was allowed to react for 60 minutes. The reaction solutionwas concentrated, and was subjected to azeotropic distillation with toluene 2 times. After adding chloroform, the mixture was basified by addition of 28% aqueous ammonia under ice cooling.

The chloroform layer was collected, washed with water once, and dried over anhydrous sodium sulfate. The solvent was distilled off, and the residue was subjected to silica gel colum chromatography (chloroform-methanol-28% aqueous ammonia = 15:1:0.1); materials of Rf 0.47 and 0.35 [Kiesel gel $60F_{254}$ plate; chloroform-methanol-28%aqueous ammonia(15:1:0.1)] was obtained. The material of Rf 0.47 is 5-methoxy-4-(3,4-dimethoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (m.p. 118-119 °C, recrystallized from chloroform-n-hexane) (680 mg), and the material of Rf 0.35 is 7-methoxy-4-(3,4-dimethoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (m.p. 119-120 °C, ethyl acetate-n-hexane recrystallization) (670 mg).

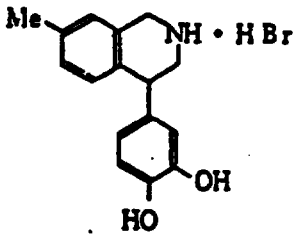
(2) 640 mg of 7-methoxy-4-(3,4-dimethoxyphenyl)-1,2,3,4-tetrahydroisoquinoline was dissolved in 13 ml of 48% aqueous hydrogen bromide, and the mixture was heated under reflux under an argon gas stream for 3 hours. The reaction solution was cooled, and crystals which separated out were collected, affording 580 mg of 7-hydroxy-4-(3,4-dihydroxyphenyl)-1,2,3,4-tetrahydroisoquinoline hydrobromide.

Elemental analysis (as $C_{15}H_{16}NO_3Br \cdot 1/5\ H_2O$)

	C(%)	H(%)	N(%)	Br(%)
Calcd.	52.71	4.84	4.10	23.38
Found	52.66	4.79	4.07	23.63

Melting Point: above 220 °C (decomposition)
Mass spectrum (FAB) 258 ($M^+ + 1$)
NMR spectrum (d_6-DMSO, internal standard TMS)
δ (ppm): 3.22 (1H, d), 3.48 (1H, dd), 4.60 (1H, dd), 6.58 (1H, s), 6.64 (1H, s), 6.67 (1H, d)

Example 3



(1) 1.8 g of α-[[(3-methylbenzyl)amino]methyl]-3,4-dimethoxybenzyl alcohol was dissolved in 13.5 ml of trifluoroacetic acid, and after adding thereto 0.41 ml of conc. sulfuric acid under ice cooling, the mixture was allowed to react for 40 minutes. The reaction solution was concentrated, and subjected to azeotropic distillation with chloroform 2 times, and after adding chloroform, the mixture was basified by addition of 28% aqueous ammonia. The chloroform layer was collected, washed with water once, and dried over anhydrous sodium sulfate. The solvent was distilled off, and the residue was subjected to silica gel column chromatography (chloroform-methanol-28% aqueous ammonia(15:1:0.1); a material of Rf 0.46 [Kiesel gel $60F_{254}$ plate, chloroform-methanol-28% aqueous ammonia(15:1:0.1)] was collected, recrystallized from chloroform-n-hexane, and recrystallized from the same solvent system several times, giving 8~0 mg of 4-(3,4-dimethoxyphenyl)-7-methyl-1,2,3,4-tetrahydroiso quinoline, m.p. 129-131 °C.
(2) 850 mg of 4-(3,4-dimethoxyphenyl)-7-methyl-1,2,3,4-tetrahydroisoquinoline was dissolved in 17 ml of 48% hydrobromic acid, and the mixture was heated under reflux under an argon gas stream for 3 hours. The reaction solution was cooled, and the crystals obtained were collected by filtration, giving 620 mg of 4-(3,4-dihydroxyphenyl)-7-methyl-1,2,3,4-tetrahydroisoquinoline hydrobromide.
Melting point; 192-195 °C

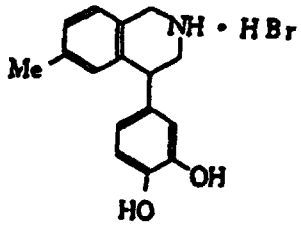
Elemental analysis (as $C_{15}H_{16}NO_3Br$)

	C(%)	H(%)	N(%)	Br(%)
Calcd.	57.16	5.40	4.17	23.76
Found	57.21	5.29	4.03	23.83

Mass Spectrum (FAB) 256 ($M^+ = 1$)
NMR spectrum (d_6-DMSO, internal standard TMS)
δ (ppm): 2.27 (3H, s), 3.26 (1H, dd), 3.59 (1H, dd) 6.48 (1H, dd), 6.55 (1H, s), 6.72 (1H, dx2), 7.02

(1H, d), 7.08 (1H, s)

Example 4



(1) 530 mg of α-[[(4-methylbenzyl)amino]methyl]-3,4-dimethoxybenzyl alcohol was dissolved in 4 ml of trifluoroacetic acid, and after adding thereto 0.12 ml of conc. sulfuric acid under ice cooling, the mixture was allowed to react for 30 minutes. The reaction solution was concentrated, and subjected to azeotropic distillation with toluene 2 times. After adding chloroform, the mixture was basified by addition of 28% aqueous ammonia.

The chloroform layer was collected, washed with water once, and dried over anhydrous sodium sulfate. The solvent was distilled off, and the residue was recrystallized from ethyl acetate-n-hexane, giving 490 mg of 4-(3,4-dimethoxyphenyl)-6-methyl-1,2,3,-4-tetrahydroisoquinoline (melting point: 94-96 • C).

(2) To 450 mg of 4-(3,4-dimethoxyphenyl)-6-methyl-1,2,3,4-tetrahydroisoquinoline was added 9 ml of 48% hydrobromic acid, and the mixture was heated under reflux under an argon gas stream for 3 hours. The reaction solution was cooled, and the crystals which separated out were collected by filtration, giving 390 mg of 4-(3,4-dihydroxyphenyl)-6-methyl-1,2,3,4-tetrahydroisoquinoline hydrobromide.

Melting point above 250 • C (decomposition)

Elemental analysis (as $C_{15}H_{16}NO_3Br$)

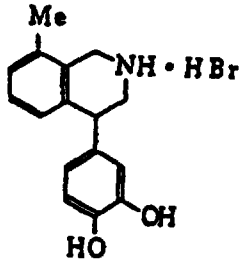
	C(%)	H(%)	N(%)	Br(%)
Calcd.	57.16	5.40	4.17	23.76
Found	56.95	5.44	4.02	24.06

Mass Spectrum (EI) 255 (M^+)

NMR spectrum (d_6-DMSO, internal standard TMS)

δ (ppm): 2.20 (3H, s), 3.28 (1H, dd), 3.64 (1H, dd), 6.50 (1H, dd), 6.56 (1H, dd), 6.56 (1H, s), 6.64 (1H, s), 6.75 (1H, d), 7.04 (1H, dd), 7.18 (1H, d)

Example 5



(1)900 mg of α-[[(2-methoxybenzylamino]amino]methyl]-3,4,-dimethoxybenzyl alcohol was dissolved in 7 ml of trifluoroacetic acid, and after adding thereto 0.21 ml of conc. sulfuric acid under ice cooling, the mixture was allowed to react for 60 minutes. The reaction solution was concentrated, and subjected to azeotropic distillation 3 times, and after adding chloroform, the mixture was basified by addition of 28% aqueous ammonia.

The chloroform layer was collected, washed with water, and dried over anhydrous sodium sulfate. The solvent was distilled off, and the residue obtained was recrystallized from ethyl acetate-n-hexane, giving 440 mg of 4-(3,4-dimethoxyphenyl)-8-methyl-1,2,3,4-tetrahydroisoquinoline, m.p. 86-88 °C.

(2) To 420 mg of 4-(3,4-dimethoxyphenyl)-8-methyl-1,2,3,4-tetrahydroisoquinoline, was added 48% hydrobromic acid, and the mixture was heated under reflux for 3 hours. After about 10 minutes, crystals separated out. The reaction mixture was cooled, and the crystals were collected by filtration, giving 420 mg of 4-(3,4-dihydroxyphenyl)-8-methyl-1,2,3,4-tetrahydroisoquinoline hydrobromide.

Melting point: above 250 °C (decomposition)

Elemental analysis (as $C_{15}H_{16}NO_3Br$)

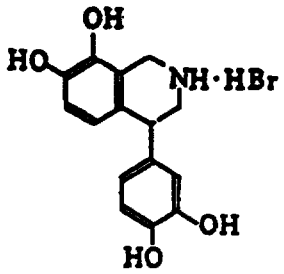
	C(%)	H(%)	N(%)	Br(%)
Calcd.	57.16	5.40	4.17	23.76
Found	57.04	5.43	4.17	23.73

Mass spectrum (FAB) 256 (M^+ = L)

NMR spectrum (d_6-DMSO, internal standard TMS)

δ (ppm): 2.28 (3H, s), 3.60 (1H, dd), 6.50 (1H, dd), 6.80 (1H, s), 6.65 (1H, d), 6.76 (1H, d), 7.12 (1H, d)

Example 6



(1) 1.0 g of α-[[2,3-dimethoxybenzyl)amino]methyl]-3,4-dimethoxybenzyl alcohol was dissolved in 7.5 ml of trifluoroacetic acid, and after adding thereto 0,23 ml of conc. sulfuric acid under ice cooling, the mixture was allowed to react for 30 minutes. The reaction solution was concentrated, and subjected to azeotropic distillation with toluene 2 times. After adding to the mixture chloroform, the mixture was basified by addition of 28% aqueous ammonia under ice cooling. After separating, the chloroform layer was collected, washed with water, and dried over anhydrous magnesium sulfate. The solvent was distilled off, and the residue thus obtained was recrystallized from chloroform-n-hexane, affording 750 mg of 7,8-dimethoxy-4-(3,4-dimethoxyphenyl)-1,2,3,4-tetrahydroisoquinoline, m.p. 109-110 °C.

(2) To 700 mg of 7,8-dimethoxy-4-(3,4-dimethoxyphenyl)-1,2,3,4-tetrahydroisoquinoline, was added 14 ml of 48% hydrobromic acid, and the mixture was heated under reflux for 3 hours under an argon gas stream. The reaction mixture was cooled, and the crystals which separated out were collected by filtration, giving 540 mg of 7,8-dihydroxy-4-(3,4-dihydroxyphenyl)-1,2,3,4-tetrahydroisoquinoline hydrobromide.

Elemental analysis (as $C_{15}H_{16}NO_4Br$)

	C(%)	H(%)	N(%)	Br(%)
Calcd.	50.87	4.55	3.95	22.56
Found	51.02	4.33	3.96	22.82

Melting point: above 230 °C (decomposition)
Mass spectrum (FAB) 274 (M^+ + 1)
NMR spectrum (d_6-DMSO; internal standard: TMS)
δ(ppm) 3.24 (1H, m), 3.52 (1H, m), 6.08 (1H, d), 6.48 (1H, dd), 6.58 (1H, s), 6.68 (1H, d), 6.76 (1H, d)

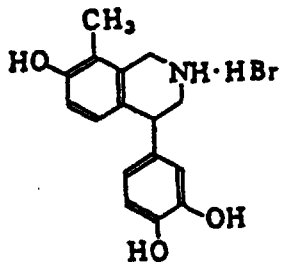
Example 7

(1) 510 mg of α-[[(3-methoxy-2-methylbenzyl)amino]methyl]-3,4-dimethoxybenzyl alcohol was dissolved in 3.8 ml of trifluoroacetic acid, 0.12 ml of conc. sulfuric acid was added dropwise under ice cooling, and the mixture was allowed to react for 30 minutes. The reaction solution was concentrated, and subjected to azeotropic distillation with toluene 2 times. The residue was dissolved in chloroform, and basified by addition of 28% aqueous ammonia. The chloroform layer was collected, washed with water, and dried over anhydrous magnesium sulfate. The solvent was distilled off, and the residue was recrystallized from ethyl acetate-n-hexane, giving 430 mg of 7-methoxy-4-(3,4-dimethoxyphenyl)-8-methyl-1,2,3,4-tetrahydroisoquinoline, m.p. 128-129 °C.
(2) To 410 mg of 7-methoxy-4-(3,4-dimethoxyphenyl)-8-methyl-1,2,3,4-tetrahydroisoquinoline was added 8.2 ml of 48% hydrobromic acid, and the mixture was heated under reflux under an argon gas stream for 3 hours. The reaction mixture was cooled, and the crystals which separated out were collected by filtration, giving 410 mg of 7-hydroxy-4-(3,4-dihydroxyphenyl)-8-methyl-1,2,3,4-tetrahydroisoquinoline hydrobromide.

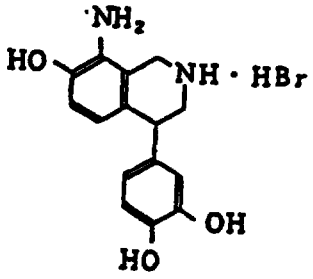
Elemental analysis (as $C_{16}H_{18}NO_3Br$)

	C(%)	H(%)	N(%)	Br(%)
Calcd.	54.56	5.15	3.98	22.69
Found	54.34	5.10	3.95	22.58

Melting point: 250 °C
Mass spectrum (FAB) 272 (M^+ + 1)
NMR spectrum (d_6-DMSO, internal standard TMS)
δ (ppm): 2.05 (1H, s), 3.35 (total 3H), 6,46 (total 3H), 2.72 (total 3H, dx2)



Example 8



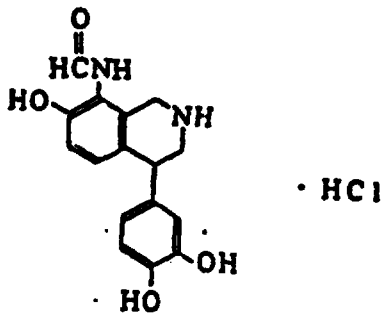
700 mg of 2-benzyl-4-(3,4-dihydroxyphenyl)-7-hydroxy-8-nitro-1,2,3,4-tetrahydroisoquinoline hydrobromide was dissolved in 14 ml of ethanol, and after adding thereto 0.07 g of 10% palladium-carbon, hydrogenation was performed at 40°C. The reaction mixture was filtered and concentrated. The residue was treated with chloroform, and the precipitates were collected by filtration and dried, affording 590 mg of 8-amino-5-(3,4-dihydroxyphenyl)-7-hydroxy-1,2,3,4-tetrahydroisoquinoline hydrobromide.

Elemental analysis (as $C_{15}H_{17}N_2O_3Br$)

	C(%)	H(%)	N(%)	Br(%)
Calcd.	51.01	4.85	7.93	22.62
Found	50.72	4.53	7.91	22.43

Mass spectrum (FAB) 273 (M^+ + 1)
NMR spectrum (d_6-DMSO, internal standard TMS)
δ (ppm): 5.96 (1H, d), 6.46 (1H, dd), 6.53 (1H, s), 6.60 (1H, d), 6.76 (1H, d)

Example 9



(1)1.03 g of 2-benzyl-4-(3,4-dihydroxyphenyl)-7-hydroxy-8-nitro-1,2,3,4-tetrahydroisoquinoline hydrobromide was suspended in 20 ml of ethanol, and after adding thereto 1 ml of Raney nickel, hydrogenation was performed at 40°C. The reaction mixture was filtered and concentrated, affording 0.88 g of 8-amino-2-benzyl-4-(3,4-dihydroxyphenyl)-7-hydroxy-1,2,3,4-tetrahydroisoquinoline hydrobromide.
(2)To a solution of 0.25 ml of formic acid in 10 ml of chloroform, was added under ice cooling 0.88 g of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, and then after 15 minutes was added dropwise 5 ml of a solution of 8-amino-2-benzyl-4-(3,4-dihydroxyphenyl)-7-hydroxy-1,2,3,4-tetrahydroisoquinoline

hydrobromide (0.88 g) in dimethylformamide. The temperature of the reaction mixture returned to room temperature, and reaction was performed for a further 30 minutes. The reaction mixture was concentrated, and treated by addition of standard buffer solution (x5). The precipitates were collected by filtration, and washed well with water, affording 450 mg of 2-benzyl-4-(3,4-dihydroxyphenyl)-8-formylamido-7-hydroxy-1,2,3,4-tetrahydrosioquinoline.

(3) 450 mg of 2-benzyl-4-(3,4-dihydroxyphenyl)-8-formamido-7-hydroxy-1,2,3,4-tetrahydroisoquinoline was dissolved in 9 ml of ethanol, and after adding thereto 0.86 ml of 2N hydrochloric acid and 0.05 g of 10% palladium-carbon, hydrogenation was performed at room temperature. The reaction mixture was filtered and concentrated. The residue was treated with isopropyl alcohol and acetonitrile, and the precipitate was collected by filtration, affording 320 mg of 4-(3,4-dihydroxyphenyl)-8-formamido-7-hydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride.

Elemental analysis (as $C_{16}H_{17}N_2O_4Cl$)

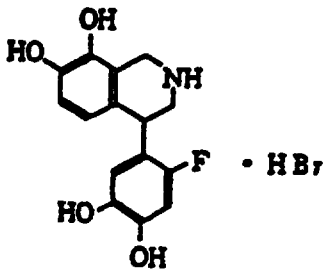
	C(%)	H(%)	N(%)	Cl(%)
Calcd.	57.06	5.09	8.32	10.53
Found	56.78	4.82	8.20	10.72

Mass spectrum (FAB) 301 ($M^+ + 1$)

NMR spectrum (d_6-DMSO, internal standard TMS)

δ (ppm): 6.56 (1H, s), 6.66 (1H, d), 6.80 (1H, d), 6.90 (1H, d), 8.28 (1H, d)

Example 10



(1) α-[[(2,3-dimethoxybenzyl)amino]methyl]-6-fluoro-3,4-dimethoxybenzyl alcohol (1.0 g) was dissolved in 7 ml of trifluoroacetic acid, and after adding thereto under ice cooling conc. sulfuric acid (0.25 ml), the mixture was stirred for 40 minutes 0.72 g of sodium acetate was added to the reaction mixture, and the mixture was concentrated. To the residue was added chloroform and water, and the mixture was basified by addition of conc. aqueous ammonia under ice cooling. After separating, the chloroform layer was collected, washed with saturated aqueous NaCl solution, and dried over anhydrous sodium sulfate. The solvent was distilled off; 0.94 g of 4-(6-fluoro-3,4-dimethoxyphenyl)-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline was obtained as a syrupy material.

(2) 0.90 g of 4-(6-fluoro-3,4-dimethoxyphenyl)-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline was dissolved in 25ml of dichloromethane, and to the mixture was added dropwise 1M boron tribromide-dichloromethane solution (27 ml) under an argon gas stream, at an internal temperature of -30 to -60°C under cooling while stirring. The mixture was stirred for 3 hours at room temperature, and 7.0 ml of methanol was added to the mixture under cooling by a dry ice-methanol bath, dropwise. The mixture was stirred for 30 minutes at room temperature, the crystals which separated out were collected, giving 0.75 g of 4-(6-fluoro-3,4-dihydroxyphenyl)-7,8-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrobromide.

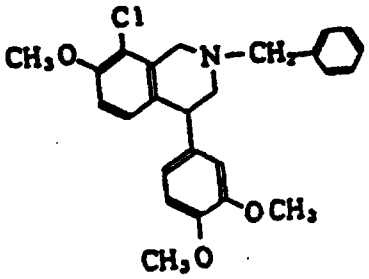
Elemental analysis (as $C_{15}H_{15}NO_4FBr$)

	C(%)	H(%)	N(%)	F(%)	Br(%)
Calcd.	48.41	4.06	3.76	5.10	21.47
Found	48.14	4.12	3.66	4.82	21.30

Melting point: above 238°C (decomposition)
Mass spectrum (FAB) 292 (M^+ + 1)
NMR spectrum (d_6-DMSO, interanl standard TMS)
δ (ppm): 5.44 (1H, m), 7.12 (1H, d), 7.43 (1H, d), 7.62 (1H, d), 7.72 (1H, d)

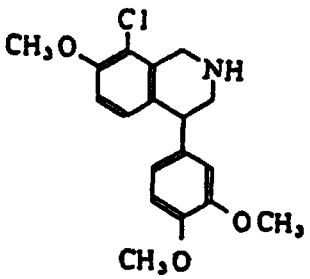
Example 11

(1)



2.02 g of 8-amino-2-benzyl-7-methoxy-4-(3,4-dimethoxyphenyl)-1,2,3,4-tetrahydroisoquinoline was dissolved in 20% hydrochloric acid, and to the solution was added dropwise a solution of 0.38 g of sodium nitrite in 1.9 ml of water, under cooling. To the mixture was added dropwise a solution of 0.55 g of cuprous chloride in 11 ml of 20% hydrochloric acid. After the reaction was over, 4.84 g of sodium hydroxide was added to the mixture, and the mixture was extracted with chloroform 2 times. The chloroform layer was collected, washed with water, and dried over anhydrous magnesium sulfate. the solvent was distilled off, and the residue was recrystallized from ethanol, giving 1.23 g of 2-benzyl-8-chloro-7-methoxy-4-(3,4-dimethoxyphenyl)-1,2,3,4-tetrahydroisoquinoline, m.p. 88-91°C.

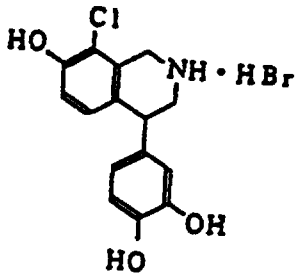
(2)



1.13 g of 2-benzyl-8-chloro-7-methoxy-4-(3,4-dimethoxyphenyl)-1,2,3,4-tetrahydroisoquinoline was dissolved in 28 ml of ethanol, and after adding thereto 0.22 ml of 12N hydrochloric acid, hydrogenation was performed by addition of 0.1 g of 10%-palladium-carbon. After the hydrogenation reaction was over, the reaction solution was filtered, and concentrated. The residue was dissolved in chloroform, washed with saturated aqueous sodium hydrogen carbonate solution and water, and dried over anhydrous magnesium sulfate. The solvent was distilled off, and the residue was recrystallized from ethyl acetate-n-hexane,

giving 580 mg of 8-chloro-7-methoxy-4-(3,4-dimethoxyphenyl)-1,2,3,4-tetrahydroisoquinoline, m.p. 130-132°C.

(3)



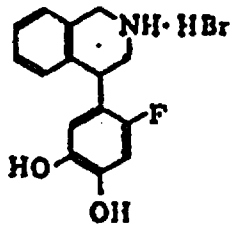
To 540 mg of 8-chloro-7-methoxy-4-(3,4-dimethoxyphenyl)-1,2,3,4-tetrahydroisoquinoline was added 11 ml of 48% hydrobromic acid, and the mixture was heated under reflux for 3 hours under an argon gas stream. After cooling, the crystals which separated out were collected by filtration, and 520 mg of 8-chloro-7-hydroxy-4-(3,4-dihydroxyphenyl)-1,2,3,4-tetrahydroisoquinoline hydrobromide was obtained.

Elemental analysis (as $C_{15}H_{15}ClNO_3Br$)

	C(%)	H(%)	N(%)
Calcd.	48.35	4.06	3.76
Found	48.32	4.05	3.75

Melting point: above 260°C (decomposition)
Mass spectrum (FAB) 292 (M^+ + 1)
NMR spectrum (d_6-DMSO), internal standard TMS)
δ ppm : 4.22 (1H, dd), 6.48 (1H, dd), 6.56 (1H, s), 6.62 (1H, d), 6.75 (1H, d), 6.92 (1H, d)

Example 12



(1) α-[(benzylamino)methyl]-6-fluoro-3,4-dimethoxybenzyl alcohol (1.25 g) was dissolved in 8.75 ml of trifluoroacetic acid, and after adding thereto 0.37 ml of conc. sulfuric acid under ice-cooling, the mixture was stirred for 70 minutes. Then, 1.07 g of sodium acetate was added to the mixture, and the reaction mixture was concentrated. To the residue was added chloroform and water, and the mixture was basified by addition of conc. aqueous ammonia under ice-cooling.

The chloroform layer was collected, washed with saturated aqueous NaCl solution, and dried over anhydrous sodium sulfate. The solvent was removed by distillation, giving 1.18 g of 4-(6-fluoro-3,4-dimethoxyphenyl)-1,2,3,4-tetrahydroisoquinoline as a syrupy material.

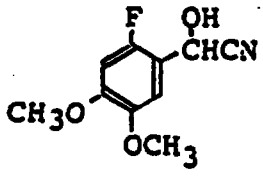
(2) 1.15 g of 4-(6-fluoro-3,4-dimethoxyphenyl)-1,2,3,4-tetrahydroisoquinoline was dissolved in 30 ml of

dichloromethane, 26. 4 ml of 1M boron tribromidedichloromethane solution was added to the solution under an argon gas stream under stirring under cooling at an internal temperature of -20 to -30 °C. The mixture was stirred for 3 hours at room temperature, and then 7.0 ml of methanol was added dropwise under cooling in dry ice - methanol bath, The mixture was stirred for 30 minutes at room temperature; the crystals which separated out were collected by filtration, affording 1.0 g of 4-(6-fluoro-3,4-dihydroxyphenyl)-1,2,3,4-tetrahydroisoquinoline hydrobromide.

Elemental analysis (as $C_{15}H_{15}NO_2FBr$)					
	C(%)	H(%)	N(%)	F(%)	Br(%)
Calcd.	52.96	4,44	4.12	5.58	23.49
Found	52.98	4.50	4.14	5.62	23.49

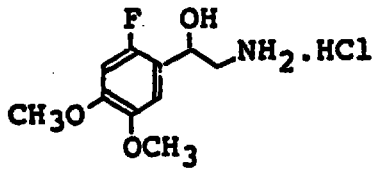
Melting point: above 237 °C (decomposition)
Mass spectrum (FAB) 260 (M^+ + 1)
NMR spectrum (d_6-DMSO, internal standard TMS)
δ (ppm): 3.12-3.80(2H, m), 4.43 (2H, br-s), 4.58 (1H, dd), 6.49 (1H, d), 6.66 (1H, d), 6.84 (1H, m), 7.12-7.36 (3H, m)

Reference Example 28



Zinc iodide (0.98 g) was added to a solution of 6-fluoro-3,4-dimethoxybenzaldehyde (5.2 g) in 55 ml tetrahydrofuran, trimethylsilyl-nitrile (4.92 ml) was further added dropwise with stirring under ice cooling in an argon gas atmosphere, and stirring under ice cooling was continued for two hours. The resulting mixture was then stirred at room temperature for four hours, 4.11 ml methanol was added under ice cooling, and the solvents were distilled off. To the residue were added 50 ml methanol and 0.65 g citric acid, and the mixture was stirred overnight at room temperature and concentrated. The residue was treated with chloroform and water, and the chloroform layer was collected and dried over anhydrous magnesium sulfate. The solvent was distilled off, and the residue was recrystallized from chloroform/n-hexane, affording 3.28 g of pure α-(cyano)-6-fluoro-3,4-dimethoxybenzyl alcohol, m.p. 112-114 °C.

Reference Example 29



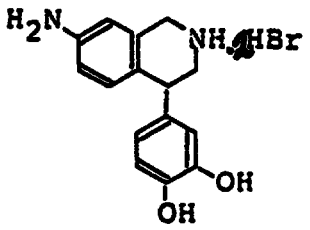
To a suspension of 3.24 g α-(cyano)-6-fluoro-3,4-dimethoxybenzyl alcohol obtained in Reference Example 28 in 20 ml tetrahydrofuran, was added dropwise 33 ml of 1M solution of borane in tetrahydrofuran with stirring in a methanol/ice bath under an argon gas atmosphere, and the resulting solution was heated under reflux for three hours. After cooling the reaction mixture in an ice bath, methanol was added until gas evolution was no longer observed, the resulting solution was stirred at room temperature for one hour, and hydrogen chloride gas was introduced until the pH fell below 1. The crystals which separated out were

collected, affording 3.34 g of α-(aminomethyl)-6-fluoro-3,4-dimethoxybenzyl alcohol hydrochloride, m.p. 223-226 °C.

Prescription

Capsules each containing a mixture of 100 mg of the compound obtained in Example 6 or 7 (free base), 200 mg of crystalline lactose and 2 mg of magnesium stearate are formed in conventional manner. One capsule is orally administered four times a day to a patient requiring renal vascular tract dilation.

Example 13



(1) A solution of 2.8 g α-[(3-aminobenzylamino)methyl]-3,4-dimethoxybenzyl alcohol obtained in Reference Example 2 in 15 ml 6N-HCl was held at 60 °C overnight with stirring, and the reaction mixture was stirred under ice cooling for one hour. The crystals which separated out were collected by filtration, chloroform and water were added, and 10% aqueous solution of caustic soda was further added under ice cooling until the aqueous layer became alkaline. The mixture was stirred well, and the chloroform layer was collected, washed with saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate. The solvent was distilled off, and the residue was recrystallized from ethyl acetate/n-hexane, affording 1.5 g of pure 7-amino-4-(3,4-dimethoxyphenyl)-1,2,3,4-tetrahydroisoquinoline, m.p. 157-159 °C.

(2) To a solution of 1.5 g 7-amino-4-(3,4-dimethoxyphenyl)-1,2,3,4-tetrahydroisoquinoline obtained above in 50 ml dichloromethane, was added dropwise 1M solution of boron tribromide in dichloromethane (25 ml) under an argon gas stream while maintaining the internal temperature at -20 °C. The reaction mixture was stirred at room temperature for three hours and then cooled to -20 °C once again, and 7 ml methanol was added dropwise at that temperature. The crystals which separated out were collected by filtration and recrystallized from ethanol, giving 1 g of pure 7-amino-4-(3,4-dimethoxyphenyl)-1,2,3,4-tetrahydroisoquinoline dihydrobromide.

(i)

Elemental analysis (as $C_{15}H_{18}Br_2N_2O_2$):				
	C(%)	H(%)	N(%)	Br(%)
Calcd.	43.09	4.34	6.70	38.22
Found	43.36	4.59	6.50	37.89

(ii) Melting point: 194-196 °C (dec.)

(iii) Mass spectrometry (FAB): 257 ($M^+ + 1$)

(iv) NMR spectrum (d_6-DMSO; internal standard: TMS):

δ (ppm) 6.56 (s, 2H), 6.72 (d, 1H) 6.92 (d, 1H), 7.12 (s, 2H)

Prescription

Capsules each containing a mixture of 100 mg of the compound obtained in Example 14 (free base), 200 mg of crystalline lactose and 2 mg of magnesium stearate were formed in conventional manner. One capsule is orally administered four times a day to a patient requiring renal vascular tract dilation.

Reference Example 30

To a suspension of 22.5 g of methanesulfonylamidobenzoic acid in 648 ml of dichloromethane was added 24,37 g of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride with stirring under ice-cooling, and stirring under ice-cooling was continued for 50 minutes. To the resulting mixture was added a suspension of 24.37 g of α-(aminomethyl)-3,4-dimethoxybenzyl alcohol hydrochloride and 15.14 ml of N-methylmorpholine in 100 ml of dichloromethane in small portions, and stirring under ice-cooling was continued for 5 hours. To the resuling mixture was added 1 N HCl (300 ml), and the dichloromethane layer was separated. The separated solution was washed once with each of 1N HCl and saturated aqueous NaCl solution, and dried over anhydrous magnesium sulfate. The solvent was distilled off, and 32.71 g of α-(N-(3-methanesulfonylamidobenzolyl)amidomethyl]-3,4-dimethoxybenzyl alcohol was obtained as foamy material.

Reference Example 31

32.7 g of α-[N-(3-methanesulfonylamidobenzolyl)amidomethyl]-3,4-dimethoxybenzyl alcohol was dissolved in 250 ml of tetrahydrofuran. To the resulting solution was added 298 ml of 1M borane-tetrahydrofuran dropwise below -30 °C. The temperature of the resulting solution was raised to room temperature, and the solution was heated under reflux for 2.5 hours. To the resulting solution was added 24.9 ml of conc. hydrochloric acid dropwise, and the solution was stirred for 30 minutes at room temperature. The solvent was distilled off, and to the residue obtained were added water and chloroform. The resulting mixture was basified with conc. aqueous ammonia, and extracted thrice with chloroform. The chloroform layers were combined, washed with saturated aqueous NaCl solution, and dried over anhydrous magnesium sulfate. The solvent was distilled off, and the residue thus obtained was subjected to silica gel column chromatography (chloroform-methanol-28% aqueous ammonia = 20:1:0.1~10:1:0.1), and a material of Rf 0.12 [Kiesel gel $60F_{254}$ plate; chloroform-methanol-28% aqueous ammonia (20:1: 0.1)] was collected, and crystallized from chloroform-n-hexane, affording 12.73 g of α-[[(3-methanesulfonylamidobenzyl)amino]-methyl]-3,4-dimethoxybenzyl alcohol, m.p. 98-100 °C.

Example 14

(1) 12.7 g of α-[[(3-methanesulfonylamidobenzyl)amino]methyl]-3,4-dimethoxybenzyl alcohol was dissolved in 250 ml of 6N hydrochloric acid; the mixture was allowed to react under an argon gas stream at 60 - 65 °C for 3 hours. To the cooled reaction mixture were added chloroform, ice and conc. aqueous ammonia, and the mixture was extracted with 5% methanol-chloroform under basic conditions. The organic layer was washed with saturated aqueous NaCl solution, and dried over anhydrous magnesium sulfate. The solvent was distilled off, and the residue thus obtained was subjected to silica gel column chromatography(chloroform-methanol-28% aqueous ammonia = 20:1:0.1~10:1:0.1), and a material of Rf 0.14 [Kiesel gel $60F_{254}$ plate; chloroform-methanol-28% aqueous ammonia = 20:1:0.1) was collected, and crystailized from chloroform-ether, affording 5.94 g of 4-(3,4-dimethoxyphenyl)-7-methanesulfonylamido-1,2,3,4-tetrahydroisoquinoline, m.p. 220-222 °C.

(2) 4.0 g of 4-(3,4-dimethoxyphenyl)-7-methanesulfonylamido-1,2,3,4-tetrahydroisoquinoline was suspended in 40 ml of dichloromethane, and after adding thereto 2.08 ml of acetic anhydride under an argon gas stream at room temperature, the mixture was allowed to react for 1 hour. To the reaction solution were added water, ice and conc. aqueous ammonia; the mixture was extracted with dichloromethane under basic conditions and the extract was washed with 1N hydrochloric acid and water, each once, and dried over anhydrous magnesium sulfate. The solvent was distilled off, and 4.46 g of 2-acetyl-4-(3,4-dimethoxyphenyl)-7-methanesulfonylamido-1,2,3,4-tetrahydroisoquinoline was obtained as syrupy material.

(3) 4.46 g of 2-acetyl-4-(3,4-dimethoxyphenyl)-7-methane-sulfonylamido-1,2,3,4-tetrahydroisoquinoline (obtained at (2) above) was dissolved in 50 ml of dichloromethane, and to the solution was added 66.2 ml of 1M borane-3Br dichloromethane solution dropwise under cooling below -28 °C under an argon gas stream. The mixture was allowed to react for 2.5 hours, and after adding dropwise 13.96 ml of methanol below -40 °C, the temperature of the reaction solution was raised to room temperature. About 30 ml of methanol was added to the solution, and the solvent was distilled off. 50 ml of toluene was added to the residue obtained, and the solvent was distilled off again, and after adding to the residue water and ethyl acetate, the mixture was extracted with ethyl acetate. The extract was washed with water and saturated aqueous NaCl solution each once, and dried over anhydrous magnesium sulfate. The solvent was distilled off, and 4.13 g of 2-acetyl-4-[3,4-dihydroxyphenyl)-7-methanesulfonylamido-1,2,3,4-

tetrahydroisoquinoline was obtained, m.p. 125-127°C.

(4) 1.7 g of 2-acetyl-4-(3,4-dihydroxyphenyl)-7-methanesulfonylamidol-1,2,3,4-tetrahydroisoquinoline obtained at (3) above was dissolved in 17 ml of ethanol and 17 ml of 2N hydrochloric acid, and the mixture was heated under reflux under an argon gas stream for 8.5 hours. The solvent was distilled off, and after adding water and ethyl acetate, the aqueous layer was separated with a separating funnel. The aqueous layer was washed with ethyl acetate 5 times, and concentrated. To the residue was added 30 ml of ethanol, and concentrating procedure was conducted 3 times, and after drying, 1.12 g of 4-(3,4-dihydroxyphenyl)-7-methanesulfonylamido-1,2,3,4-tetrahydroisoquinoline HCl salt was obtained as a foamy material.

Elemental analysis (as $C_{16}H_{18}N_2O_4SCl.1/3H_2O$)					
	C(%)	H(%)	N(%)	S(%)	Cl(%)
Calcd.	50.99	5.26	7.43	8.50	9.40
Found	51.20	5.31	7.29	8.73	9.63

Mass spectrometry (FAB): 335 (M + 1)

NMR spectrum (d_6-DMSO; internal standard: TMS)

δ (ppm) 3.02 (3H, s), 3.1-3.7 (2H, m) 4.24 (1H, m), 3.35 (2H, br-s) 6.4-7.2 (6H, m)

Reference Example 32

(1) 12.0 g of 3-ethanesulfonylamidobenzoic acid was suspended in 360 ml of dichloromethane, and after adding thereto under ice cooling while stirring 12.04 g of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, the mixture was stirred for 30 minutes. To the mixture was added a suspension of 12.23 g of α-(aminomethyl)-3,4-dimethoxybenzyl alcohol hydrochloride and 7.48 ml of N-methylmorpholine in 60 ml of dichloromethane, slowly. The mixture was stirred overnight under ice cooling. After adding 1N hydrochloric acid (200 ml), the dichloromethane layer was collected, washed with 1N hydrochloric acid and saturated aqueous NaCl solution each once, and dried over anhydrous magnesium sulfate. The solvent was distilled off, giving 20.35 g of α-[N-(3-ethanesulfonylamidobenzoyl)amidomethyl]-3,4-dimethoxybenzyl alcohol as a foamy material.

(2) 20.0 g of α-[N-(3-ethanesulfonylamidobenzoyl)amidomethyl]-3,4-dimethoxybenzyl alcohol was dissolved in 150 ml of tetrahydrofuran, and to the mixture was added dropwise 1M borane-tetrahydrofuran solution (176 ml) below -20°C. The solution was raised gradually to room temperature, and the mixture was heated under reflux for 2.5 hours. To the mixture was added 7.13 ml of methanol under cooling by a methanol-ice bath, and the mixture was heated under reflux for 30 minutes. To the solution was added 14.7 ml of conchydrochloric acid (under cooling by methanol-ice bath) dropwise, and the mixture was stirred at room temperature for 30 minutes, and the solvent was distilled off. To the residue was added water and chloroform, and the mixture was basified with conc. aqueous ammonia and extracted with chloroform 3 times. The chloroform layer was collected, washed with saturated aqueous NaCl solution, and dried over anhydrous magnesium sulfate. The solvent was distilled off, and the residue was subjected to column chromatography (chloroform-methanol-28% aqueous ammonia = 20:1:0.1-10:1:0.1), and a material of Rf 0.13 [Kiesel gel 60F_{254} plate, chloroform-methanol-28% aqueous ammonia = 20:1:0.1) was collected, giving 13.81 g of alpha-[[(3-ethanesulfonylamidobenzyl)amino]methyl]-3,4-dimethoxybenzyl-alcohol.

Example 15

1.0 g of 2-acetyl-4-(3,4-dihydroxyphenyl)-7-ethanesulfonylamido-1,2,3,4-tetrahydroisoquinoline was dissolved in 10 ml of ethanol and 10 ml of 2N hydrochloric acid, and the mixture was heated under reflux overnight. The solvent was distilled off, and after adding water and ethyl acetate, the aqueous layer was collected, washed with ethyl acetate twice, and concentrated. To the residue was added 30 ml of ethanol, and the concentration procedures were repeated 3 times. The residue was crystallized from isopropanol, giving 0.90 g of 4-(3,4-dihydroxyphenyl)-7-ethanesulfonylamido-1,2,3,4-tetrahydroisoquinoline.1-isopropanol.1-HCl salt.

Melting point: 161-162°C

Elemental analysis (as $C_{17}H_{21}N_2O_4SCl.C_3H_7OH$)					
	C(%)	H(%)	N(%)	S(%)	Cl(%)
Calcd.	53.98	6.57	6.30	7.21	7.97
Found	53.74	6.50	6.25	7.29	8.17

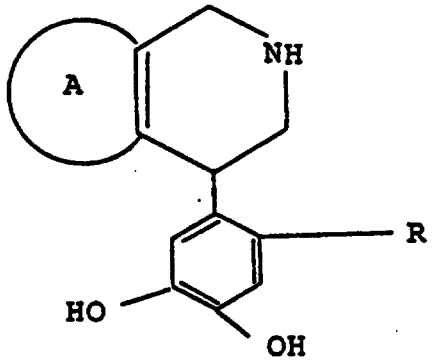
Mass spectrum (FAB) 349 (M +1)
NMR spectrum (d_6-DMSO, internal standard TMS)
(ppm): 1.21 (3H, t), 3.10(2H, t), 3.2-3.9 (2H, m), 4.20(1H, m), 4.34(2H, br-s), 6.4-7.2(6H, m)

The starting material of the above compound has melting point of 117-119 °C, and was prepared in conventional manner.

The following compounds were also prepared.
4-(3,4-dimethoxyphenyl)-7-ethanesulfonylamido-1,2,3,4-tetrahydroisoquinoline, m.p. 209-211 °C.
2-acetyl-4-(3,4-dimethoxyphenyl)-7-ethanesulfonylamido-1,2,3,4-tetrahdydroisoquinoline (a foamy material).

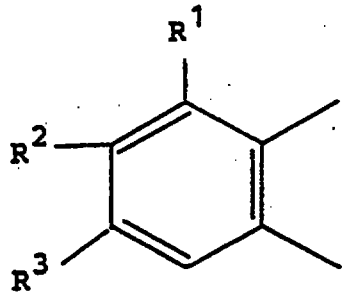
Claims

1. A compound of formula (I) or a salt thereof :



(I)

wherein  is



R^1 is hydrogen, C_1-C_5 alkyl, hydroxyl, halogen, amino, or C_1-C_6 acylamino;
R^2 is hydrogen, C_1-C_5 alkyl, hydroxyl, amino, or C_1-C_5 alkylsulfonylamino;
R^3 is hydrogen, C_1-C_5 alkyl, or hydroxyl; and
R is hydrogen or halogen;
with the proviso that when R^1 is other than C_1-C_5 alkyl, R^2, R^3 and R are not all hydrogens.

2. A compound according to claim 1 which is 7,8-dihydroxy-4-(3,4-dihydroxyphenyl)-1,2,3,4-tetrahydroisoquinoline or a salt thereof.

3. A compound according to claim 1 which is 7-hydroxy-4-(3,4-dihydroxyphenyl)-8-methyl-1,2,3,4-tetrahydroisoquinoline or a salt thereof.

Elemental analysis (as $C_{17}H_{21}N_2O_4SCl.C_3H_7OH$)					
	C(%)	H(%)	N(%)	S(%)	Cl(%)
Calcd.	53.98	6.57	6.30	7.21	7.97
Found	53.74	6.50	6.25	7.29	8.17

Mass spectrum (FAB) 349 (M +1)
NMR spectrum (d_6-DMSO, internal standard TMS)
(ppm): 1.21 (3H, t), 3.10(2H, t), 3.2-3.9 (2H, m), 4.20(1H, m), 4.34(2H, br-s), 6.4-7.2(6H, m)

The starting material of the above compound has melting point of 117-119 °C, and was prepared in conventional manner.

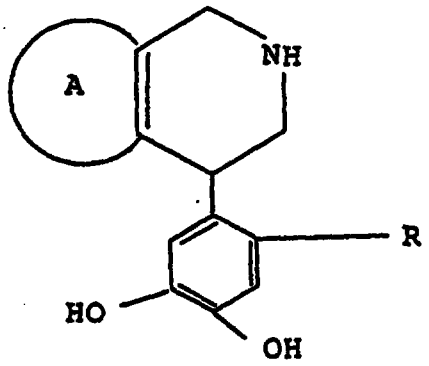
The following compounds were also prepared.

4-(3,4-dimethoxyphenyl)-7-ethanesulfonylamido-1,2,3,4-tetrahydroisoquinoline, m.p. 209-211 °C.

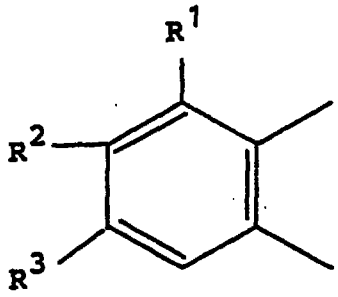
2-acetyl-4-(3,4-dimethoxyphenyl)-7-ethanesulfonylamido-1,2,3,4-tetrahdydroisoquinoline (a foamy material).

Claims

1. A compound of formula (I) or a salt thereof :



(I)

wherein  is 

R^1 is hydrogen, C_1-C_5 alkyl, hydroxyl, halogen, amino, or C_1-C_6 acylamino;
R^2 is hydrogen, C_1-C_5 alkyl, hydroxyl, amino, or C_1-C_5 alkylsulfonylamino;
R^3 is hydrogen, C_1-C_5 alkyl, or hydroxyl; and
R is hydrogen or halogen;
with the proviso that when R^1 is other than C_1-C_5 alkyl, R^2, R^3 and R are not all hydrogens.

2. A compound according to claim 1 which is 7,8-dihydroxy-4-(3,4-dihydroxyphenyl)-1,2,3,4-tetrahydroisoquinoline or a salt thereof.

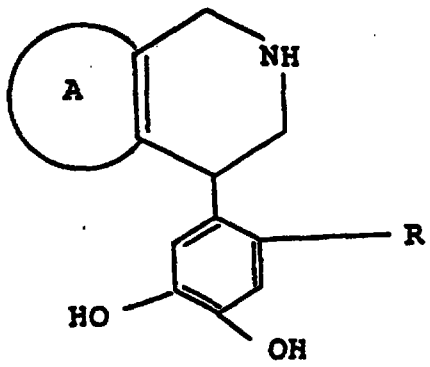
3. A compound according to claim 1 which is 7-hydroxy-4-(3,4-dihydroxyphenyl)-8-methyl-1,2,3,4-tetrahydroisoquinoline or a salt thereof.

* C L M S *

4. A compound according to claim 1 which is 4-(3,4-dihydroxyphenyl)-7-methanesulfonylamido-1,2,3,4-tetrahydroisoquinoline or a salt thereof.

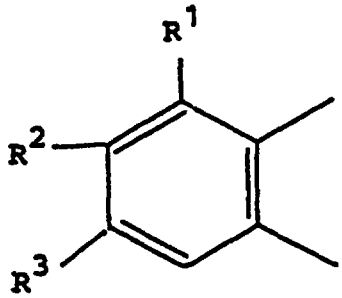
5. A pharmaceutical composition containing a pharmacologically acceptable compound according to any preceding claim.

6. A process for preparing a compound of formula I, or a salt thereof :

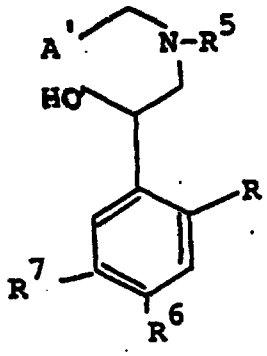


(I)

wherein  is

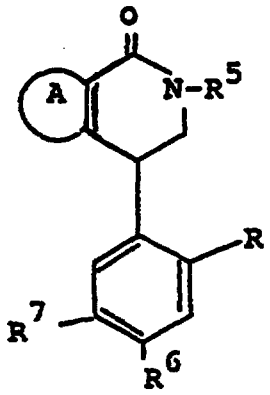


R^1 is hydrogen, C_1-C_5 alkyl, hydroxyl, halogen, amino, or C_1-C_6 acylamino;
R^2 is hydrogen, C_1-C_5 alkyl, hydroxyl, amino, or C_1-C_5 alkylsulfonylamido;
R^3 is hydrogen, C_1-C_5 alkyl, or hydroxyl; and
R is hydrogen or halogen;
with the proviso that when R^1 is other than C_1-C_5 alkyl, R^2, R^3 and R are not all hydrogens.
the process comprising
a) intramolecular cyclization of compound II



II

followed by removal of the protective group(s) when required
or
b) reduction of compound V



V

followed by removal of protective group(s) when required;
wherein R^6 and R^7 are hydroxyl groups which may optionally be protected; R^5 is hydrogen atom or a protective group for the nitrogen atom; and A' is a monovalent version of

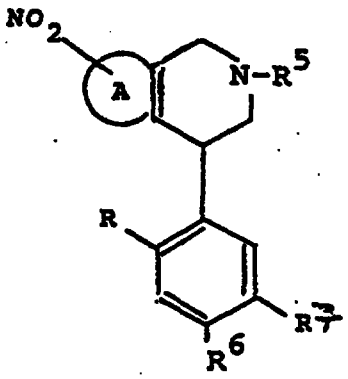


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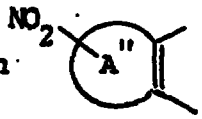
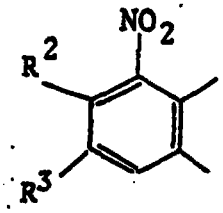
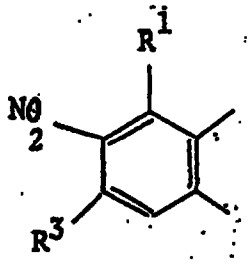
7. A process according to claim 6, wherein the cyclizing agent is chosen from hydrochloric acid, sulfuric acid, sulfuric acid in trifluoroacetic acid, polyphosphoric acid, esters of polyphosphoric acid, methanesulfonic acid in dichloromethane, hydrogen bromide, and Lewis acids (e.g. boron trifluoride, aluminum chloride and stannic chloride).

8. A process according to claim 6 wherein the reducing agent is chosen from borane, diborane, lithium aluminum hydride, sodium borohydride plus propionic acid, aluminum hydride diisobutyl or aluminum hydride bis(2-methoxyethoxy)sodium,

9. A process for preparing a compound according to claim 1, which comprises reduction of nitro compound III



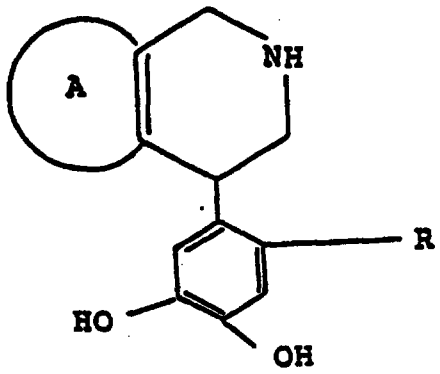
III

wherein  is  or 

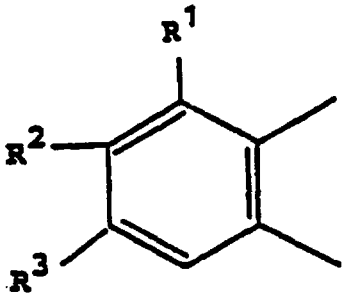
followed by removal of protective group(s) when required wherein R^6 and R^7 are hydroxyl groups which may optionally be protected; and R^5 is a hydrogen atom or a protective group for the nitrogen atom.

Revendications

1. Un composé de formule (I) ou un sel de celui-ci :



(I)

dans lequel  est 

R^1 est un hydrogène, un alcoyle en C_1-C_5, un hydroxyle, un halogène, un amino ou un acylamino en C_1-C_6 ;
R^2 est un hydrogène, un alcoyle en C_1-C_5, un hydroxyle, un amino ou un alkylsulfonylamino en C_1-C_5 ;
R^3 est un hydrogène, un alcoyle en C_1-C_5 ou un hydroxyle, et ;
R est un hydrogène ou un halogène ;

à la condition que quand R^1 est autre qu'un alcoyle en C_1-C_5,R^2, R^3 et R ne sont pas tous des hydrogènes.

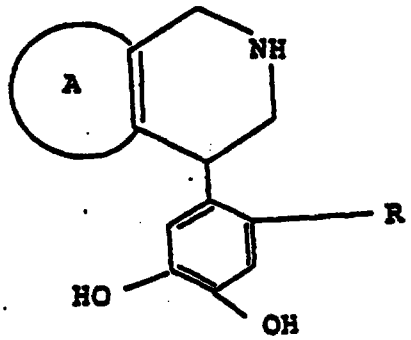
2. Un composé conforme à la revendication 1 qui est la 7,8-dihydroxy-4-(3,4-dihydroxyphényl)-1,2,3,4-tétrahydroisoquinoléine ou un sel de celle-ci.

3. Un composé conforme a la revendication 1 qui est la 7-hydroxy-4-(3,4-dihydroxyphényl)-8-méthyl-12,2,3,4-tétrahydroisoquinoléine ou un sel de celle-ci.

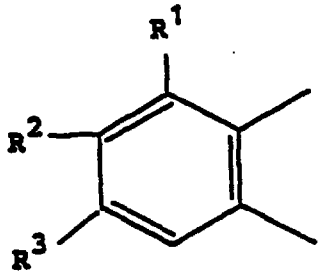
4. Un composé conforme a la revendication 1 qui est la 4-(3,4-dihydroxyphényl)-7-méthanesulfonylamido-1,2,3,4-tétrahydroisoquinoléine ou un sel de celle-ci.

5. Une composition pharmaceutique contenant un composé pharmacologiquement acceptable conforme à l'une quelconque des revendications précédentes.

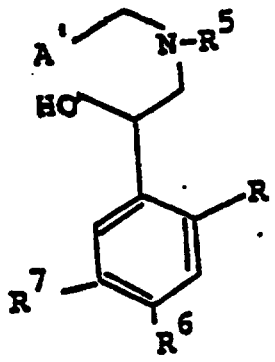
6. Un procédé pour préparer un composé de formule I ou un sel de celui-ci:



(I)

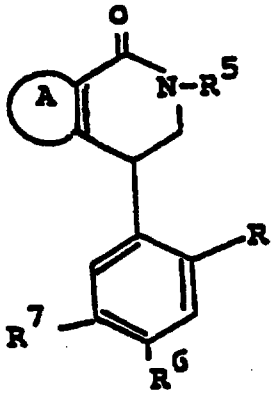
dans lequel  est 

R^1 est un hydrogène, un alcoyle en C_1-C_5, un hydroxyle, un halogène, un amino ou un acylamino en C_1-C_6 ;
R^2 est un hydrogène, un alcoyle en C_1-C_5, un hydroxyle, un amino ou un alkylsulfonylamino en C_1-C_5 ;
R^3 est un hydrogène, un alcoyle en C_1-C_5 ou un hydroxyle; et R est un hydrogène ou un halogène ;
à la condition que quand R^1 est autre qu'un alcoyle en C_1-C_5,R^2, R^3 et R ne sont pas tous des hydrogènes.
le procédé comprenant
a) une cyclisation intramoléculaire du composé II



II

suivie par l'enlèvement du (des) groupe (s) protecteur (s) quand cela est exigé
ou
b) la réduction du composé V



V

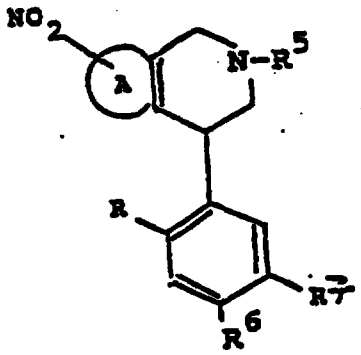
suivie par l'enlèvement du (des) groupe (s) protecteur (s) quand cela est exigé ; dans lequel R^6 et R^7 sont de groupements hydroxyles qui peuvent être éventuellement protégés ; R^5 est un atome d'hydrogène ou un groupement protecteur pour l'atome d'azote et A' est une version monovalente de



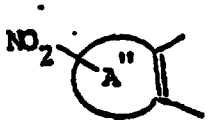
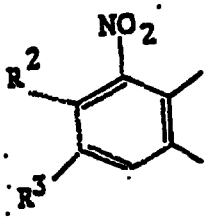
7. Un procédé conforme à la revendication 6, dans lequel l'agent de cyclisation est choisi parmi l'acide chlorhydrique, l'acide sulfurique, l'acide sulfurique dans de l'acide trifluoroacétique, l'acide polyphosphorique, les esters d'acide polyphosphorique, l'acide méthane-sulfonique dans le dichlorométhane, le bromure d'hydrogène, et les acides de Lewis (par exemple trifluorure de bore, chlorure d'aluminium et chlorure d'étain).

8. Un procédé conforme à la revendication 6 dans lequel, l'agent réducteur est choisi parmi le borane, le diborane, l'hydrure de lithium et d'aluminium, l'hydroborure de sodium plus l'acide propionique, un hydrure d'aluminium et de diisobutyle ou un hydrure d'aluminium et de bis (2-méthoxyéthoxy) sodium.

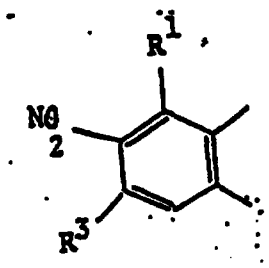
9. Un procédé pour préparer un composé conforme à la revendication 1 qui comprend la réduction du composé nitro III



III

dans lequel  est 

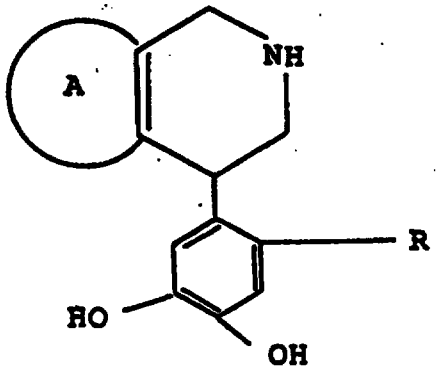
ou



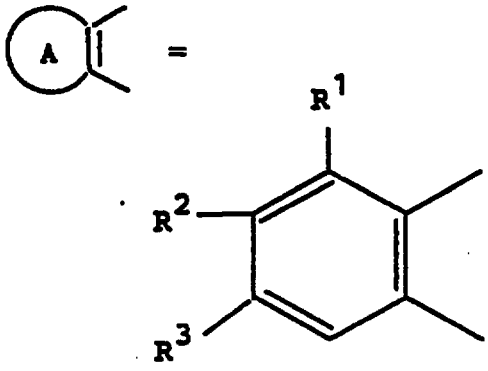
suivi par l'enlèvement du (des) groupement (s) protecteur (s) quand cela est exigé, dans lequel R^6 et R^7 sont des groupements hydroxyles qui peuvent être éventuellement protégés et R^5 est un atome d'hydrogène ou un groupement protecteur pour l'atome d'azote.

Patentansprüche

1. Verbindung der Formel (I) oder ein Salz davon



(I)

in der  ist,

wobei R^1 Wasserstoff, C_1-C_5-Alkyl, Hydroxyl, Halogen, Amino oder C_1-C_6-Acylamino ist;
R^2 Wasserstoff, C_1-C_5-Alkyl, Hydroxyl, Amino oder C_1-C_5-Alkylsulfonylamino ist;
R^3 Wasserstoff, C_1-C_5-Alkyl oder Hydroxyl ist und
R Wasserstoff oder Halogen bedeutet,
mit der Maßgabe, daß, wenn R^1 nicht C_1-C_5-Alkyl ist, R^2, R^3 und R nicht alle Wasserstoffatome bedeuten.

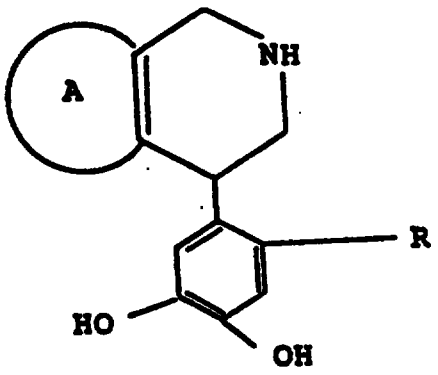
2. Verbindung nach Anspruch 1, die 7,8-Dihydroxy-4-(3,4-dihydroxyphenyl)-1,2,3,4-tetrahydroisochinolin oder ein Salz davon ist.

3. Verbindung nach Anspruch 1, die 7-Hydroxy-4-(3,4-dihydroxyphenyl)-8-methyl-1,2,3,4-tetrahydroisochinolin oder ein Salz davon ist.

4. Verbindung nach Anspruch 1, die 4-(3,4-Dihydroxyphenyl)-7-methansulfonylamido-1,2,3,4-tetrahydroisochinolin oder ein Salz davon ist.

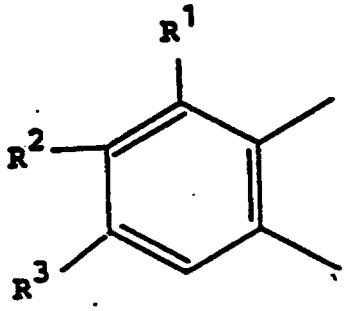
5. Pharmazeutisches Mittel, enthaltend eine pharmakologisch annehmbare Verbindung nach einem der vorangehenden Ansprüche.

6. Verfahren zur Herstellung einer Verbindung der Formel I oder eines Salzes davon



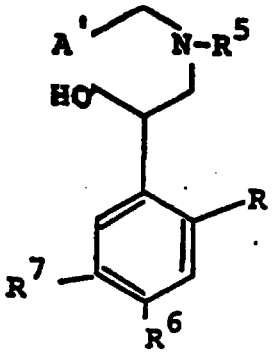
(I)

in der A =  ist,



wobei R^1 Wasserstoff, C_1-C_5-Alkyl, Hydroxyl, Halogen, Amino oder C_1-C_6-Acylamino ist;
R^2 Wasserstoff, C_1-C_5-Alkyl, Hydroxyl, Amino oder C_1-C_5-Alkylsulfonylamino ist;
R^3 Wasserstoff, C_1-C_5-Alkyl oder Hydroxyl ist und
R Wasserstoff oder Halogen bedeutet,
mit der Maßgabe, daß, wenn R^1 nicht C_1-C_5-Alkyl ist, R^2, R^3 und R nicht alle Wasserstoffatome bedeuten,
wobei das Verfahren umfaßt

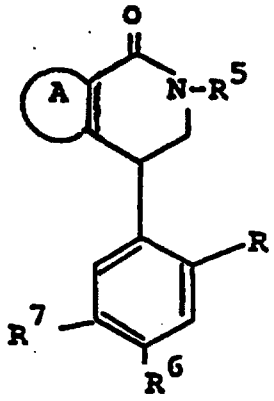
a) intramolekulare Cyclisierung der Verbindung II



II

und anschließende Entfernung der Schutzgruppe(n), soweit erforderlich, oder

b) Reduktion der Verbindung V



V

und anschließende Entfernung der Schutzgruppe(n), wenn erforderlich, wobei R^6 und R^7 Hydroxylgruppen sind, die gegebenenfalls geschützt sein können, R^5 ein Wasserstoffatom oder eine Schutzgruppe für das Stickstoffatom ist und A' eine einwertige Version von

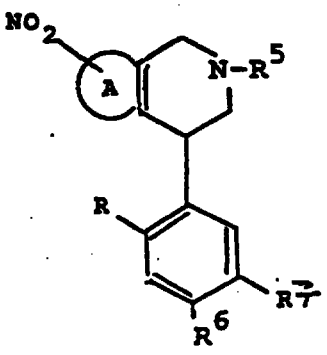


ist.

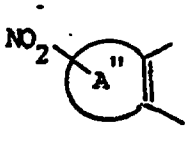
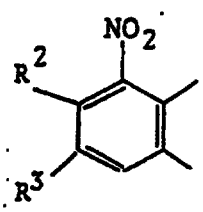
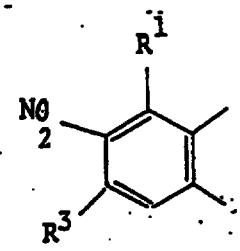
7. Verfahren nach Anspruch 6, wobei das Cyclisierungsmittel ausgewählt ist aus Chlorwasserstoffsäure (Salzsäure), Schwefelsäure, Schwefelsäure in Trifluoressigsäure, Polyphosphorsäure, Estern von Polyphosphorsäure, Methansulfonsäure in Dichlormethan, Bromwasserstoffsäure und Lewis Säure (z.B. Bortrifluorid, Aluminiumchlorid und Zinn-IV-chlorid).

8. Verfahren nach Anspruch 6, wobei das Reduktionsmittel ausgewählt ist aus Boran, Diboran, Lithiumaluminiumhydrid, Natriumborhydrid plus Propionsäure, Aluminiumhydrid-diisobutyl oder Aluminium-hydrid-bis(2-methoxyethoxy)natrium.

9. Verfahren zur Herstellung einer Verbindung nach Anspruch 1, umfassend die Reduktion der Nitroverbindung III



III

wobei  =  oder  ist,

und anschließende Entfernung der Schutzgruppe(n), soweit erforderlich, wobei R^6 und R^7 Hydroxylgruppen sind, die gegebenenfalls geschützt sein können, und R^5 ein Wasserstoffatom oder eine Schutzgruppe für das Stickstoffatom bedeutet.