Description

The present invention relates to novel pyridoindole derivatives and a pharmaceutically acceptable salt thereof. More particularly, it relates to novel pyridoindole derivatives and a pharmaceutically acceptable salt thereof which have pharmacological activities such as 5-hydroxytryptamine (5-HT) antagonism and the like, to processes for preparation thereof, to a pharmaceutical composition comprising the same and to a use of the same as a medicament.

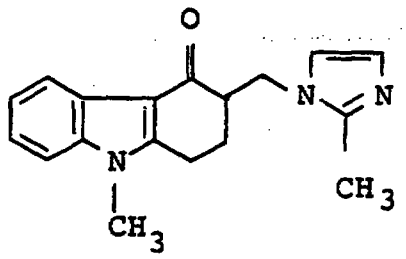
Accordingly, one object of the present invention is to provide novel pyridoindole derivatives and a pharmaceutically acceptable salt thereof, which are useful as a potent and selective antagonist of 5-HT receptor.

Another object of the present invention is to provide processes for preparation of said pyridoindole derivatives or a salt thereof.

A further object of the present invention is to provide a pharmaceutical composition comprising, as an active ingredient, said pyridoindole derivatives or a pharmaceutically acceptable salt thereof.

Still further object of the present invention is to provide a use of said pyridoindole derivatives or a pharmaceutically acceptable salt thereof as a 5-HT antagonist useful for treating or preventing central nervous system (CNS) disorders such as psychosis (e.g. schizophrenia, mania, etc.), anxiety, and depression; pains or aches such as headaches (e.g. migraine, cluster headaches, vascular headaches, etc.) and neuralgia (e.g. trigeminal neuralgia, etc.); gastrointestinal disorders such as symptoms of gastrointestinal dysfunction such as occur with, for example, dyspepsia, peptic ulcer, reflux oesophagitis and flatulence, and irritable bowel syndrome (IBS); nausea or vomiting, each of which may be associated with cancer therapy; motion sickness; and the like in human being or animals, particularly nausea and vomiting.

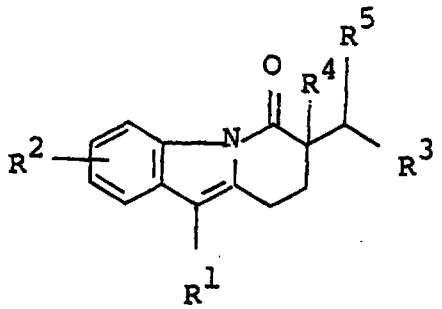
With regard to the states of the arts in this field, for example, the following compound is known.



(Japanese Patent Gazette KOKAI 60-214784)

As a result of an extensive study, the inventors of the present invention could obtain the pyridoindole derivatives which have strong pharmacological activities.

The pyridoindole derivatives of the present invention are novel and can be represented by the formula (I) :



(I)

wherein

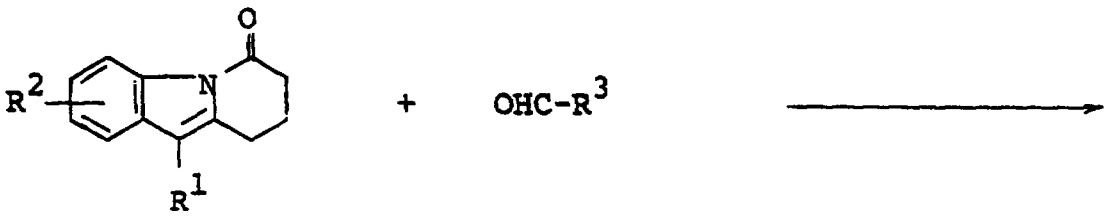
R^1 is		hydrogen, lower alkyl or lower alkenyl,
R^2 is		hydrogen, lower alkyl or halogen,
R^3 is		imidazolyl or pyridyl, each of which may have suitable substituent(s), and
R^4 is		hydrogen, lower alkyl, lower alkenyl or hydroxy(lower)alkyl and
R^5 is		hydrogen, hydroxy or acyloxy, or

R^4 and R^5 are linked together to form an additional bond.

With regard to the compound (I) of the present invention, it is to be noted that there may be one or more optically isomeric pairs due to the presence of one or more asymmetric carbon atom(s) and these isomers or a mixture thereof are included within a scope of the compound (I) of the present invention.

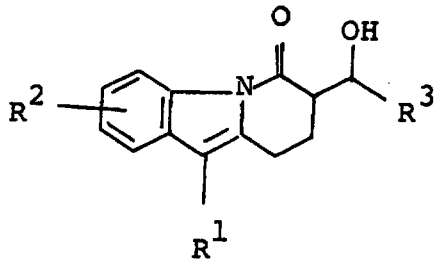
According to the present invention, the object compound (I) can be prepared by the following processes :

Process 1



(II) (III)

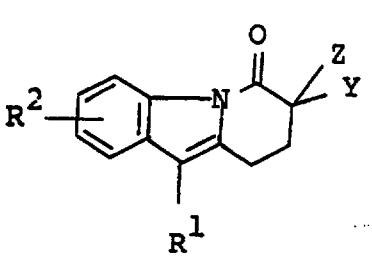
or a salt thereof



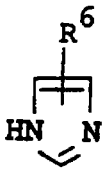
(Ia)

or a salt thereof

Process 2 :

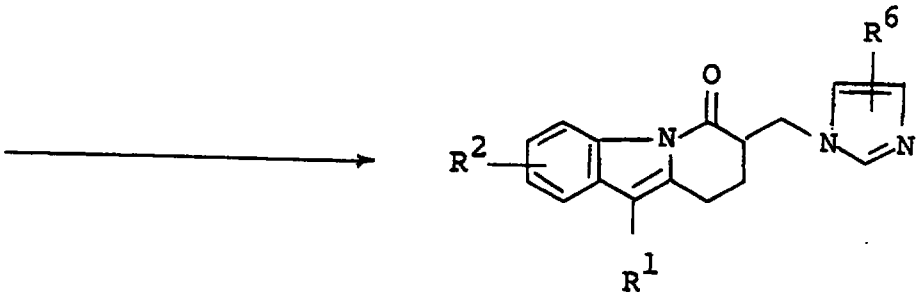


(IV)



(V)

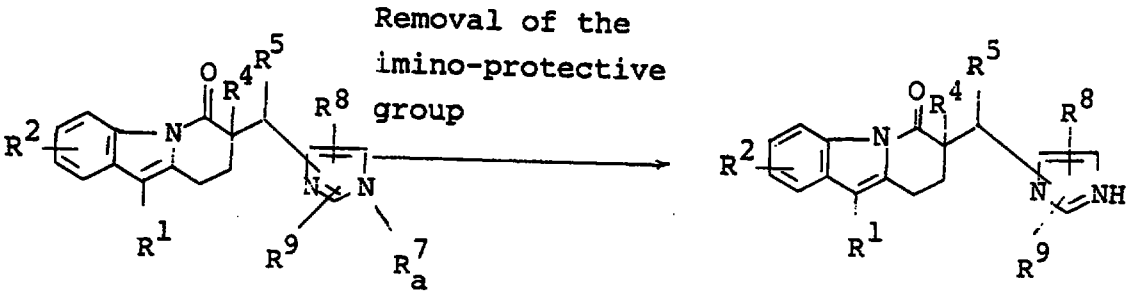
or a salt thereof



(Ib)

or a salt thereof

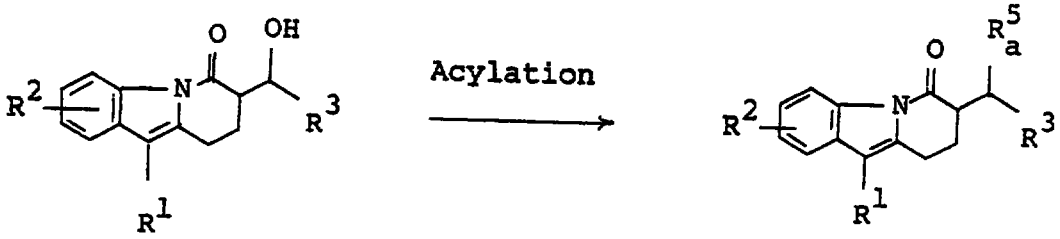
Process 3 :



(Ic)
or a salt thereof

(Id)
or a salt thereof

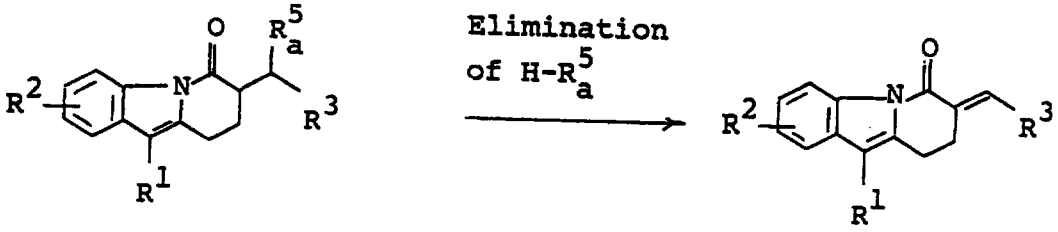
Process 4 :



(Ia)
or a salt thereof

(Ie)
or a salt thereof

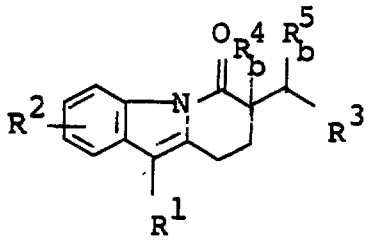
Process 5:



(Ie)
or a salt thereof

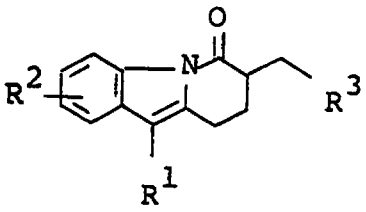
(If)
or a salt thereof

Process 6 :



(Ig)
or a salt thereof

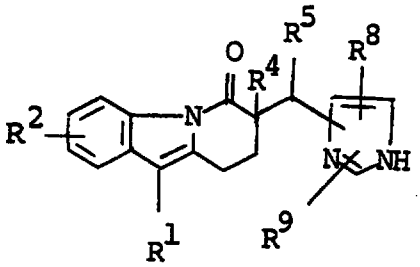
Reduction



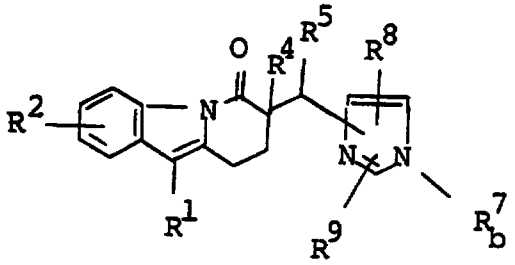
(Ih)
or a salt thereof

Process 7 :

R_b^7X
(VI)
or a salt thereof

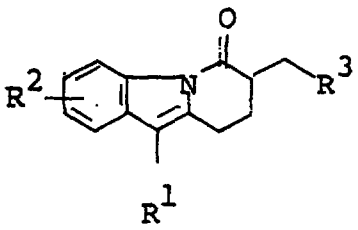


(Id)
or a salt thereof



(Ii)
or a salt thereof

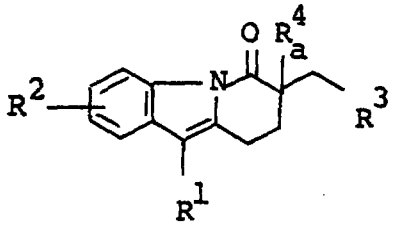
Process 8 :



Introduction of R^4_a

(Ij)

or a salt thereof



(Ik)

or a salt thereof

wherein

R^1, R^2, R^3, R^4 and R^5 are	each as defined above,
R^4_a is	lower alkyl, lower alkenyl or hydroxy(lower)alkyl,
R^5_a is	acyloxy,
R^4_b is	hydrogen and R^5_b is hydroxy or acyloxy, or
R^4_b and R^5_b are	linked together to form an additional bond,
R^6, R^8 and R^9 are	each hydrogen or lower alkyl,
R^7_a is	imino-protective group,
R^7_b is	lower alkyl,
X is	acid residue, and
Y is	N,N-di(lower)alkylaminomethyl and
Z is	hydrogen or Y and Z are combined to from methylene.

Suitable salt of the compounds (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (Ik), (III), (V) and (VI) are conventional non-toxic, pharmaceutically acceptable salt and may include a salt with a base or an acid addition salt such as a salt with an inorganic base, for example, an alkali metal salt (e.g. sodium salt, potassium salt, cesium salt, etc.), an alkaline earth metal salt (e.g. calcium salt, magnesium salt, etc.), an ammonium salt; a salt with an organic base, for example, an organic amine salt (e.g. triethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc.), etc.; an inorganic acid addition salt (e.g. hydrochloride, hydrobromide, sulfate, phosphate, etc.); an organic carboxylic or sulfonic acid addition salt (e.g. formate, acetate, trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate, p-toluenesulfonate, etc.); a salt with a basic or acidic amino acid (e.g. arginine, aspartic acid, glutamic acid, etc.); and the like, and the preferable example thereof is an acid addition salt.

In the above and subsequent descriptions of the present specification, suitable examples and illustrations of the various definitions which the present invention include within the scope thereof are explained in detail as follows.

The term "lower" is intended to mean 1 to 6 carbon atoms, preferably 1 to 4 carbon atoms, unless otherwise indicated.

Suitable "lower alkyl" may include straight or branched one, having 1 to 6 carbon atom(s), such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, pentyl, hexyl, preferably one having 1 to 4 carbon atoms, and the like, in which the most preferred one is methyl, ethyl or propyl.

Suitable "lower alkenyl" may include vinyl, 1-propenyl, allyl, 1-butenyl, 2-butenyl, 2-pentenyl, and the like, preferably one having 2 to 4 carbon atoms, in which the most preferred one is allyl.

Suitable "hydroxy(lower)alkyl" is lower alkyl as mentioned above which is substituted by hydroxy and may include hydroxymethyl, hydroxyethyl, hydroxypropyl, and the like, in which the most preferred one is hydroxymethyl.

Suitable "halogen" means fluoro, chloro, bromo and iodo, in which the most preferred one is chloro.

Suitable "imidazolyl" means 1H-imidazolyl-1-yl, 1H-imidazol-2-yl, 1H-imidazol-4-yl and 1H-imidazol-5-yl.

Suitable "pyridyl" means 2-pyridyl, 3-pyridyl and 4-pyridyl.

Suitable substituent in the terms "imidazolyl or pyridyl, each of which may have suitable substituent(s)" is conventional one used in a pharmaceutical field and may include lower alkyl as mentioned above, imino-protective group as mentioned below, and the like.

Suitable acyl moiety in the term "acyloxy" may include conventional one derived, for example, from carboxylic, carbonic, sulfonic and carbamic acids, and the preferable example thereof is lower alkanoyl (e.g. formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, etc.), lower alkanesulfonyl (e.g. mesyl, ethanesulfonyl, propanesulfonyl, etc.), and the like, in which the most preferred one is acetyl.

These acyl group may be substituted with suitable substituent(s) such as halogen (e.g. chlorine, bromine, iodine, fluorine).

Suitable "imino-protective group" may include conventional one, and the preferable example thereof is ar(lower)alkyl such as mono-(or di- or tri-)phenyl(lower)alkyl (e.g. benzyl, benzhydryl, trityl, etc.), acyl such as N,N-di(lower)alkylsulfamoyl (e.g. N,N-dimethylsulfamoyl, etc.), lower alkanesulfonyl (e.g. mesyl, etc.), arenesulfonyl (e.g. tosyl, etc.), and the like, in which the most preferred one is trityl, benzyl or N,N-dimethylsulfamoyl.

Suitable "acid residue" may include halogen as mentioned above, and the like.

Suitable "N,N-di(lower)alkylaminomethyl" may include N,N-dimethylaminomethyl, and the like.

Particularly, the preferred embodiments of R^1, R^2, R^3, R^4 and R^5 are as follows.

R^1 is hydrogen; lower alkyl such as methyl, ethyl, propyl, etc.; or lower alkenyl such as allyl, etc.;

R^2 is hydrogen; lower alkyl such as methyl, etc.; or halogen such as chloro;

R^3 is 1H-imidazolyl which may have one or more, preferably one to three substituent(s) selected from lower alkyl and imino-protective group such as 2-lower alkyl-1H-imidazol-1-yl (e.g. 2-methyl-1H-imidazol-1-yl, etc.), 1H-imidazol-2-yl, 1-ar(lower)alkyl-1H-imidazol-2-yl (e.g. 1-trityl-1H-imidazol-2-yl, etc.), 1-ar(lower)alkyl-5-lower alkyl-1H-imidazol-4-yl (e.g. 5-methyl-1-trityl-1H-imidazol-4-yl, 1-benzyl-5-methyl-1H-imidazol-4-yl, etc.), 5-lower alkyl-1H-imidazol-4-yl (e.g. 5-methyl-1H-imidazol-4-yl, etc.), 1-ar(lower)alkyl-1H-imidazol-4-yl (e.g. 1-trityl-1H-imidazol-4-yl, etc.), 1H-imidazol-4-yl, 2-lower alkyl-5-lower alkyl-1H-imidazol-4-yl (e.g. 2,5-dimethyl-1H-imidazol-4-yl, etc.), 1-ar(lower)alkyl-2-lower alkyl-1H-imidazol-4-yl (e.g. 2-methyl-1-trityl-imidazol-4-yl, etc.), 2-lower alkyl-1H-imidazol-4-yl (e.g. 2-methyl-1H-imidazol-4-yl, etc.), 1-lower alkyl-1H-imidazol-4-yl (e.g. 1-methyl-1H-imidazol-4-yl, etc.), 1-lower alkyl-5-lower alkyl-1H-imidazol-4-yl (e.g. 1,5-dimethyl-1H-imidazol-4-yl, etc.) and 1-di(lower)alkylaminosulfonyl-5-lower alkyl-1H-imidazol-4-yl (e.g. 1-dimethylaminosulfonyl-5-methyl-1H-imidazol-4-yl, etc.), 1-lower alkyl-1H-imidazol-5-yl (e.g. 1-methyl-1H-imidazol-5-yl, etc.) and 1-lower alkyl-4-lower alkyl-1H-imidazol-5-yl (e.g. 1,4-dimethyl-1H-imidazol-5-yl, etc.);
pyridyl which may have lower alkyl such as 3-pyridyl which may have suitable substituent(s) such as 3-pyridyl and 2-lower alkyl-3-pyridyl (e.g. 2-methyl-3-pyridyl, etc.); and

R^4 is hydrogen;
lower alkyl such as methyl, ethyl, etc.; lower alkenyl such as allyl, etc.; or hydroxy(lower)alkyl such as hydroxymethyl, etc.; and

R^5 is hydrogen;
hydroxy; or
acyloxy such as lower alkanoyloxy (e.g. acetoxy, etc.), and the like; or

R^4 and R^5 are linked together to form an additional bond.

The processes 1 to 8 for preparing the object compound (I) of the present invention are explained in detail in the following.

Process 1 :

The object compound (Ia) or a salt thereof can be prepared by reacting the compound (II) with the compound (III) or a salt thereof.

The present reaction is usually carried out in the presence of a base such as alkyl lithium (e.g. n-butyllithium, etc.), alkali metal hydride (e.g. sodium hydride, potassium hydride, etc), and the like.

The present reaction is usually carried out in a solvent such as dioxane, dimethylsulfoxide, dimethylformamide, diethylformamide, dimethylacetamide, benzene, hexane, tetrahydrofuran, or any other solvent which does not adversely affect the reaction.

The reaction temperature is not critical and the reaction is usually carried out under cooling, at ambient temperature or under heating.

Process 2 :

The object compound (Ib) or a salt thereof can be prepared by reacting the compound (IV) with the compound (V) or a salt thereof.

The reaction is usually carried out in a solvent such as water, alcohol [e.g. methanol, ethanol, propanol, etc.], acetic acid, diethyl ether, dioxane, tetrahydrofuran, methylene chloride, chloroform, N,N-dimethylformamide, dimethylsulfoxide, or any other organic solvent which does not adversely influence the reaction, or a mixture thereof.

The reaction temperature is not critical and the reaction is usually carried out at ambient temperature, under warming or under heating.

Process 3 :

The object compound (Id) or a salt thereof can be prepared by subjecting the compound (Ic) or a salt thereof to removal reaction of the imino-protective group.

Suitable method for this removal may include conventional one such as hydrolysis, reduction, or the like. The hydrolysis is preferably carried out in the presence of the base or an acid.

Suitable base may include, for example, an inorganic base such as alkali metal hydroxide (e.g. sodium hydroxide, potassium hydroxide, etc.), alkaline earth metal hydroxide (e.g. magnesium hydroxide, calcium hydroxide, etc.), alkali metal carbonate, (e.g. sodium carbonate, potassium carbonate, etc.), alkaline earth metal carbonate (e.g. magnesium carbonate, calcium carbonate, etc.), alkali metal bicarbonate (e.g. sodium bicarbonate, potassium bicarbonate, etc.), alkali metal acetate (e.g. sodium acetate, potassium acetate, etc.), alkaline earth metal phosphate (e.g. magnesium phosphate, calcium phosphate, etc.), alkali metal hydrogen phosphate (e.g. disodium hydrogen phosphate, dipotassium hydrogen phosphate, etc.), or the like, and an organic base such as trialkylamine (e.g. trimethylamine, triethylamine, etc.), picoline, N-methylpyrrolidine, N-methylmorpholine, 1,5-diazabicyclo[4,3,0]non-5-one, 1,4-diazabicyclo[2,2,2]octane, 1,5-diazabicyclo[5,4,0]undecene-5 or the like. The hydrolysis using a base is often carried out in water or a hydrophilic organic solvent or a mixed solvent thereof.

Suitable acid may include an organic acid (e.g. formic acid, acetic acid, propionic acid, etc.) and an inorganic acid (e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, etc.).

The present hydrolysis is usually carried out in an organic solvent, water or a mixed solvent thereof.

The reaction temperature is not critical, and the reaction is usually carried out at ambient temperature or under warming or heating.

The reduction may include catalytic reduction and chemical reduction as explained in Process 6 and can be carried out by a conventional method.

The method applied for this removal reaction can be selected depending on the kind of the imino0protective group.

The present removal reaction includes, within its scope, the case that hydroxy or acyloxy for R^5, or the additional bond formed by linkage of R^4 and R^5 is eliminated during the reaction or at the post-treating step of the present process.

In such cases, the reaction is preferably carried out in the presence of catalyst (e.g. palladium on carbon, etc.), ammonium formate and acetic acid under heating.

Process 4 :

The object compound (Ie) or a salt thereof can be prepared by reacting the compound (Ia) or a salt thereof with an acylating agent.

The compound (Ia) may be used in the form of its conventional reactive derivative at the hydroxy group.

The acylating agent can be represented by the compound of the formula :

R_a^5 - H

in which R_a^5 is acyloxy as defined above and its conventional reactive derivative at the hydroxy group.

The suitable example may be an acid halide (e.g. acid chloride, etc.), an acid anhydride, (e.g. acetic anhydride, etc.), an activated amide, an activated ester, and the like.

The reaction is usually carried out in a conventional solvent such as water, acetone, dioxane, acetonitrile, chloroform, dichloromethane, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide, pyridine or any other organic solvent which does not adversely influence the reaction. These conventional solvents may also be used in a mixture with water.

The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

The reaction may also be carried out in the presence of an inorganic or organic base such as an alkali metal bicarbonate, tri(lower)alkylamine, pyridine, N-(lower)-alkylmorphorine, N,N-di(lower)alkylbenzylamine, and the like.

Process 5 :

The object compound (If) or a salt thereof can be prepared by subjecting the compounds (Ie) or a salt thereof to elimination reaction of HR_a^5 group.

The elimination reaction can usually be carried out by an inorganic base such as alkali metal hydride (e.g. sodium hydride, potassium hydride, etc.), or the like, and an organic base such as trialkylamine (e.g. trimethylamine, triethylamine, etc.), picoline, N-methylpyrrolidine, N-methylmorpholine, 1,5-diazabicyclo-[4.3.0]non-5-ene, 1,4-diazabicyclo[2.2.2]octane, 1,8-diazabicyclo[5.4.0]undec-7-ene, or the like.

The present reaction is usually carried out in a solvent such as dioxane, dimethyl sulfoxide, dimethylformamide, diethylformamide, dimethylacetamide, benzene, tetrahydrofuran, toluene, or any other solvent which does not adversely affect the reaction.

The reaction temperature is not critical and the reaction is usually carried out under cooling, at ambient temperature or under heating.

Process 6 :

The object compound (Ih) or a salt thereof can be prepared by subjecting a compound (Ig) or a salt thereof to reduction reaction.

The reaction can be carried out in a conventional manner, for example, chemical reduction or catalytic reduction.

Suitable reducing agents to be used in chemical reduction are a metal hydride compound such as aluminum hydride compound [e.g. lithium aluminum hydride, sodium aluminum hydride, aluminum hydride, lithium trimethoxy-aluminum hydride, lithium tri-t-butoxyaluminum hydride, etc.], borohydride compound [e.g. sodium borohydride, lithium borohydride, sodium cyanoborohydride, tetramethylammonium borohydride, etc.], borane, diborane, aluminum halide [e.g. aluminum chloride, etc.], phosphorus trihalide [e.g. phosphorus trichloride, phosphorus tribromide, etc.], ferrous oxalate, a combination of metal [e.g. tin, zinc, iron, etc.] or metallic compound [e.g. chromium chloride, chromium acetate, etc.] and an organic or inorganic acid [e.g. formic acid, acetic acid, propionic acid, trifluoroacetic acid, p-toluenesulfonic acid, hydrochloric acid, hydrobromic acid, etc.] or the like.

Suitable catalysts to be used in catalytic reduction are conventional ones such as platinum catalyst [e.g. platinum plate, spongy platinum, platinum black, colloidal platinum, platinum oxide, platinum wire, etc.], palladium catalyst [e.g. spongy palladium, palladium black, palladium oxide, palladium on carbon, colloidal palladium, palladium on barium sulfate, palladium on barium carbonate etc.], nickel catalyst [e.g. reduced nickel, nickel oxide, Raney nikel, etc.], cobalt catalyst [e.g. reduced cobalt, Raney cobalt, etc.], iron catalyst [e.g. reduced iron, Raney iron, etc.], copper catalyst [e.g. reduced copper, Raney copper, Ullman copper, etc.] or the like.

The preferable manner is catalytic reduction.

The reaction is usually carried out in a solvent such as water, alcohol [e.g. methanol, ethanol, propanol, etc.], acetic acid, diethyl ether, dioxane, tetrahydrofuran, methylene chloride, chloroform, N,N-dimethylformamide, dimethylsulfoxide, or any other organic solvent which odes not adversely influence the reaction, or a mixture thereof.

The reaction is preferably carried out in the presence of ammonium formate.

The reaction is preferably carried out under somewhat milder conditions such as under cooling to warming.

The present reaction includes, within its scope, the case that the imino-protective group on R_a^3 is eliminated during the reaction or at the past-treating step of the present process.

Process 7 :

The object compound (Ii) or a salt thereof can be prepared by reacting the compound (Id) or a salt thereof with the compound (VI).

The present reaction is usually carried out in the presence of a base such as alkyl lithium (e.g. n-butyl lithium, etc.), alkali metal hydride (e.g. sodium hydride, potassium hydride, etc.), di(lower)alkylamine (e.g. diisopropylamine, etc.), tri(lower)alkylamine (e.g. trimethylamine, triethylamine, etc.), pyridine or its derivative (e.g. picoline, lutidine, 4-dimethylaminopyridine, etc.), or the like.

The present reaction is usually carried out in a solvent such as dioxane, dimethyl sulfoxide, dimethylformamide, diethylformamide, dimethylacetamide, benzene, tetrahydrofuran, or any other solvent which does not adversely affect the reaction. In case that the base to be used is liquid, it can also be used as a solvent.

The reaction temperature is not critical and the reaction is usually carried out under cooling, at ambient temperature or under heating.

Process 8 :

The object compound (Ik) or a salt thereof can be prepared by subjecting the compound (Ij) or a salt thereof to introduction reaction of R_a^4 .

In case that R_a^4 to be introduced is lower alkyl or lower alkenyl, the introducing agent of R_a^4 can be represented by the compound of the formula :

$R_a^4 X^1$

in which

R_a^4 is lower alkyl or lower alkenyl, and

X^1 is acid residue as defined above.

In case that R_a^4 to be introduced is hydroxy(lower)alkyl, the introducing agent of R_a^4 can be represented by the compound of the formula :

$(R^{10}CHO)_n$

in which

R^{10} is hydrogen or lower alkyl, and

n is integer.

This reaction can be carried out in substantially the same manner as Process 7, and therefore the reaction mode and reaction conditions [e.g. solvents, bases, reaction temperature, etc.] of this reaction are to be referred to those as explained in Process 7.

Among the starting compounds (II), (III), (IV), (V) and (VI), some of them are new and such compounds can be prepared by the methods of Preparations mentioned below.

The object compound (I) of the present invention can be isolated and purified in a conventional manner, for example, extraction, precipitation, fractional crystallization, recrystallization, chromatography, and the like.

The object compound (I) thus obtained can be converted to its salt by a conventional method.

The optically active isomers of the object compound (I) can be resolved by a conventional method such as a resolution by reacting a mixture of isomers with an optically active reagent. Such reagents include optically active acids (e.g., benzyloxycarbonyl-L-phenylalanine, di-p-toluoyltartaric acid, etc.) or acid derivatives such as acid chloride (e.g., l-menthoxyacetyl chloride, etc.) or acid anhydride and the like.

The object compound (I) of the present invention are novel and exhibit pharmacological activities such as 5-HT antagonism, especially, 5-HT_3 antagonism, and the like and therefore are useful as 5-HT antagonist for treating or preventing central nervous system (CNS) disorders such as psychosis (e.g. schizophrenia, mania, etc.), anxiety, and depression; pains or aches such as headaches (e.g. migraine, cluster headaches, vascular headaches, etc.), and neuralgia (e.g. trigeminal neuralgia, etc.); gastrointestinal disorders such as symptoms of gastrointestinal dysfunction such as occur with, for example, dyspepsia, peptic ulcer, reflux oesophagitis and flatulence, and irritable bowel syndrome (IBS); nausea or vomiting, each of which may be associated with cancer therapy; motion sickness; and the like.

Further, it is expected that the object compound (I) of the present invention are useful as therapeutical and/or preventive agents for obesity; lung embolism; arrhythmia; withdrawal syndrome resulting from addition to a drug or substance of abuse; stress-related psychiatric disorders; rhinitis; and serotonin-induced nasal disorders, and the like.

In order to illustrate the usefulness of the object compounds (I), pharmacological activity of representative compound of the present invention are shown below.

[1] Test Compound

① 8,9-Dihydro-7-[(hydroxy)(5-methyl-1H-imidazol-4-yl)methyl]-10-methylpyrido[1,2-a]indol-6(7H)-one maleate (isomer B)
(hereinafter referred to as Compound ①)
② 8,9-Dihydro-7-[(1H-imidazol-4-yl)methyl]-10-methylpyrido[1,2-a]indol-6(7H)-one
(hereinafter referred to as Compound ②)
③ (+)-8,9-Dihydro-10-methyl-7-[(5-methyl-1H-imidazol-4-yl)methyl]pyrido[1,2-a]indol-6(7H)-one hydrochloride
(hereinafter referred to as Compound ③)
④ 8,9-Dihydro-7,10-dimethyl-7-[(5-methyl-1H-imidazol-4-yl)methyl]pyrido[1,2-a]indol-6(7H)-one
(hereinafter referred to as Compound ④)

[2] Test

(A) Inhibition of Benzold-Jarisch reflex

Test Method :

Male Sprague -Dawley rats weighing 260-350 g were anesthetized intraperitoneally with 1.25 g/kg urethane.

Blood pressure and heart rate were monitored continuously from the left common carotid artery with a pressure transducer. A right femoral vein was connulated for the intravenous injection (iv) of drugs. The trachea was also connulated to ease the respiration.

Rats were given a rapid bolus injection of 2-methyl-5-hydroxytryptamine (32 µg/kg, iv) to establish the control bradycardic response. Once the heart rate returned to base line, the rats were given the test compound (iv), followed by 5-minutes interval and another bolus injection of 2-methyl-5-hydroxytryptamine (32 ug/kg, iv).

Test Result :

Compound	ED_{50} (µg/kg)
①	5.9
②	1.8
③	0.9
④	1.1

(B) Inhibition of Cisplatin-induced vomiting

Test Method :

Nonfasted female beagles weighing about 10 kg were administered test compound or saline intravenously twice 10 minutes prior to and 90 minutes after Cisplatin dosing (3.2 mg/kg, iv).

Cisplatin was dissolved in 0.9% warm saline with a final concentration of 3 mg/ml and used immediately. The beagles were observed for vomiting for up to 5 hours following Cisplatin administration.

Test Result :

Compound	ED_{50} (μg/kg)
③	1.1

For therapeutic or preventive administration, the object compound (I) of the present invention are used in the form of conventional pharmaceutical preparation which contains said compound as an active ingredient, in admixture with pharmaceutically acceptable carriers such as an organic or inorganic solid or liquid excipient which is suitable for oral, parenteral and external administration. The pharmaceutical preparations may be in solid form such as tablet, granule, powder, capsule, or liquid form such as solution, suspension, syrup, emulsion, lemonade and the like.

If needed, there may be included in the above preparations auxiliary substances, stabilizing agents, wetting agents and other commonly used additives such as lactose, citric acid, tartaric acid, stearic acid, magnesium stearate, terra alba, sucrose, corn starch, talc, gelatin, agar, pectin, peanut oil, olive oil, cacao butter, ethylene glycol, and the like.

While the dosage of the compound (I) may vary from and also depend upon the age, conditions of the patient, a kind of diseases or conditions, a kind of the compound (I) to be applied, etc. In general amounts between 0.01 mg and about 500 mg or even more per day may be administered to a patient. An average single dose of about 0.05 mg, 0.1 mg, 0.25 mg, 0.5 mg, 1 mg, 20 mg, 50 mg, 100 mg of the object compound (I) of the present invention may be used in treating diseases.

The following Preparations and Examples are given for the purpose of illustrating the present invention.

Preparation 1

To a suspension of p-chlorophenylhydrazine hydrochloride (8.52 g) in toluene (100 ml) were added 2-methylcyclohexane-1,3-dione (5.0 g) and 40% sulfuric acid (40 ml), and the mixture was stirred at 80-85 °C for 4 hours. After cooling, the organic layer was separated. The aqueous layer was extracted with toluene. The organic layers were combined and washed with aqueous sodium bicarbonate, water, and brine. After dried over sodium sulfate, the organic layer was evaporated. The residue was recrystallized from methanol to give 2-chloro-8,9-dihydro-10-methylpyrido[1,2-a]indol-6(7H)-one (4.63 g).

mp : 102-103 °C

IR (Nujol) : 1690, 1675, 1625 cm^{-1}

NMR ($CDCl_3$, δ) : 2.08 (2H, quint, J=6Hz), 2.12 (3H, s), 2.75 (2H, t, J=6Hz), 2.88 (2H, t, J=6Hz), 7.21 (1H, dd, J=8.5Hz, J=2Hz), 7.35 (1H, d, J=2Hz), 8.32 (1H, d, J=8.5Hz)

Preparation 2

8,9-Dihydro-2,10-dimethylpyrido[1,2-a]indol-6(7H)-one was prepared in a similar manner to that of Preparation 1.

mp : 106-107 °C

IR (Nujol) : 1705, 1675, 1620 cm^{-1}

NMR ($CDCl_3$, δ) : 2.06 (2H, quint, J=6Hz), 2.15 (3H, s), 2.45 (3H, s), 2.74 (2H, t, J=6Hz), 2.88 (2H, t, J=6Hz), 7.10 (1H, d, J=8.5Hz), 7.20 (1H, s), 8.29 (1H, d, J=8.5Hz)

Preparation 3

To a solution of diisopropylamine (1.21 g) in tetrahydrofuran (15 ml) at -70 °C under a nitrogen atmosphere was added 1.64 M n-butyllithium in hexane (7.3 ml). After being stirred at the same temperature for 20 minutes, the mixture was treated with a solution of 8,9-dihydro-10-methylpyrido[1,2-a]-indol-6(7H)-one (1.99 g) in tetrahydrofuran (20 ml) over 5 minutes. The mixture was stirred at -70 °C for 30 minutes and N,N-dimethylmethyleneammonium iodide (2.41 g) was added in one portion. The reaction temperature was allowed to gradually come to -40 °C over 1 hour and 20 minutes. The reaction mixture was diluted with water and extracted with methylene chloride three times. The organic layer was washed with water twice and brine, dried over anhydrous magnesium sulfate, and evaporated in vacuo. The oil obtained was purified by silica gel column chromatography (1-5% methanol-methylene chloride). The first eluted fraction contained 8,9-dihydro-10-methyl-7-methylenepyrido[1,2-a]indol-6(7H)-one (0.16 g) as an oil.

IR (Nujol) : 1680, 1615, 1185 cm^{-1}

NMR ($CDCl_3$, δ) : 2.13 (3H, s), 2.60-3.10 (4H, m), 5.60 (1H, s), 6.36 (1H, s), 7.30 (3H, s), 8.43 (1H, m)

The second eluted fraction contained 8,9-dihydro-10-methyl-7-(dimethylaminomethyl)pyrido[1,2-a]indol-6(7H)-one (1.15 g).

mp : 70-76 °C

IR (Nujol) : 1685, 1615 cm^{-1}

NMR ($CDCl_3$, δ) : 1.70-2.10 (2H, m), 2.13 (3H, s), 2.23 (6H, s), 2.70-3.10 (5H, m), 7.30 (3H, m), 8.40 (1H, m)

Preparation 4

To a solution of 5-methyl-1H-imidazole-4-carbaldehyde (1.10 g) and triethylamine (1.67 ml) in acetonitrile (15 ml) at room temperature was added dimethylsulfamoyl chloride (1.18 ml). The solution was stirred at 45 °C for 20 hours. The reaction mixture was diluted with chilled water and extracted three times with methylene chloride. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, and evaporated in vacuo. The residue was purified by silica gel column chromatography (2% methanol-methylene chloride) to give crystals (1.57 g). Recrystallization from toluene-hexane gave 4-formyl-N,N-dimethyl-5-methyl-1H-imidazole-1-sulfonamide (1.16 g).

mp : 100-108 °C

IR (Nujol) : 1690, 1560, 1190, 1165 cm^{-1}

NMR (DMSO-d_6, δ) : 2.73 (3H, s), 2.98 (6H, s), 7.91 (1H, s), 10.03 (1H, s)

Example 1

(a) To a solution of diisopropylamine (1.89 g) in tetrahydrofuran (30 ml) at -70 °C under a nitrogen atmosphere was added 1.64 M n-butyllithium in hexane (11.5 ml). After being stirred at the same temperature for 20 minutes, the mixture was treated with a solution of 8,9-dihydro-10-methylpyrido[1,2-a]indol-6(7H)-one (3.39 g) in tetrahydrofuran (39 ml) over 15 minutes. The mixture was stirred at -70 °C for 30 minutes, and a solution of 5-methyl-1-trityl-1H-imidazole-4-carbaldehyde (6.0 g) in tetrahydrofuran (75 ml) was added dropwise over 20 minutes. After the mixture was stirred at -70 °C for further 55 minutes, it was diluted with water and extracted with methylene chloride. The organic layer was washed with water twice and brine, dried over anhydrous magnesium sulfate, and evaporated in vacuo to give 8,9-dihydro-7-[(hydroxy)(5-methyl-1-trityl-1H-imidazol-4-yl)methyl]-10-methylpyrido[1,2-a]indol-6(7H)-one. The product was a mixture of two diastereoisomers.

(b) The obtained oil contained two products which showed close Rf values (0.5 and 0.4 respectively) by TLC (2% methanol-chloroform). Separation with silica gel column chromatography (0.8% methanol-methylene chloride) gave two fractions. The first eluted fraction, being a mixture of two products, was crystallized from chloroform-ethyl acetate-hexane to give one isomer with an upper Rf value of 8,9-dihydro-7-[(hydroxy)(5-methyl-1-trityl-1H-imidazol-4-yl)methyl]-10-methylpyrido[1,2-a]indol-6(7H)-one (3.8 g), which was designated as the isomer A.

mp : 153-169 °C

IR (Nujol) : 1680, 1620, 1230 cm^{-1}

NMR (DMSO-d_6, δ) : 1.40 (3H, s), 2.10 (3H, s), 2.00 (2H, m), 2.60-3.20 (3H, m), 5.00-5.30 (2H, m), 6.70-7.50 (19H, m), 8.27 (1H, m)

The second eluted fraction and the filtrate of the first eluted one were combined and evaporated in vacuo, giving predominantly the other isomer with a lower Rf value of 8,9-dihydro-7-[(hydroxy)(5-methyl-1-

trityl-1H-imidazol-4-yl)methyl]-10-methylpyrido[1,2-a]indol-6(7H)-one (1.9 g) as an amorphous powder, which was designated as the isomer B.

NMR (DMSO-d_6, δ) : 1.43 (3H, s), 2.10 (3H, s), 2.10 (2H, m), 2.50-3.30 (3H, m), 5.10 (1H, d, J=6Hz), 5.33 (1H, m), 6.90-7.50 (19H, m), 8.27 (1H, m)

Example 2

A solution of the isomer A of 8,9-dihydro-7-[(hydroxy)(5-methyl-1-trityl-1H-imidazol-4-yl)methyl]-10-methylpyrido[1,2-a]indol-6(7H)-one (0.9 g) in acetic acid-water [3.5:1, 45 ml) was stirred at 55°C for 2.5 hours. After evaporation of the solvent, the residue was partitioned between water and methylene chloride and neutralized with an aqueous sodium bicarbonate solution to give a precipitate. Collection of the precipitate, followed by washing with water and methylene chloride, gave crystals (0.363 g), which was treated with maleic acid (0.136 g) in hot methanol (20 ml). The solution obtained was evaporated in vacuo to give an oil, which was crystallized from methanol-ether to give the isomer A of 8,9-dihydro-7-[(hydroxy)(5-methyl-1H-imidazol-4-yl)methyl]-10-methylpyrido[1,2-a]indol-6(7H)-one maleate (0.45 g).

mp : 189-190°C

IR (Nujol) : 1685, 1635, 1615, 1575 cm^{-1}

NMR (DMSO-d_6, δ) : 1.60-2.10 (2H, m), 2.10 (3H, s), 2.27 (3H, s), 2.66-3.40 (3H, m), 5.40 (1H, d, J=4.5Hz), 6.00 (2H, s), 7.10-7.50 (3H, m), 8.20 (1H, m), 8.73 (1H, s)

Example 3

A solution of the isomer B of 8,9-dihydro-7-[(hydroxy)(5-methyl-1-trityl-1H-imidazol-4-yl)methyl]-10-methylpyrido[1,2-a]indol-6(7H)-one (1 g) in acetic acid-water (4:1, 40 ml) was stirred at 45°C for 4 hours and then at 60°C for 2 hours. After evaporation of the solvent, the residue was diluted with water, neutralized with an aqueous sodium bicarbonate solution, and extracted three time with methylene chloride. The organic layer combined was washed with water and brine, dried over anhydrous magnesium sulfate, and evaporated in vacuo. Purification of the residue with silica gel column chromatography (8% methanol-methylene chloride) gave an oil (0.41 g). A solution of the oil (0.41 g) in methanol (10 ml) was treated with maleic acid (0.155 g) and evaporated. The obtained residue was crystallized from methanol-ether to give the isomer B of 8,9-dihydro-7-[(hydroxy)(5-methyl-1H-imidazol-4-yl)methyl]-10-methylpyrido[1,2-a]indol-6-(7H)-one maleate (0.50 g).

mp : 155-161°C

IR (Nujol) : 2500-3200, 1715, 1690, 1650, 1620, 1530 cm^{-1}

NMR (DMSO-d_6, δ) : 2.10 (3H, s), 1.70-2.30 (3H, m), 2.23 (3H, s), 2.70-3.30 (3H, m), 5.57 (1H, d, J=3Hz), 6.00 (2H, s), 7.10-7.50 (3H, m), 8.27 (1H, m), 8.80 (1H, s), 12.50-14.50 (2H, br s)

Example 4

Acetic anhydride (5 ml) was added to a solution of 8,9-dihydro-7-[(hydroxy)(5-methyl-1-trityl-1H-imidazol-4-yl)methyl]-10-methylpyrido[1,2-a]indol-6(7H)-one (4 g, a mixture of the isomers A and B) in pyridine (50 ml). After being stirred at room temperature for 20 hours, the solution was evaporated in vacuo. Silica gel column chromatography (1% methanol-methylene chloride) of the oil obtained gave 7-[(acetoxy)-(5-methyl-1-trityl-1H-imidazol-4-yl)methyl]-8,9-dihydro-10-methylpyrido[1,2-a]indol-6(7H)-one (4.30 g) as an amorphous powder.

IR (Nujol) : 1730, 1685, 1625, 1235 cm^{-1}

Example 5

To a solution of 7-[(acetoxy)(5-methyl-1-trityl-1H-imidazol-4-yl)methyl]-8,9-dihydro-10-methylpyrido[1,2-a]indol-6(7H)-one (4.30 g) in toluene (60 ml) at room temperature was added 1,8-diazabicyclo[5.4.0]undec-7-ene (5 ml). After being stirred at 55°C for 6 hours, the solution was diluted with chilled water. The organic layer separated was washed with water three times and brine, dried over anhydrous magnesium sulfate, and evaporated in vacuo. Purification of the oil obtained with silica gel column chromatography (0.5% methanol-methylene chloride) gave 8,9-dihydro-10-methyl-7-[(5-methyl-1-trityl-1H-imidazol-4-yl)methylene]pyrido[1,2-a]indol-6(7H)-one (3.60 g) as an amorphous powder.

IR (Nujol) : 1675, 1625, 1610, 1140 cm^{-1}

NMR (DMSO-d_6, δ) : 1.60 (3H, s), 2.17 (3H, s), 2.93 (2H, m), 3.60 (2H, m), 6.90-7.70 (20H, m), 8.40 (1H,

m)

Example 6

A mixture of 8,9-dihydro-10-methyl-7-[(5-methyl-1-trityl-1H-imidazol-4-yl)methylene]pyrido[1,2-a]indol-6-(7H)-one (2.0 g) and 10% palladium on carbon (0.4 g) in N,N-dimethylformamide-ethanol (6:1, 49 ml) was hydrogenated at an atmospheric pressure for 6 hours. After filtration of the catalyst, the filtrate was evaporated in vacuo to give 8,9-dihydro-10-methyl-7-[(5-methyl-1-trityl-1H-imidazol-4-yl)methyl]pyrido[1,2-a]indol-6(7H)-one as an oil, which was used in the next reaction without purification.

Example 7

(a) A solution of crude 8,9-dihydro-10-methyl-7-[(5-methyl-1-trityl-1H-imidazol-4-yl)methyl]pyrido[1,2-a]-indol-6(7H)-one in acetic acid (50 ml) and water (15 ml) was stirred at 45 °C for 2 hours and then at 65 °C for 2 hours. After evaporation of the solvent, the residue was diluted with water, neutralized with an aqueous sodium bicarbonate solution, and extracted three times with methylene chloride. The organic layer combined was washed with water and brine, dried over anhydrous magnesium sulfate, and evaporated in vacuo. Purification of the residue with silica gel column chromatography (10% methanol-methylene chloride) gave 8,9-dihydro-10-methyl-7-[(5-methyl-1H-imidazol-4-yl)methyl]pyrido[1,2-a]indol-6(7H)-one (1.0 g) as crystals.

mp : 226-229 °C

IR (Nujol) : 1690, 1615, 1325 cm^{-1}

NMR (DMSO-d_6, δ) : 1.60-2.10 (2H, m), 2.10 (6H, s), 2.50-3.40 (5H, m), 7.17-7.60 (3H, m), 7.37 (1H, s), 8.33 (1H, m), 11.60 (1H, s)

(b) The above obtained crystals were treated with maleic acid (0.396 g) in methanol (30 ml). After evaporation of the solvent, the residue obtained was crystallized from methanol-ether to give 8,9-dihydro-10-methyl-7-[(5-methyl-1H-imidazol-4-yl)methyl]pyrido[1,2-a]indol-6(7H)-one maleate (1.06 g).

mp : 176-178 °C

IR (Nujol) : 2200-2600, 1690, 1640, 1620, 1555 cm^{-1}

NMR (DMSO-d_6, δ) : 1.66-2.20 (2H, m), 2.13 (3H, s), 2.23 (3H, s), 2.60-3.40 (5H, m), 6.00 (2H, s), 7.10-7.60 (3H, m), 8.27 (1H, m), 8.77 (1H, s), 11.00-14.00 (2H, m)

Example 8

A solution of 8,9-dihydro-10-methyl-7-[(5-methyl-1-triyl-1H-imidazol-4-yl)methylene]pyrido[1,2-a]indol-6-(7H)-one (0.9 g) in acetic acid-water (4:1, 50 ml) was stirred at 60 °C for 2.5 hours.
After evaporation of the solvent, the residue was diluted with an aqueous sodium bicarbonate solution and extracted with methylene chloride. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, and evaporated in vacuo. Purification of the residue with silica gel column chromatography (2% methanol-chloroform), followed by recrystallization from methanol-chloroform-hexane, gave 8,9-dihydro-10-methyl-7-[(5-methyl-1H-imidazol-4-yl)methylene]pyrido[1,2-a]indol-6(7H)-one (0.41 g).

mp : 252-255 °C

IR (Nujol) : 1665, 1625, 1595, 1555, 1140 cm^{-1}

NMR (DMSO-d_6, δ) : 2.16 (3H, s), 2.33 (3H, s), 2.96 (2H, t, J = 6Hz), 3.53 (2H, t, J = 6Hz), 7.10-7.60 (3H, m), 7.63 (1H, s), 7.70 (1H, s), 8.40 (1H, m)

Example 9

(a) 8,9-Dihydro-7-[(hydroxy)(5-methyl-1-trityl-1H-imidazol-4-yl)methyl]-10-propylpyrido[1,2-a]indol-6(7H)-one was prepared in a similar manner to that of Example 1-(a).

IR (Nujol) : 1705, 1610, 1230 cm^{-1}

The product was a mixture of two diastereoisomers and used in the next reaction without separation.

(b) A solution of 8,9-dihydro-7-[(hydroxy)(5-methyl-1-trityl-1H-imidazol-4-yl)methyl]-10-propylpyrido[1,2-a]indol-6(7H)-one (1.65 g) in a mixture of acetic acid and water (4:1, 90 ml) was stirred at 60 °C for 4 hours. After evaporation of the solvent, the residue was diluted with as aqueous sodium bicarbonate solution and extracted three times with methylene chloride. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, and evaporated in vacuo. The crystalline residue was suspended in a mixture of methanol and chloroform and filtered to give one isomer of 8,9-dihydro-7-[-

(hydroxy)(5-methyl-1H-imidazol-4-yl)methyl]-10-propylpyrido[1,2-a]indol-6(7H)-one with an upper Rf value in silica gel thin layer chromatography (TLC) (6% methanol-chloroform) (0.27 g), which was designated as the isomer A. The filtrate was evaporated and purified by silica gel column chromatography (6% methanol-methylene chloride). The fractions eluted first contained the isomer A and the fractions eluted later contained another isomer of 8,9-dihydro-7-[(hydroxy)(5-methyl-1H-imidazol-4-yl)methyl]-10-propylpyrido[1,2-a]indol-6(7H)-one with a lower Rf value in TLC, which was designated as the isomer B.

The isomer A combined was recrystallized from methanol to give 326 mg of the product.

mp : 190-192 °C

IR (Nujol) : 3430, 1690, 1660, 1620 cm^{-1}

NMR (DMSO-d_6, δ) : 0.89 (3H, t, J=9Hz), 1.57 (2H, m), 2.17 (5H, br s), 2.54 (2H, t, J=7Hz), 2.60-3.00 (2H, m), 3.20 (1H, m), 4.80-5.80 (2H, m), 7.23 (2H, m), 7.36 (1H, s), 7.50 (1H, m), 8.30 (1H, m), 11.68 (1H, s)

The isomer B was recrystallized from methanol-chloroform-hexane to give 302 mg of the product.

mp : 220-223 °C

IR (Nujol) : 3230, 1660, 1615, 1590 cm^{-1}

NMR (DMSO-d_6, δ) : 0.90 (3H, t, J=7.2Hz), 1.58 (2H, m), 2.04 (2H, m), 2.19 (3H, s), 2.60 (2H, t, J=7.2Hz), 2.60-3.20 (2H, m), 3.33 (1H, m), 5.25 (1H, br s), 5.57 (1H, br s), 7.25 (2H, m), 7.42 (1H, s), 7.50 (1H, m), 8.36 (1H, m), 11.70 (1H, s)

Example 10

7-[(Acetoxy)(5-methyl-1-trityl-1H-imidazol-4-yl)methyl]-8,9-dihydro-10-propylpyrido[1,2-a]indol-6(7H)-one was prepared in a similar manner to that of Example 4 as an amorphous powder.

IR (Nujol) : 1725, 1695, 1610 cm^{-1}

Example 11

8,9-Dihydro-7-[(5-methyl-1-trityl-1H-imidazol-4-yl)methylene]-10-propylpyrido[1,2-a]indol-6(7H)-one was prepared in a similar manner to that of Example 5 as an amorphous powder.

IR (Nujol) : 1675, 1615 cm^{-1}

Example 12

8,9-Dihydro-7-[(5-methyl-1-trityl-1H-imidazol-4-yl)methyl]-10-propylpyrido[1,2-a]indol-6(7H)-one was prepared in a similar manner to that of Example 6.

Example 13

The suspension of 8,9-dihydro-10-methyl-7-[(-5-methyl-1H-imidazol-4-yl)methyl]pyrido[1,2-a]indol-6(7H)-one (2.0 g) in methanol (60 ml) was treated with hydrogen chloride in ethanol and then diluted with hot aqueous ethanol (water:ethanol, 1:4) to give a clear solution. After filtration of the insoluble materials, the filtrate was evaporated under reduced pressure to about 40 ml and allowed to stand at room temperature overnight. Filtration, followed by washing with ethanol, gave 8,9-dihydro-10-methyl-7-[(5-methyl-1H-imidazol-4-yl)methyl]pyrido[1,2-a]indol-6(7H)-one hydrochloride (2.10 g) as crystals.

mp : >250 °C

IR (Nujol) : 1695, 1635, 1520 cm^{-1}

NMR (DMSO-d_6, δ) : 1.66-2.10 (2H, m), 2.13 (3H, s), 2.23 (3H, s), 2.60-3.40 (5H, m), 7.27 (2H, m), 7.43 (1H, m), 8.23 (1H, m), 8.90 (1H, s)

Example 14

8,9-Dihydro-7-[(5-methyl-1H-imidazol-4-yl)methyl]-10-propylpyrido[1,2-a]indol-6(7H)-one hydrochloride was prepared in a similar manner to that of Example 7-(a), and then Example 13.

mp : 193-199 °C

IR (Nujol) : 3350, 1690, 1660, 1640, 1615 cm^{-1}

NMR (DMSO-d_6, δ) : 0.90 (3H, t, J=7.3Hz), 1.68 (2H, m), 1.70-2.20 (2H, m), 2.27 (3H, s), 2.60 (2H, t, J=7.3Hz), 2.65-3.50 (5H, m), 7.26 (2H, m), 7.52 (1H, m), 8.33 (1H, m), 8.96 (1H, s), 14.45 (2H, br s)

Example 15

8,9-Dihydro-7-[(hydroxy)(1-trityl-1H-imidazol-4-yl)methyl]-10-methylpyrido[1,2-a]indol-6(7H)-one (a mixture of the isomers A and B) was prepared in a similar manner to that of Example 1-(a).

IR (Nujol) : 1710, 1685, 1660 cm^{-1}

NMR ($CDCl_3$, δ) : 5.53 (1H, m), 3.51 (1H, d, J=7Hz), 5.20 (1H, m), 4.66 (1H, d, J=4Hz)

Example 16

7-[(Acetoxy)(1-trityl-1H-imidazol-4-yl)methyl]-8,9-dihydro-10-methylpyrido[1,2-a]indol-6(7H)-one was prepared in a similar manner to that of Example 4.

IR (Nujol) : 1735, 1680 cm^{-1}

NMR ($CDCl_3$, δ) : 1.95 (3H, s), 2.14 (3H, s)

Example 17

8,9-Dihydro-10-methyl-7-[(1-trityl-1H-imidazol-4-yl)methylene]pyrido[1,2-a]indol-6(7H)-one was prepared in a similar manner to that of Example 5.

mp : 179-181 °C

IR (Nujol) : 1670, 1620, 1610 cm^{-1} NMR (DMSO-d_6, δ) : 8.35 (1H, dd, J=6Hz, J=3Hz), 7.7-6.9 (21H, m), 3.44 (2H, br t, J=6Hz), 2.97 (2H, br t, J=6Hz), 2.16 (3H, s)

Example 18

8,9-Dihydro-10-methyl-7-[(1-trityl-1H-imidazol-4-yl)methyl]pyrido[1,2-a]indol-6(7H)-one was prepared in a similar manner to that of Example 6, which was used in the next reaction without purification.

Example 19

To a mixture of acetic acid (50 ml) and water (15 ml), was added 8,9-dihydro-10-methyl-7-[(1-trityl-1H-imidazol-4-yl)methyl]pyrido[1,2-a]indol-6(7H)-one (4.93 g), and stirred at 60 °C for 2 hours. After being cooled, the precipitates were filtered off. The filtrate was neutralized with aqueous 8N-sodium hydroxide solution, and extracted with chloroform. The organic layer was washed with brine, dried over sodium sulfate, and evaporated. The residue was crystallized from diisopropyl ether-ethyl acetate (5:1, V/V) to give 8,9-dihydro-7-[(1H-imidazol-4-yl)methyl]-10-methylpyrido[1,2-a]indol-6(7H)-one (1.84 g).

mp : 156-157 °C

IR (Nujol) : 1685 cm^{-1}

NMR (DMSO-d_6, δ) : 8.34 (1H, dt, J=6Hz, J=3Hz, J=3Hz), 7.76 (1H, s), 7.46 (1H, dd, J=6Hz, J=3Hz), 7.4-7.2 (2H, m), 6.94 (1H, s), 3.25 (1H, dd, J=7Hz, J=2Hz), 3.2-3.0 (2H, m), 2.9-2.7 (2H, m), 2.13 (3H, s), 2.2-2.0 (1H, m), 1.8-1.6 (1H, m)

MS (m/e) : 279 (M^+)

Example 20

(+)-Di-p-toluoyl-D-tartaic acid (4.68 g) and 8,9-dihydro-10-methyl-7-[(5-methyl-1H-imidazol-4-yl)methyl]-pyrido[1,2-a]indol-6(7H)-one (3.55 g) were dissolved in hot methanol (200 ml). After removal of the solvent (100 ml), the solution was diluted with ethanol (200 ml) and allowed to stand at 5 °C for 3 days. The precipitates formed was collected and washed with methanol. Recrystallization of the precipitates from methanol (200 ml) at 5 °C gave crystals, which were neutralized with an aqueous sodium bicarbonate solution and extracted with chloroform. The chloroform layer was washed with water, dried over anhydrous magnesium sulfate, and evaporated in vacuo. The crystals obtained were purified by silica gel column chromatography (10% methanol-chloroform) and then recrystallized from methanol-chloroform-hexane. After filtration of the crystals, the filtrate was evaporated in vacuo to give (-)-8,9-dihydro-10-methyl-7-[(5-methyl-1H-imidazol-4-yl)methyl]pyrido[1,2-a]indol-6(7H)-one (0.4 g) with $[\alpha]_D^{25}$ =-56° (C=1.0, 10% methanol-chloroform) as crystals. A part of the crystals (200 mg) were treated with hydrochloric acid in methanol and recrystallized from methanol-ether to give (-)-8,9-dihydro-10-methyl-7-[(5-methyl-1H-imidazol-4-yl)methyl]-pyrido[1,2-a]indol-6(7H)-one hydrochloride (0.2 g).

mp : >250 °C

Example 21

(+)-8,9-Dihydro-10-methyl-7-[(5-methyl-1H-imidazol-4-yl)methyl]pyrido[1,2-a]indol-6(7H)-one hydrochloride was prepared in a similar manner to that of Example 20 except that (-)-di-p-toluoyl-L-tartaric acid was used in place of (+)-di-p-toluoyl-D-tartaric acid.

Hydrochloride : mp. >250 °C

The free base $[\alpha]_D^{25}$ = +60° (C=1, 10% methanol-chloroform)

Example 22

To a solution of diisopropylamine (658 mg) in tetrahydrofuran (8 ml) at -70 °C under nitrogen atmosphere was added 1.64 M butyllithium in hexane (3.96 ml). After being stirred at the same temperature for 20 minutes, the mixture was treated with a solution of 8,9-dihydropyrido[1,2-a]indol-6(7H)-one (1.21 g) in tetrahydrofuran (12 ml) over 15 minutes. The mixture was stirred at -70 °C for 30 minutes, and a solution of 5-methyl-1-trityl-1H-imidazole-4-carbaldehyde (2.29 g) in tetrahydrofuran (20 ml) was added dropwise over 20 minutes. After the mixture was stirred at -70 °C for further 60 minutes and at ambient temperature for 2 hours, it was diluted with water and neutralized with an aqueous solution of oxalic acid. Separated organic layer was washed with brine, dried over anhydrous magnesium sulfate, and evaporated in vacuo to give 8,9-dihydro-7-[(hydroxy)(5-methyl-1-trityl-1H-imidazol-4-yl)methyl]pyrido[1,2-a]indol-6(7H)-one (2.21 g) as an amorphous powder. The product was a mixture of two diastereoisomers.

mp : 85-90 °C

IR (Nujol) : 1690, 1590 cm^{-1}

NMR ($CDCl_3$, δ) : 1.46 (3H, s), 1.6-2.4 (2H, m), 2.8-3.5 (3H, m), 4.8-5.2 (1H, m), 6.29 (1H, s), 7.0-7.4 (18H, m), 8.3-8.5 (1H, m)

Example 23

A solution of 8,9-dihydro-7-[(hydroxy)(5-methyl-1-trityl-1H-imidazol-4-yl)methyl]pyrido[1,2-a]indol-6(7H)-one (1.1 g) in acetic acid-water (3:1, 48 ml) was stirred at 65 °C for 90 minutes. After evaporation of the solvent, the residue was diluted with water, neutralized with an aqueous solution of sodium hydrogencarbonate, and extracted with chloroform. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and evaporated in vacuo. The obtained amorphous powder contained two products which showed close Rf values (0.3 and 0.4 respectively) by TLC (20% methanol-chloroform). Separation with silica gel column chromatography (10% methanol-chloroform) gave two fractions. The residue obtained from the first eluted fraction was dissolved in ethyl acetate and treated with hydrogen chloride in ether to give one isomer with an upper Rf value of 8,9-dihydro-7-[(hydroxy)(5-methyl-1H-imidazol-4-yl)methyl]pyrido-[1,2-a]indol-6(7H)-one hydrochloride (86.1 mg), which was designated as the isomer A.

mp : 180-183 °C (dec.)

IR (Nujol) : 3300, 1680, 1595 cm^{-1}

NMR (DMSO-d_6, δ) : 1.5-2.0 (1H, m), 2.32 (3H, s), 2.8-3.6 (5H, m), 5.48 (1H, br s), 6.43 (1H, s), 7.1-7.6 (3H, m), 8.2-8.3 (1H, m), 8.94 (1H, s), 14.3 (1H, s)

MS (m/e) : 295 (M^+)

The second eluted fraction was evaporated in vacuo, followed by recrystallization from ethyl acetate to give the other isomer with a lower Rf value of 8,9-dihydro-7-[(hydroxy)(5-methyl-1H-imidazol-4-yl)methyl]-pyrido[1,2-a]indol-6(7H)-one (45 mg), which was designated as the isomer B.

mp : 186-188 °C (dec.)

IR (Nujol) : 3400, 1655, 1590 cm^{-1}

NMR (DMSO-d_6, δ) : 1.8-2.2 (2H, m), 2.20 (3H, s), 2.7-3.3 (3H, m), 5.30 (1H, br s), 5.58 (1H, s), 6.41 (1H, s), 7.2-7.6 (3H, m), 7.43 (1H, s), 8.3-8.4 (1H, m)

MS (m/e) : 295 (M^+)

Example 24

Acetic anhydride (1.26 g) was added to a solution of 8,9-dihydro-7-[(hydroxy)(5-methyl-1-trityl-1H-imidazol-4-yl)methyl]pyrido[1,2-a]indol-6(7H)-one (1.34 g, a mixture of the isomers A and B) in pyridine (20 ml). After being stirred at 60 °C for 2 hours, the solution was evaporated in vacuo. The residue obtained was diluted with chloroform and neutralized with an aqueous sodium hydrogencarbonate solution. The separated organic layer was dried over anhydrous magnesium sulfate and evaporated in vacuo to give 7-[(acetoxy)(5-

methyl-1-trityl-1H-imidazol-4-yl)methyl]-8,9-dihydropyrido[1,2-a]indol-6(7H)-one as an oil, which was used in the next reaction without purification.

Example 25

To a solution of 7-[(acetoxy)(5-methyl-1-trityl-1H-imidazol-4-yl)methyl]-8,9-dihydropyrido[1,2-a]indol-6-(7H)-one in toluene (30 ml) at room temperature was added 1,8-diazabicyclo[5.4.0]undec-7-ene (762 mg). After being stirred at 55 °C for 2 hours, the solution was evaporated in vacuo. The residue was diluted with chloroform, washed with water, and dried over anhydrous magnesium sulfate. After evaporation of the solvent, the residue obtained was purified with silica gel column chromatography (eluent:chloroform) to give 8,9-dihydro-7-[(5-methyl-1-trityl-1H-imidazol-4-yl)methylene]pyrido[1,2-a]indol-6(7H)-one (1.3 g).

mp : 214-217 °C

IR (Nujol) : 1675, 1620, 1570 cm^{-1}

NMR (DMSO-d_6, δ) : 1.61 (3H, s), 3.03 (2H, t, J=6.87Hz), 3.60 (2H, t, J=6.87Hz), 6.47 (1H, s), 7.0-7.7 (20H, m), 8.3-8.5 (1H, m)

Example 26

8,9-Dihydro-7-[(5-methyl-1H-imidazol-4-yl)methyl]pyrido[1,2-a]indol-6(7H)-one hydrochloride was prepared from 8,9-dihydro-7-[(5-methyl-1-trityl-1H-imidazol-4-yl)methylene]pyrido[1,2-a]indol-6(7H)-one in a similar manner to that of Example 36.

mp : 262-264 °C (dec.)

IR (Nujol) : 1695, 1640, 1595 cm^{-1}

NMR (DMSO-d_6, δ) : 1.7-2.1 (2H, m), 2.27 (3H, s), 2.8-3.4 (5H, m), 6.45 (1H, s), 7.2-7.6 (3H, m), 8.2-8.4 (1H, m), 8.98 (1H, s)

MS (m/e) : 279 (M^+)

Example 27

To a solution of diisopropylamine (557 mg) in tetrahydrofuran (15 ml) at -70 °C under a nitrogen atmosphere was added 1.64 M butyllithium in hexane (3.35 ml). After being stirred at the same temperature for 20 minutes, the mixture was treated with a solution of 8,9-dihydro-10-methylpyrido[1,2-a]indol-6(7H)-one (995 mg) in tetrahydrofuran (10 ml) over 15 minutes. The mixture was stirred at -70 °C for 30 minutes, and a solution of 1-trityl-1H-imidazole-2-carbaldehyde (1.69 g) in tetrahydrofuran (20 ml) was added dropwise over 10 minutes. After the mixture was stirred at -70 °C for further 70 minutes, it was diluted with chilled water, neutralized with an aqueous solution of oxalic acid, and extracted with chloroform. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and evaporated in vacuo. Purification of the residue with silica gel column chromatography (20% ethyl acetate-chloroform) gave 8,9-dihydro-7-[(hydroxy)(1-trityl-1H-imidazol-2-yl)methyl]-10-methylpyrido[1,2-a]indol-6(7H)-one (1.85 g)

mp : 209-210 °C (dec.)

IR (Nujol) : 3300, 1660, 1615 cm^{-1}

NMR ($CDCl_3$, δ) : 1.1-1.2 (1H, m), 1.9-2.2 (1H, m), 2.08 (3H, s), 2.4-2.7 (2H, m), 3.2-3.4 (1H, m), 4.5-4.7 (2H, m), 6.9-7.3 (20H, m), 8.2-8.4 (1H, m)

MS (m/e) : 519 (M^+)

Example 28

A solution of 8,9-dihydro-7-[(hydroxy)(1-trityl-1H-imidazol-2-yl)methyl]-10-methylpyrido[1,2-a]indol-6-(7H)-one (376 mg) in acetic acid (15 ml) and water (5 ml) was stirred at 60 °C for 2.5 hours. After evaporation of the solvent, the residue was diluted with water, neutralized with an aqueous solution of sodium hydrogencarbonate, and extracted three times with chloroform. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and evaporated in vacuo. Purification of the residue with silica gel column chromatography (15% methanol-chloroform), followed by recrystallization from methanol, gave 8,9-dihydro-7-[(hydroxy)(1H-imidazol-2-yl)methyl]-10-methylpyrido[1,2-a]indol-6(7H)-one (148 mg).

mp : 199-200 °C

IR (Nujol) : 3400, 1668, 1620 cm^{-1}

NMR ($CDCl_3$, δ) : 1.8-2.1 (2H, m), 2.15 (3H, s), 2.7-2.9 (1H, s), 3.0-3.2 (2H, m), 3.61 (2H, br s), 5.24 (1H,

d, J=6.07Hz), 6.99 (1H, s), 7.00 (1H, s), 7.2-7.5 (3H, m), 8.3-8.5 (1H, m)
MS (m/e) : 295 (M^+)

Example 29

7-[(Acetoxy)(1-trityl-1H-imidazol-2-yl)methyl]-8,9-dihydro-10-methylpyrido[1,2-a]indol-6(7H)-one was prepared in a similar manner to that of Example 4, which was used in the next reaction without purification.

Example 30

8,9-Dihydro-10-methyl-7-[(1-trityl-1H-imidazol-2-yl)methylene]pyrido[1,2-a]indol-6(7H)-one was prepared in a similar manner to that of Example 5.
mp : 222-224 °C (dec.)
IR (Nujol) : 1670, 1620, 1600 cm^{-1}
NMR (DMSO-d_6, δ) : 2.13 (3H, s), 2.7-3.1 (2H, m), 3.2-3.4 (2H, m), 6.8-7.5 (21H, m), 8.11 (1H, dd, J=2.93Hz, 6.81Hz)

Example 31

A mixture of 8,9-dihydro-10-methyl-7-[(1-trityl-1H-imidazol-2-yl)methylene]pyrido[1,2-a]indol-6(7H)-one (950 mg), ammonium formate (573 mg) and 10% palladium on carbon (285 mg) in acetic acid (19 ml) was stirred at 110 °C for 1 hour. After filtration of the catalyst, the filtrate was evaporated in vacuo. The residue was diluted with chloroform. The chloroform solution was washed with 1N hydrochloric acid (5 ml x 2) to give a precipitate which was collected, washed with water, and dried to give 8,9-dihydro-10-methyl-7-[(1H-imidazol-2-yl)methyl]pyrido[1,2-a]indol-6(7H)-one hydrochloride (445.6 mg).
mp : >270 °C
IR (Nujol) : 2660, 1665, 1630 cm^{-1}
NMR (DMSO-d_6, δ) : 1.8-2.1 (2H, m), 2.15 (3H, s), 2.8-3.8 (6H), 7.2-7.3 (2H, m), 7.4-7.5 (1H, m), 7.61 (2H, s), 8.2-8.3 (1H, m), 14.6 (1H, br s)
MS (m/e) : 279 (M^+)

Example 32

7-[(1-Benzyl-1H-2,5-dimethylimidazol-4-yl)(hydroxy)methyl]-8,9-dihydro-10-methylpyrido[1,2-a]indol-6-(7H)-one was prepared in a similar manner to that of Example 27.
mp : 121-124 °C
IR (Nujol) : 3400, 1670, 1620 cm^{-1}
NMR ($CDCl_3$, δ) : 1.4-1.6 (2H, m), 1.7-2.0 (2H, m), 2.06 (3H, s), 2.19 (3H, s), 2.36 (3H, s), 2.7-2.9 (1H, m), 5.0-5.9 (3H, m), 6.9-7.1 (2H, m), 7.2-7.5 (6H, m), 8.3-8.5 (1H, m)

Example 33

A mixture of 7-[(1-benzyl-1H-2,5-dimethylimidazol-4-yl)(hydroxy)methyl]-8,9-dihydro-10-methylpyrido-[1,2-a]indol-6(7H)-one (1.70 g), ammoniumformate (7.78 g) and 10% palladium on carbon (0.5 g) in acetic acid (30 ml) was stirred at 120 °C for 4 hours. After filtration of the catalyst, the filtrate was evaporated in vacuo. The residue was diluted with chloroform, washed with 10% aqueous solution of sodium hydrogencarbonate, and dried over anhydrous magnesium sulfate. After the solvent was evaporated in vacuo, the residue was subjected to column chromatography on silica gel (10% methanol-chloroform). Fractions containing the product were combined and evaporated in vacuo. The residue was crystallized from ethyl acetate to give 8,9-dihydro-10-methyl-7-[(2,5-dimethyl-1H-imidazol-4-yl)methyl]pyrido[1,2-a]indol-6(7H)-one (0.36 g).
mp : 219-221 °C
IR (Nujol) : 1690, 1620, 1545 cm^{-1}
NMR (DMSO-d_6, δ) : 1.6-1.85 (1H, m), 1.9-2.1 (1H, m), 2.05 (3H, s), 2.13 (3H, s), 2.19 (3H, s), 2.5-2.8 (2H, m), 2.9-3.2 (3H, m), 7.2-7.3 (2H, m), 7.4-7.5 (1H, m), 8.3-8.4 (1H, m)
MS (m/e) : 307 (M^+)

Example 34

(a) To a solution of diisopropylamine (1.01 g) in tetrahydrofuran (15 ml) at -70 °C under a nitrogen atmosphere was added 1.64 M butyllithium in hexane (6.1 ml). After being stirred at the same temperature for 20 minutes, the mixture was treated with a solution of 8,9-dihydro-10-methylpyrido[1,2-a]indol-6(7H)-one (1.99 g) in tetrahydrofuran (25 ml) over 20 minutes. The mixture was stirred at -70 °C for 30 minutes, and a solution of 2-methyl-3-pyridinecarbaldehyde (1.21 g) in tetrahydrofuran (20 ml) was added dropwise over 20 minutes. After the mixture was stirred at -70 °C for further 60 minutes and at ambient temperature for 60 minutes, it was diluted with water and adjusted to pH 9 with oxalic acid. The separated organic layer was washed with brine, dried over anhydrous magnesium sulfate, and evaporated in vacuo, to give 8,9-dihydro-7-[(hydroxy)(2-methylpyridin-3-yl)methyl]-10-methylpyrido[1,2-a]indol-6(7H)-one.

The product was a mixture of two diastereoisomers.

(b) The obtained oil contained two products which showed close Rf values (0.3 and 0.4 respectively) by TLC (20% ethyl acetate-chloroform). Separation with silica gel column chromatography (20% ethyl acetate-chloroform) gave two fractions. The solid obtained from the first eluted fraction was treated with hydrogen chloride in a mixture of ethyl acetate-chloroform-ether to give one isomer with an upper Rf value of 8,9-dihydro-7-[(hydroxy)(2-methylpyridin-3-yl)methyl]-10-methylpyrido[1,2-a]indol-6(7H)-one hydrochloride (0.45 g), which was designated as the isomer A.

mp : 232-233 °C (dec.)

IR (Nujol) : 3260, 2500, 1690, 1610 cm^{-1}

NMR (DMSO-d_6, δ) : 2.15 (3H, s), 2.23 (2H, t, J=5.51Hz), 2.85 (3H, s), 2.7-3.0 (1H, m), 3.1-3.4 (2H, m), 5.30 (1H, d, J=2.18Hz), 7.1-7.5 (3H, m), 7.94 (1H, dd, J=5.76Hz, 6.99Hz), 8.1-8.3 (1H, m), 8.6-8.8 (2H, m)

MS (m/e) : 320 (M^+)

The second eluted fraction was evaporated in vacuo, and treated in a similar manner to that of an upper Rf value to give the other isomer with a lower Rf value of 8,9-dihydro-7-[(hydroxy)(2-methylpyridin-3-yl)-methyl]-10-methylpyrido[1,2-a]indol-6(7H)-one hydrochloride (74.3 mg), which was designated as the isomer B.

mp : 213-214 °C (dec.)

IR (Nujol) : 3200, 2500, 1690, 1615 cm^{-1}

NMR (DMSO-d_6, δ) : 1.6-1.8 (2H, m), 1.9-2.0 (1H, m), 2.15 (3H, s), 2.6-2.9 (1H, m), 2.80 (3H, s), 3.0-3.3 (2H, m), 5.83 (1H, s), 7.2-7.4 (3H, m), 7.95 (1H, dd, J=5.44Hz, 7.42Hz), 8.3-8.4 (1H, m), 8.57 (1H, d, J=7.42Hz), 8.71 (1H, d, J=5.45Hz)

MS (m/e) : 320 (M^+)

Example 35

Acetic anhydride (2.24 g) was added to a solution of 8,9-dihydro-7-[(hydroxy)(2-methylpyridin-3-yl)-methyl]-10-methylpyrido[1,2-a]indol-6(7H)-one (1.35 g, a mixture of the isomers A and B) in pyridine (20 ml). After being stirred at 60 °C for 2 hours, the solution was evaporated in vacuo. The residue was diluted with chloroform, washed with brine, dried over anhydrous magnesium sulfate, and evaporated in vacuo. The residue and 1,8-diazabicyclo[5.4.0]undec-7-ene (1.27 g) were dissolved in toluene (30 ml). The solution was stirred at 60 °C for 2 hours and evaporated in vacuo. The residue was crystallized from ethyl acetate to give 8,9-dihydro-10-methyl-7-[(2-methylpyridin-3-yl)methylene]pyrido[1,2-a]indol-6(7H)-one (0.92 g).

mp : 182-183 °C

IR (Nujol) : 1675, 1630, 1610 cm^{-1}

NMR (DMSO-d_6, δ) : 2.17 (3H, s), 2.51 (3H, s), 2.6-3.0 (4H, m), 7.2-7.4 (3H, m), 7.4-7.6 (1H, m), 7.70 (1H, d, J=7.4Hz), 7.88 (1H, s), 8.3-8.6 (2H, m)

MS (m/e) : 302 (M^+)

Example 36

A mixture 8,9-dihydro-10-methyl-7-[(2-methylpyridin-3-yl)methylene]pyrido[1,2-a]indole-6(7H)-one (820 mg), ammonium formate (854 mg) and 10% palladium on carbon (0.3 g) in acetic acid (30 ml)was stirred at 110 °C for 1 hour. After filtration of the catalyst, the filtrate was evaporated in vacuo. The residue was diluted with 5% methanol in chloroform, washed with 5% aqueous solution of sodium hydrogencarbonate and brine, dried over anhydrous magnesium sulfate, and evaporated in vacuo. Purification of the residue with silica gel column chromatography (5% methanol-chloroform) gave 0.7 g of crystals, which were dissolved in a mixture of chloroform and ethyl acetate and treated with hydrogen chloride in ether to give

8,9-dihydro-10-methyl-7-[(2-methylpyridin-3-yl)methyl]pyrido[1,2-a]indol-6(7H)-one hydrochloride (0.43 g).

mp : 237-239 °C (dec.)

IR (Nujol) : 1690, 1615, 1545 cm^{-1}

NMR (DMSO-d_6, δ) : 1.8-2.1 (2H, m), 2.15 (3H, s), 2.82 (3H, s), 2.9-3.7 (5H, m), 7.2-7.3 (2H, m), 7.4-7.6 (1H, m), 7.87 (1H, dd, J=5.80, 6.67Hz), 8.2-8.4 (1H, m), 8.46 (1H, d, J=6.67Hz), 8.68 (1H, dd, J=1.33, 6.67Hz)

MS (m/e) : 304 (M^+)

Example 37

8,9-Dihydro-7-[(hydroxy)(pyridin-3-yl)methyl]-10-methylpyrido[1,2-a]indol-6(7H)-one was prepared in a similar manner to that of Example 27.

mp : 83-86 °C

IR (Nujol) : 1685, 1615 cm^{-1}

NMR (DMSO-d_6, δ) : 1.6-2.1 (2H, m), 2.14 (3H, d, J=1.24Hz), 2.5-3.1 (3H, m), 3.76 (1/2H, br s), 5.10 (1/2H, d, J=8.7Hz), 5.44 (1/2H, s), 5.80 (1/2H, s), 7.2-7.4 (4H, m), 7.7-7.9 (1H, m), 8.4-8.7 (3H, m)

Example 38

8,9-Dihydro-10-methyl-7-[(pyridin-3-yl)methylene]pyrido[1,2-a]indol-6(7H)-one was prepared in a similar manner to that of Example 35.

mp : 102-103 °C

IR (Nujol) : 1670, 1630, 1615 cm^{-1}

NMR (DMSO-d_6, δ) : 2.20 (3H, s), 2.9-3.1 (4H, m), 7.2-7.5 (4H, m), 7.7-7.8 (1H, m), 7.96 (1H, s), 8.4-8.6 (1H, m), 8.60 (1H, dd, J=1.60, 4.83Hz), 8.69 (1H, d, J=2.2Hz)

MS (m/e) : 288 (M^+)

Example 39

A solution of 8,9-dihydro-10-methyl-7-[(pyridin-3-yl)methylene]pyrido[1,2-a]indol-6(7H)-one (520 mg), ammonium formate (568 mg) and 10% palladium on carbon (200 mg) in acetic acid (20 ml) was stirred at 110 °C for 2 hours. After filtration of the catalyst, the filtrate was evaporated in vacuo. The residue was diluted with 10% methanol-chloroform. The solution was washed with 5% aqueous solution of sodium hydrogencarbonate and brine, dried over anhydrous magnesium sulfate, and evaporated in vacuo. Purification of the residue with silica gel chromatography (5% methanol-chloroform), followed by recrystallization from ethyl acetate-ether, gave 8,9-dihydro-10-methyl-7-[(pyridin-3-yl)methyl]pyrido[1,2-a]indol-6(7H)-one (273 mg).

mp : 158-160 °C

IR (Nujol) : 1690, 1675, 1620 cm^{-1}

NMR ($CDCl_3$, δ) : 0.9-2.0 (2H, m), 2.13 (3H, s), 2.4-3.6 (5H, m), 7.0-7.7 (5H, m), 8.3-8.6 (3H, m)

MS (m/e) : 290 (M^+)

Example 40

To a solution of diisopropylamine (557 mg) in tetrahydrofuran (7.5 ml) at -70 °C under a nitrogen atmosphere was added 1.64 M butyllithium in hexane (3.35 ml). After being stirred at the same temperature for 20 minutes, the mixture was treated with a solution of 8,9-dihydro-10-methylpyrido[1,2-a]indol-6(7H)-one (995 mg) in tetrahydrofuran (10 ml) over 15 minutes. The mixture was stirred at -70 °C for 40 minutes, and a solution of 2-methyl-1-trityl-1H-imidazole-4-carbaldehyde (1.76 g) in tetrahydrofuran (20 ml) was added dropwise over 15 minutes. After the mixture was stirred at -70 °C for 1 hour and at ambient temperature for 1 hour, it was diluted with water and neutralized with a aqueous solution of oxalic acid. The organic layer was separated and the aqueous layer was extracted with chloroform. The organic layers were combined and washed with brine and dried over anhydrous magnesium sulfate. After the solvent was evaporated in vacuo, the residue was subjected to a column chromatography on silica gel (20% ethyl acetate-chloroform). The fractions containing the product were combined and evaporated in vacuo. The residue was crystallized from n-hexane-ether to give 8,9-dihydro-7-[(hydroxy)(2-methyl-1-trityl-1H-imidazol-4-yl)methyl]-10-methylpyrido[1,2-a]indol-6(7H)-one (2.06 g).

mp : 135-136 °C

IR (Nujol) : 1690, 1670, 1620 cm^{-1}

NMR ($CDCl_3$, δ) : 0.8-1.0 (1H, m), 1.61 (3H, s), 1.65 (3H, s), 1.8-2.2 (1H, m), 2.7-3.4 (3H, m), 4.9-5.1 (1H, m), 5.5-5.6 (1H, m), 6.66 (1/2H, s), 6.71 (1/2H, s), 7.0-7.5 (18H, m), 8.3-8.5 (1H, m)

Example 41

8,9-Dihydro-7-[(hydroxy)(2-methyl-1H-imidazol-4-yl)methyl]-10-methylpyrido[1,2-a]indol-6(7H)-one was prepared in a similar manner to that of Example 28.

mp : 210-211 °C

IR (Nujol) : 3200, 1660, 1630, 1575, 1530 cm^{-1}

NMR (DMSO-d_6, δ) : 1.7-2.1 (2H, m), 2.13 (3H, s), 2.45 (3H, s), 2.6-2.8 (1H, m), 3.0-3.2 (2H, m), 3.33 (1H, br s), 5.27 (1H, d, J=4.85Hz), 5.48 (1H, br s), 6.78 (1H, s), 7.2-7.3 (2H, m), 7.4-7.5 (1H, m), 8.3-8.4 (1H, m)

MS (m/e) : 309 (M^+)

Example 42 Acetic anhydride (1.31 g) was added to a solution of 8,9-dihydro-7-[(hydroxy)(2-methyl-1-trityl-1H-imidazol-4-yl)methyl]-10-methylpyrido[1,2-a]indol-6(7H)-one (1.42 g) in pyridine (20 ml). After being stirred at room temperature for 6 hours, the solution was evaporated in vacuo. The residue was diluted with chloroform, washed with 5% aqueous solution of sodium hydrogencarbonate and brine, and dried over anhydrous magnesium sulfate. After the solvent was evaporated in vacuo, the residue was subjected to column chromatography on silica gel (5% methanol-chloroform). The fractions containing the product were evaporated in vacuo and crystallized from n-hexane-ether to give 7-[(acetoxy)(2-methyl-1-trityl-1H-imidazol-4-yl)methyl]-8,9-dihydro-10-methylpyrido[1,2-a]indol-6(7H)-one (1.3 g).

mp : 183-188 (dec.)

IR (Nujol) : 1730, 1685, 1625 cm^{-1}

NMR (DMSO-d_6, δ) : 1.43 (3/2H, s), 1.52 (3/2H, s), 1.86 (3/2H, s), 2.02 (3/2H, s), 2.14 (3H, s), 1.9-2.3 (2H, m), 2.7-3.2 (2H, m), 3.31 (1H, s), 3.33 (1H, s), 6.4-6.6 (1H, m), 6.9-7.4 (18H, m), 8.1-8.4 (1H, m)

MS (m/e) : 593 (M^+)

Example 43

8,9-Dihydro-10-methyl-7-[(2-methyl-1-trityl-1H-imidazol-4-yl)methylene]pyrido[1,2-a]indol-6(7H)-one was prepared in a similar manner to that of Example 5.

mp : 232-233 °C (dec.)

IR (Nujol) : 1680, 1620, 1610 cm^{-1}

NMR (DMSO-d_6, δ) : 1.60 (3H, s), 2.18 (3H, s), 2.9-3.1 (2H, m), 3.4-3.6 (2H, m), 7.0-7.6 (20H, m), 8.3-8.4 (1H, m)

MS (m/e) : 533 (M^+)

Example 44

8,9-Dihydro-10-methyl-7-[(2-methyl-1H-imidazol-4-yl)methyl]pyrido[1,2-a]indol-6(7H)-one hydrochloride was prepared in a similar manner to that of Example 31.

mp : >250 °C

IR (Nujol) : 3260, 1680, 1630 cm^{-1}

NMR (DMSO-d_6, δ) : 1.7-1.9 (1H, m), 2.0-2.2 (1H, m), 2.14 (3H, s), 2.56 (3H, s), 2.7-3.5 (6H, m), 7.2-7.3 (2H, m), 7.31 (1H, s), 7.4-7.5 (1H, m), 8.3-8.4 (1H, m), 14.39 (1H, br s)

MS (m/e) : 293 (M^+)

Example 45

To a solution of 8,9-dihydro-7-[(1H-imidazol-4-yl)methyl]-10-methylpyrido[1,2-a]indol-6(7H)-one (1.4 g) in N,N-dimethylformamide (14 ml) at 5 °C was added sodium hydride (60% in mineral oil) (220 mg). After stirring for 1 hour at 5 °C, methyl iodide (852 mg) in dimethylformamide (5 ml) was added dropwise at 5 °C for 10 minutes. The mixture was stirred at 5 °C for 1 hour and at 20 °C for 2 hours. After evaporation of the solvent, the residue was diluted with 5% methanol-chloroform. The organic layer was washed twice with brine, dried over anhydrous magnesium sulfate, and evaporated in vacuo. The obtained residue contained two products which showed close Rf values (0.5 and 0.4 respectively) by TLC (20% methanol-chloroform).

Separation with silica gel column chromatography (5% methanol-chloroform) gave two fractions. The first eluted fraction, containing a mixture of two products, was concentrated. The crystalline residue was recrystallized from ethyl acetate to give 8,9-dihydro-10-methyl-7-[(1-methyl-1H-imidazol-4-yl)methyl]pyrido-[1,2-a]indol-6(7H)-one (0.4 g).

mp : 99-100 °C

IR (Nujol) : 1685, 1675, 1615 cm^{-1}

NMR ($CDCl_3$, δ) : 1.8-2.3 (2H, m), 2.15 (3H, s), 2.6-3.2 (4H, m), 3.33 (1H, dd, J=3.83, 13.71Hz), 3.62 (3H, s), 6.73 (1H, s), 7.2-7.5 (4H, m)

MS (m/e) : 293 (M^+)

The second elution was evaporated in vacuo to give 8,9-dihydro-10-methyl-7-[(1-methyl-1H-imidazol-5-yl)methyl]pyrido[1,2-a]indol-6(7H)-one (0.03 g).

mp : 117-118 °C

IR (Nujol) : 1688, 1668, 1620 cm^{-1}

NMR (DMSO-d_6, δ) : 1.7-2.2 (2H, m), 2.14 (3H, s), 2.7-2.9 (2H, m), 3.0-3.3 (3H, m), 3.33 (3H, s), 6.72 (1H, s), 7.2-7.3 (2H, m), 7.4-7.4 (1H, m), 7.52 (1H, s), 8.3-8.4 (1H, m)

MS (m/e) : 293 (M^+)

Example 46

8,9-Dihydro-7-[(1,5-dimethyl-1H-imidazol-4-yl)methyl]-10-methylpyrido[1,2-a]indol-6(7H)-one and 8,9-dihydro-7-[(1,4-dimethyl-1H-imidazol-5-yl)methyl-10-methylpyrido[1,2-a]indol-6(7H)-one were prepared in a similar manner to that of Example 45.

8,9-Dihydro-7[(1,5-dimethyl-1H-imidazol-4-yl)methyl]-10-methylpyrido[1,2-a]indol-6(7H)-one.

mp : 169-170 °C

IR (Nujol) : 1686, 1630, 1570 cm^{-1}

NMR ($CDCl_3$, δ) : 1.81-1.97 (1H, m), 2.15 (3H, s), 2.19 (3H, s), 2.1-2.3 (1H, m), 2.6-2.8 (2H, m), 3.0-3.2 (2H, m), 3.36 (1H, q, J=4.23, 14.5Hz), 3.51 (3H, s), 7.2-7.3 (2H, m), 7.33 (1H, s), 8.37-8.41 (1H, m), 8.4-8.5 (1H, m)

MS (m/e) : 307 (M^+)

8,9-Dihydro-7-[(1,4-dimethyl-1H-imidazol-5-yl)methyl]-10-methylpyrido[1,2-a]indol-6(7H)-one.

mp : 193-194 °C

IR (Nujol) : 1688, 1636, 1570

NMR ($CDCl_3$, δ) : 1.7-1.83 (1H, m), 2.0-2.15 (2H, m), 2.17 (6H, s), 2.6-2.8 (3H, m), 3.0-3.2 (1H, m), 3.4-3.6 (1H, m), 3.60 (3H, s), 7.26-7.32 (2H, m), 7.35 (1H, s), 7.38-7.43 (1H, m), 8.39-8.43 (1H, m)

MS (m/e) : 307 (M^+)

Example 47

To a solution of diisopropylamine (263 mg) in tetrahydrofuran (3 ml) at -70 °C under a nitrogen atmosphere was added 1.64 M butyllithium in hexane (1.75 ml). After being stirred at the same temperature for 20 minutes, the mixture was treated with a solution of 8,9-dihydro-10-methyl-7-[(5-methyl-1-trityl-1H-imidazol-4-yl)methyl]pyrido[1,2-a]indol-6(7H)-one (1.07 g) in tetrahydrofuran (5 ml) over 15 minutes. The mixture was stirred at -65 °C for 30 minutes and at -25 °C for 40 minutes and a solution of methyl iodide (282 mg) in tetrahydrofuran (3 ml) was added dropwise at -65 °C over 10 minutes. After the mixture was stirred at -65 °C for 30 minutes and at -20 °C for 1 hour, it was diluted with water and neutralized with an aqueous solution of oxalic acid. The resultant mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and evaporated in vacuo. Purification of the residue with silica gel column chromatography (5% ethyl acetate-chloroform) gave 8,9-dihydro-7,10-dimethyl-7-[(5-methyl-1-trityl-1H-imidazol-4-yl)methyl]pyrido[1,2-a]indol-6(7H)-one (0.73 g).

mp : 116-118 °C

IR (Nujol) : 1680, 1625, 1580 cm^{-1}

NMR ($CDCl_3$, δ) : 1.30 (3H, s), 1.36 (3H, s), 1.9-2.1 (1H, m), 2.17 (3H, s), 2.3-2.5 (1H, m), 2.93 (2H, ABq, J=14.3Hz), 2.8-3.3 (2H, m), 7-7.4 (19H, m), 8.4-8.5 (1H, m)

MS (m/e) : 549 (M^+)

Example 48

8,9-Dihydro-7,10-dimethyl-7-[(5-methyl-1H-imidazol-4-yl)methyl]pyrido[1,2-a]indol-6(7H)-one was prepared in a similar manner to that of Example 28.

mp : 163-164 °C

IR (Nujol) : 1680, 1625, 1585 cm^{-1}

NMR ($CDCl_3$, δ) : 1.39 (3H, s), 1.9-2.1 (2H, m), 2.14 (3H, s), 2.19 (3H, s), 2.71 (1H, d, J=14.7Hz), 2.8-3.3 (2H, m), 3.27 (1H, d, J=14.7Hz), 7.2-7.5 (4H, m), 8.4-8.5 (1H, m)

MS (m/e) : 307 (M^+)

Example 49

To a solution of diisopropylamine (1.44 ml) in tetrahydrofuran (5 ml) at -60 °C under a nitrogen atmosphere was added 1.64 M butyllithium in hexane (6.3 ml). After being stirred at the same temperature for 30 minutes, the mixture was treated with a solution of 2-chloro-8,9-dihydro-10-methylpyrido[1,2-a]indol-6(7H)-one (2.0 g) in tetrahydrofuran (25 ml) over 10 minutes. The mixture was stirred at -70 °C for 20 minutes, and a solution of 5-methyl-1-trityl-1H-imidazol-4-carbaldehyde (3.32 g) in tetrahydroruran (45 ml) was added dropwise over 30 minutes. After the mixture was stirred at -70 °C for further 2 hours, it was diluted with water (70 ml) and dichloromethane (70 ml). After neutralization with hydrochloric acid, the organic layer was separated, washed with water twice and brine, dried over sodium sulfate, and evaporated in vacuo. The obtained oil was tritulated with dichloromethane and diisopropyl ether (1:5, V/V) to give colorless powder, which contains two diastereoisomers of 2-chloro-8,9-dihydro-7-[(hydroxy)(5-methyl-1-trityl-1H-imidazol-4-yl)methyl]-10-methylpyrido[1,2-a]indol-6(7H)-one (2.24 g).

IR (Nujol) : 1705, 1615, 1590 cm^{-1}

Example 50

A solution of the mixture of two diastereoisomers of 2-chloro-8,9-dihydro-7-[(hydroxy)(5-methyl-1-trityl-1H-imidazol-4-yl)methyl]-10-methylpyrido[1,2-a]indol-6(7H)-one (0.50 g) in acetic acid-water (5:2, 7 ml) was stirred at 60 °C for 2 hours. After evaporation of the solvent, the residue was partitioned between water and chloroform and neutralized with an aqueous sodium hydroxide, to give precipitates. The organic layer and the precipitates were contained and chromatographed on silica gel eluted by chloroform-methanol (0-10% V/V), to give two isomers of 2-chloro-8,9-dihydro-10-methyl-7[(hydroxy(5-methyl-1H-imidazol-4-yl)methyl]-pyrido[1,2-a]indol-6(7H)-one (0.037 g), respectively.

isomer A : (upper Rf on TLC (silica gel, chloroform-methanol 9:1 V/V)

mp : 193-195 °C

IR (Nujol) : 1660, 1630 cm^{-1}

NMR (DMSO-d_6, δ) : 1.8-2.1 (2H, m), 2.10 (3H, s), 2.17 (3H, s), 2.6-3.2 (3H, m), 5.26 (2H, br s), 7.25 (1H, dd, J=2Hz, J=9Hz), 7.36 (1H, s), 7.52 (1H, d, J=2Hz), 8.24 (1H, d, J=9Hz), 11.70 (1H, br s)

MS (m/z) : 343 (M^+)

isomer B : (lower Rf on TLC)

mp : 185-188 °C

IR (Nujol) : 1680, 1620 cm^{-1}

NMR (DMSO-d_6, δ) : 1.9-2.1 (2H, m), 2.13 (3H, s), 2.19 (3H, s), 2.6-3.3 (3H, m), 5.28 (1H, br s), 5.54 (1H, s), 7.28 (1H, dd, J=2Hz, J=8.5Hz), 7.45 (1H, s), 7.55 (1H, d, J=2Hz), 8.32 (1H, d, J=8.5Hz), 11.80 (1H, br s)

MS (m/z) : 343 (M^+)

Example 51

To a solution of 2-chloro-8,9-dihydro-7-[(hydroxy)(5-methyl-1-trityl-1H-imidazol-4-yl)methyl]-10-methylpyrido[1,2-a]indol-6(7H)-one (1.64 g) in dichloromethane (32 ml) were added pyridine (0.83 ml) and acetic anhydride (0.53 ml). The solution was refluxed for 24 hours. After being cooled, the solution was washed with water twice and brine, dried over sodium sulfate, and evaporated, to give 7-[(acetoxy)(5-methyl-1-trityl-1H-imidazol-4-yl)methyl]-2-chloro-8,9-dihydro-10-methylpyrido[1,2-a]indol-6(7H)-one (1.49 g).

IR (Nujol) : 1725, 1690, 1615 cm^{-1}

Example 52

To a solution of 7-[(acetoxy)(5-methyl-1-trityl-1H-imidazol-4-yl)methyl]-2-chloro-8,9-dihydro-10-methylpyrido[1,2-a]indol-6(7H)-one (1.40 g) in toluene (15 ml) was added 1.8-diazabicyclo[5.4.0]undec-7-ene (0.37 ml), and the mixture was refluxed for 2 hours. After being cooled, the solution was washed with water and brine, dried over sodium sulfate, evaporated, and triturated in diisopropyl ether, to give 2-chloro-8,9-dihydro-10-methyl-7-[(5-methyl-1-trityl-1H-imidazol-4-yl)methylene]pyrido[1,2-a]indol-6(7H)-one (1.11 g).

mp : 224-227 °C

IR (Nujol) : 1685, 1620 cm^{-1}

NMR ($CDCl_3$, δ) : 1.67 (3H, s), 2.17 (3H, s), 2.98 (2H, t, J=6.5Hz), 3.66 (2H, t, J=6.5Hz), 7.1-7.5 (19H, m), 7.73 (1H, s), 8.42 (1H, d, J=9Hz)

Example 53

To a solution of 2-chloro-8,9-dihydro-10-methyl-7-[(5-methyl-1-trityl-1H-imidazol-4-yl)methylene]pyrido-[1,2-a]indol-6(7H)-one(0.95 g) in acetic acid (47.5 ml) was added zinc powder (1.09 g) and the mixture was refluxed for 2.5 hours. The resulting precipitates were filtered off, and the filtrate was evaporated in vacuo. The residue was diluted in chloroform, washed with aqueous sodium bicarbonate, solution, water, and brine, dried over sodium sulfate, and chromatographed on silica gel eluted by chloroform-methanol (0-5% V/V), to give 2-chloro-8,9-dihydro-10-methyl-7-[(5-methyl-1H-imidazol-4-yl)methyl]pyrido[1,2-a]indol-6(7H)-one (0.50 g).

mp : 244-246 °C

IR (Nujol) : 1683, 1620 cm^{-1}

NMR (DMSO-d_6, δ) : 1.7-2.1 (2H, m), 2.10 (3H, s), 2.12 (3H, s), 2.6-3.5 (5H, m), 7.28 (1H, dd, J=2Hz, J=9Hz), 7.41 (1H, s), 7.55 (1H, d, J=2Hz), 8.30 (1H, d, J=9Hz), 11.60 (1H, br s)

MS (m/z) : 327 (M^+)

Example 54

8,9-Dihydro-2,10-dimethyl-7-[(hydroxy)(5-methyl-1-trityl-1H-imidazol-4-yl)methyl]pyrido[1,2-a]indol-6-(7H)-one was prepared in a similar manner to that of Example 49.

IR (Nujol) : 1675, 1615 cm^{-1}

Example 55

8,9-Dihydro-2,10-dimethyl-7-[(5-methyl-1H-imidazol-4-yl)methyl]pyrido[1,2-a]indol-6(7H)-one was prepared in a similar manner to that of Example 56.

mp : 255-258 °C

IR (Nujol) : 1677, 1620 cm^{-1}

NMR ($CDCl_3$, MeOH-d_4, δ) : 1.6-2.3 (2H, m), 2.13 (3H, s), 2.17 (3H, s), 2.43 (3H, s), 2.5-3.1 (5H, m), 7.08 (1H, d, J=9Hz), 7.19 (1H, s), 7.39 (1H, s), 8.28 (1H, d, J=9Hz)

M/S (m/z) : 307 (M^+)

Example 56

To a solution of 8,9-dihydro-7-[(hydroxy)(5-methyl-1-trityl-1H-imidazol-4-yl)methyl]-10-methylpyrido[1,2-a]indol-6(7H)-one (4.6 g) in acetic acid (92 ml) were added 10% palladium on carbon (2.3 g) and ammonium formate (7.89 g), and the mixture was refluxed gently for 3 hours. After being cooled, the catalyst was filtered off. The filtrate was evaporated, and diluted with water (50 ml) and diisopropyl ether (50 ml). Aqueous sodium hydroxide was added to neutralized the solution. Resulted precipitates were collected, and washed with water and diisopropyl ether successively, to give 8,9-dihydro-10-methyl-7-[(5-methyl-1H-imidazol-4-yl)methyl]pyrido[1,2-a]indol-6(7H)-one (1.87 g).

mp : 225-227 °C

IR (Nujol) : 1615, 1690 cm^{-1}

NMR (DMSO-d_6, δ) : 1.5-2.2 (2H, m), 2.12 (6H, s), 2.5-3.3 (5H, m), 7.2-7.3 (2H, m), 7.39 (1H, s), 7.45 (1H, m), 8.34 (1H, m)

MS (m/z) : 293 (M^+)

Example 57

7-[(Acetoxy)(5-methyl-1-trityl-1H-imidazol-4-yl)methyl]-8,9-dihydro-10-methylpyrido[1,2-a]indol-6(7H)-one was converted into 8,9-dihydro-10-methyl-7-[(5-methyl-1H-imidazol-4-yl)methyl]pyrido[1,2-a]indol-6(7H)-one in a similar manner to that of Example 56.

IR (Nujol) : 1615, 1690 cm^{-1}

Example 58

8,9-Dihydro-10-methyl-7-[(5-methyl-1-trityl-1H-imidazol-4-yl)methylene]pyrido[1,2-a]indol-6(7H)-one was converted into 8,9-dihydro-10-methyl-7-[(5-methyl-1H-imidazol-4-yl)methyl]pyrido[1,2-a]indol-6(7H)-one in a similar manner to that of Example 67.

IR (Nujol) : 1615, 1690 cm^{-1}

Example 59

(+)-Di-p-toluoyl-D-tartaric acid (45.50 g) and 8,9-dihydro-10-methyl-7-[(5-methyl-1H-imidazol-4-yl)-methyl]pyrido[1,2-a]indol-6(7H)-one (34.55 g) were dissolved in a mixture of chloroform-methanol (3:7, 2.35 *l*) at 70 • C. The solution was allowed to stand at 5 • C for 7 days to give crystals (31.0 g). The crystals (30.8 g) were dissolved in N,N-dimethylformamide (69 ml) at 80 • C. The resulting solution was diluted successively with chloroform (69 ml) and methanol (323 ml) and then allowed to stand at 5 • C for 5 days to give the (+)-di-p-toluoyl-D-tartaric acid salt (17.75 g).

mp : 178-180 • C

The crystals were dissolved in N,N-dimethylformamide (53 ml) at 80 • C. The solution was diluted with 10% methanol-chloroform (180 ml) and water (270 ml). The mixture was treated with 2N aqueous sodium hydroxide solution (14 ml) to neutralize the salt. The organic layer was washed with water three times, dried over anhydrous magnesium sulfate, and evaporated in vacuo to give crystalline (+)-8,9-dihydro-10-methyl-7-[(5-methyl-1H-imidazol-4-yl)methyl]pyrido[1,2-a]indol-6(7H)-one (7.1 g) with $[\alpha]_D^{25}$ = +63 (C=1.0, 10% methanol-chloroform).

The crystals were dissolved in hot methanol (160 ml) containing 12N hydrochloric acid (4.5 ml). After evaporation of the solvent to 70 ml, the solution was diluted with ether and allowed to stand at 5 • C for 2 days. The crystals were collected and dried to give (+)-8.9-dihydro-10-methyl-7-[(5-methyl-1H-imidazol-4-yl)methyl]pyrido[1,2-a]indol-6(7H)-one hydrochloride (7.3 g).

mp : >250 • C

IR (Nujol) : 1700, 1635, 1520, 1310 cm^{-1}

NMR (DMSO-d_6, δ) : 1.75-2.20 (2H, m), 2.14 (3H, s), 2.26 (3H, s), 2.73-3.40 (5H, m), 7.26 (2H, m), 7.49 (1H, m), 8.32 (1H, m), 8.98 (1H, s), 14.55 (2H, br s)

$[\alpha]_D^{20}$ = + 14.1 (C=2, methanol)

Example 60

10-Allyl-8,9-dihydro-7-[(hydroxy)(5-methyl-1-trityl-1H-imidazol-4-yl)methyl]pyrido[1,2-a]indol-6(7H)-one was prepared in a similar manner to that of Example 64 as an amorphous powder.

IR (Nujol) : 1685, 1615, 1225 cm^{-1}

Example 61

7-[(Acetoxy)(5-methyl-1-trityl-1H-imidazol-4-yl)methyl]-10-allyl-8,9-dihydropyrido[1,2-a]indol-6(7H)-one was prepared in a similar manner to that of Example 65 as an amorphous powder.

IR (Nujol) : 1730, 1685, 1610 cm^{-1}

Example 62

10-Allyl-8,9-dihydro-7-[(5-methyl-1-trityl-1H-imidazol-4-yl)methylene]pyrido[1,2-a]indol-6(7H)-one was prepared in a similar manner to that of Example 66.

mp : 211-214 • C

IR (Nujol) : 1685, 1620, 1350, 1140 cm^{-1}

NMR (DMSO-d_6, δ) : 1.61 (3H, s), 3.00 (2H, m), 3.43 (2H, d, J=7Hz), 3.57 (2H, m), 5.00-5.15 (2H, m),

5.95 (1H, m), 7.10-7.59 (20H, m), 8.37 (1H, m)

Example 63

A mixture of 10-allyl-8,9-dihydro-7-[(5-methyl-1-trityl-1H-imidazol-4-yl)methylene]pyrido[1,2-a]indol-6-(7H)-one and zinc powder (2.0 g) in acetic acid (30 ml) was stirred vigorously at 100 °C for 2 hours. Zinc powder (1.5 g) was added and the mixture was heated for further 1 hour. After being cooled to room temperature, the insoluble material was filtered and washed with acetic acid. After evaporation of the solvent, the residue was diluted with water and washed twice with toluene. The toluene layer was extracted with 0.5N hydrochloric acid. The combined aqueous layers were neutralized with aqueous sodium bicarbonate solution and extracted three times with chloroform. The chloroform layer was washed with water twice and brine, dried over anhydrous magnesium sulfate, and evaporated in vacuo. Chromatography (silica gel, 5% methanol-chloroform) of the residue, followed by recrystallization from methanol-chloroform-hexane, gave 10-allyl-8,9-dihydro-7-[(5-methyl-1H-imidazol-4-yl)methyl]pyrido[1,2-a]indol-6(7H)-one (0.63 g).

mp : 215-217 °C

IR (Nujol) : 1690, 1635, 1615, 1295 cm^{-1}

NMR (DMSO-d_6, δ) : 1.80 (1H, m), 2.00 (1H, m), 2.10 (3H, s), 2.60-2.80 (2H, m), 2.95-3.15 (3H, m), 3.38 (2H, d, J = 6Hz), 4.99-5.12 (2H, m), 5.90 (1H, m), 7.24 (2H, m), 7.40 (1H, s), 7.50 (1H, m), 8.35 (1H, m), 11.60 (1H, br s)

Example 64

To a solution of diisopropylamine (1.85 g) in tetrahydrofuran (15 ml) at -70 °C under a nitrogen atmosphere was added 1.49 M butyllithium in hexane (11.5 ml). After being stirred at the same temperature for 35 minutes, the mixture was treated with a solution of 10-ethyl-8,9-dihydropyrido[1,2-a]indol-6(7H)-one (3.2 g) in tetrahydrofuran (20 ml) over 5 minutes. The mixture was stirred at -70 °C for 40 minutes, and a solution of 5-methyl-1-trityl-1H-imidazol-4-carbaldehyde (5.81 g) in tetrahydrofuran (65 ml) was added dropwise over 30 minutes. After the mixture was stirred at -70 °C for 2 hours and then at room temperature for 1 hour, it was diluted with chilled water, neutralized with aqueous oxalic acid solution, and extracted with methylene chloride three times. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, and evaporated in vacuo. The oil obtained was purified by silica gel column chromatography (1% methanol-chloroform) to give 10-ethyl-8,9-dihydro-7-[(hydroxy)(5-methyl-1-trityl-1H-imidazol-4-yl)-methyl]pyrido[1,2-a]indol-6(7H)-one (6.8 g) as an amorphous powder. The product was a mixture of two diastereoisomers.

IR (Nujol) : 1685, 1615, 1225 cm^{-1}

Example 65

Acetic anhydride (2.0 ml) was added to a solution of 10-ethyl-8,9-dihydro-7-[(hydroxy)(5-methyl-1-trityl-1H-imidazol-4-yl)methyl]pyrido[1,2-a]indol-6(7H)-one (2.15 g) in pyridine (10 ml). After being stirred at room temperature for 20 hours, the solution was evaporated in vacuo. The residue was dissolved in toluene (30 ml) and the solution was evaporated in vacuo to remove pyridine and acetic anhydride. This operation was repeated further three times to give 7-[(acetoxy)(5-methyl-1-trityl-1H-imidazol-4-yl)methyl]-10-ethyl-8,9-dihydropyrido[1,2-a]indol-6(7H)-one as an amorphous powder. This crude product was used in the next reaction without further purification.

IR (Nujol) : 1730, 1690, 1615, 1230 cm^{-1}

Example 66

To a solution of 7-[(acetoxy)(5-methyl-1-trityl-1H-imidazol-4-yl)methyl]-10-ethyl-8,9-dihydropyrido[1,2-a]-indol-6(7H)-one (2.06 g) in toluene (30 ml) at room temperature was added 1,8-diazabicyclo[5.4.0]undec-7-ene (1.2 ml). After being stirred at 75 °C for 3 hours, the solution was diluted with chilled water. The organic layer separated was washed with aqueous oxalic acid solution, water, and brine, dried over anhydrous sodium sulfate, and evaporated in vacuo. The residue was triturated with methanol and filtered to give 10-ethyl-8,9-dihydro-7-[(5-methyl-1-trityl-1H-imidazol-4-yl)methylene]pyrido[1,2-a]indol-6(7H)-one (1.41 g).

mp : 217-220 °C

IR (Nujol) : 1680, 1620, 1340 cm^{-1}

NMR (DMSO-d_6, δ) : 1.18 (3H, t, J = 7.5Hz), 1.61 (3H, s), 2.67 (2H, m), 2.98 (2H, m), 3.58 (2H, m), 7.10-

7.60 (20H, m), 8.37 (1H, m)

Example 67

A mixture of 10-ethyl-8,9-dihydro-7-[(5-methyl-1-trityl-1H-imidazol-4-yl)methylene]pyrido[1,2-a]indol-6-(7H)-one (1.0 g), 10% palladium on carbon (0.25 g), and ammonium formate (0.5 g) in acetic acid (14 ml) was stirred at 90°C for 1 hour and 45 minutes and cooled to room temperature. After filtration of the catalyst, the filtrate was evaporated in vacuo and the residue was suspended in 0.5N hydrochloric acid. The aqueous layer was washed twice with toluene, made basic with aqueous sodium bicarbonate solution, and extracted three times with chloroform. The chloroform layer was washed with water twice and brine, dried over anhydrous magnesium sulfate, and evaporated to give crystals. Recrystallization from chloroform-methanol gave 10-ethyl-8,9-dihydro-7-[(5-methyl-1H-imidazol-4-yl)methyl]pyrido[1,2-a]indol-6(7H)-one (0.319 g).

mp : 222-224°C

IR (Nujol) : 1690, 1618, 1300, 1185 cm^{-1}

NMR (DMSO-d_6, δ) : 1.15 (3H, t, J=7.5Hz), 1.75 (1H, m), 1.97 (1H, m), 2.10 (3H, s), 2.50-2.84 (4H, m), 2.95-3.19 (3H, m), 7.25 (2H, m), 7.41 (1H, s), 7.51 (1H, m), 8.35 (1H, m), 11.62 (1H, br s)

Example 68

To a solution of diisopropylamine (395 mg) in tetrahydrofuran (5 ml) at -70°C under a nitrogen atmosphere was added 1.64 M butyllithium in hexane (2.62 ml). After being stirred at the same temperature for 20 minutes, the mixture was treated with a solution of 8,9-dihydro-10-methyl-7-[(5-methyl-1-trityl-1H-imidazol-4-yl)methyl]pyrido[1,2-a]indol-6(7H)-one (1.61 g) in tetrahydrofuran (5 ml) over 15 minutes. The mixture was stirred at -65°C for 30 minutes and at -30 ~ -40°C for 30 minutes and a solution of allyl bromide (363 mg) in tetrahydrofuran (5 ml) was added dropwise at -65°C over 10 minutes. After the mixture was stirred at -65°C for 1 hour, at -20°C for 1 hour and at ambient temperature for 1 hour. The resultant mixture was washed with water (10 ml x 2) and brine, dried over anhydrous magnesium sulfate and evaporated in vacuo. Purification of the residue with silica gel column chromatography (5% ethyl acetate-chloroform) gave 7-allyl-8,9-dihydro-10-methyl-7-[(5-methyl-1-trityl-1H-imidazol-4-yl)methyl] pyrido-[1,2-a]indol-6(7H)-one (1.15 g).

mp : 83-85°C

IR (Nujol) : 1670, 1610 cm^{-1}

NMR ($CDCl_3$, δ) : 1.32 (3H, s), 2.22 (3H, s), 2.0-2.4 (4H, m), 2.7-3.2 (4H, m), 5.0-5.2 (2H, m), 5.7-6.0 (1H, m), 7.0-7.5 (19H, m), 8.3-8.5 (1H, m)

Example 69

7-Allyl-8,9-dihydro-10-methyl-7-[(5-methyl-1H-imidazol-4-yl)methyl]pyrido[1,2-a]indol-6(7H)-one was prepared in a similar manner to that of Example 71.

mp : 209-210°C

IR (Nujol) : 1680, 1640, 1590 cm^{-1}

NMR (DMSO-d_6, δ) : 1.8-2.4 (4H, m), 2.03 (3H, s), 2.13 (3H, s), 2.6-3.1 (4H, m), 5.0-5.2 (2H, m), 4.7-6.0 (1H, m), 7.2-7.5 (3H, m), 7.38 (1H, s), 8.2-8.4 (1H, m), 11.6 (1H, br s)

MS (m/e) : 333 (M^+)

Example 70

7-Ethyl-8,9-dihydro-10-methyl-7-[(5-methyl-1-trityl-1H-imidazol-4-yl)methyl]pyrido[1,2-a]indol-6(7H)-one was prepared in a similar manner to that of Example 68.

mp : 83-98°C

IR (Nujol) : 1680, 1630 cm^{-1}

NMR ($CDCl_3$, δ) : 0.96 (3H, t, J=7.38Hz), 1.33 (3H, s), 1.4-1.7 (1H, m), 1.9-2.4 (4H, m), 2.2 (3H, s), 2.83, 3.04 (2H, ABq, J=14.3Hz), 2.8-3.1 (1H, m), 7.0-7.5 (19H, m), 8.4-8.5 (1H, m)

Example 71

A solution of 7-ethyl-8,9-dihydro-10-methyl-7-[(5-methyl-1-trityl-1H-imidazol-4-yl)methyl]pyrido[1,2-a] indol-6(7H)-one (0.45 g) in acetic acid (10 ml) and water (2.5 ml) was stirred at 60°C for 2 hours. After evaporation of the solvent, the residue was diluted with ether (10 ml) and an aqueous solution of sodium hydrogencarbonate (10 ml). The resultant mixture was stirred for 30 minutes at ambient temperature. The insoluble material was collected, washed with water and ether, and dried to give crystalline 7-ethyl-8,9-dihydro-10-methyl-7-[(5-methyl-1H-imidazol-4-yl)methyl]pyrido[1,2-a]indol-6(7H)-one (0.20 g).

mp : 202-204°C

IR (Nujol) : 1685, 1625, 1600 cm^{-1}

NMR (DMSO-d_6, δ) : 0.87 (3H, t, J=7.8Hz), 1.4-1.6 (1H, m), 1.7-2.2 (3H, m), 2.07 (3H, s), 2.13 (3H, s), 2.71, 2.90 (2H, ABq, J=14.3Hz), 2.9-3.2 (2H, m), 7.2-7.5 (3H, m), 7.36 (1H, s), 8.3-8.4 (1H, m), 11.61 (1H, s)

Example 72

8,9-Dihydro-7-hydroxymethyl-10-methyl-7-[(5-methyl-1-trityl-1H-imidazol-4-yl)methyl]pyrido[1,2-a]indol-6(7H)-one was prepared in a similar manner to that of Example 68 except for using paraformaldehyde in place of allyl bromide.

mp : 85-88°C

IR (Nujol) : 1680, 1620 cm^{-1}

NMR ($CDCl_3$, δ) : 1.26 (3H, s), 2.0-2.1 (2H, m), 2.16 (3H, s), 2.85-3.19 (2H, ABq, J=14.8Hz), 3.00 (2H, t, J=6.3Hz), 3.71, 4.07 (2H, ABq, J=11.8Hz), 7.1-7.5 (19H, m), 8.3-8.4 (1H, m)

Example 73

A solution of 8,9-dihydro-7-hydroxymethyl-10-methyl-7-[(5-methyl-1-trityl-1H-imidazol-4-yl)methyl] pyrido[1,2-a]indol-6(7H)-one (0.6 g) in acetic acid (15 ml) and water (3 ml) was stirred at 60°C for an hour. After evaporation of the solvent, the residue was diluted with chloroform, washed with an aqueous solution of sodium hydrogencarbonate and brine, dried over anhydrous magnesium sulfate, and evaporated in vacuo. The residue was dissolved with ethyl acetate and treated with hydrogen chloride in ether to give 8,9-dihydro-7-hydroxymethyl-10-methyl-7-[(5-methyl-1H-imidazol-4-yl)methyl]pyrido[1,2-a]indol-6(7H)-one hydrochloride (0.18 g).

mp : 230-260°C (dec.)

IR (Nujol : 3350, 1680, 1620 cm^{-1}

NMR (DMSO-d_6, δ) : 1.8-2.3 (2H, m), 2.14 (6H, m), 2.9-3.5 (6H, m), 3.56, 3.77 (2H, ABq, J=10.7Hz), 7.2-7.5 (3H, m), 8.2-8.3 (1H, m), 8.91 (1H, s), 14.2 (1H, br s)

Example 74

A mixture of 8,9-dihydro-10-methyl-7-(dimethylaminomethyl)pyrido[1,2-a]indol-6(7H)-one (0.65 g), 2-methylimidazole (0.76 g), 2N hydrochloric acid (1.27 ml), and isopropyl alcohol (4 ml) was heated at 100°C for 3 hours and 15 minutes. After evaporation of the solvent, the residue obtained was dissolved in methylene chloride. The methylene chloride solution was washed with water and brine, dried over anhydrous magnesium sulfate, and evaporated in vacuo. Purification with neutral alumina column chromatography (0.5% methanol-methylene chloride), followed by recrystallization with ethyl acetate-hexane, gave 8,9-dihydro-10-methyl-7-[(2-methyl-1H-imidazol-1-yl)methyl]pyrido[1,2-a]indol-6(7H)-one (0.40 g).

mp : 120-121°C

IR (Nujol) : 1665, 1615, 1520, 1280 cm^{-1}

NMR (DMSO-d_6, δ) : 1.60-1.90 (2H, m), 2.10 (3H, s), 2.30 (3H, s), 2.66-3.40 (3H, m), 4.13 (1H, dd, J=8, 15Hz), 4.50 (1H, dd, J=5, 15Hz), 6.73 (1H, s), 7.03 (1H, s), 7.10-7.50 (3H, m), 8.30 (1H, m)

Example 75

A mixture of 8,9-dihydro-10-methyl-7-methylenepyrido[1,2-a]indol-6(7H)-one (142 mg), 2-methylimidazole (180 mg), isopropyl alcohol (1 ml) and water (0.4 ml) was heated at 100°C for 3 hours. The reaction mixture was purified by a procedure analogous to that of Example 74 to give 8,9-dihydro-10-

methyl-7-[(2-methyl-1H-imidazol-1-yl)methyl]pyrido[1,2-a]indol-6(7H)-one (60 mg).
mp : 120-121 °C

Example 76

8,9-Dihydro-7-[(hydroxy)[5-methyl-1-(N,N-dimethylsulfamoyl)-1H-imidazol-4-yl]methyl]-10-methylpyrido-[1,2-a]indol-6(7H)-one was prepared in a similar manner to that of Example 64 as an amorphous powder.
IR (Nujol) : 1685, 1620, 1170 cm^{-1}

Example 77

7-[(Acetoxy)[5-methyl-1-(N,N-dimethylsulfamoyl)-1H-imidazol-4-yl]methyl]-8,9-dihydro-10-methylpyrido-[1,2-a]indol-6(7H)-one was prepared in a similar manner to that of Example 65 as an amorphous powder.
IR ($CHCl_3$) : 1730, 1695, 1630, 1170 cm^{-1}

Example 78

8,9-Dihydro-10-methyl-7-[[5-methyl-1-(N,N-dimethylsulfamoyl)-1H-imidazol-4-yl]methylene]pyrido[1,2-a]-indol-6(7H)-one was prepared in a similar manner to that of Example 66.
mp : 200-205 °C
IR (Nujol) : 1680, 1625, 1350, 1160 cm^{-1}
NMR (DMSO-d_6, δ) : 2.19 (3H, s), 2.52 (3H, s), 2.93 (6H, s), 2.98 (2H, t, J=7Hz), 3.51 (2H, t, J=7Hz), 7.29 (2H, m), 7.51 (1H, m), 7.61 (1H, s), 8.27 (1H, s), 8.39 (1H, m)

Example 79

A mixture of 8,9-dihydro-10-methyl-7-[[5-methyl-1-(N,N-dimethylsulfamoyl)-1H-imidazol-4-yl]methylene]-pyrido[1,2-a]indol-6(7H)-one (0.83 g), ammonium formate (0.75 g), and 10% palladium on carbon (0.1 g) in acetic acid (10 ml) was stirred at 90 °C for 3 hours and cooled to room temperature. After filtration of the catalyst, the filtrate was evaporated in vacuo. The residue was made basic with aqueous sodium bicarbonate solution and extracted with methylene chloride three times. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, and evaporated in vacuo. Chromatography of the obtained oil (silica gel, 0.5% methanol-chloroform) gave three fractions. The first eluted fractions contained the starting material (166 mg). The second eluted fractions contained 8,9-dihydro-10-methyl-7-[[5-methyl-1-(N,N-dimethylsulfamoyl)-1H-imidazol-4-yl]methyl]pyrido[1,2-a]indol-6(7H)-one (130 mg) as an oil.
IR ($CHCl_3$) : 1685, 1625, 1165, 970 cm^{-1}
NMR ($CDCl_3$, δ) : 1.85 (1H, m), 2.16 (3H, s), 2.16 (1H, m), 2.36 (3H, s), 2.70-2.90 (2H, m), 2.88 (6H, s), 3.02-3.13 (2H, m), 3.35 (1H, dd, J=4.5, 15Hz), 7.28 (2H, m), 7.41 (1H, m), 7.85 (1H, s), 8.44 (1H, m)
The third eluted fractions gave 8,9-dihydro-10-methyl-7-[(5-methyl-1H-imidazol-4-yl)methyl]pyrido [1,2-a]indol-6(7H)-one (90 mg) which was recrystallized from methanol to give crystals (40 mg).
mp : 224-226 °C
IR (Nujol) : 1690, 1620, 1325, 1300 cm^{-1}

Example 80

A mixture of 8,9-dihydro-10-methyl-7-[[5-methyl-1-(N,N-dimethylsulfamoyl)-1H-imidazol-4-yl]methyl]-pyrido[1,2-a]indol-6(7H)-one(93 mg), 3N hydrochloric acid (3 ml), and ethanol (2 ml) was heated at 90 °C for 2.5 hours. After evaporation of the solvent, the residue was neutralized with aqueous sodium bicarbonate solution and extracted three times with chloroform. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, and evaporated in vacuo. Chromatography of the residue (solvent, 4% methanol-chloroform) gave 8,9-dihydro-10-methyl-7-[(5-methyl-1H-imidazol-4-yl)methyl]pyrido[1,2-a]-indol-6(7H)-one (42 mg).
mp : 224-226 °C
IR (Nujol) : 1690, 1620, 1325, 1300 cm^{-1}

Preparation 5

To a suspension of 5-methyl-1H-imidazole-4-carbaldehyde (20 g) in N,N-dimethylformamide (100 ml) was added triethylamine (20.5 g) and p-toluenesulfonyl chloride (38 g). The mixture was stirred under ice-cooling for two hours. The reaction mixture was diluted with water (600 ml) and separated organic layer was filtered. The residue obtained was suspended in methanol (100 ml). After being stirred at ambient temperature for two hours, the mixture was cooled and filtered to give 5-methyl-1-tosyl-1H-imidazole-4-carbaldehyde (40.3 g).

NMR ($CDCl_3$, δ) : 2.47 (3H, s), 2.61 (3H, s), 7.42 (2H, d, J=8Hz), 7.87 (2H, d, J=8Hz), 8.14 (1H, s), 9.94 (1H, s)

MS (m/e) : 264 (M^+)

Example 81

8,9-Dihydro-7-[(hydroxy)(5-methyl-1-tosyl-1H-imidazol-4-yl)methyl]-10-methylpyrido[1,2-a]indol-6(7H)-one was prepared in a similar manner to that of Example 64.

NMR (DMSO-d_6, δ) : 2.11 (3H, s), 2.29 (3H, s), 1.90-2.10 (2H, m), 2.39 (3H, s), 2.70 (1H, m), 3.05 (1H, m), 3.20 (1H, m), 5.22 (1H, t, J=5Hz), 5.35 (1H, d, J=5Hz), 7.2 (2H, m), 7.4 (1H, m), 7.45 (2H, d, J=8Hz), 7.85 (2H, d, J=8Hz), 8,17 (1H, s), 8.2 (1H, m)

MS (m/e) : 463 (M^+)

Example 82

7-[(Acetoxy)(5-methyl-1-tosyl-1H-imidazol-4-yl)methyl]-8.9-dihydro-10-methylpyrido[1,2-a]indol-6(7H)-one was prepared in a similar manner to that of Example 65.

NMR (DMSO-d_6, δ) : 2.00 (3H, s), 1.90-2.10 (2H, m), 2.11 (3H, s), 2.28 (3H, s), 2.39 (3H, s), 2.80 (1H, m), 3.00 (1H, m), 3.50 (1H, m), 6.29 (1H, d, J=7Hz), 7.20-7.30 (2H, m), 7.40 (1H, m), 7.40 (2H, d, J=8Hz), 7.87 (2H, d, J=8Hz), 8.10 (1H, m), 8.27 (1H, s)

MS (m/e) : 445 (M^+-$OCOCH_3$)

Example 83

8,9-Dihydro-10-methyl-7-[(5-methyl-1-tosyl-1H-imidazol-4-yl)methylene]pyrido[1,2-a]indol-6(7H)-one was prepared in a similar manner to that of Example 66.

NMR (DMSO-d_6, δ) : 2.17 (3H, s), 2.50 (3H, s), 2.51 (3H, s), 2.95 (2H, t, J=7Hz), 3.45 (2H, t, J=7Hz), 7.20-7.30 (2H, m), 7.52 (2H, d, J=8Hz), 7.49 (1H, s), 8.00 (2H, d, J=8Hz), 8.30 (1H, m), 8.54 (1H, s)

MS (m/e) : 445 (M^+)

Example 84

To a solution of 8,9-dihydro-10-methyl-7-[(5-methyl-1-tosyl-1H-imidazol-4-yl)methylene]pyrido[1,2-a]-indol-6(7H)-one (1.0 g) in the mixture of tetrahydrofuran (10 ml) and methanol (10 ml) was added 2N-sodium hydroxide. The mixture was heated at 80°C for 5 hours. After being cooled, the reaction mixture was neutralized with acetic acid, and added water (40 ml). The precipitates were filtered to give 8,9-dihydro-10-methyl-7-[(5-methyl-1H-imidazol-4-yl)methylene]pyrido[1,2-a]indol-6(7H)-one (0.5 g).

NMR (DMSO-d_6, δ) : 2.18 (3H, s), 2.36 (3H, s), 2.95 (2H, t, J=6.0Hz), 3.58 (2H, t, J=6.0Hz), 7.64 (1H, s), 7.74 (1H, s), 7.20-7.30 (2H, m), 7.50-7.60 (1H, m), 8.30-8.40 (1H, m), 12.34 (1H, s)

MS (m/e) : 291 (M^+)

Example 85

8,9-Dihydro-10-methyl-7-[(5-methyl-1H-imidazol-4-yl)methyl]pyrido[1,2-a]indol-6(7H)-one was prepared in a similar manner to that of Example 39.

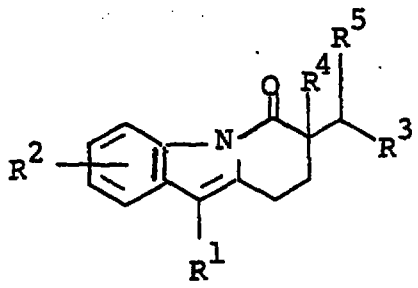
NMR (DMSO-d_6, δ) : 1.60-2.10 (2H, m), 2.13 (3H, s), 2.18 (3H, s), 2.70-3.30 (5H, m), 7.20-7.30 (3H, m), 7.44-7.51 (1H, m), 8.21 (1H, s), 8.28-8.34 (1H, m)

* C L M S *

Claims

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

1. A compound of the formula :



wherein

R^1 is hydrogen,(C_1-C_6)alkyl or(C_2-C_6)alkenyl

R^2 is hydrogen,(C_1-C_6)alkyl or halogen,

R^3 is imidazolyl or pyridyl, each of which may have suitable substituent(s), selected from (C_1-C_6)alkyl and imino-protective group,

and R^4 is hydrogen,(C_1-C_6)alkyl, (C_2-C_6) alkenyl or hydroxy(C_1-C_6)alkyl and R^5 is hydrogen, hydroxy or acyloxy, or

R^4 and R^5 are linked together to form an additional bond,

and pharmaceutically acceptable salts thereof.

2. A compound of claim 1, wherein

R^3 is imidazolyl which may have one to three substituent(s) selected from(C_1-C_6)alkyl and imino-protective group.

3. A compound of claim 2, wherein

R^3 is 2-(C_1-C_6)alkyl-1H-imidazol-1-yl, 1H-imidazol-2-yl, 1-ar(C_1-C_6)alkyl-1H-imidazol-2-yl, 1-ar(C_1-C_6)alkyl-5-(C_1-C_6)alkyl-1H-imidazol-4-yl, 5-(C_1-C_6)alkyl-1H-imidazol-4-yl, 1-ar(C_1-C_6)alkyl-1H-imidazol-4-yl, 1H-imidazol-4-yl, 2-(C_1-C_6)alkyl-5-(C_1-C_6)alkyl-1H-imidazol-4-yl, 1-ar(C_1-C_6)alkyl-2-(C_1-C_6) alkyl-1H-imidazol-4-yl, 2-(C_1-C_6)alkyl-1H-imidazol-4-yl, 1-(C_1-C_6)alkyl-1H-imidazol-4-yl, 1-(C_1-C_6)alkyl-5-(C_1-C_6)-alkyl-1H-imidazol-4-yl, 1-di(C_1-C_6)alkylaminosulfonyl-5-(C_1-C_6)alkyl-1H-imidazol-4-yl, 1-(C_1-C_6)alkyl-1H-imidazol-5-yl or 1-(C_1-C_6)alkyl-4-(C_1-C_6)alkyl-1H-imidazol-5-yl.

4. A compound of claim 3, wherein

R^1 is (C_1-C_6)alkyl,

R^2 is hydrogen,

R^3 is 1-mono or di or triphenyl(C_1-C_6)alkyl-5-(C_1-C_6) alkyl-1H-imidazol-4-yl, 5-(C_1-C_6)-alkyl-1H-imidazol-4-yl or 1-di(C_1-C_6)alkylaminosulfonyl-5-(C_1-C_6)alkyl-1H-imidazol-4-yl, and

R^4 is hydrogen and R^5 is hydrogen, hydroxy or (C_1-C_6) alkanoyloxy, or

R^4 and R^5 are linked together to form an additional bond.

5. A compound of claim 4, wherein

R^3 is 5-(C_1-C_6)alkyl-1H-imidazol-4-yl, and

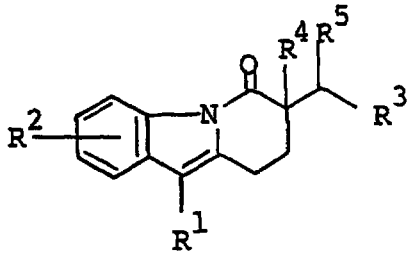
R^4 and R^5 are each hydrogen.

6. A compound of claim 5, which is 8,9-dihydro-10-methyl-7-[(5-methyl-1H-imidazol-4-yl)methyl]pyrido[1,2-a]indol-6(7H)-one or its acid addition salt.

7. A compound of claim 6, which is (+)8,9-dihydro-10-methyl-7-[(5-methyl-1H-imidazol-4-yl)methyl]pyrido[1,2-a]indol-6(7H)-one or its hydrochloride or its maleate.

* C L M S *

8. A process for preparing a compound of the formula :



wherein

R^1 is hydrogen, $(C_1\text{-}C_6)$alkyl or$(C_2\text{-}C_6)$ alkenyl,

R^2 is hydrogen, $(C_1\text{-}C_6)$alkyl or halogen,

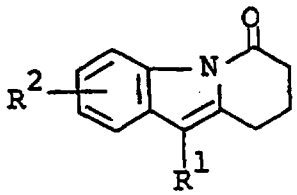
R^3 is imidazolyl or pyridyl, each of which may have suitable substituent(s), selected from $(C_1\text{-}C_6)$alkyl and imino-protective group

and R^4 is hydrogen, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl or hydroxy$(C_1\text{-}C_6)$alkyl and R^5 is hydrogen, hydroxy or acyloxy, or

R^4 and R^5 are linked together to form an additional bond,

or a salt thereof which comprises

(1) reacting a compound of the formula :



wherein

R^1 and R^2 are each as defined above,

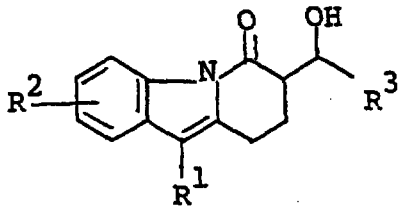
with a compound of the formula :

OHC - R^3

wherein

R^3 is as defined above,

or a salt thereof, to give a compound of the formula :

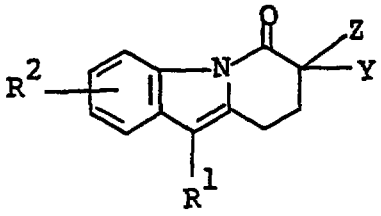


wherein

R^1, R^2 and R^3 are each as defined above,

or a salt thereof, or

(2) reacting a compound of the formula :



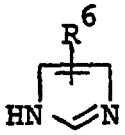
wherein

R^1 and R^2 are each as defined above, and

Y is N,N-di(C_1-C_6)alkylaminomethyl and

Z is hydrogen, or Y and Z are combined to form methylene,

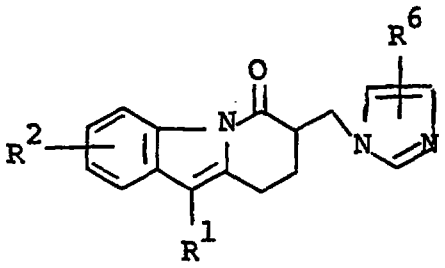
with a compound of the formula :



wherein

R^6 is hydrogen or (C_1-C_6)alkyl,

or a salt thereof, to give a compound of the formula :

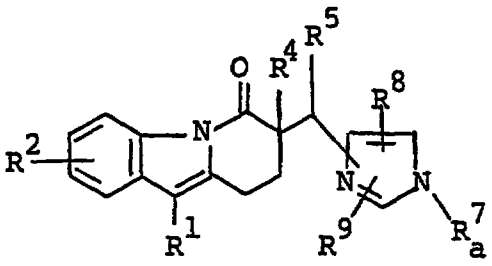


wherein

R^1, R^2 and R^6 are each as defined above,

or a salt thereof, or

(3) subjecting a compound of the formula :



wherein

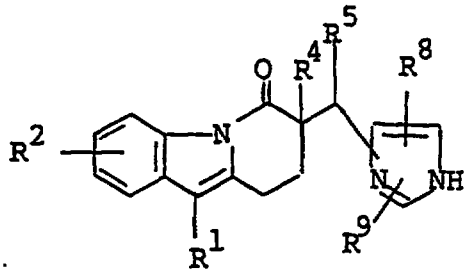
R^1, R^2, R^4 and R^5 are each as defined above,

R_a^7 is imino-protective group, and

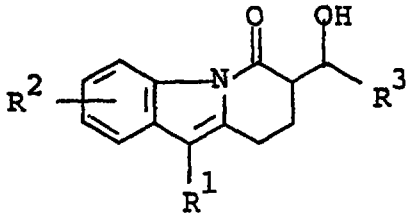
R^8 and R^9 are each hydrogen or (C_1-C_6)alkyl,

or a salt thereof, to removal reaction of the imino-protective group, to give a compound of the

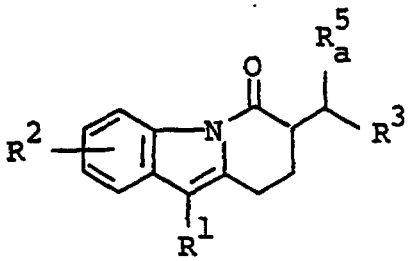
formula :



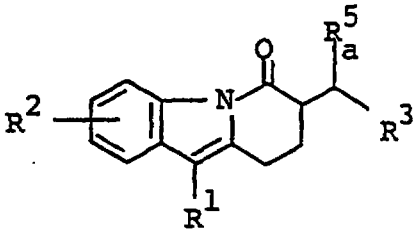
wherein
R^1, R^2, R^4, R^5, R^8 and R^9 are each as defined above,
or a salt thereof, or
(4) subjecting a compound of the formula :



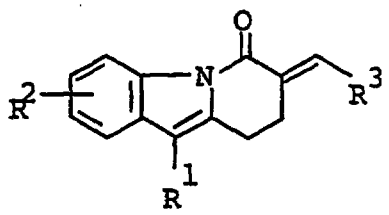
wherein
R^1, R^2 and R^3 are each as defined above,
or a salt thereof, to acylation reaction, to give a compound of the formula :



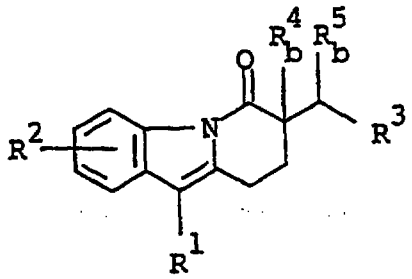
wherein
R^1, R^2 and R^3 are each as defined above, and
R_a^5 is acyloxy,
or a salt thereof, or
(5) subjecting a compound of the formula :



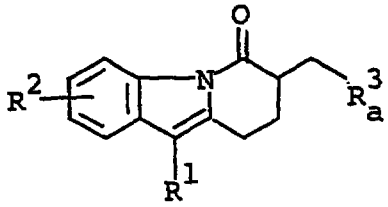
wherein
R^1, R^2, R^3 and R_a^5 are each as defined above,
or a salt thereof, to elimination reaction of H-R_a^5, to give a compound of the formula :



wherein
R^1, R^2 and R^3 are each as defined above,
or a salt thereof, or
(6) subjecting a compound of the formula :

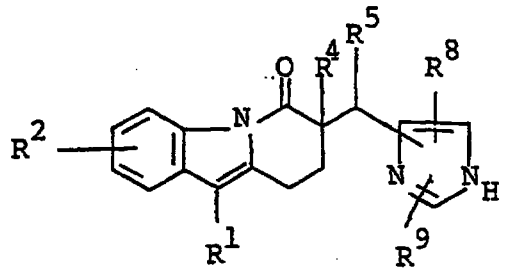


wherein
R^1, R^2 and R^3 are each as defined above, and
R_b^4 is hydrogen and R_b^5 is hydroxy or acyloxy, or
R_b^4 and R_b^5 are linked together to form an additional bond,
or a salt thereof, to reduction, to give a compound of the formula :



wherein
R^1, R^2 and R_a^3 are each as defined above,
or a salt thereof, or

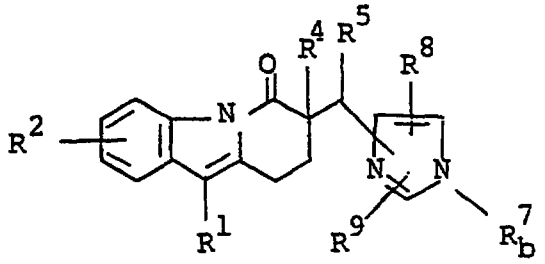
(7) reacting a compound of the formula :



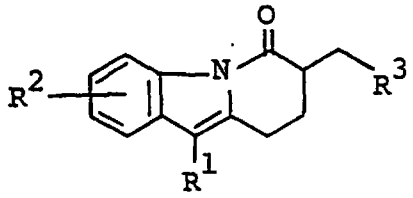
wherein
R^1, R^2, R^4, R^5, R^8 and R^9 are each as defined above,
or a salt thereof, with a compound of the formula :

R_b^7 X

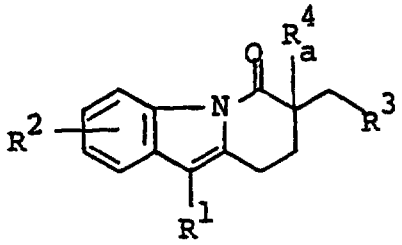
wherein
R_b^7 is $(C_1$-$C_6)$ alkyl, and
X is acid residue,
or a salt thereof, to give a compound of the formula :



wherein
R^1, R^2, R^4, R^5, R_b^7, R^8 and R^9 are each as defined above,
or a salt thereof, or
(8) subjecting a compound of the formula :



wherein
R^1, R^2 and R^3 are each as defined above,
or a salt thereof, to introduction of R_a^4, to give a compound of the formula :



wherein
R^1, R^2 and R^3 are each as defined above, and
R^4_a is $(C_1\text{-}C_6)$ alkyl, $(C_2\text{-}C_6)$ alkenyl or hydroxy $(C_1\text{-}C_6)$alkyl,
or a salt thereof.

9. A pharmaceutical composition comprising a compound of claim 1 or pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable, substantially non-toxic carrier or excipient.

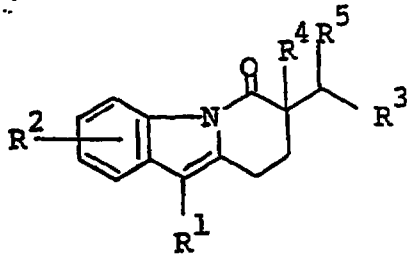
10. Use of a compound of claim 1 or pharmaceutically acceptable salt thereof for the manufacture of a medicament for use as 5-hydroxytryptamine antagonist.

11. A compound of claim 1 or a pharmaceutically acceptable salt thereof for use as a medicament.

12. A compound of claim 1 or a pharmaceutically acceptable salt thereof for use as a 5-hydroxytryptamine antagonist.

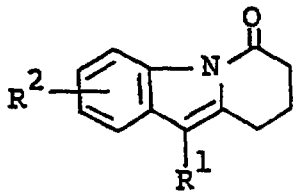
Claims for the following Contracting State : ES

1. A process for preparing a compound of the formula :



wherein
R^1 is hydrogen, $(C_1\text{-}C_6)$alkyl or$(C_2\text{-}C_6)$ alkenyl,
R^2 is hydrogen, $(C_1\text{-}C_6)$alkyl or halogen,
R^3 is imidazolyl or pyridyl, each of which may have suitable substituent(s),
selected from $(C_1\text{-}C_6)$alkyl and imino-protective group
and R^4 is hydrogen, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl or hydroxy$(C_1\text{-}C_6)$alkyl and R^5 is hydrogen, hydroxy or acyloxy, or
R^4 and R^5 are linked together to form an additional bond,
or a salt thereof which comprises

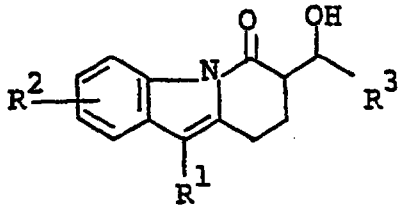
(1) reacting a compound of the formula :



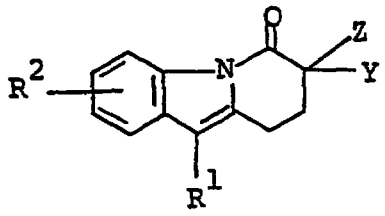
wherein
R^1 and R^2 are each as defined above,
with a compound of the formula :

OHC - R^3

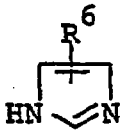
wherein
R^3 is as defined above,
or a salt thereof, to give a compound of the formula :



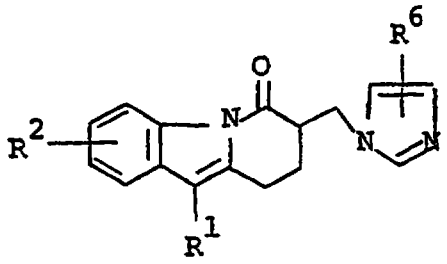
wherein
R^1, R^2 and R^3 are each as defined above,
or a salt thereof, or
(2) reacting a compound of the formula :



wherein
R^1 and R^2 are each as defined above, and
Y is N,N-di(C_1-C_6)alkylaminomethyl and
Z is hydrogen, or Y and Z are combined to form methylene,
with a compound of the formula :



wherein
R^6 is hydrogen or (C_1-C_6)alkyl,
or a salt thereof, to give a compound of the formula :

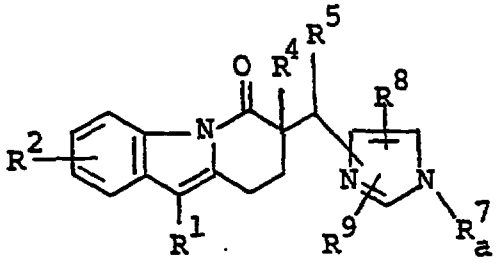


wherein

R^1, R^2 and R^6 are each as defined above,

or a salt thereof, or

(3) subjecting a compound of the formula :

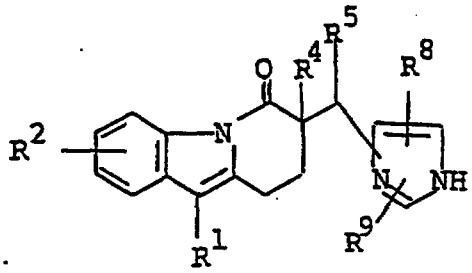


wherein

R^1, R^2, R^4 and R^5 are each as defined above,

R_a^7 is imino-protective group, and R^8 and R^9 are each hydrogen or (C_1-C_6) alkyl,

or a salt thereof, to removal reaction of the imino-protective group, to give a compound of the formula :

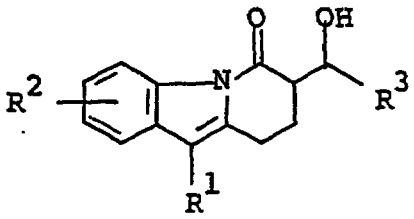


wherein

R^1, R^2, R^4, R^5, R^8 and R^9 are each as defined above,

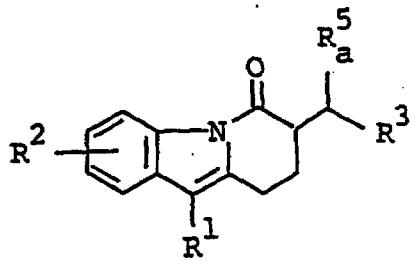
or a salt thereof, or

(4) subjecting a compound of the formula :

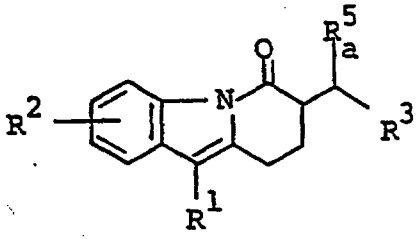


wherein

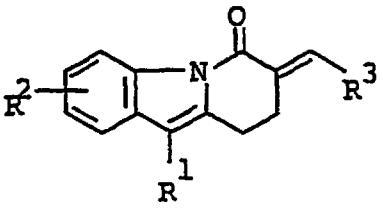
R^1, R^2 and R^3 are each as defined above,
or a salt thereof, to acylation reaction, to give a compound of the formula :



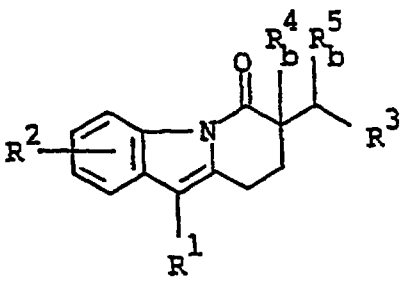
wherein
R^1, R^2 and R^3 are each as defined above, and
R_a^5 is acyloxy,
or a salt thereof, or
(5) subjecting a compound of the formula :



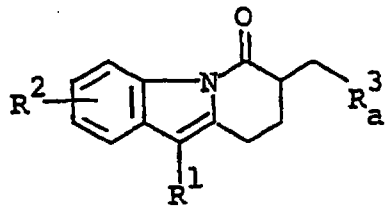
wherein
R^1, R^2, R^3 and R_a^5 are each as defined above,
or a salt thereof, to elimination reaction of H-R_a^5, to give a compound of the formula :



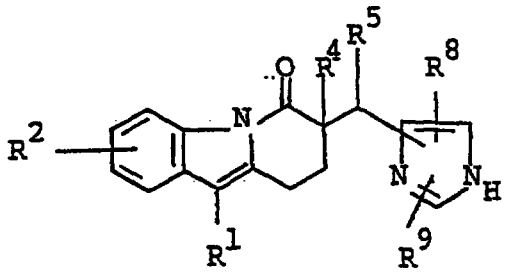
wherein
R^1, R^2 and R^3 are each as defined above,
or a salt thereof, or
(6) subjecting a compound of the formula :



wherein
R^1, R^2 and R^3 are each as defined above, and
R_b^4 is hydroxy and R_b^5 is hydroxy or acyloxy, or
R_b^4 and R_b^5 are linked together to form an additional bond,
or a salt thereof, to reduction, to give a compound of the formula :



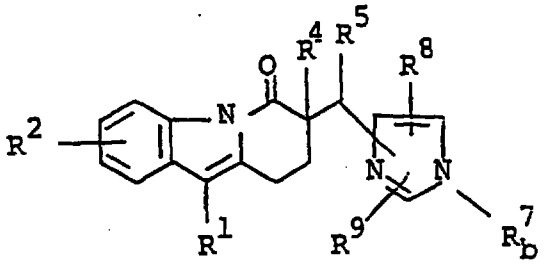
wherein
R^1, R^2 and R_a^3 are each as defined above,
or a salt thereof, or
(7) reacting a compound of the formula :



wherein
R^1, R^2, R^4, R^5, R^8 and R^9 are each as defined above,
or a salt thereof, with a compound of the formula :

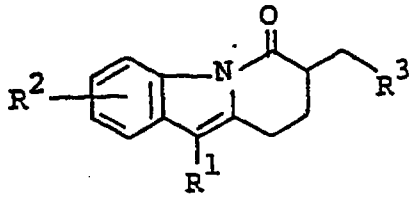
R_b^7X

wherein
R_b^7 is $(C_1\text{-}C_6)$ alkyl, and
X is acid residue,
or a salt thereof, to give a compound of the formula :



wherein
R^1, R^2, R^4, R^5, R_b^7 R^8 and R^9 are each as defined above,
or a salt thereof, or

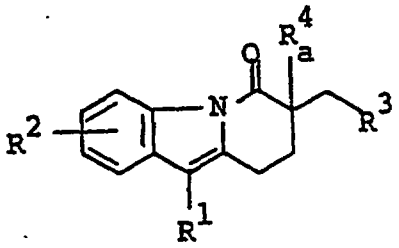
(8) subjecting a compound of the formula :



wherein

R^1, R^2 and R^3 are each as defined above,

or a salt thereof, to introduction of R^4_a, to give a compound of the formula :



wherein

R^1, R^2 and R^3 are each as defined above, and

R^4_a is $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$ alkenyl or hydroxy $(C_1\text{-}C_6)$alkyl,

or a salt thereof.

2. A process of claim 1, wherein

R^3 is imidazolyl which may have one to three substituent(s) selected from lower alkyl and imino-protective group.

3. A process of claim 2, wherein

R^3 is 2-lower alkyl-1H-imidazol-1-yl, 1H-imidazol-2-yl, 1-ar(lower)alkyl-1H-imidazol-2-yl, 1-ar(lower)alkyl-5-lower alkyl-1H-imidazol-4-yl, 5-lower alkyl-1H-imidazol-4-yl, 1-ar(lower)alkyl-1H-imidazol-4-yl, 1H-imidazol-4-yl, 2-lower alkyl-5-lower alkyl-1H-imidazol-4-yl, 1-ar(lower)alkyl-2-lower alkyl-1H-imidazol-4-yl, 2-lower alkyl-1H-imidazol-4-yl, 1-lower alkyl-1H-imidazol-4-yl, 1-lower alkyl-5-lower alkyl-1H-imidazol-4-yl, 1-di(lower)alkylaminosulfonyl-5-lower alkyl-1H-imidazol-4-yl, 1-lower alkyl-1H-imidazol-5-yl or 1-lower alkyl-4-lower alkyl-1H-imidazol-5-yl.

4. A process of claim 3, wherein

R^1 is lower alkyl,

R^2 is hydrogen,

R^3 is 1-mono or di or triphenyl(lower)alkyl-5-lower alkyl-1H-imidazol-4-yl, 5-lower alkyl-1H-imidazol-4-yl or 1-di(lower)alkylaminosulfonyl-5-lower alkyl-1H-imidazol-4-yl, and

R^4 is hydrogen and R^5 is hydrogen, hydroxy or lower alkanoyloxy, or

R^4 and R^5 are linked together to form an additional bond.

5. A process of claim 4, wherein

R^3 is 5-lower alkyl-1H-imidazol-4-yl, and

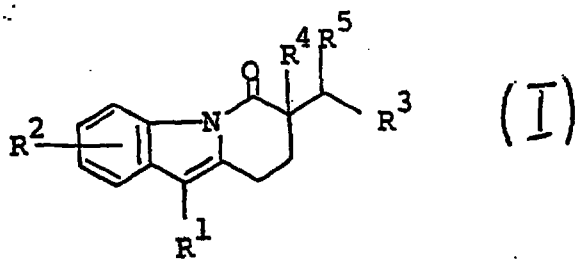
R^4 and R^5 are each hydrogen.

6. A process of claim 5, for preparing 8,9-dihydro-10-methyl-7-[(5-methyl-1H-imidazol-4-yl)methyl]pyrido[1,2-a]indol-6(7H)-one or its acid addition salt.

7. A process of claim 6, for preparing (+)8,9-dihydro-10-methyl-7-[(5-methyl-1H-imidazol-4-yl)methyl]pyrido[1,2-a]indol-6(7H)-one or its hydrochloride or its maleate.

Claims for the following Contracting State : GR

1. A process for preparing a compound of the formula :



(I)

wherein

R^1 is hydrogen, (C_1-C_6)alkyl or(C_2-C_6) alkenyl,

R^2 is hydrogen, (C_1-C_6) alkyl or halogen,

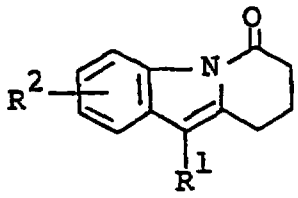
R^3 is imidazolyl or pyridyl, each of which may have suitable substituent(s), selected from (C_1-C_6)alkyl and imino-protective group

and R^4 is hydrogen, (C_1-C_6)alkyl, (C_2-C_6)alkenyl or hydroxy(C_1-C_6)alkyl and R^5 is hydrogen, hydroxy or acyloxy, or

R^4 and R^5 are linked together to form an additional bond,

or a salt thereof which comprises

(1) reacting a compound of the formula :



wherein

R^1 and R^2 are each as defined above,

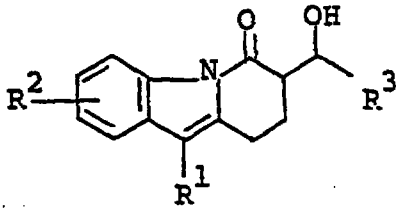
with a compound of the formula :

OHC - R^3

wherein

R^3 is as defined above,

or a salt thereof, to give a compound of the formula :



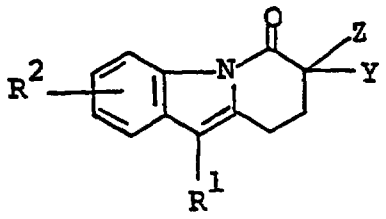
wherein

R^1, R^2 and R^3 are each as defined above,

* C L M S *

or a salt thereof, or

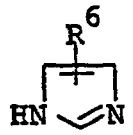
(2) reacting a compound of the formula :



wherein

R^1 and R^2 are	each as defined above, and
Y is	N,N-di(C_1-C_6)alkylaminomethyl and
Z is	hydrogen, or Y and Z are combined to form methylene,

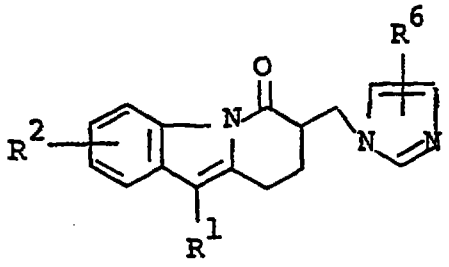
with a compound of the formula :



wherein

R^6 is	hydrogen or (C_1-C_6)alkyl,

or a salt thereof, to give a compound of the formula :

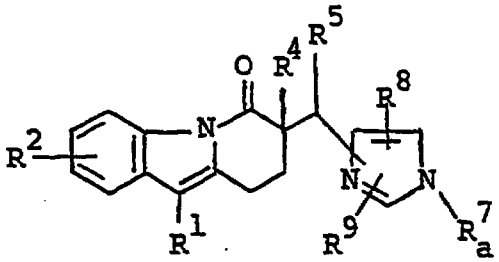


wherein

R^1, R^2 and R^6 are	each as defined above,

or a salt thereof, or

(3) subjecting a compound of the formula :

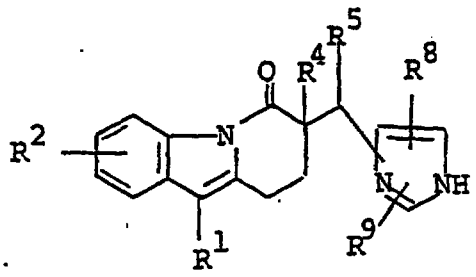


wherein

R^1, R^2, R^4 and R^5 are	each as defined above,
R^7_a is	imino-protective group, and
R^8 and R^9	are each hydrogen or (C_1-C_6)alkyl,

or a salt thereof, to removal reaction of the imino-protective group, to give a compound of the

formula :

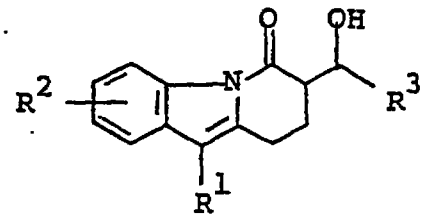


wherein

R^1, R^2, R^4, R^5, R^8 and R^9 are each as defined above,

or a salt thereof, or

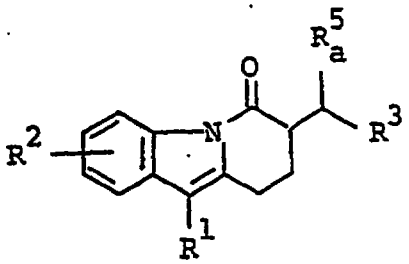
(4) subjecting a compound of the formula :



wherein

R^1, R^2 and R^3 are each as defined above,

or a salt thereof, to acylation reaction, to give a compound of the formula :



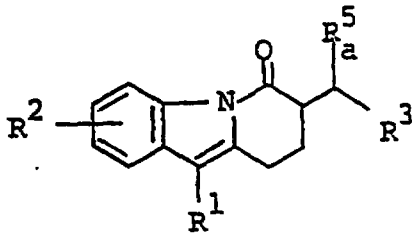
wherein

R^1, R^2 and R^3 are each as defined above, and

R_a^5 is acyloxy,

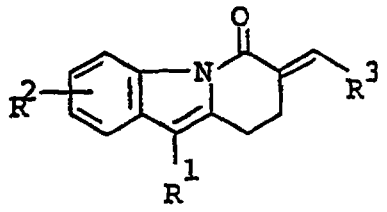
or a salt thereof, or

(5) subjecting a compound of the formula :

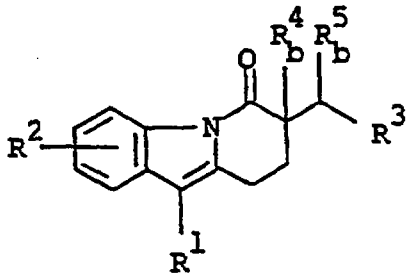


wherein

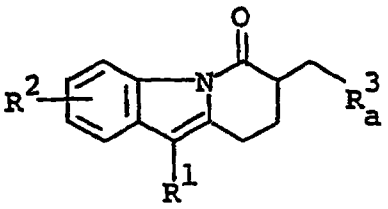
R^1, R^2, R^3 and R_a^5 are each as defined above,
or a salt thereof, to elimination reaction of H-R_a^5, to give a compound of the formula :



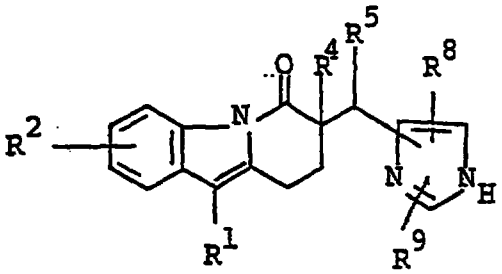
wherein
R^1, R^2 and R^3 are each as defined above,
or a salt thereof, or
(6) subjecting a compound of the formula :



wherein
R^1, R^2 and R^3 are each as defined above, and
R_b^4 is hydrogen and R_b^5 is hydroxy or acyloxy, or
R_b^4 and R_b^5 are linked together to form an additional bond,
or a salt thereof, to reduction, to give a compound of the formula :



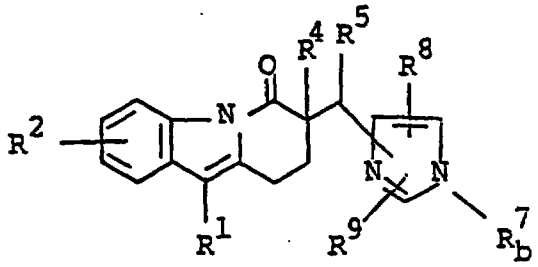
wherein
R^1, R^2 and R_a^3 are each as defined above,
or a salt thereof, or
(7) reacting a compound of the formula :



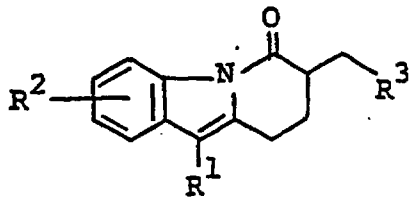
wherein
R^1, R^2, R^4, R^5, R^8 and R^9 are each as defined above,
or a salt thereof, with a compound of the formula :

$R_b^7 X$

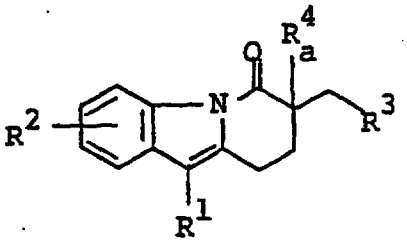
wherein
R_b^7 is $(C_1\text{-}C_6)$ alkyl, and
X is acid residue,
or a salt thereof, to give a compound of the formula :



wherein
R^1, R^2, R^4, R^5, R_b^7, R^8 and R^9 are each as defined above,
or a salt thereof, or
(8) subjecting a compound of the formula :



wherein
R^1, R^2 and R^3 are each as defined above,
or a salt thereof, to introduction of R_a^4, to give a compound of the formula :



wherein
R^1, R^2 and R^3 are each as defined above, and
R_a^4 is $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$ alkenyl or hydroxy$(C_1\text{-}C_6)$alkyl,
or a salt thereof.

2. A process of claim 1, wherein
R^3 is imidazolyl which may have one to three substituent(s) selected from lower alkyl and imino-protective group.

* C L M S *

3. A process of claim 2, wherein
R^3 is 2-lower alkyl-1H-imidazol-1-yl, 1H-imidazol-2-yl, 1-ar(lower)alkyl-1H-imidazol-2-yl, 1-ar(lower)alkyl-5-lower alkyl-1H-imidazol-4-yl, 5-lower alkyl-1H-imidazol-4-yl, 1-ar(lower)alkyl-1H-imidazol-4-yl, 1H-imidazol-4-yl, 2-lower alkyl-5-lower alkyl-1H-imidazol-4-yl, 1-ar(lower)alkyl-2-lower alkyl-1H-imidazol-4-yl, 2-lower alkyl-1H-imidazol-4-yl, 1-lower alkyl-1H-imidazol-4-yl, 1-lower alkyl-5-lower alkyl-1H-imidazol-4-yl, 1-di(lower)alkylaminosulfonyl-5-lower alkyl-1H-imidazol-4-yl, 1-lower alkyl-1H-imidazol-5-yl or 1-lower alkyl-4-lower alkyl-1H-imidazol-5-yl.

4. A process of claim 3, wherein

R^1 is	lower alkyl,
R^2 is	hydrogen,
R^3 is	1-mono or di or triphenyl(lower)alkyl-5-lower alkyl-1H-imidazol-4-yl, 5-lower alkyl-1H-imidazol-4-yl or 1-di(lower)alkylaminosulfonyl-5-lower alkyl-1H-imidazol-4-yl, and
R^4 is	hydrogen and R^5 is hydrogen, hydroxy or lower alkanoyloxy, or
R^4 and R^5 are	linked together to form an additional bond.

5. A process of claim 4, wherein

R^3 is	5-lower alkyl-1H-imidazol-4-yl, and
R^4 and R^5 are	each hydrogen.

6. A process of claim 5, for preparing
8,9-dihydro-10-methyl-7-[(5-methyl-1H-imidazol-4-yl)methyl]pyrido[1,2-a]indol-6(7H)-one or its acid addition salt.

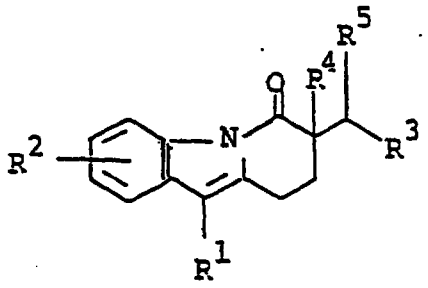
7. A process of claim 6, for preparing
(+)8,9-dihydro-10-methyl-7-[(5-methyl-1H-imidazol-4-yl)methyl]pyrido[1,2-a]indol-6(7H)-one or its hydrochloride or its maleate.

8. Modification of the processes according to any of the claims 1 to 7, wherein the compound of the formula (I) is brought into a pharmaceutically acceptable form by admixture or presentation of said compound with at least one pharmaceutically acceptable carrier or diluent.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Eine Verbindung der Formel:



worin R^1 Wasserstoff, (C_1-C_6)Alkyl oder (C_2-C_6)Alkenyl ist, R^2 Wasserstoff, (C_1-C_6)Alkyl oder Halogen ist, R^3 Imidazolyl oder Pyridyl ist, wovon jedes geeignete Substituent(en), ausgewählt aus (C_1-C_6)Alkyl und einer Imino-Schutzgruppe, aufweisen kann, und R^4 Wasserstoff, (C_1-C_6)Alkyl, (C_2-C_6)Alkenyl oder Hydroxy-(C_1-C_6)alkyl ist, und R^5 Wasserstoff, Hydroxy oder Acyloxy ist, oder R^4 und R^5 miteinander verbunden sind, um eine zusätzliche Bindung zu bilden, und pharmazeutisch verträgliche Salze davon.

2. Eine Verbindung nach Anspruch 1, worin R^3 Imidazol ist, das einen bis drei Substituent(en), ausgewählt aus (C_1-C_6)Alkyl und einer Imino-Schutzgruppe, aufweisen kann.

3. Eine Verbindung nach Anspruch 2, worin R^3 2-(C_1-C_6)-Alkyl-1H-imidazol-1-yl, 1H-Imidazol-2-yl, 1-Ar(C_1-C_6)alkyl-1H-imidazol-2-yl, 1-Ar(C_1-C_6)alkyl-5-(C_1-C_6)alkyl-1H-imidazol-4-yl, 5-(C_1-C_6)Alkyl-1H-imidazol-4-yl, 1-Ar(C_1-C_6)alkyl-1H-imidazol-4-yl, 1H-Imidazol-4-yl, 2-(C_1-C_6)Alkyl-5-(C_1-C_6)alkyl-1H-imidazol-4-yl, 1-Ar(C_1-C_6)alkyl-2-(C_1-C_6)alkyl-1H-imidazol-4-yl, 2-(C_1-C_6)Alkyl-1H-imidazol-4-yl, 1-(C_1-C_6)Alkyl-1H-imidazol-4-yl, 1-(C_1-C_6)Alkyl-5-(C_1-C_6)alkyl-1H-imidazol-4-yl, 1-Di(C_1-C_6)alkylaminosulfonyl-5-(C_1-C_6)alkyl-1H-imidazol-4-yl, 1-(C_1-C_6)Alkyl-1H-imidazol-5-yl oder 1-(C_1-C_6)Alkyl-4-(C_1-C_6)-alkyl-1H-imidazol-5-yl ist.

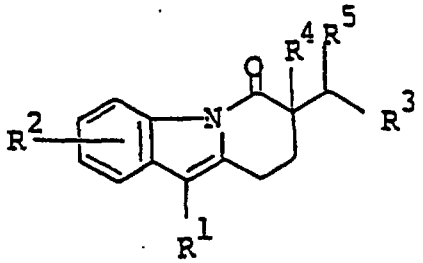
4. Eine Verbindung nach Anspruch 3, worin R^1 (C_1-C_6)Alkylist, R^2 Wasserstoff ist, R^3 1-Mono- oder Di- oder Triphenyl-(C_1-C_6)alkyl-5-(C_1-C_6)alkyl-1H-imidazol-4-yl, 5-(C_1-C_6)Alkyl-1H-imidazol-4-yl oder 1-Di-(C_1-C_6)alkylaminosulfonyl-5-(C_1-C_6)-alkyl-1H-imidazol-4-yl ist, und R^4 Wasserstoff ist, und R^5 Wasserstoff, Hydroxy oder (C_1-C_6)Alkanoyloxy ist, oder R^4 und R^5 miteinander verbunden sind, um eine zusätzliche Bindung zu bilden.

5. Eine Verbindung nach Anspruch 4, worin R^3 5-(C_1-C_6)Alkyl-1H-imidazol-4-yl ist und R^4 und R^5 jeweils Wasserstoff sind.

6. Eine Verbindung nach Anspruch 5, die 8,9-Dihydro-10-methyl-7-[(5-methyl-1H-imidazol-4-yl)methyl]-pyrido[1,2-a]indol-6(7H)-on oder ihr Säureadditionssalz ist.

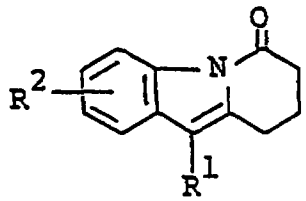
7. Eine Verbindung nach Anspruch 6, die (+)8,9-Dihydro-10-methyl-7-[(5-methyl-1H-imidazol-4-yl)methyl]-pyrido[1,2-a]indol-6(7H)-on oder ihr Hydrochlorid oder ihr Maleat ist.

8. Ein Verfahren zur Herstellung einer Verbindung der Formel:



worin R^1 Wasserstoff, (C_1-C_6)Alkyl oder (C_2-C_6)Alkenyl ist, R^2 Wasserstoff, (C_1-C_6)Alkyl oder Halogen ist, R^3 Imidazolyl oder Pyridyl ist, wovon jedes geeignete Substituent(en), ausgewählt aus (C_1-C_6)Alkyl und einer Imino-Schutzgruppe, aufweisen kann, und R^4 Wasserstoff, (C_1-C_6)Alkyl, (C_2-C_6)Alkenyl oder Hydroxy(C_1-C_6)alkyl ist, und R^5 Wasserstoff, Hydroxy oder Acyloxy ist, oder R^4 und R^5 miteinander verbunden sind, um eine zusätzliche Bindung zu bilden, oder eines Salzes davon, das umfaßt:

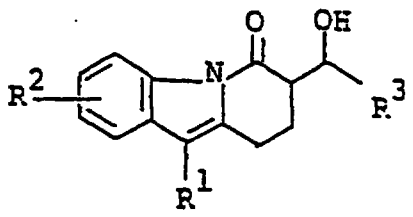
(1) Reagieren einer Verbindung der Formel:



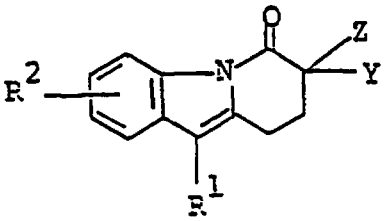
worin R^1 und R^2 jeweils wie oben definiert sind, mit einer Verbindung der Formel:

OHC - R^3

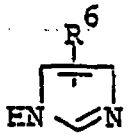
worin R^3 wie oben definiert ist, oder einem Salz davon, um eine Verbindung der Formel:



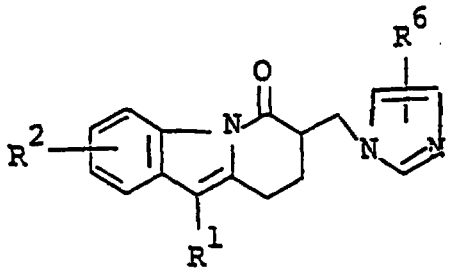
worin R^1, R^2 und R^3 jeweils wie oben definiert sind, oder ein Salz davon zu ergeben, oder
(2) Reagieren einer Verbindung der Formel:



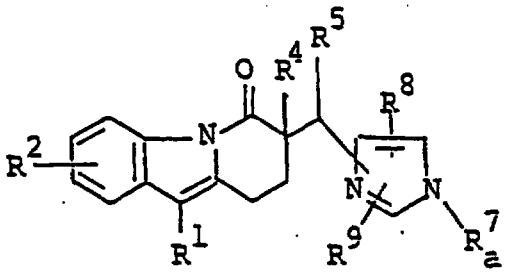
worin R^1 und R^2 jeweils wie oben definiert sind, und Y N,N-Di(C_1-C_6)alkylaminomethyl ist, und Z Wasserstoff ist, oder Y und Z vereint sind, um Methylen zu bilden, mit einer Verbindung der Formel:



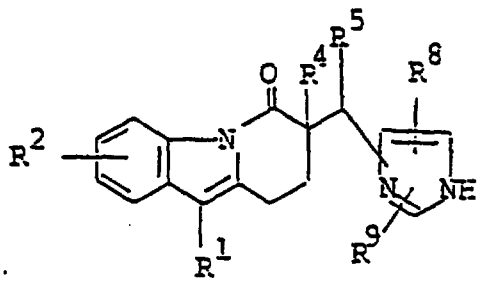
worin R^6 Wasserstoff oder (C_1-C_6)Alkyl ist, oder einem Salz davon, um eine Verbindung der Formel:



worin R^1, R^2 und R^5 jeweils wie oben definiert sind, oder ein Salz davon zu ergeben, oder
(3) Unterwerfen einer Verbindung der Formel:

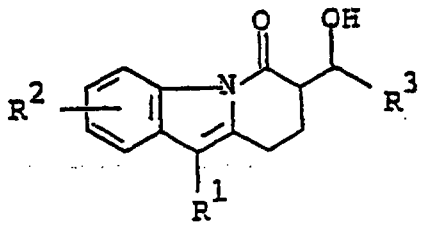


worin R^1, R^2, R^4 und R^5 jeweils wie oben definiert sind, $R^7{}_a$ eine Imino-Schutzgruppe ist, und R^8 und R^9 jeweils Wasserstoff oder (C_1-C_6)Alkyl ist, oder eines Salzes davon, der Entfernungsreaktion der Imino-Schutzgruppe, um eine Verbindung der Formel:

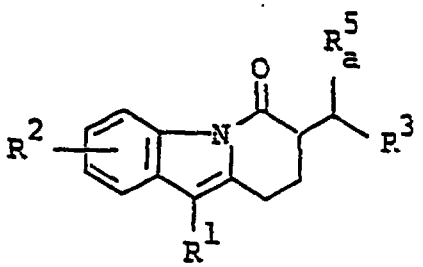


worin R^1, R^2, R^4, R^5, R^8 und R^9 jeweils wie oben definiert sind, oder ein Salz davon zu ergeben, oder

(4) Unterwerfen einer Verbindung der Formel:

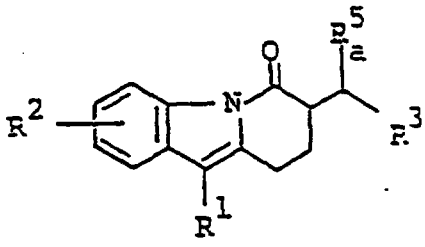


worin R^1, R^2 und R^3 jeweils wie oben definiert sind, oder eines Salzes davon der Acylierungsreaktion, um eine Verbindung der Formel:

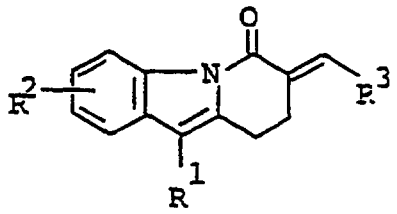


worin R^1, R^2 und R^3 jeweils wie oben definiert sind, und $R^5{}_a$ Acyloxy ist, oder ein Salz davon zu ergeben, oder

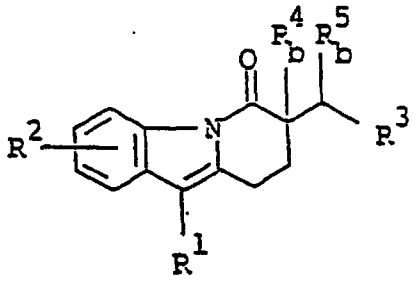
(5) Unterwerfen einer Verbindung der formel:



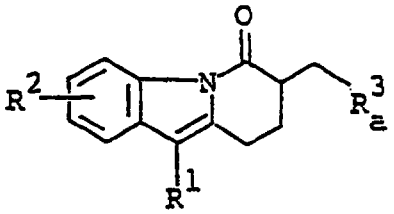
worin R^1, R^2, R^3 und $R^5{}_a$ jeweils wie oben definiert sind, oder eines Salzes davon der Eliminierungsreaktion von H-$R^5{}_a$, um eine Verbindung der Formel:



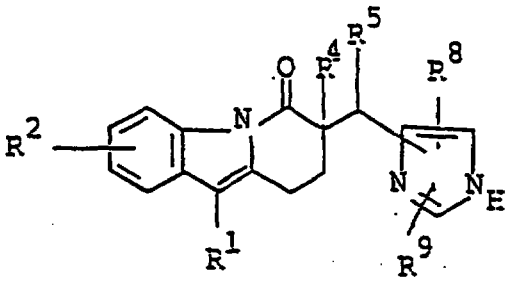
worin R^1, R^2 und R^3 jeweils wie oben definiert sind, oder ein Salz davon zu ergeben, oder
(6) Unterwerfen einer Verbindung der Formel:



worin R^1, R^2 und R^3 jeweils wie oben definiert sind, und $R^4{}_b$ Wasserstoff ist, und $R^5{}_b$ Hydroxy oder Acyloxy ist, oder $R^4{}_b$ und $R^5{}_b$ miteinander verbunden sind, um eine zusätzliche Bindung zu bilden, oder eines Salzes davon der Reduktion, um eine Verbindung der Formel:



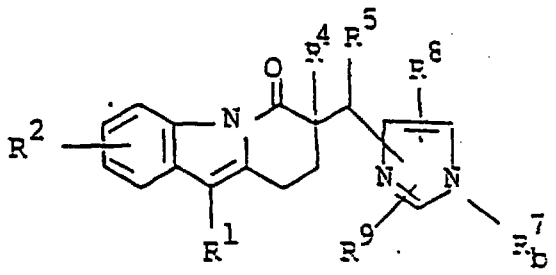
worin R^1, R^2 und $R^3{}_a$ jeweils wie oben definiert sind, oder ein Salz davon zu ergeben, oder
(7) Reagieren einer Verbindung der Formel:



worin R^1, R^2, R^4, R^5, R^8 und R^9 jeweils wie oben definiert sind, oder eines Salzes davon, mit einer Verbindung der Formel:

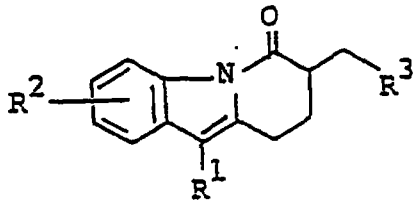
$R^7{}_bX$

worin $R^7{}_b$ (C_1-C_6)Alkyl ist, und X ein Säurerest ist, oder einem Salz davon, um eine Verbindung der Formel:

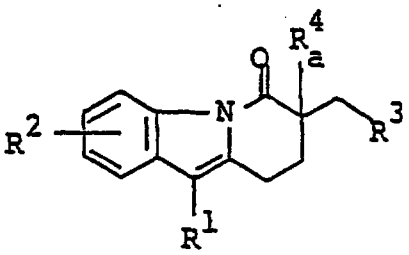


worin R^1, R^2, R^4, R^5, $R^7{}_b$, R^8 und R^9 jeweils wie oben definiert sind, oder ein Salz davon zu ergeben, oder

(8) Unterwerfen einer Verbindung der Formel:



worin R^1, R^2 und R^3 jeweils wie oben definiert sind, oder eines Salzes davon der Einführung von $R^4{}_a$, um eine Verbindung der Formel:



worin R^1, R^2 und R^3 jeweils wie oben definiert sind, und $R^4{}_a$ (C_1-C_6)Alkyl, (C_2-C_6)Alkenyl oder Hydroxy(C_1-C_6)alkyl ist, oder ein Salz davon zu ergeben.

9. Eine pharmazeutische Zusammensetzung, die eine Verbindung nach Anspruch 1 oder ein pharmazeutisch verträgliches Salz davon in Verbindung mit einem pharmazeutisch verträglichen, im wesentlichen nichttoxischen Träger oder Exzipienten umfaßt.

10. Verwendung einer Verbindung nach Anspruch 1 oder eines pharmazeutisch verträglichen Salzes davon zur Herstellung eines Medikamentes zur Verwendung als 5-Hydoxytryptamin-Antagonist.

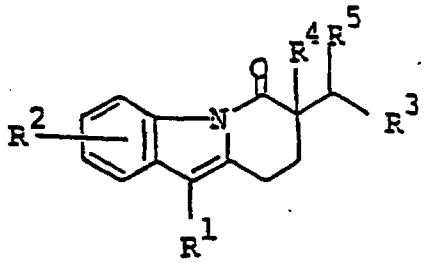
11. Eine Verbindung nach Anspruch 1 oder eines pharmazeutisch verträglichen Salzes davon zur Verwendung als Medikament.

12. Eine Verbindung nach Anspruch 1 oder eines pharmazeutisch verträglichen Salzes davon zur Verwendung als 5-Hydroxytryptamin-Antagonist.

* C L M S *

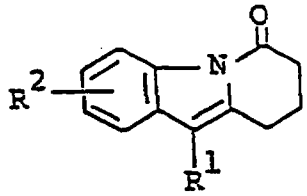
Patentansprüche für folgenden Vertragsstaat : ES

1. Ein Verfahren zur Herstellung einer Verbindung der Formel:



worin R^1 Wasserstoff, (C_1-C_6)Alkyl oder (C_2-C_6)Alkenyl ist, R^2 Wasserstoff, (C_1-C_6)Alkyl oder Halogen ist, R^3 Imidazolyl oder Pyridyl ist, wovon jedes geeignete Substituent(en), ausgewählt aus (C_1-C_6)Alkyl und einer Imino-Schutzgruppe, aufweisen kann, und R^4 Wasserstoff, (C_1-C_6)Alkyl, (C_2-C_6)Alkenyl oder Hydroxy(C_1-C_6)alkyl ist, und R^5 Wasserstoff, Hydroxy oder Acyloxy ist, oder R^4 und R^5 miteinander verbunden sind, um eine zusätzliche Bindung zu bilden, oder eines Salzes davon, das umfaßt:

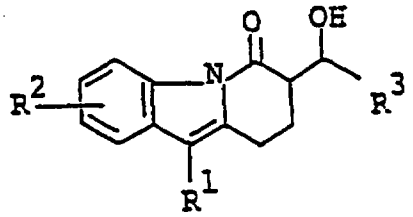
(1) Reagieren einer Verbindung der Formel:



worin R^1 und R^2 jeweils wie oben definiert sind, mit einer Verbindung der Formel:

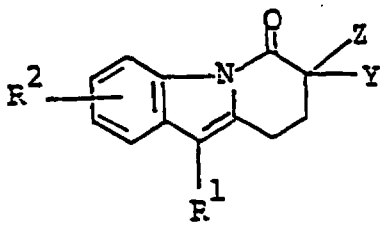
OHC - R^3

worin R^3 wie oben definiert ist, oder einem Salz davon, um eine Verbindung der Formel:



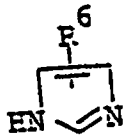
worin R^1, R^2 und R^3 jeweils wie oben definiert sind, oder ein Salz davon zu ergeben, oder

(2) Reagieren einer Verbindung der Formel:

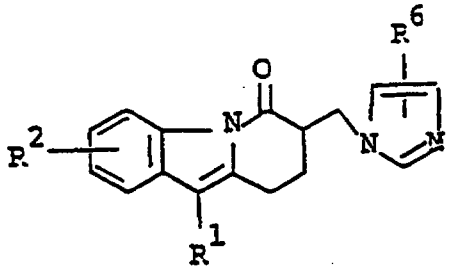


worin R^1 und R^2 jeweils wie oben definiert sind, und Y N,N-Di(C_1-C_6)alkylaminomethyl ist, und Z

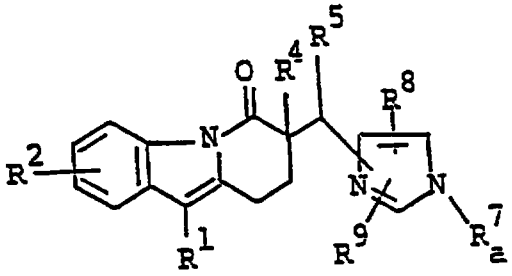
Wasserstoff ist, oder Y und Z vereint sind, um Methylen zu bilden, mit einer Verbindung der Formel:



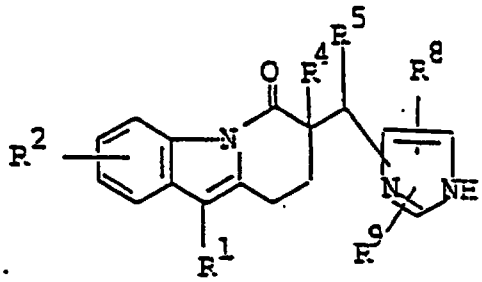
worin R^6 Wasserstoff oder (C_1-C_6)Alkyl ist, oder einem Salz davon, um eine Verbindung der Formel:



worin R^1, R^2 und R^5 jeweils wie oben definiert sind, oder ein Salz davon zu ergeben, oder
(3) Unterwerfen einer Verbindung der Formel:

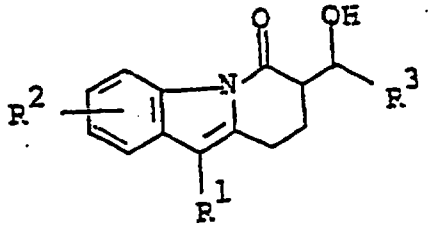


worin R^1, R^2, R^4 und R^5 jeweils wie oben definiert sind, $R^7{}_a$ eine Imino-Schutzgruppe ist, und R^8 und R^9 jeweils Wasserstoff oder (C_1-C_6)Alkyl ist, oder eines Salzes davon, der Entfernungsreaktion der Imino-Schutzgruppe, um eine Verbindung der Formel:

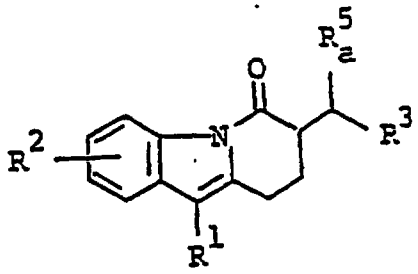


worin R^1, R^2, R^4, R^5, R^8 und R^9 jeweils wie oben definiert sind, oder ein Salz davon zu ergeben, oder

(4) Unterwerfen einer Verbindung der Formel:

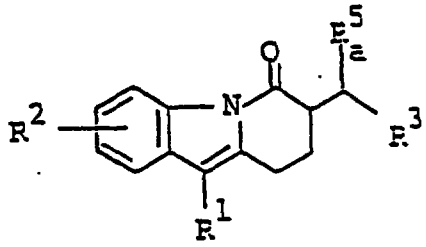


worin R^1, R^2 und R^3 jeweils wie oben definiert sind, oder eines Salzes davon der Acylierungsreaktion, um eine Verbindung der Formel:

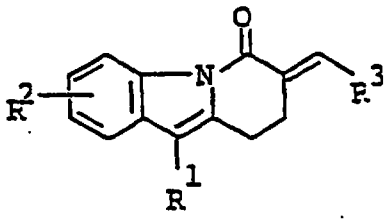


worin R^1, R^2 und R^3 jeweils wie oben definiert sind, und $R^5{}_a$ Acyloxy ist, oder ein Salz davon zu ergeben, oder

(5) Unterwerfen einer Verbindung der formel:

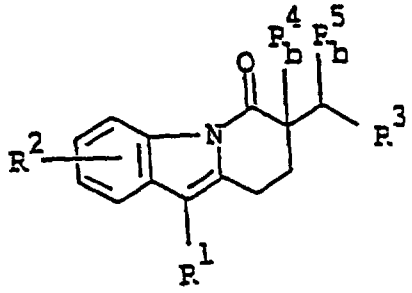


worin R^1, R^2, R^3 und $R^5{}_a$ jeweils wie oben definiert sind, oder eines Salzes davon der Eliminierungsreaktion von H-$R^5{}_a$, um eine Verbindung der Formel:

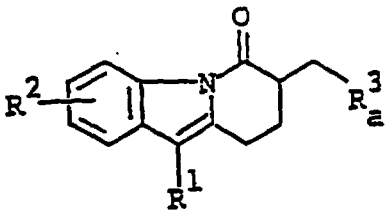


worin R^1, R^2 und R^3 jeweils wie oben definiert sind, oder ein Salz davon zu ergeben, oder

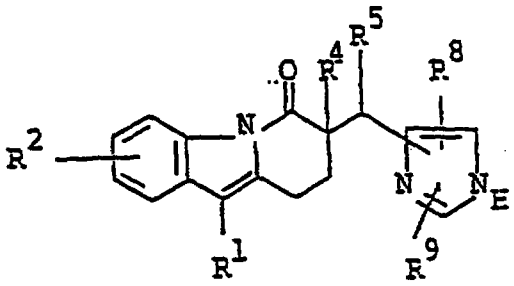
(6) Unterwerfen einer Verbindung der Formel:



worin R^1, R^2 und R^3 jeweils wie oben definiert sind, und $R^4{}_b$ Wasserstoff ist, und $R^5{}_b$ Hydroxy oder Acyloxy ist, oder $R^4{}_b$ und $R^5{}_b$ miteinander verbunden sind, um eine zusätzliche Bindung zu bilden, oder eines Salzes davon der Reduktion, um eine Verbindung der Formel:



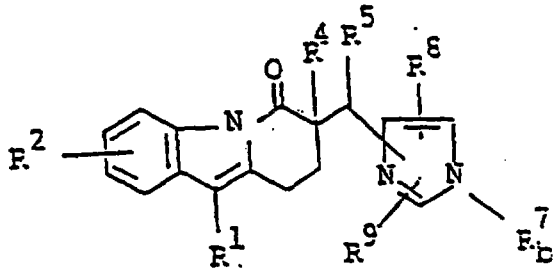
worin R^1, R^2 und $R^3{}_a$ jeweils wie oben definiert sind, oder ein Salz davon zu ergeben, oder
(7) Reagieren einer Verbindung der Formel:



worin R^1, R^2, R^4, R^5, R^8 und R^9 jeweils wie oben definiert sind, oder eines Salzes davon, mit einer Verbindung der Formel:

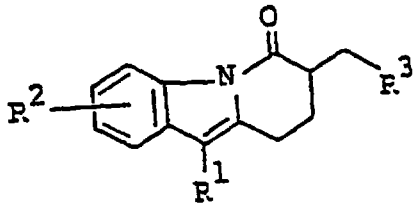
$R^7{}_bX$

worin $R^7{}_b$ (C_1-C_6)Alkyl ist, und X ein Säurerest ist, oder einem Salz davon, um eine Verbindung der Formel:

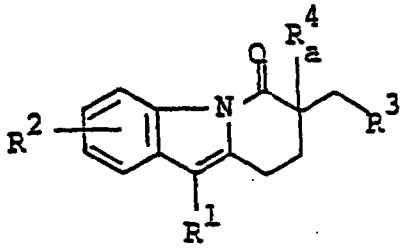


worin R^1, R^2, R^4, R^5, $R^7{}_b$, R^8 und R^9 jeweils wie oben definiert sind, oder ein Salz davon zu ergeben, oder

(8) Unterwerfen einer Verbindung der Formel:



worin R^1, R^2 und R^3 jeweils wie oben definiert sind, oder eines Salzes davon der Einführung von $R^4{}_a$, um eine Verbindung der Formel:



worin R^1, R^2 und R^3 jeweils wie oben definiert sind, und $R^4{}_a$ (C_1-C_6)Alkyl, (C_2-C_6)Alkenyl oder Hydroxy(C_1-C_6)alkyl ist, oder ein Salz davon zu ergeben.

2. Ein Verfahren nach Anspruch 1, worin R^3 Imidazol ist, das einen bis drei Substituent(en), ausgewählt aus (C_1-C_6)Alkyl und einer Imino-Schutzgruppe, aufweisen kann.

3. Ein Verfahren nach Anspruch 2, worin R^3 2-(C_1-C_6)-Alkyl-1H-imidazol-1-yl, 1H-Imidazol-2-yl, 1-Ar(C_1-C_6)alkyl-1H-imidazol-2-yl, 1-Ar(C_1-C_6)alkyl-5-(C_1-C_6)alkyl-1H-imidazol-4-yl, 5-(C_1-C_6)Alkyl-1H-imidazol-4-yl, 1-Ar(C_1-C_6)alkyl-1H-imidazol-4-yl, 1H-Imidazol-4-yl, 2-(C_1-C_6)Alkyl-5-(C_1-C_6)alkyl-1H-imidazol-4-yl, 1-Ar(C_1-C_6)alkyl-2-(C_1-C_6)alkyl-1H-imidazol-4-yl, 2-(C_1-C_6)Alkyl-1H-imidazol-4-yl, 1-(C_1-C_6)Alkyl-1H-imidazol-4-yl, 1-(C_1-C_6)Alkyl-5-(C_1-C_6)alkyl-1H-imidazol-4-yl, 1-Di(C_1-C_6)alkylaminosulfonyl-5-(C_1-C_6)alkyl-1H-imidazol-4-yl, 1-(C_1-C_6)Alkyl-1H-imidazol-5-yl oder 1-(C_1-C_6)Alkyl-4-(C_1-C_6)-alkyl-1H-imidazol-5-yl ist.

4. Ein Verfahren nach Anspruch 3, worin R^1 (C_1-C_6)Alkyl ist, R^2 Wasserstoff ist, R^3 1-Mono- oder Di- oder Triphenyl-(C_1-C_6)alkyl-5-(C_1-C_6)alkyl-1H-imidazol-4-yl, 5-(C_1-C_6)Alkyl-1H-imidazol-4-yl oder 1-Di(C_1-C_6)alkylaminosulfonyl-5-(C_1-C_6)-alkyl-1H-imidazol-4-yl ist, und R^4 Wasserstoff ist, und R^5 Wasserstoff, Hydroxy oder (C_1-C_6)Alkanoyloxy ist, oder R^4 und R^5 miteinander verbunden sind, um eine zusätzliche Bindung zu bilden.

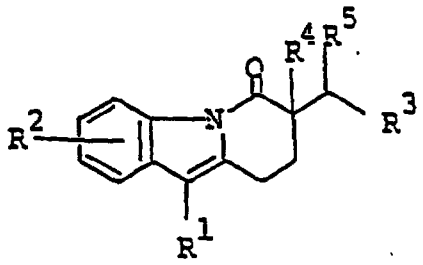
5. Ein Verfahren nach Anspruch 4, worin R^3 5-(C_1-C_6)-Alkyl-1H-imidazol-4-yl ist und R^4 und R^5 jeweils Wasserstoff sind.

6. Ein Verfahren nach Anspruch 5, zur Herstellung von 8,9-Dihydro-10-methyl-7-[(5-methyl-1H-imidazol-4-yl)methyl]-pyrido[1,2-a]indol-6(7H)-on oder ihres Säureadditionssalzes.

7. Ein Verfahren nach Anspruch 6, zur Herstellung von (+)8,9-Dihydro-10-methyl-7-[(5-methyl-1H-imidazol-4-yl)methyl]pyrido[1,2-a]indol-6(7H)-on oder ihres Hydrochlorid oder ihres Maleates.

Patentansprüche für folgenden Vertragsstaat : GR

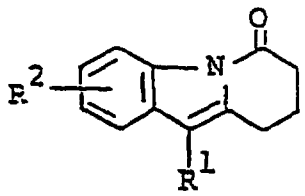
1. Ein Verfahren zur Herstellung einer Verbindung der Formel:



(I)

worin R^1 Wasserstoff, (C_1-C_6)Alkyl oder (C_2-C_6)Alkenyl ist, R^2 Wasserstoff, (C_1-C_6)Alkyl oder Halogen ist, R^3 Imidazolyl oder Pyridyl ist, wovon jedes geeignete Substituent(en), ausgewählt aus (C_1-C_6)Alkyl und einer Imino-Schutzgruppe, aufweisen kann, und R^4 Wasserstoff, (C_1-C_6)Alkyl, (C_2-C_6)Alkenyl oder Hydroxy(C_1-C_6)alkyl ist, und R^5 Wasserstoff, Hydroxy oder Acyloxy ist, oder R^4 und R^5 miteinander verbunden sind, um eine zusätzliche Bindung zu bilden, oder eines Salzes davon, das umfaßt:

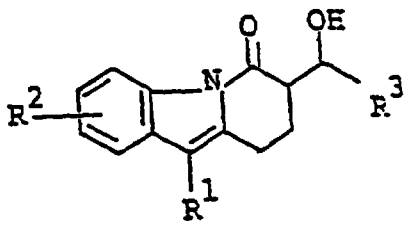
(1) Reagieren einer Verbindung der Formel:



worin R^1 und R^2 jeweils wie oben definiert sind, mit einer Verbindung der Formel:

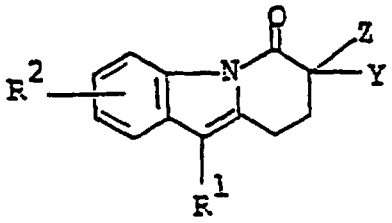
OHC - R^3

worin R^3 wie oben definiert ist, oder einem Salz davon, um eine Verbindung der Formel:

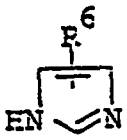


worin R^1, R^2 und R^3 jeweils wie oben definiert sind, oder ein Salz davon zu ergeben, oder

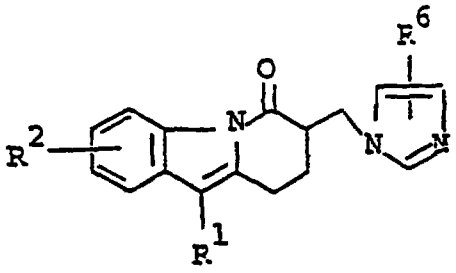
(2) Reagieren einer Verbindung der Formel:



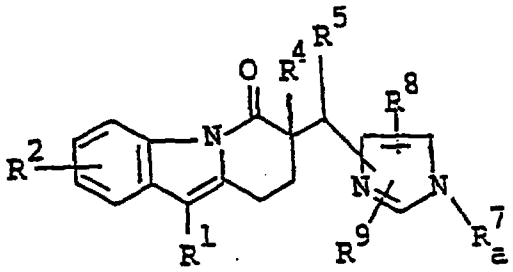
worin R^1 und R^2 jeweils wie oben definiert sind, und Y N,N-Di(C_1-C_6)alkylaminomethyl ist, und Z Wasserstoff ist, oder Y und Z vereint sind, um Methylen zu bilden, mit einer Verbindung der Formel:



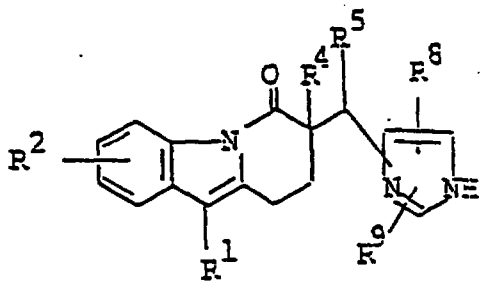
worin R^6 Wasserstoff oder (C_1-C_6)Alkyl ist, oder einem Salz davon, um eine Verbindung der Formel:



worin R^1, R^2 und R^6 jeweils wie oben definiert sind, oder ein Salz davon zu ergeben, oder
(3) Unterwerfen einer Verbindung der Formel:

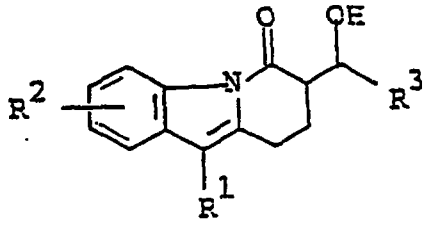


worin R^1, R^2, R^4 und R^5 jeweils wie oben definiert sind, $R^7{}_a$ eine Imino-Schutzgruppe ist, und R^8 und R^9 jeweils Wasserstoff oder (C_1-C_6)Alkyl ist, oder eines Salzes davon, der Entfernungsreaktion der Imino-Schutzgruppe, um eine Verbindung der Formel:

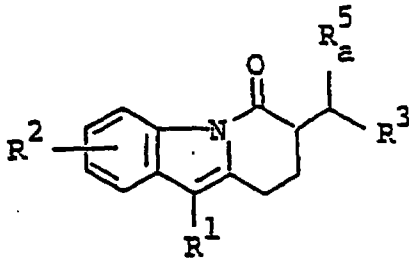


worin R^1, R^2, R^4, R^5, R^8 und R^9 jeweils wie oben definiert sind, oder ein Salz davon zu ergeben, oder

(4) Unterwerfen einer Verbindung der Formel:

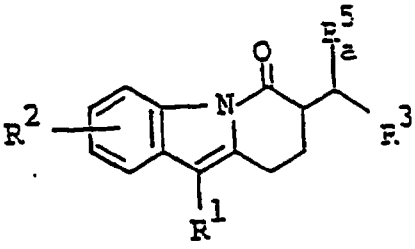


worin R^1, R^2 und R^3 jeweils wie oben definiert sind, oder eines Salzes davon der Acylierungsreaktion, um eine Verbindung der Formel:

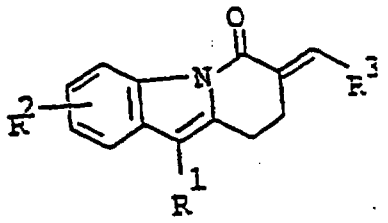


worin R^1, R^2 und R^3 jeweils wie oben definiert sind, und $R^5{}_a$ Acyloxy ist, oder ein Salz davon zu ergeben, oder

(5) Unterwerfen einer Verbindung der formel:

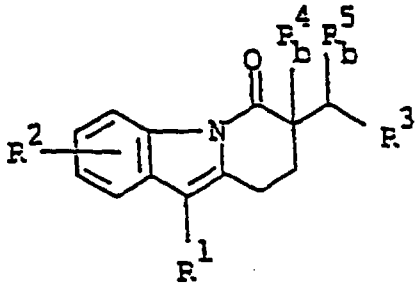


worin R^1, R^2, R^3 und $R^5{}_a$ jeweils wie oben definiert sind, oder eines Salzes davon der Eliminierungsreaktion von H-$R^5{}_a$, um eine Verbindung der Formel:

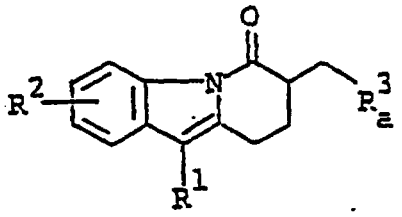


worin R^1, R^2 und R^3 jeweils wie oben definiert sind, oder ein Salz davon zu ergeben, oder

(6) Unterwerfen einer Verbindung der Formel:

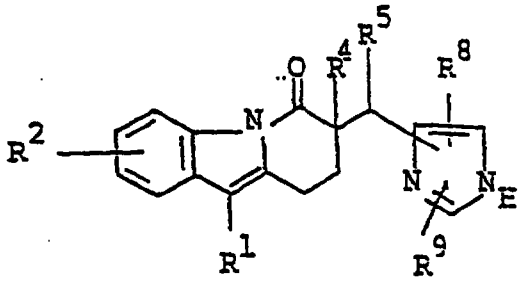


worin R^1, R^2 und R^3 jeweils wie oben definiert sind, und $R^4{}_b$ Wasserstoff ist, und $R^5{}_b$ Hydroxy oder Acyloxy ist, oder $R^4{}_b$ und $R^5{}_b$ miteinander verbunden sind, um eine zusätzliche Bindung zu bilden, oder eines Salzes davon der Reduktion, um eine Verbindung der Formel:



worin R^1, R^2 und $R^3{}_a$ jeweils wie oben definiert sind, oder ein Salz davon zu ergeben, oder

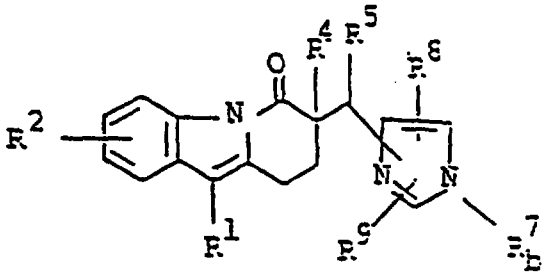
(7) Reagieren einer Verbindung der Formel:



worin R^1, R^2, R^4, R^5, R^8 und R^9 jeweils wie oben definiert sind, oder eines Salzes davon, mit einer Verbindung der Formel:

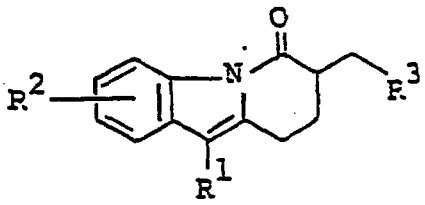
$R^7{}_bX$

worin $R^7{}_b$ (C_1-C_6)Alkyl ist, und X ein Säurerest ist, oder einem Salz davon, um eine Verbindung der Formel:

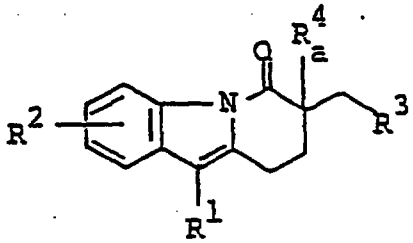


worin R^1, R^2, R^4, R^5, R^{7}_b, R^8 und R^9 jeweils wie oben definiert sind, oder ein Salz davon zu ergeben, oder

(8) Unterwerfen einer Verbindung der Formel:



worin R^1, R^2 und R^3 jeweils wie oben definiert sind, oder eines Salzes davon der Einführung von R^{4}_a, um eine Verbindung der Formel:



worin R^1, R^2 und R^3 jeweils wie oben definiert sind, und R^{4}_a (C_1-C_6)Alkyl, (C_2-C_6)Alkenyl oder Hydroxy(C_1-C_6)alkyl ist, oder ein Salz davon zu ergeben.

2. Ein Verfahren nach Anspruch 1, worin R^3 Imidazol ist, das einen bis drei Substituent(en), ausgewählt aus (C_1-C_6)Alkyl und einer Imino-Schutzgruppe, aufweisen kann.

3. Ein Verfahren nach Anspruch 2, worin R^3 2-(C_1-C_6)Alkyl-1H-imidazol-1-yl, 1H-Imidazol-2-yl, 1-Ar(C_1-C_6)alkyl-1H-imidazol-2-yl, 1-Ar(C_1-C_6)alkyl-5-(C_1-C_6)alkyl-1H-imidazol-4-yl, 5-(C_1-C_6)Alkyl-1H-imidazol-4-yl, 1-Ar(C_1-C_6)alkyl-1H-imidazol-4-yl, 1H-Imidazol-4-yl, 2-(C_1-C_6)Alkyl-5-(C_1-C_6)alkyl-1H-imidazol-4-yl, 1-Ar(C_1-C_6)alkyl-2-(C_1-C_6)alkyl-1H-imidazol-4-yl, 2-(C_1-C_6)Alkyl-1H-imidazol-4-yl, 1-(C_1-C_6)Alkyl-1H-imidazol-4-yl, 1-(C_1-C_6)Alkyl-5-(C_1-C_6)alkyl-1H-imidazol-4-yl, 1-Di(C_1-C_6)alkylaminosulfonyl-5-(C_1-C_6)alkyl-1H-imidazol-4-yl, 1-(C_1-C_6)Alkyl-1H-imidazol-5-yl oder 1-(C_1-C_6)Alkyl-4-(C_1-C_6)alkyl-1H-imidazol-5-yl ist.

4. Ein Verfahren nach Anspruch 3, worin R^1 (C_1-C_6)Alkyl ist, R^2 Wasserstoff ist, R^3 1-Mono- oder Di- oder Triphenyl(C_1-C_6)alkyl-5-(C_1-C_6)alkyl-1H-imidazol-4-yl, 5-(C_1-C_6)Alkyl-1H-imidazol-4-yl oder 1-Di(C_1-C_6)-alkylaminosulfonyl-5-(C_1-C_6)alkyl-1H-imidazol-4-yl ist, und R^4 Wasserstoff ist, und R^5 Wasserstoff, Hydroxy oder (C_1-C_6)Alkanoyloxy ist, oder R^4 und R^5 miteinander verbunden sind, um eine zusätzliche Bindung zu bilden.

5. Ein Verfahren nach Anspruch 4, worin R^3 5-(C_1-C_6)-Alkyl-1H-imidazol-4-yl ist und R^4 und R^5 jeweils Wasserstoff sind.

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6. Ein Verfahren nach Anspruch 5, zur Herstellung von 8,9-Dihydro-10-methyl-7-[(5-methyl-1H-imidazol-4-yl)methyl]-pyrido[1,2-a]indol-6(7H)-on oder ihres Säureadditionssalzes.

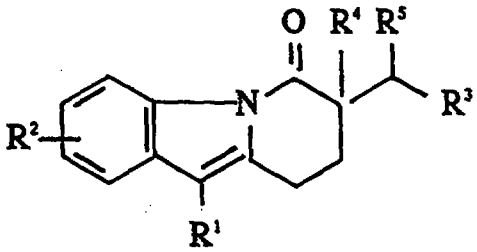
7. Ein Verfahren nach Anspruch 6, zur Herstellung von (+)8,9-Dihydro-10-methyl-7-[(5-methyl-1H-imidazol-4-yl)methyl]-pyrido[1,2-a]indol-6(7H)-on oder ihres Hydrochlorid oder ihres Maleates.

8. Modifizierung der Verfahren gemäß irgendeinem der Ansprüche 1 bis 7, worin die Verbindung der Formel (I) durch Zusammenmischen oder Präsentation der genannten Verbindung mit wenigstens einem pharmazeutisch verträglichen Träger oder Verdünnungsmittel in eine pharmazeutisch verträgliche Form gebracht wird.

Revendications

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

1. Composé de la formule :



dans laquelle

R^1 est un hydrogène, un (C_1-C_6)alkyle ou un (C_2-C_6)alcényle,

R^2 est un hydrogène, un (C_1-C_6)alkyle ou un halogène,

R^3 est un imidazolyle ou un pyridyle, chacun des deux pouvant avoir un ou plusieurs substituants appropriés choisis parmi les (C_1-C_6)alkyles et le groupe imino-protecteur et R^4 est un hydrogène, un (C_1-C_6)alkyle, un (C_2-C_6)alcényle ou un hydroxy(C_1-C_6)alkyle et R^5 est un hydrogène, un hydroxy ou un acyloxy, ou

R^4 et R^5 sont liés ensemble pour former une liaison additionnelle,

ainsi que les sels de celui-ci acceptables sur le plan pharmaceutique.

2. Composé de la revendication 1, dans lequel
R^3 est un imidazolyle qui peut avoir un à trois substituants choisis parmi les groupes (C_1-C_6)alkyles et le groupe imino-protecteur.

3. Composé de la revendication 2, dans lequel
R^3 est un 2-(C_1-C_6)alkyl-1H-imidazol-1-yle, un 1H-imidazol-2-yle, un 1-ar(C_1-C_6)alkyl-1H-imidazol-2-yle, un 1-ar(C_1-C_6)alkyl-5-(C_1-C_6)alkyl-1H-imidazol-4-yle, un 5-(C_1-C_6)alkyl-1H-imidazol-4-yle, un 1-ar(C_1-C_6)alkyl-1H-imidazol-4-yle, un 1H-imidazol-4-yle, un 2-(C_1-C_6)alkyl-5-(C_1-C_6)alkyl-1H-imidazol-4-yle, un 1-ar(C_1-C_6)alkyl-2-(C_1-C_6)alkyl-1H-imidazol-4-yle, un 2-(C_1-C_6)-alkyl-1H-imidazol-4-yl, un 1-(C_1-C_6)alkyl-1H-imidazol-4-yle, un 1-(C_1-C_6)alkyl-5-(C_1-C_6)-alkyl-1H-imidazol-4-yle, un di(C_1-C_6) alkylaminosulfonyl-5-(C_1-C_6)alkyl-1H-imidazol-4-yle, un 1-(C_1-C_6)alkyl-1H-imidazol-5-yle, ou un 1-(C_1-C_6)alkyl-4-(C_1-C_6)-alkyl-1H-imidazol-5-yle.

4. Composé de la revendication 3, dans lequel
R^1 est un (C_1-C_6)alkyle,
R^2 est un hydrogène,
R^3 est un 1-mono-, un di- ou un triphényl(C_1-C_6)alkyl-5-(C_1-C_6)alkyl-1H-imidazol-4-yle, un 5-(C_1-C_6)-alkyl-1H-imidazol-4-yle ou un 1-di(C_1-C_6)alkylaminosulfonyl-5-(C_1-C_6)alkyl-1H-imidazol-4-yle et
R^4 est un hydrogène et R^5 est un hydrogène, un hydroxy ou un (C_1-C_6)alcanoyloxy ou
R^4 et R^5 sont liés ensemble pour former une liaison additionnelle.

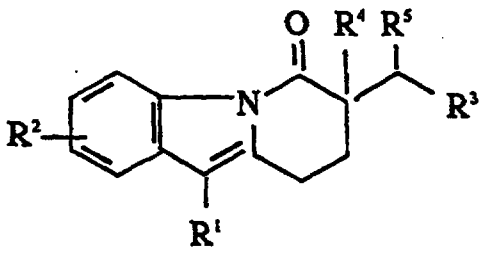
* C L M S *

5. Composé de la revendication 4, dans lequel
R^3 est un 5-(C_1-C_6)alkyl-1H-imidazol-4-yle et
R^4 et R^5 sont chacun un hydrogène.

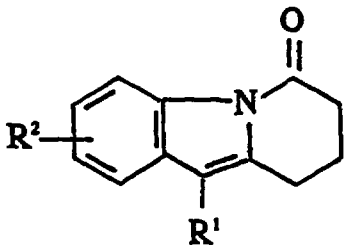
6. Composé de la revendication 5, qui est la 8,9-dihydro-10-méthyl-7-[(5-méthyl-1H-imidazol-4-yl)méthyl]-pyrido[1,2-a]indol-6(7H)one ou un sel d'addition de celui-ci avec un acide.

7. Composé de la revendication 6, qui est la (+)8,9-dihydro-10-méthyl-7-[(5-méthyl-1H-imidazol-4-yl)-méthyl]pyrido[1,2-a]indol-6(7H)one, son chlorhydrate ou son maléate.

8. Procédé de préparation d'un composé de la formule :



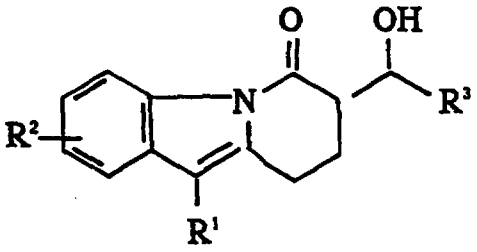
dans laquelle
R^1 est un hydrogène, un (C_1-C_6)alkyle ou un (C_2-C_6)alcényle, R^2 est un hydrogène, un (C_1-C_6)-alkyle ou un halogène,
R^3 est un imidazolyle ou un pyridyle, chacun des deux pouvant avoir un ou plusieurs substituants appropriés choisis parmi les (C_1-C_6)alkyles et le groupe imino-protecteur et R^4 est un hydrogène, un (C_1-C_6)alkyle, un (C_2-C_6)alcényle ou un hydroxy(C_1-C_6)alkyle et R^5 est un hydrogène, un hydroxy ou un acyloxy, ou
R^4 et R^5 sont liés ensemble pour former une liaison additionnelle,
ou un sel de celui-ci, qui comprend de
(1) faire réagir un composé de la formule :



dans laquelle
R^1 et R^2 sont définis chacun comme ci-dessus, avec un composé de la formule :

OHC - R^3

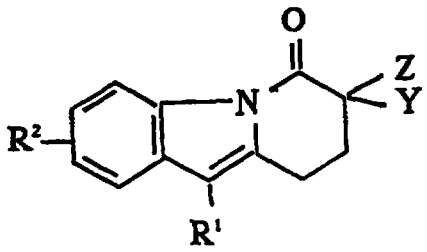
dans laquelle
R^3 est défini comme ci-dessus, ou un sel de celui-ci, pour donner un composé de la formule :



dans laquelle

R^1, R^2 et R^3 sont définis chacun comme ci-dessus, ou un sel de celui-ci, ou

(2) de faire réagir un composé de la formule :



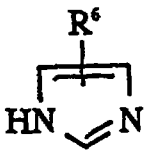
dans laquelle

R^1 et R^2 sont définis chacun comme ci-dessus et

Y est un N,N-di(C_1-C_6)alkylaminométhyle et

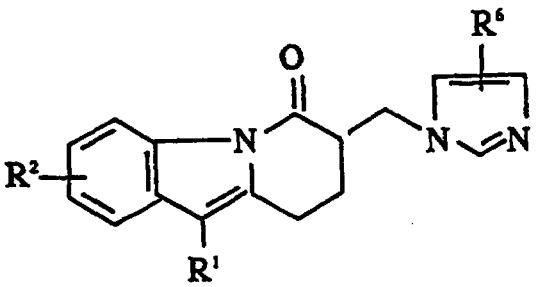
Z est un hydrogène ou Y et Z sont combinés pour former un méthylène,

avec un composé de la formule :



dans laquelle

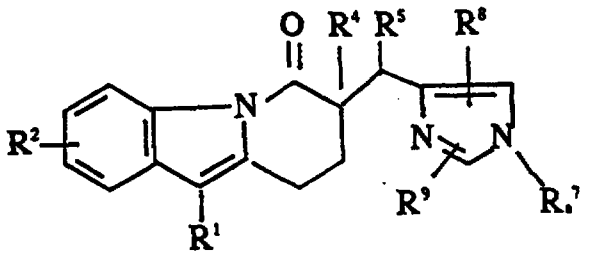
R^6 est un hydrogène ou un (C_1-C_6)alkyle ou un sel de celui-ci, pour donner un composé de la formule :



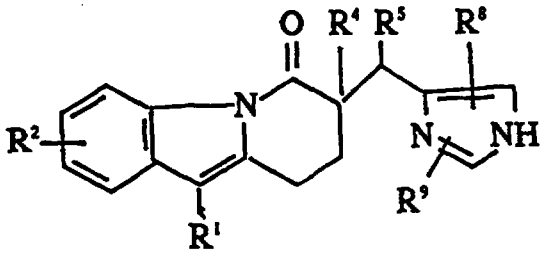
dans laquelle

R^1, R^2 et R^6 sont définis chacun comme ci-dessus ou un sel de celui-ci, ou

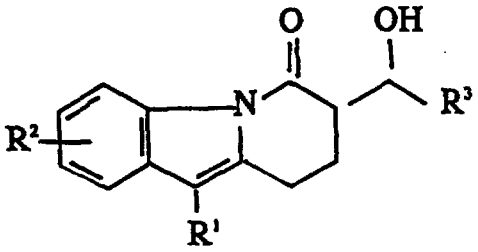
(3) de soumettre un composé de la formule :



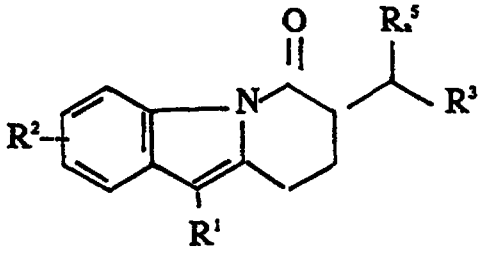
dans laquelle
R^1, R^2, R^4 et R^5 sont définis chacun comme ci-dessus,
R_a^7 est un groupe imino-protecteur et
R^8 et R^9 sont chacun un hydrogène ou un (C_1-C_6)alkyle,
ou un sel de celui-ci, à une réaction d'élimination du groupe imino-protecteur, pour donner un composé de la formule :



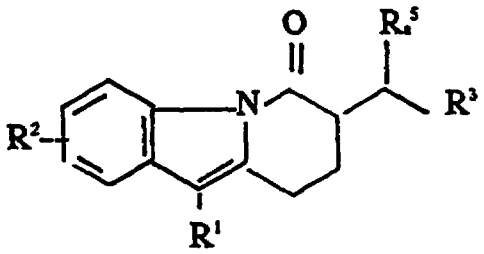
dans laquelle
R^1, R^2, R^4, R^5, R^8 et R^9 sont définis chacun comme ci-dessus,
ou un sel de celui-ci, ou
(4) de soumettre un composé de la formule :



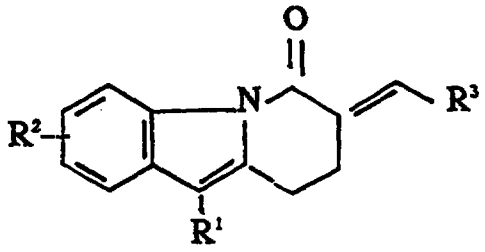
dans laquelle
R^1, R^2 et R^3 sont définis chacun comme ci-dessus,
ou un sel de celui-ci, à une réaction d'acylation, pour donner un composé de la formule :



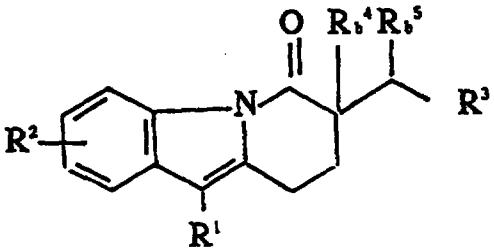
dans laquelle
R^1, R^2, et R^3 sont définis chacun comme ci-dessus et
R^5 est un acyloxy,
ou un sel de celui-ci, ou
(5) de soumettre un composé de la formule :



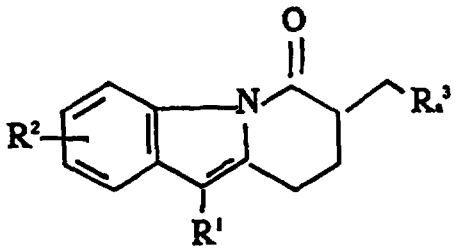
dans laquelle
R^1, R^2, R^3 et R_a^5 sont définis chacun comme ci-dessus ou un sel de celui-ci, à une réaction d'élimination de H-R_a^5, pour donner un composé de la formule :



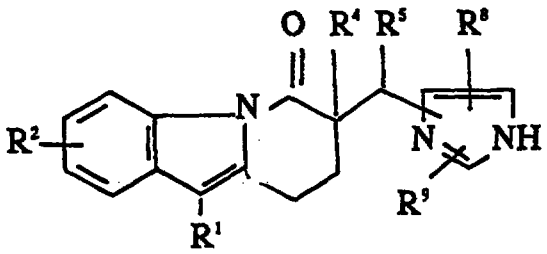
dans laquelle
R^1, R^2 et R^3 sont définis chacun comme ci-dessus, ou un sel de celui-ci, ou
(6) de soumettre un composé de la formule :



dans laquelle
R^1, R^2 et R^3 sont définis chacun comme ci-dessus et
R_b^4 est un hydrogène et R_b^5 est un hydroxy ou un acyloxy ou
R_b^4,et R_b^5 sont liés ensemble pour former une liaison additionnelle,
ou un sel de celui-ci, à une réduction pour donner un composé de la formule :



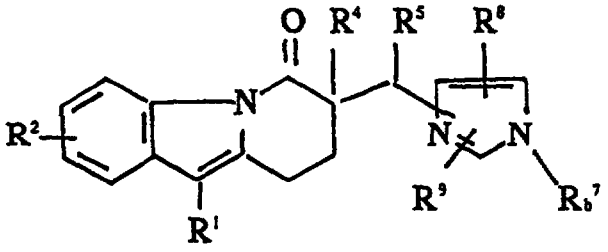
dans laquelle
R^1, R^2 et R_a^3 sont définis chacun comme ci-dessus, ou un sel de celui-ci, ou
(7) de faire réagir un composé de la formule :



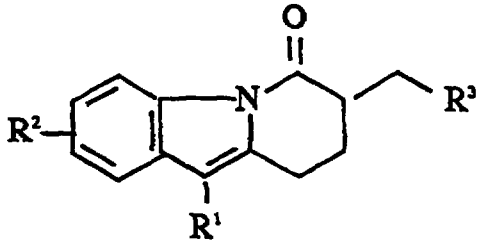
dans laquelle
R^1, R^2, R^4, R^5, R^8 et R^9 sont définis chacun comme ci-dessus, ou un sel de celui-ci, avec un composé de la formule :

R_b^7X

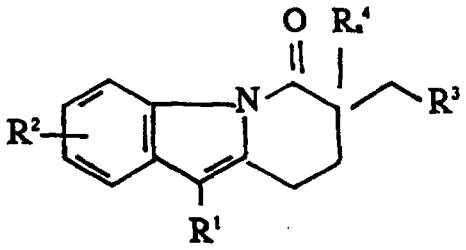
dans laquelle
R_b^7 est un (C_1-C_6)alkyle et
X est un résidu acide,
ou un sel de celui-ci pour donner un composé de la formule :



dans laquelle
R^1, R^2, R^4, R^5, R_b^7, R^8 et R^9 sont définis chacun comme ci-dessus, ou un sel de celui-ci, ou
(8) de soumettre un composé de la formule :



dans laquelle
R^1, R^2 et R^3 sont définis chacun comme ci-dessus, ou un sel de celui-ci, à l'introduction de R_a^4, pour donner un composé de la formule :



dans laquelle
R^1, R^2 et R^3 sont définis chacun comme ci-dessus et
$R^4{}_a$ est un (C_1-C_6)alkyle, un (C_2-C_6)alcényle ou un hydroxy(C_1-C_6)alkyle,
ou un sel de celui-ci.

9. Composition pharmaceutique comprenant un composé de la revendication 1 ou un sel de celui-ci acceptable sur le plan pharmaceutique en association avec un vecteur ou un excipient sensiblement non toxique et acceptable sur le plan pharmaceutique.

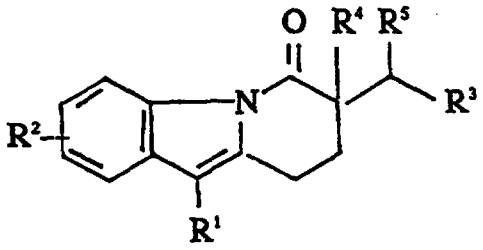
10. Utilisation d'un composé de la revendication 1 ou un sel de celui-ci acceptable sur le plan pharmaceutique, pour la fabrication d'un médicament servant d'antagoniste de la 5-hydroxytryptamine.

11. Composé de la revendication 1 ou un sel de celui-ci acceptable sur le plan pharmaceutique, pour une utilisation comme médicament.

12. Composé de la revendication 1 ou un sel acceptable de celui-ci sur le plan pharmaceutique servant d'antagoniste de la 5-hydroxytryptamine.

Revendications pour l'Etat contractant suivant : ES

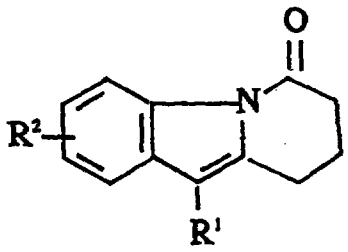
1. Procédé de préparation d'un composé de la formule :



(I)

dans laquelle
R^1 est un hydrogène, un (C_1-C_6)alkyle ou un (C_2-C_6)alcényle,
R^2 est un hydrogène, un (C_1-C_6)alkyle ou un halogène,
R^3 est un imidazolyle ou un pyridyle, chacun des deux pouvant avoir un ou plusieurs substituants appropriés choisis parmi les (C_1-C_6)alkyles et le groupe imino-protecteur et R^4 est un hydrogène, un (C_1-C_6)alkyle, un (C_2-C_6)alcényle ou un hydroxy(C_1-C_6)alkyle et R^5 est un hydrogène, un hydroxy ou un acyloxy, ou
R^4 et R^5 sont liés ensemble pour former une liaison additionnelle,
ou un sel de celui-ci, qui comprend de

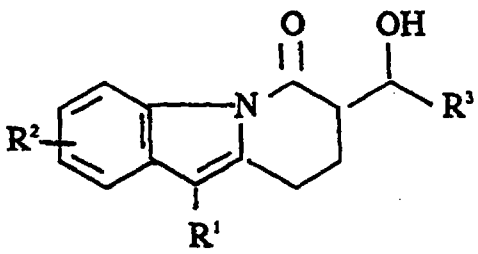
(1) faire réagir un composé de la formule :



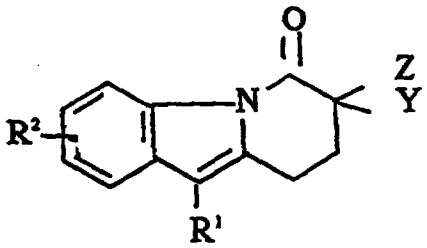
dans laquelle
R^1 et R^2 sont définis chacun comme ci-dessus, avec un composé de la formule :

OHC - R^3

dans laquelle
R^3 est défini comme ci-dessus, ou un sel de celui-ci, pour donner un composé de la formule :



dans laquelle
R^1, R^2 et R^3 sont définis chacun comme ci-dessus, ou un sel de celui-ci, ou
(2) de faire réagir un composé de la formule :

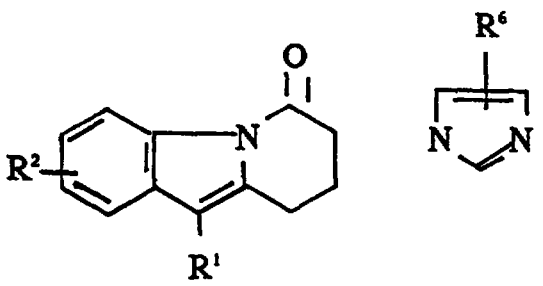


dans laquelle
R^1 et R^2 sont définis chacun comme ci-dessus et
Y est un N,N-di(C_1-C_6)alkylaminométhyle et
Z est un hydrogène ou Y et Z sont combinés pour former un méthylène,
avec un composé de la formule :



dans laquelle

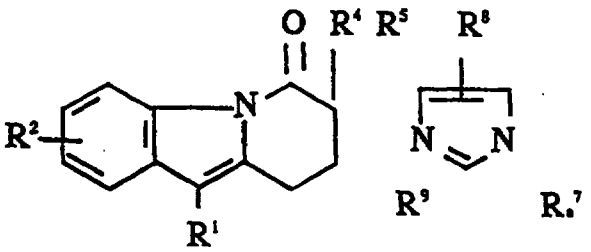
R^6 est un hydrogène ou un (C_1-C_6)alkyle ou un sel de celui-ci, pour donner un composé de la formule :



dans laquelle

R^1, R^2 et R^6 sont définis chacun comme ci-dessus ou un sel de celui-ci, ou

(3) de soumettre un composé de la formule :



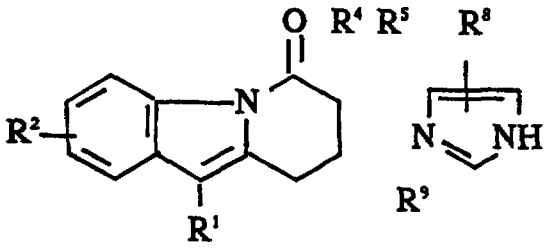
dans laquelle

R^1, R^2, R^4 et R^5 sont définis chacun comme ci-dessus,

R_a^7 est un groupe imino-protecteur et

R^8 et R^9 sont chacun un hydrogène ou un (C_1-C_6)alkyle,

ou un sel de celui-ci, à une réaction d'élimination du groupe imino-protecteur, pour donner un composé de la formule :

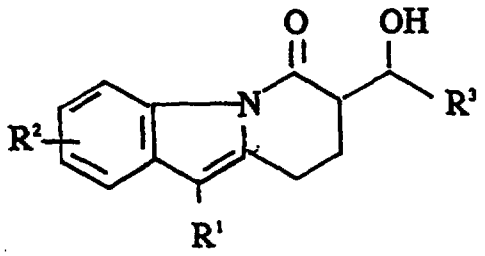


dans laquelle

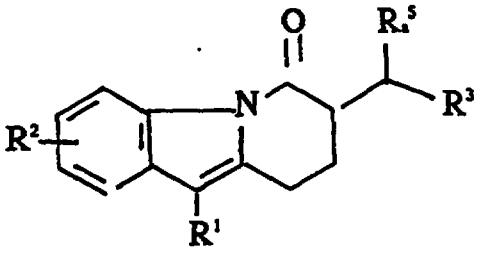
R^1, R^2, R^4, R^5, R^8 et R^9 sont définis chacun comme ci-dessus,

ou un sel de celui-ci, ou

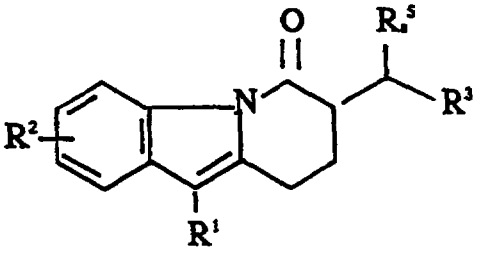
(4) de soumettre un composé de la formule :



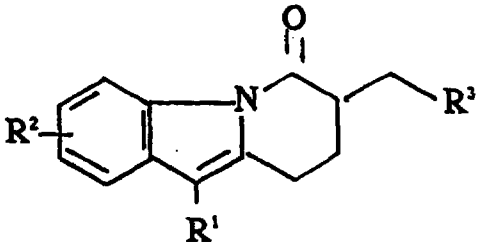
dans laquelle
R^1, R^2 et R^3 sont définis chacun comme ci-dessus,
ou un sel de celui-ci, à une réaction d'acylation, pour donner un composé de la formule :



dans laquelle
R^1, R^2, et R^3 sont définis chacun comme ci-dessus et
R_a^5 est un acyloxy,
ou un sel de celui-ci, ou
(5) de soumettre un composé de la formule :

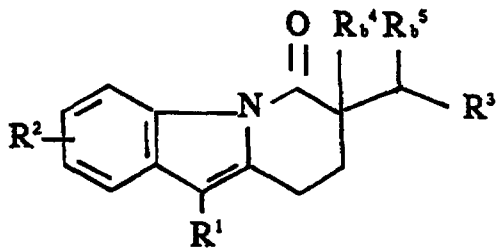


dans laquelle
R^1, R^2, R^3 et R_a^5 sont définis chacun comme ci-dessus
ou un sel de celui-ci, à une réaction d'élimination de H-R_a^5, pour donner un composé de la formule :

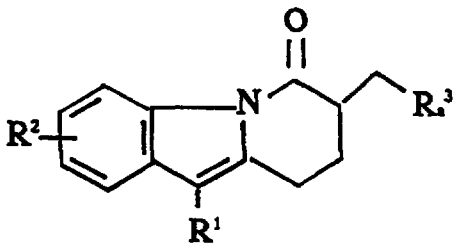


dans laquelle
R^1, R^2 et R^3 sont définis chacun comme ci-dessus,

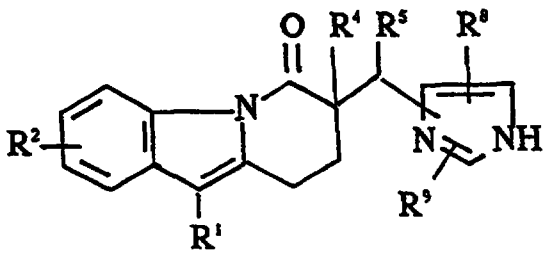
ou un sel de celui-ci, ou
(6) de soumettre un composé de la formule :



dans laquelle
R^1, R^2 et R^3 sont définis chacun comme ci-dessus et
R_b^4 est un hydrogène et R_b^5 est un hydroxy ou un acyloxy ou
R_b^4 et R_b^5 sont liés ensemble pour former une liaison additionnelle,
ou un sel de celui-ci, à une réduction pour donner un composé de la formule :



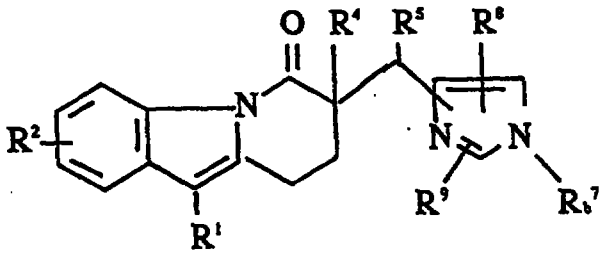
dans laquelle
R^1, R^2 et R_a^3 sont définis chacun comme ci-dessus,
ou un sel de celui-ci, ou
(7) de faire réagir un composé de la formule :



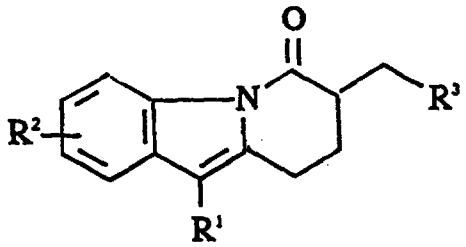
dans laquelle
R^1, R^2, R^4, R^5, R^8 et R^9 sont définis chacun comme ci-dessus,
ou un sel de celui-ci, avec un composé de la formule :

R_b^7X

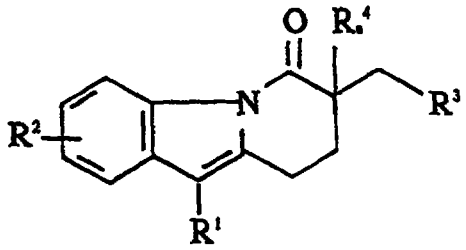
dans laquelle
R_b^7 est un (C_1-C_6)alkyle et
X est un résidu acide,
ou un sel de celui-ci pour donner un composé de la formule :



dans laquelle
R^1, R^2, R^4, R^5, R_b^7, R^8 et R^9 sont définis chacun comme ci-dessus,
ou un sel de celui-ci, ou
(8) de soumettre un composé de la formule :



dans laquelle
R^1, R^2 et R^3 sont définis chacun comme ci-dessus,
ou un sel de celui-ci, à l'introduction de R_a^4, pour donner un composé de la formule :



dans laquelle
R^1, R^2 et R^3 sont définis chacun comme ci-dessus et
$R^4{}_a$ est un (C_1-C_6)alkyle, un (C_2-C_6)alcényle ou un hydroxy(C_1-C_6)alkyle,
ou un sel de celui-ci.

2. Procédé selon la revendication 1, dans lequel
R^3 est un imidazolyle qui peut avoir un à trois substituants choisis parmi les groupes alkyles inférieurs et le groupe imino-protecteur.

3. Procédé selon la revendication 2, dans lequel
R^3 est un 2-(alkyle inférieur)-1H-imidazol-1-yle, un 1H-imidazol-2-yle, un 1-ar(alkyle inférieur)-1H-imidazol-2-yle, un 1-ar(alkyle inférieur)-5-(alkyle inférieur)-1H-imidazol-4-yle, un 5-(alkyle inférieur)-1H-imidazol-4-yle, un 1-ar(alkyle inférieur)-1H-imidazol-4-yle, un 1H-imidazol-4-yle, un 2-(alkyle inférieur)-5-(alkyle inférieur)-1H-imidazol-4-yle, un 1-ar(alkyle inférieur)-2-(alkyle inférieur)-1H-imidazol-4-yle, un 2-(alkyle inférieur)-1H-imidazol-4-yl, un 1-(alkyle inférieur)-1H-imidazol-4-yle, un 1-(alkyle inférieur)-5-(alkyle inférieur)-1H-imidazol-4-yle, un di(alkyle inférieur)aminosulfonyl-5-(alkyle inférieur)-1H-imidazol-4-yle, un 1-(alkyle inférieur)-1H-imidazol-5-yle, ou un 1-(alkyle inférieur)-4-(alkyle inférieur)-1H- imidazol-

* C L M S *

5-yle.

4. Procédé selon la revendication 3, dans lequel
R^1 est un alkyle inférieur,
R^2 est un hydrogène,
R^3 est un 1-mono-, un di- ou un triphényl(alkyle inférieur)-5-(alkyle inférieur)-1H-imidazol-4-yle, un 5-(alkyle inférieur)-1H-imidazol-4-yle ou un 1-di(alkyle inférieur)aminosulfonyl-5-(alkyle inférieur)-1H-imidazol-4-yle et
R^4 est un hydrogène et R^5 est un hydrogène, un hydroxy ou un alcanoyloxy inférieur ou
R^4 et R^5 sont liés ensemble pour former une liaison additionnelle.

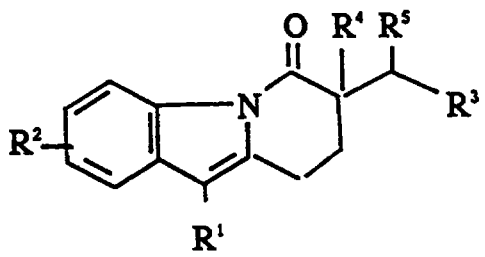
5. Procédé selon la revendication 4, dans lequel
R^3 est un 5-(alkyle inférieur)-1H-imidazol-4-yle et
R^4 et R^5 sont chacun un hydrogène.

6. Procédé selon la revendication 5, pour préparer la 8,9-dihydro-10-méthyl-7-[(5-méthyl-1H-imidazol-4-yl)méthyl]pyrido[1,2-a]indol-6-(7H)one ou un sel d'addition de celui-ci avec un acide.

7. Procédé selon la revendication 6, pour préparer la (+)8,9-dihydro-10-méthyl-7-[(5-méthyl-1H-imidazol-4-yl)méthyl]pyrido[1,2-a]indol-6(7H)one,son chlorhydrate ou son maléate.

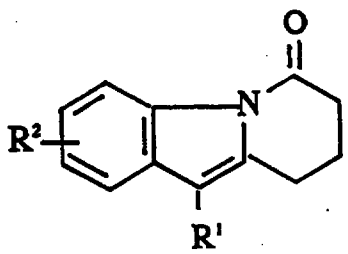
Revendications pour l'Etat contractant suivant : GR

1. Procédé de préparation d'un composé de la formule :



(I)

dans laquelle
R^1 est un hydrogène, un (C_1-C_6)alkyle ou un (C_2-C_6)alcényle,
R^2 est un hydrogène, un (C_1-C_6)alkyle ou un halogène,
R^3 est un imidazolyle ou un pyridyle, chacun des deux pouvant avoir un ou plusieurs substituants appropriés choisis parmi les (C_1-C_6)alkyles et le groupe imino-protecteur et
R^4 est un hydrogène, un (C_1-C_6)alkyle, un (C_2-C_6)alcényle ou un hydroxy(C_1-C_6)alkyle et R^5 est un hydrogène, un hydroxy ou un acyloxy, ou
R^4 et R^5 sont liés ensemble pour former une liaison additionnelle,
ou un sel de celui-ci, qui comprend de
(1) faire réagir un composé de la formule :

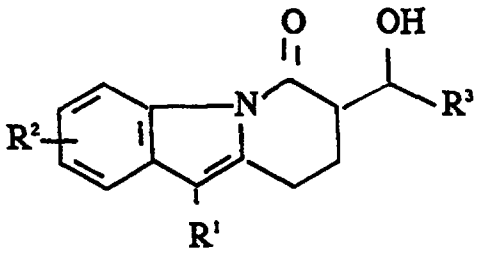


dans laquelle
R^1 et R^2 sont définis chacun comme ci-dessus, avec un composé de la formule :

OHC - R^3

dans laquelle

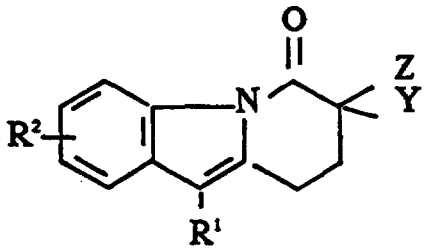
R^3 est défini comme ci-dessus, ou un sel de celui-ci, pour donner un composé de la formule :



dans laquelle

R^1, R^2 et R^3 sont définis chacun comme ci-dessus, ou un sel de celui-ci, ou

(2) de faire réagir un composé de la formule :



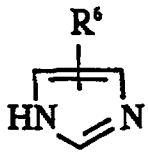
dans laquelle

R^1 et R^2 sont définis chacun comme ci-dessus et

Y est un N,N-di(C_1-C_6)alkylaminométhyle et

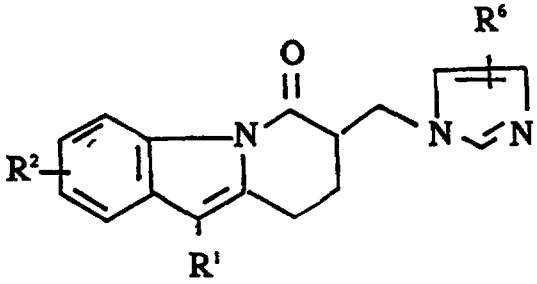
Z est un hydrogène ou Y et Z sont combinés pour former un méthylène,

avec un composé de la formule :

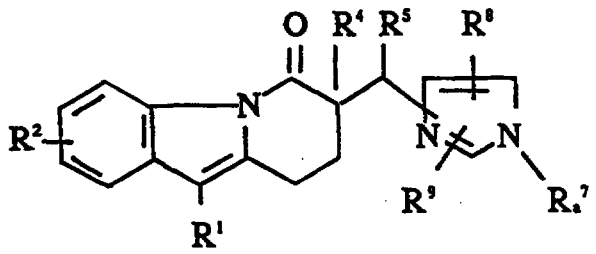


dans laquelle

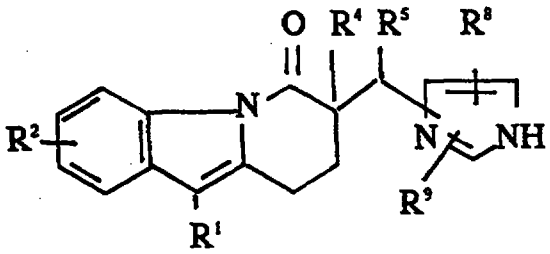
R^6 est un hydrogène ou un (C_1-C_6)alkyle ou un sel de celui-ci, pour donner un composé de la formule :



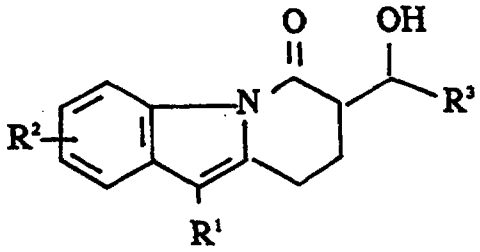
dans laquelle
R^1, R^2 et R^6 sont définis chacun comme ci-dessus
ou un sel de celui-ci, ou
(3) de soumettre un composé de la formule :



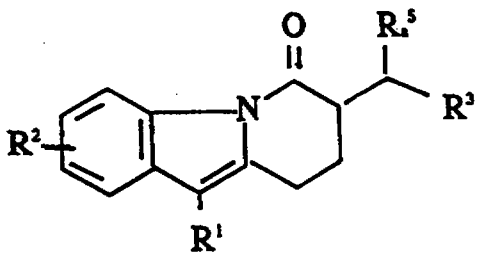
dans laquelle
R^1, R^2, R^4 et R^5 sont définis chacun comme ci-dessus,
R_a^7 est un groupe imino-protecteur et
R^8 et R^9 sont chacun un hydrogène ou un (C_1-C_6)alkyle,
ou un sel de celui-ci, à une réaction d'élimination du groupe imino-protecteur, pour donner un composé de la formule :



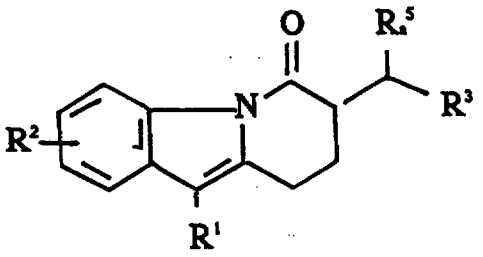
dans laquelle
R^1, R^2, R^4, R^5, R^8 et R^9 sont définis chacun comme ci-dessus,
ou un sel de celui-ci, ou
(4) de soumettre un composé de la formule :



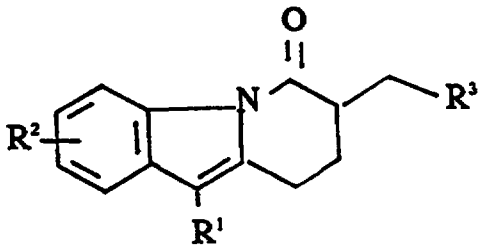
dans laquelle
R^1, R^2 et R^3 sont définis chacun comme ci-dessus,
ou un sel de celui-ci, à une réaction d'acylation, pour donner un composé de la formule :



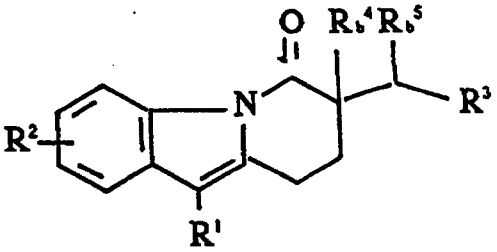
dans laquelle
R^1, R^2, et R^3 sont définis chacun comme ci-dessus et
R_a^5 est un acyloxy,
ou un sel de celui-ci, ou
(5) de soumettre un composé de la formule :



dans laquelle
R^1, R^2, R^3 et R_a^5 sont définis chacun comme ci-dessus
ou un sel de celui-ci, à une réaction d'élimination de H-R_a^5, pour donner un composé de la formule :

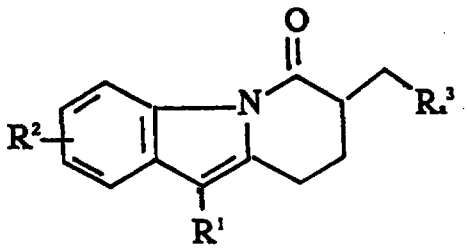


dans laquelle
R^1, R^2 et R^3 sont définis chacun comme ci-dessus,
ou un sel de celui-ci, ou
(6) de soumettre un composé de la formule :

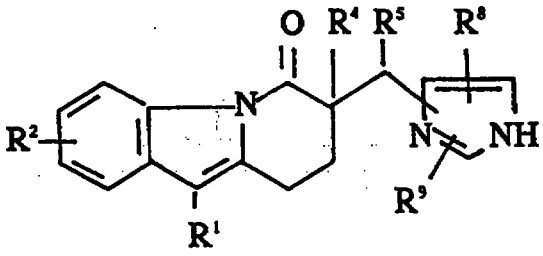


dans laquelle

R^1, R^2 et R^3 sont définis chacun comme ci-dessus et
R_b^4 est un hydrogène et R_b^5 est un hydroxy ou un acyloxy ou
R_b^4 et R_b^5 sont liés ensemble pour former une liaison additionnelle,
ou un sel de celui-ci, à une réduction pour donner un composé de la formule :



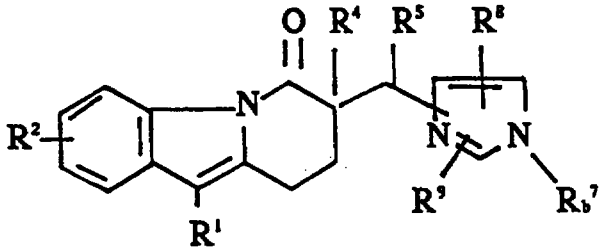
dans laquelle
R^1, R^2 et R_a^3 sont définis chacun comme ci-dessus,
ou un sel de celui-ci, ou
(7) de faire réagir un composé de la formule :



dans laquelle
R^1, R^2, R^4, R^5, R^8 et R^9 sont définis chacun comme ci-dessus,
ou un sel de celui-ci, avec un composé de la formule :

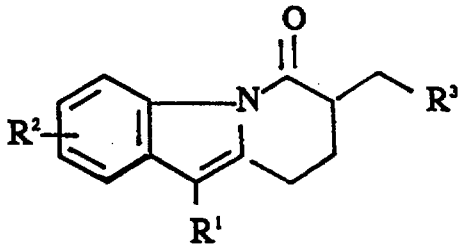
R_b^7X

dans laquelle
R_b^7 est un $(C_1\text{-}C_6)$alkyle et
X est un résidu acide,
ou un sel de celui-ci pour donner un composé de la formule :

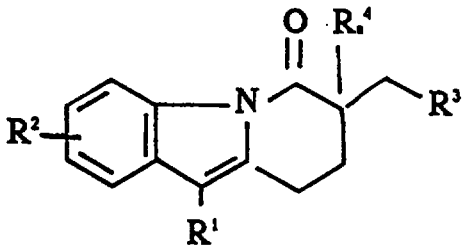


dans laquelle
R^1, R^2, R^4, R^5, R_b^7, R^8 et R^9 sont définis chacun comme ci-dessus,
ou un sel de celui-ci, ou

(8) de soumettre un composé de la formule :



dans laquelle
R^1, R^2 et R^3 sont définis chacun comme ci-dessus,
ou un sel de celui-ci, à l'introduction de R_a^4, pour donner un composé de la formule :



dans laquelle
R^1, R^2 et R^3 sont définis chacun comme ci-dessus et
$R^4{}_a$ est un (C_1-C_6)alkyle, un (C_2-C_6)alcényle ou un hydroxy(C_1-C_6)alkyle,
ou un sel de celui-ci.

2. Procédé selon la revendication 1, dans lequel
R^3 est un imidazolyle qui peut avoir un à trois substituants choisis parmi les groupes alkyles inférieurs et le groupe imino-protecteur.

3. Procédé selon la revendication 2, dans lequel
R^3 est un 2-(alkyle inférieur)-1H-imidazol-1-yle, un 1H-imidazol-2-yle, un 1-ar(alkyle inférieur)-1H-imidazol-2-yle, un 1-ar(alkyle inférieur)-5-(alkyle inférieur)-1H-imidazol-4-yle, un 5-(alkyle inférieur)-1H-imidazol-4-yle, un 1-ar(alkyle inférieur)-1H-imidazol-4-yle, un 1H-imidazol-4-yle, un 2-(alkyle inférieur)-5-(alkyle inférieur)-1H-imidazol-4-yle, un 1-ar(alkyle inférieur)-2-(alkyle inférieur)-1H-imidazol-4-yle, un 2-(alkyle inférieur)-1H-imidazol-4-yl, un 1-(alkyle inférieur)-1H-imidazol-4-yle, un 1-(alkyle inférieur)-5-(alkyle inférieur)-1H-imidazol-4-yle, un di(alkyle inférieur)aminosulfonyl-5-(alkyle inférieur)-1H-imidazol-4-yle, un 1-(alkyle inférieur)-1H-imidazol-5-yle, ou un 1-(alkyle inférieur)-4-(alkyle inférieur)-1H- imidazol-5-yle.

4. Procédé selon la revendication 3, dans lequel
R^1 est un alkyle inférieur,
R^2 est un hydrogène,
R^3 est un 1-mono-, un di- ou un triphényl(alkyle inférieur)-5-(alkyle inférieur)-1H-imidazol-4-yle, un 5-(alkyle inférieur)-1H-imidazol-4-yle ou un 1-di(alkyle inférieur)aminosulfonyl-5-(alkyle inférieur)-1H-imidazol-4-yle et
R^4 est un hydrogène et R^5 est un hydrogène, un hydroxy ou un alcanoyloxy inférieur ou
R^4 et R^5 sont liés ensemble pour former une liaison additionnelle.

5. Procédé selon la revendication 4, dans lequel
R^3 est un 5-(alkyle inférieur)-1H-imidazol-4-yle et
R^4 et R^5 sont chacun un hydrogène.

* C L M S *

6. Procédé selon la revendication 5, pour préparer la 8,9-dihydro-10-méthyl-7-[(5-méthyl-1H-imidazol-4-yl)méthyl]pyrido[1,2-a]indol-6-(7H)one ou un sel d'addition de celui-ci avec un acide.

7. Procédé selon la revendication 6, pour préparer la (+)8,9-dihydro-10-méthyl-7-[(5-méthyl-1H-imidazol-4-yl)méthyl]pyrido[1,2-a]indol-6(7H)one,son chlorhydrate ou son maléate.

8. Modification des procédés selon une quelconque des revendications 1 à 7, dans laquelle le composé de la formule (I) est mis sous une forme acceptable sur le plan pharmaceutique par mélange ou par adjonction audit composé d'au moins d'un vecteur ou d'un diluant acceptable sur le plan pharmaceutique.