

- [54] Title: BICYCLIC AMINE COMPOUND
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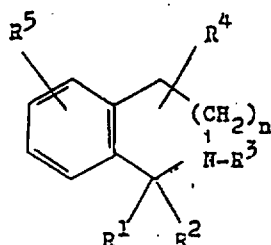
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[57] A B S T R A C T

The present invention relates to novel bicyclic amine compound and a pharmaceutically acceptable salt thereof which is an N-methyl-D-aspartate (an excitatory amino acid) receptor antagonist and useful as an anticonvulsant and a drug for treatment of the delayed neuronal death induced, for instance, by cerebral ischemia, for example, in case of cardiac arrest, to a process for the preparation thereof, to a pharmaceutical composition comprising the same, and to a use of the same as a medicament in treatment of convulsion and delayed neuronal death in human being or animal, and which compound is represented by the following general formula (I):

(see page 2)



(I)

wherein R^1 is lower alkyl,

R^2 is aryl which may have one or more suitable substituent(s), cyclo(lower)alkyl or heterocyclic group,

R^3 is hydrogen, lower alkyl which may have one or more suitable substituent(s), lower alkenyl, or acyl which may have one or more suitable substituent(s),

R^4 is hydrogen, lower alkyl, or hydroxy(lower)alkyl,

R^5 is hydrogen, lower alkyl, halogen, or protected amino, and

n is an integer of 1 or 2.

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BICYCLIC AMINE COMPOUND AND
A PROCESS FOR THE PREPARATION THEREOF

The present invention relates to novel bicyclic amine compound and a pharmaceutically acceptable salt thereof.

More particularly, it relates to novel bicyclic amine compound and a pharmaceutically acceptable salt thereof,
5 which is an N-methyl-D-aspartate (an excitatory amino acid) receptor antagonist and useful as an anticonvulsant and a drug for treatment of the delayed neuronal death induced, for instance, by cerebral ischemia, for example, in case of cardiac arrest, to a process for the
10 preparation thereof, to a pharmaceutical composition comprising the same, and to a use of the same as a medicament in treatment of convulsion and delayed neuronal death in human being or animal.

15 Accordingly, one object of the present invention is to provide novel bicyclic amine compound and a pharmaceutically acceptable salt thereof, which is useful as stated above.

Another object of the present invention is to provide

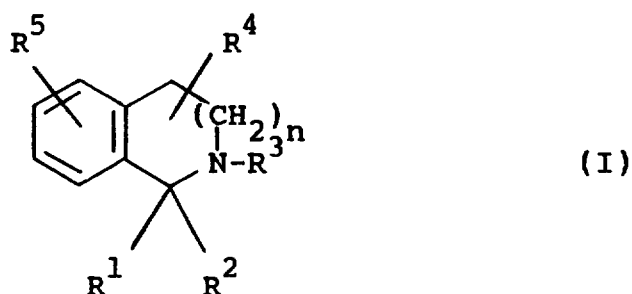
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a process for the preparation of novel bicyclic amine compound and a salt thereof.

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

Still further object of the present invention is to provide a use of said bicyclic amine compound and a pharmaceutically acceptable salt thereof as a medicament in the treatment of convulsion and delayed neuronal death in human being or animal.

The object bicyclic amine compound of the present invention is novel and can be represented by the following general formula (I).



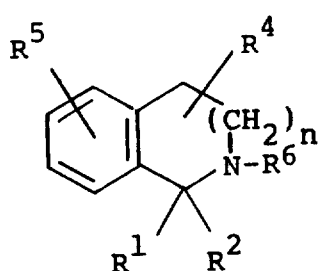
wherein R^1 is lower alkyl,
 R^2 is aryl which may have one or more suitable substituent(s), cyclo(lower)alkyl or heterocyclic group,
 R^3 is hydrogen, lower alkyl which may have one or more suitable substituent(s), lower alkenyl, or acyl which may have one or more suitable substituent(s),
 R^4 is hydrogen, lower alkyl, or hydroxy(lower)-alkyl,
 R^5 is hydrogen, lower alkyl, halogen, or protected amino, and

n is an integer of 1 or 2.

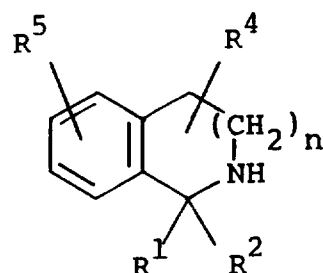
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According to the present invention, the novel bicyclic amine compound (I) can be prepared by the processes illustrated in the following reaction schemes.

Process 1



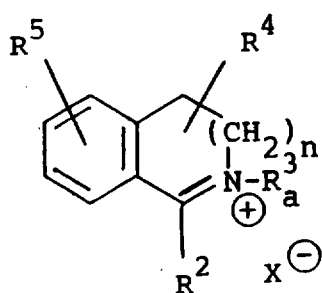
elimination reaction
of the amino
protective group



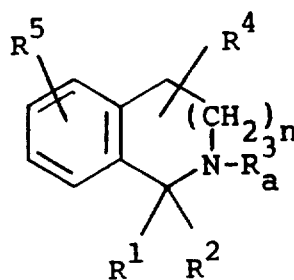
(II)
or a salt thereof

(Ia)
or a salt thereof

Process 2



lower alkylating
agent

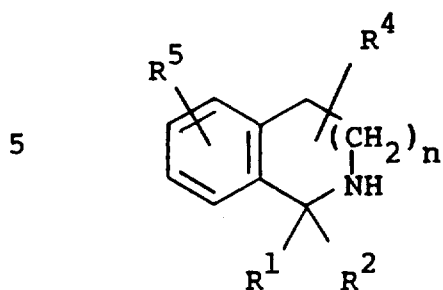


(III)
or a salt thereof

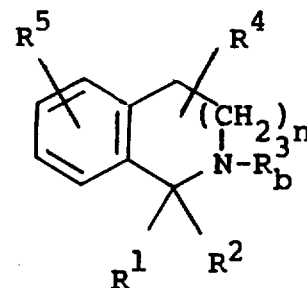
(Ib)
or a salt thereof

Process 3

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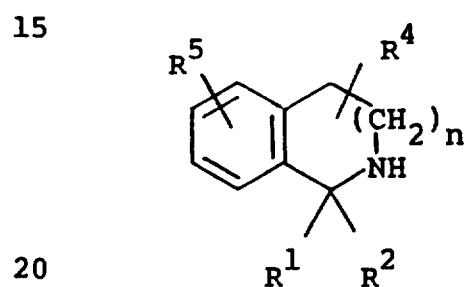
R_b^3-Y (IV)
or a salt
thereof



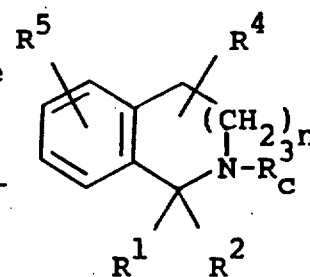
10 (Ia)
or a salt thereof

(Ic)
or a salt thereof

Process 4



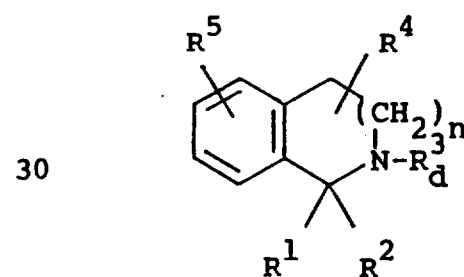
introduction reaction
of acyl which may have
one or more suitable
substituent(s)



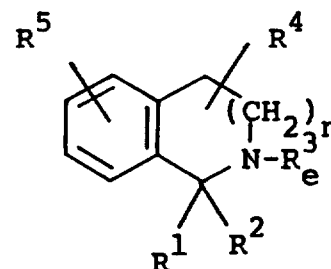
(Ia)
or a salt thereof

(Id)
or a salt thereof

Process 5



cyclic amine
(V)
or a salt
thereof

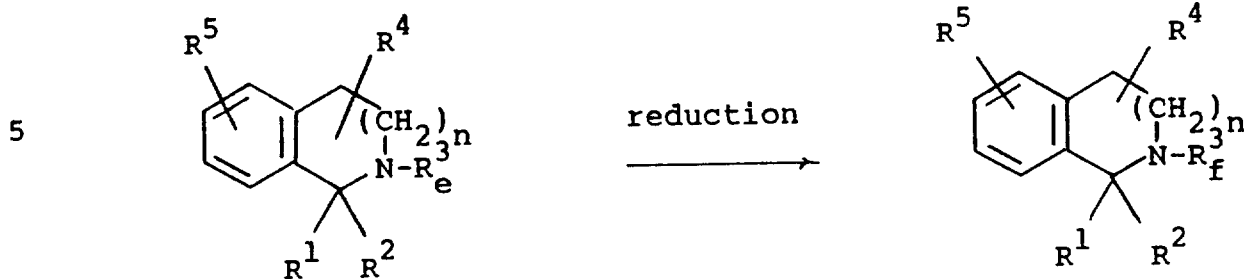


35 (Ie)
or a salt thereof

(If)
or a salt thereof

Process 6

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10 (If)
or a salt thereof

(Ig)
or a salt thereof

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

15 R_a^3 is lower alkyl which may have one or more
suitable substituent(s), lower alkenyl, or
acyl which may have one or more suitable
substituent(s),

R_b^3 is lower alkyl which may have one or more
suitable substituent(s), or lower alkenyl,

20 R_c^3 is acyl which may have one or more suitable
substituent(s),

R_d^3 is lower alkanoyl having halogen,

R_e^3 is lower alkanoyl having cyclic amino,

R_f^3 is lower alkyl having cyclic amino,

25 R^6 is amino protective group,

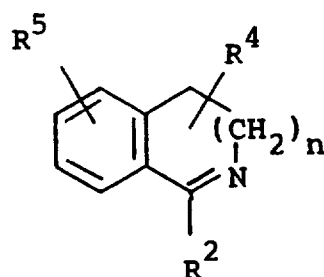
$X^\ominus$ is an anion, and

Y is a leaving group.

30 The starting compounds (II) and (III) to be used in
these processes are novel and can be prepared by the
processes illustrated in the following reaction schemes.

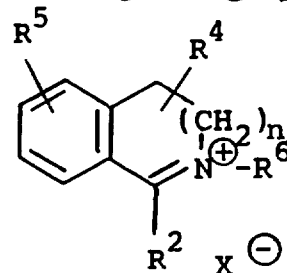
Process For The Preparation of The Starting Compound (II)

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introduction reaction
of the amino
protective group

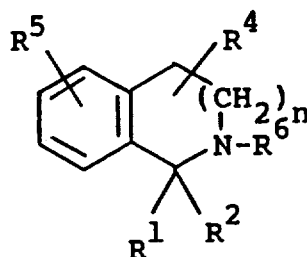
Step A



or a salt thereof

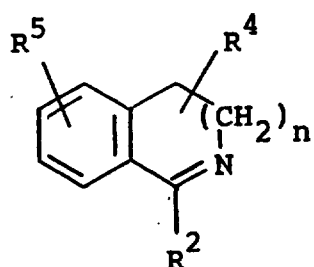
15 lower alkylating
agent

Step B



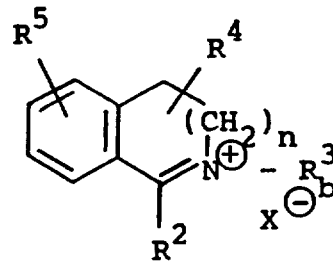
or a salt thereof

Process For The Preparation of The Starting Compound (III)



$R_b^3 - Y$ (IV)
or a salt
thereof

Step C



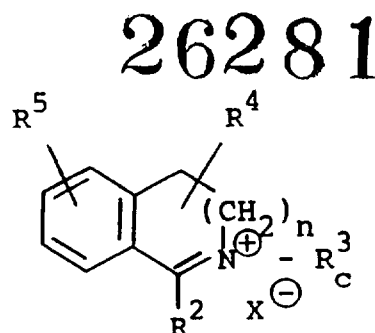
35 or a salt thereof

or a salt thereof



introduction reaction
of acyl which may have
one or more suitable
substituent(s)

Step D



(IIIb)

or a salt thereof

wherein R^1 , R^2 , R_b^3 , R_c^3 , R^4 , R^5 , R^6 , n , $X^\ominus$ and Y are each
as defined above.

The object compound (I), (Ia), (Ib), (Ic), (Id),
(Ie), (If), (Ig) and the starting compound (II) include
stereomers due to the existence of the asymmetric carbon
atom therein. Said stereomers are also included within
the scope of the present invention.

Suitable pharmaceutically acceptable salt of the
object compound (I) is a conventional non-toxic salt and
may include an acid addition salt such as an organic acid
salt (e.g. acetate, trifluoroacetate, maleate, tartrate,
methanesulfonate, benzenesulfonate, formate,
toluenesulfonate, etc.), an inorganic acid salt (e.g.
hydrochloride, hydrobromide, hydriodide, sulfate,
phosphate, etc.), a salt with an amino acid (e.g.
arginine, aspartic acid, glutamic acid, etc.), or the
like.

In the above and following descriptions of the
present specification, suitable example and illustrations
of the various definitions which the present invention

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include within the scope thereof are explained in detail as follows.

The term "lower" is intended to mean 1 to 6 carbon atom(s) unless otherwise indicated.

5 Suitable "lower alkyl" may include straight or branched ones such as methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, pentyl, hexyl or the like, in which the preferred one may be (C₁-C₄)alkyl and the most preferred one may be methyl and ethyl.

10 Suitable example of "suitable substituent(s)" in "lower alkyl which may have one or more suitable substituent(s)" may include aryl (e.g. phenyl, naphthyl, pentalenyl, indenyl, etc.), cyclic amino such as 5- or 6-membered one having at least one nitrogen atom (e.g.
15 1-pyrrolidinyl, 1-imidazolidinyl, 1-pyrrolinyl, piperidino, 1-piperazinyl, morpholino, etc.) and the like.

 Suitable "lower alkyl which may have one or more suitable substituent(s)" may include lower alkyl as mentioned above which may have one or more (preferably 1
20 to 3) suitable substituent(s) as mentioned above, in which the preferred one may be lower alkyl, lower alkyl having aryl and lower alkyl having cyclic amino, the more preferred one may be lower alkyl, lower alkyl having phenyl and lower alkyl having 6-membered cyclic amino, the
25 much more preferred one may be (C₁-C₄)alkyl, (C₁-C₄)alkyl having phenyl and (C₁-C₄)alkyl having piperidino, and the most preferred one may be methyl, ethyl, phenethyl and 2-piperidinoethyl.

 Suitable "aryl" in "aryl which may have one or more
30 suitable substituent(s)" may include phenyl, naphthyl, pentalenyl, indenyl, and the like, and suitable example of "suitable substituent(s)" in this group may include lower alkyl as mentioned above, lower alkoxy (e.g. methoxy, ethoxy, propoxy, butoxy, t-butoxy, pentyloxy, hexyloxy,
35 etc.), halogen (e.g. fluoro, chloro, bromo and iodo) and

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the like.

The preferred "aryl which may have one or more suitable substituent(s)" may be phenyl which may have 1 to 3 suitable substituent(s) selected from a group consisting of lower alkyl, lower alkoxy and halogen, the more preferred one may be phenyl, phenyl having lower alkyl (e.g. o-tolyl, m-tolyl, p-tolyl, 2-ethylphenyl, 3-propylphenyl, 4-butylphenyl, 3-t-butylphenyl, 4-pentylphenyl, 2-hexylphenyl, etc.), phenyl having lower alkoxy (e.g. 2-methoxyphenyl, 4-methoxyphenyl, 3-ethoxyphenyl, 4-propoxyphenyl, 2-butoxyphenyl, 3-t-butoxyphenyl, 2-pentyloxyphenyl, 4-hexyloxyphenyl, etc.) and phenyl having halogen (e.g. 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-bromophenyl, 4-iodophenyl, etc.), and the most preferred one may be phenyl, p-tolyl, 4-methoxyphenyl, 3-fluorophenyl, 4-fluorophenyl, 2-chlorophenyl, 3-chlorophenyl and 4-chlorophenyl.

Suitable "cyclo(lower)alkyl" may include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl, in which the preferred one may be cyclo(C₄-C₆)alkyl and the more preferred one may be cyclohexyl.

Suitable "heterocyclic group" may be the conventional ones having at least one hetero atom such as oxygen, sulfur, nitrogen or the like and suitable example thereof may include unsaturated 5- or 6-membered ones having 1 to 3 hetero atom(s) such as furyl, thienyl, pyrrolyl, thiazolyl, isothiazolyl, isoxazolyl, dioxolyl (e.g. 1,3-dioxolyl, etc.), dithiolyl (e.g. 1,3-dithiolyl, etc.), 1,2-oxathiolyl (e.g. 3H-1,2-oxathiolyl, etc.), pyrazolyl, 2,3-dihydrofuryl, 2,3-dihydrothienyl, pyrrolinyl, 4,5-dihydrothiazolyl, thiadiazolyl (e.g., 1,2,4-thiadiazolyl, etc.), pyranyl (e.g. 2H-pyranyl, etc.), thiinyl (e.g. 4H-thiinyl, etc.), pyridyl,

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1,3-oxathiinyl (e.g. 4H-1,3-oxathiinyl, etc.),
1,4-dioxinyl, 1,3-dithiinyl (e.g. 6H-1,3-dithiinyl, etc.),
1,3-oxazinyl (e.g. 6H-1,3-oxazinyl, etc.), 1,4-thiazinyl
(e.g. 2H-1,4-thiazinyl, etc.), pyrimidinyl,
5 1,2,5-thiadiazinyl (e.g. 6H-1,2,5-thiadiazinyl, etc.), or
the like;

saturated 5- or 6-membered ones having 1 to 3 hetero
atom(s) such as oxolanyl, thiolanyl, pyrrolidinyl,
thiazolidinyl (e.g. 1,3-thiazolidinyl, etc.), oxathiolanyl
10 (e.g. 1,2-oxathiolanyl, etc.), isoxazolidinyl,
1,3-dioxolanyl, 1,3-dithiolanyl, 1,3,4-dioxathiolanyl,
oxanyl, dioxanyl (e.g. 1,4-dioxanyl, etc.), dithianyl
(e.g. 1,3-dithianyl, etc.), 1,3,5-oxadithianyl, piperidyl,
piperazinyl, perhydro-1,4-thiazinyl,
15 perhydro-1,3-oxazinyl, perhydro-1,2,5-thiadiazinyl, or the
like; and the like, in which the preferred one may be
unsaturated 5- or 6-membered heterocyclic group having 1
to 3 oxygen or sulfur atom(s), the more preferred one may
be unsaturated 5-membered heterocyclic group having 1 to 2
20 oxygen or sulfur atom(s) and the most preferred one may be
furyl and thienyl.

Suitable "lower alkenyl" may include straight or
branched ones having 2 to 6 carbon atoms such as vinyl,
allyl, isopropenyl, 2-butenyl, 4-pentenyl, 1-hexenyl or
25 the like, in which the preferred one may be (C₂-C₄)alkenyl
and the most preferred one may be allyl.

Suitable "acyl" may include lower alkanoyl (e.g.
formyl, acetyl, propionyl, butyryl, valeryl, pivaloyl,
hexanoyl, etc.), lower alkoxycarbonyl (e.g.
30 methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl,
butoxycarbonyl, t-butoxycarbonyl, pentyloxycarbonyl,
hexyloxycarbonyl, etc.), and the like and said "acyl" may
have one or more (preferably 1 to 3) suitable
substituent(s) such as aforesaid halogen, aforesaid cyclic
35 amino, or the like.

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The preferred "acyl which may have one or more suitable substituent(s)" may be lower alkanoyl, lower alkanoyl having halogen, lower alkanoyl having cyclic amino, the more preferred one may be lower alkanoyl having halogen and lower alkanoyl having 6-membered cyclic amino, the much more preferred one may be (C₂-C₄)alkanoyl having halogen and (C₂-C₄)alkanoyl having piperidino, and the most preferred one may be 2-chloroacetyl and 2-piperidinoacetyl.

Suitable "hydroxy(lower)alkyl" may include hydroxymethyl, 2-hydroxyethyl, 2-hydroxypropyl, 1-hydroxybutyl, 1-hydroxymethyl-1-methylethyl, 3-hydroxypentyl, 6-hydroxyhexyl, in which the preferred one may be hydroxy(C₁-C₄)alkyl and the more preferred one may be hydroxymethyl.

Suitable "protected amino" may be amino group protected by conventional amino protective group such as ar(lower)alkyl as explained below, aforesaid acyl or the like, in which the preferred one may be lower alkoxy-carbonylamino (e.g. methoxycarbonylamino, ethoxycarbonylamino, propoxycarbonylamino, butoxycarbonylamino, t-butoxycarbonylamino, pentyloxycarbonylamino, hexyloxycarbonylamino, etc.), the more preferred one may be (C₁-C₄)alkoxy-carbonylamino and the most preferred one may be ethoxycarbonylamino.

Suitable "amino protective group" may be conventional ones to be used in this field of the art and, for example, may include ar(lower)alkyl such as phenyl(lower)alkyl (e.g. benzyl, phenethyl, etc.), diphenyl(lower)alkyl (e.g. benzhydryl, etc.), triphenyl(lower)alkyl (e.g. trityl, etc.) or the like, each of which may have aforesaid lower alkoxy; and the like, in which the preferred one may be phenyl(lower)alkyl which may have lower alkoxy, the more preferred one may be phenyl(C₁-C₄)alkyl which may have (C₁-C₄)alkoxy and the most preferred one may be benzyl and

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4-methoxybenzyl.

Suitable "anion" may be formate, acetate, trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate, toluenesulfonate, halogen anion (e.g. chloride, bromide, iodide), sulfate, phosphate, or the like.

Suitable "a leaving group" may include halogen as mentioned before, acyloxy such as lower alkanoyloxy (e.g. acetoxy, etc.), sulfonyloxy (e.g. mesyloxy, tosyloxy, etc.) or the like, and the like.

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

Process 1

The compound (Ia) or a salt thereof can be prepared by subjecting the compound (II) or a salt thereof to elimination reaction of the amino protective group.

Suitable salts of the compounds (Ia) and (II) can be referred to the ones as exemplified for the compound (I).

This reaction is carried out in accordance with a conventional method such as hydrolysis, reduction, oxydation or the like.

The hydrolysis is preferably carried out in the presence of a base or an acid including Lewis acid. Suitable base may include an inorganic base and an organic base such as an alkali metal [e.g. sodium, potassium, etc.], an alkaline earth metal [e.g. magnesium, calcium, etc.], the hydroxide or carbonate or bicarbonate thereof, trialkylamine [e.g. trimethylamine, triethylamine, etc.], picoline, 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.

Suitable acid may include an organic acid [e.g.

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formic acid, acetic acid, propionic acid, trichloroacetic acid, trifluoroacetic acid, etc.] and an inorganic acid [e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, hydrogen chloride, hydrogen bromide, etc.]. The elimination using Lewis acid such as trihaloacetic acid [e.g. trichloroacetic acid, trifluoroacetic acid, etc.] or the like is preferably carried out in the presence of cation trapping agents [e.g. anisole, phenol, etc.].

The reaction is usually carried out in a solvent such as water, an alcohol [e.g. methanol, ethanol, etc.], methylene chloride, tetrahydrofuran, a mixture thereof or any other solvent which does not adversely influence the reaction. A liquid base or acid can be also used as the solvent. The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

The reduction method applicable for the elimination reaction may include chemical reduction and catalytic reduction.

Suitable reducing agents to be used in chemical reduction are 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.].

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

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reduced iron, Raney iron, etc.], copper catalysts [e.g. reduced copper, Raney copper, Ullman copper, etc.] and the like.

5 The reduction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, methanol, ethanol, propanol, N,N-dimethylformamide, or a mixture thereof. Additionally, in case that the abovementioned acids to be used in chemical reduction are in liquid, they can also be
10 used as a solvent. Further, a suitable solvent to be used in catalytic reduction may be the above-mentioned solvent, and other conventional solvent such as diethyl ether, dioxane, tetrahydrofuran, acetic acid, etc., or a mixture thereof.

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

20 The oxydation method applicable for the elimination reaction may include oxydation using an oxydating agent such as cerium compound (e.g. ceric ammonium nitrate, etc.) or the like.

25 The oxydation is usually carried out in a conventional solvent such as water, alcohol (e.g. methanol, ethanol, etc.), acetonitrile or any other solvent which does not adversely influence the reaction.

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

30 Process 2

The compound (Ib) or a salt thereof can be prepared by reacting the compound (III) or a salt thereof with a lower alkylating agent.

35 Suitable salts of the compounds (Ib) and (III) can be referred to the ones as exemplified for the compound (I).

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Suitable examples for said lower alkylating agent may be so-called Grignard type reagent shown in the formula : R^1MgY (wherein R^1 is lower alkyl and Y is halogen, each explained before) (e.g. methylmagnesium bromide, ethylmagnesium bromide, propylmagnesium iodide, etc.), metalated lower alkyl (e.g. methyl lithium, ethyl lithium, etc.) or the like.

The reaction is usually carried out in a solvent such as diethyl ether, tetrahydrofuran or any other solvent which does not adversely affect the reaction.

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

Process 3

The compound (Ic) or a salt thereof can be prepared by reacting the compound (Ia) or a salt thereof with the compound (IV) or a salt thereof.

Suitable salts of the compounds (Ic) and (IV) can be referred to the ones as exemplified for the compound (I).

The present reaction may be carried out in a solvent such as water, phosphate buffer, acetone, chloroform, acetonitrile, nitrobenzene, methylene chloride, ethylene chloride, formamide, N,N-dimethylformamide, methanol, ethanol, diethyl ether, tetrahydrofuran, dimethyl sulfoxide, or any other organic solvent which does not adversely affect the reaction, preferably in ones having strong polarities. Among the solvents, hydrophilic solvents may be used in a mixture with water. When the compound (IV) is in liquid, it can also be used as a solvent.

The reaction is preferably conducted in the presence of a base, for example, inorganic base such as alkali metal hydride (e.g. sodium hydride, etc.), alkali metal hydroxide, alkali metal carbonate, alkali metal bicarbonate, organic base such as trialkylamine, and the

like.

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

5 The present reaction is preferably carried out in the presence of alkali metal halide [e.g. sodium iodide, potassium iodide, etc.], alkali metal thiocyanate [e.g. sodium thiocyanate, potassium thiocyanate, etc.] or the like.

10 Process 4

15 The compound (Id) or a salt thereof can be prepared by subjecting the compound (Ia) or a salt thereof to introduction reaction of acyl which may have one or more suitable substituent(s).

Suitable salt of the compound (Id) can be referred to the ones as exemplified for the compound (I).

20 This introduction reaction can be carried out by reacting the compound (Ia) or a salt thereof with an acid corresponding to acyl group to be introduced or its reactive derivative at the carboxy group or a salt thereof.

25 Suitable reactive derivative at the carboxy group may include an acid halide (e.g. acid chloride, etc.), an acid anhydride, an activated amide, an activated ester and the like, which are used conventionally in this field of the art.

30 This reaction is usually carried out in a conventional solvent such as methylene chloride, chloroform or the like.

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

Process 5

35 The compound (If) or a salt thereof can be prepared

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by reacting the compound (Ie) or a salt thereof with the compound (V) or a salt thereof.

Suitable salts of the compounds (Ie), (If) and (V) can be referred to the ones as exemplified for the compound (I).

This reaction can be carried out according to a similar manner to that as explained in Process 3.

Process 6

The compound (Ig) or a salt thereof can be prepared by subjecting the compound (If) or a salt thereof to reduction.

Suitable salt of the compound (Ig) can be referred to the ones as exemplified for the compound (I).

Suitable reducing agent for this reduction may include lithium aluminum hydride, sodium borohydride and the like.

This reaction is usually carried out in a conventional solvent such as tetrahydrofuran, diethyl ether or the like.

The reaction temperature is not critical and the reaction can be carried out under cooling to heating.

When the compound (I) thus obtained in these processes is a racemic mixture, this mixture can be separated into each stereomer according to a conventional manner.

The processes for preparing the starting compounds (II) and (III) of the present invention are explained in detail in the following.

Step A

The compound (VII) can be prepared by subjecting the compound (VI) or a salt thereof to introduction reaction

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of the amino protective group.

Suitable salt of the compound (VI) can be referred to the ones as exemplified for the compound (I).

The introduction reaction of the amino protective group in this step can be carried out by reacting the compound (VI) or a salt thereof with a suitable agent for introducing the amino protective group.

Suitable examples of said agent may be ar(lower)alkyl halide which may have aforesaid lower alkoxy such as phenyl(lower)alkyl halide which may have lower alkoxy (e.g. benzyl iodide, 3-methoxybenzyl iodide, benzyl bromide, 4-methoxybenzyl bromide, phenethyl chloride, etc.), diphenyl(lower)alkyl halide (e.g. benzhydryl chloride, etc.), triphenyl(lower)alkyl halide (e.g. trityl bromide, etc.) or the like.

This introduction reaction may be carried out in a suitable solvent such as chloroform, acetonitrile, nitrobenzene, N,N-dimethylformamide or any other solvent which does not adversely affect the reaction.

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

Step B

The compound (II) or a salt thereof can be prepared by reacting the compound (VII) with a lower alkylating agent.

This reaction can be carried out according to a similar manner to that as explained in Process 2.

Step C

The compound (IIIa) or a salt thereof can be prepared by reacting the compound (VI) or a salt thereof with the compound (IV) or a salt thereof.

Suitable salt of the compound (IIIa) can be referred

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to the ones as exemplified for the compound (I).

This reaction can be carried out according to a similar manner to that as explained in Process 3.

5 Step D

The compound (IIIb) or a salt thereof can be prepared by subjecting the compound (VI) or a salt thereof to introduction reaction of acyl which may have one or more suitable substituent(s).

10 Suitable salt of the compound (IIIb) can be referred to the ones as exemplified for the compound (I).

This reaction can be carried out according to a similar manner to that as explained in Process 4.

15 The object bicyclic amine compound (I) of the present invention is an N-methyl-D-aspartate receptor antagonist and useful as an anticonvulsant and a drug for treatment of the delayed neuronal death induced, for instance, by cerebral ischemia, for example, in case of cardiac arrest
20 in myocardial infarction.

In order to show the usefulness of the object compound (I), we set forth the representative test results in the following.

25

Test 1 : the effect against the convulsion

[I] Test Compound

1-Methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline hydrochloride (the compound of Example 1)

30

[III] Test Method

Six- to seven-week-old ICR male mice (5 mice per one group) were used for this experiment.

35 Test compound dissolved in saline was administered intraperitoneally (dose : 100 mg/kg) to each mouse (Test Group).

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To the Control Group, only saline was administered.
30 minutes after said administration, N-methyl-D-
aspartate (0.32 μ g) was injected intracerebroventricularly
to each mouse. Then, each mouse was put into a plastic
cage and observed for 10 minutes to confirm the occurrence
of clonic and tonic seizures.

[III] Test Results

The latency of initial seizure (second) (mean value $\pm$
standard error) was shown in the following table.

	Latency (second)
Control group	5.0 $\pm$ 0.7
Test Group	> 600**

** P < 0.01

Test 2 : the effect against the convulsion

[I] Test Compound

(+)-1-Methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline
hydrochloride (the compound of Example 4)

[II] Test Method

the same as used in Test 1

[III] Test Results

The latency of initial seizure (second) (mean value $\pm$
standard error) was shown in the following table.

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	Latency (second)
Control group	8.4 ± 0.5
Test Group	> 600**

** P < 0.01

Test 3 : the effect against the delayed neuronal death

[I] Test Compound

1-Methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline
hydrochloride (the compound of Example 1)

[II] Test Method

The effect on ischemia-induced delayed hippocampal
neurodegeneration was examined according to the following
method :

Eight- to nine-week-old male Wistar rats were used
for this experiment.

The vertebral arteries were cauterized within the
alar foramina and the common carotid arteries were exposed
and looped with surgical suture under anesthesia with
thiopental sodium (50 mg/kg i.p.).

Next day, the both carotid arteries were occluded
with aneurysm clips for 20 minutes under a slight ether
anesthesia. The test compound suspended in 0.5%
methylcellulose (dose : 100 mg/kg) was administered
intraperitoneally 10 minutes prior to ischemic insult
(Test Group). To Control Group, only 0.5% methylcellulose
was administered.

Seven days after the recirculation, rats were
perfusion-fixed with fixative consisting of 1.5% glutamic
dialdehyde and 1.0% paraformaldehyde in 0.1M phosphate
buffer (pH = 7.4). Perfusion was performed at a pressure

of 160 cm H₂O.

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Neuronal cell damage was assessed by counting the number of pyramidal neurons appearing normal in a 1 mm length of CA 1 pyramidal cell layer from each hippocampus in coronal sections (3 ~ 4 μ m) stained by cresyl violet corresponding to 1.9-2.1 mm posterior to the bregma.

[III] Test Results

The number of normal pyramidal neurons in CA 1 (cells/mm) (mean value $\pm$ standard error) in each group was shown in the following table.

group	the number of rats to be used	the number of normal pyramidal neurons in CA 1
Normal Group	8	136.0 $\pm$ 3.1
Control Group	7	20.9 $\pm$ 13.4
Test Group	4	88.3 $\pm$ 27.5*

* P < 0.05 : compared with the control group

Test 4 : the effect against the delayed neuronal death

[I] Test Compound

(+)-1-Methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline hydrochloride (the compound of Example 4)

[II] Test Method

The effect on ischemia-induced delayed hippocampal neurodegeneration was examined according to the following method :

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Eight- to nine-week-old male Wistar rats were used for this experiment.

The vertebral arteries were cauterized within the alar foramina and the common carotid arteries were exposed and looped with surgical suture under anesthesia with thiopental sodium (50 mg/kg i.p.).

Next day, the both carotid arteries were occluded with aneurysm clips for 20 minutes under a slight ether anesthesia. The test compound suspended in 0.5% methylcellulose (dose : 32 mg/kg) was administered intraperitoneally 10 minutes prior to ischemic insult (Test Group). To Control Group, only 0.5% methylcellulose was administered.

Seven days after the recirculation, rats were perfusion-fixed with fixative consisting of 1.5% glutamic dialdehyde and 1.0% paraformaldehyde in 0.1M phosphate buffer (pH = 7.4). Perfusion was performed at a pressure of 160 cm H₂O.

Neuronal cell damage was assessed by counting the number of pyramidal neurons appearing normal in a 1 mm length of CA 1 pyramidal cell layer from each hippocampus in coronal sections (3 ~ 4 μ m) stained by cresyl violet corresponding to 1.9-2.1 mm posterior to the bregma.

[III] Test Results

The number of normal pyramidal neurons in CA 1 (cells/mm) (mean value $\pm$ standard error) in each group was shown in the following table.

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group	the number of rats to be used	the number of normal pyramidal neurons in CA 1
Normal Group	8	136.0 ± 3.1
Control Group	7	20.9 ± 13.4
Test Group	5	107.2 ± 16.9**

** P < 0.01 : compared with the control group

Test 5 : the effect against the delayed neuronal death

[I] Test Compound

(+)-1-Methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline
hydrochloride (the compound of Example 4)

[II] Test Method

The effect on ischemia-induced delayed hippocampal
neurodegeneration was examined according to the following
method :

Eight- to ten-week-old male gerbils were used for
this experiment.

The both common carotid arteries were exposed under
local anesthesia with lidocaine and were occluded with
aneurysm clips for 5 minutes. The test compound dissolved
in saline (dose : 10 mg/kg) was administered
intraperitoneally 30 minutes prior to ischemic insult
(Test Group). To Control Group, only saline was
administered.

Four days after the recirculation, gerbils were
perfusion-fixed with fixative consisting of 1.5% glutamic
dialdehyde and 1.0% paraformaldehyde in 0.1M phosphate
buffer (pH = 7.4). Perfusion was performed at a pressure
of 160 cm H₂O.

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Neuronal cell damage was assessed by counting the number of pyramidal neurons appearing normal in a 1 mm length of CA 1 pyramidal cell layer from each hippocampus in coronal sections (3 - 4 μ m) stained by cresyl violet corresponding to 0.5 - 1 mm posterior to the bregma.

[IIII] Test Results

The number of normal pyramidal neurons in CA 1 (cells/mm) (mean value $\pm$ standard error) in each group was shown in the following table.

group	the number of gerbils to be used	the number of normal pyramidal neurons in CA 1
Normal Group	7	201.0 $\pm$ 6.5**
Control Group	7	3.9 $\pm$ 0.9
Test Group	7	91.9 $\pm$ 30.2**

** p < 0.01 : compared with the control group

For therapeutic administration, the object compound (I) and pharmaceutically acceptable salts thereof 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

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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, a kind of the compound (I) to be applied, etc. In general, amounts between 1 mg and about 6,000 mg or even more per day may be administered to a patient. An average single dose of about 50 mg, 100 mg, 250 mg, 500 mg, 1000 mg, 2000 mg of the object compound (I) of the present invention may be used.

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

Preparation 1

A mixture of 1-phenyl-3,4-dihydroisoquinoline (1.0 g) and benzyliodide (1.26 g) in acetonitrile (7 ml) was refluxed for 1 hour. After allowing to cool to room temperature, the reaction mixture was evaporated in vacuo and the residual precipitate was recrystallized from a mixture of diethyl ether (5 ml) and acetonitrile (3 ml). The crystal was collected by filtration, washed with diethyl ether and dried in vacuo to give 1-phenyl-2-benzyl-3,4-dihydroisoquinolinium iodide (1.52 g).

mp : 208-209°C

IR (Nujol) : 1620, 1600, 1565 cm^{-1}

NMR (DMSO- d_6 , δ) : 3.52 (2H, t, J=7Hz), 4.20 (2H, t, J=7Hz), 5.10 (2H, s), 6.96-7.83 (14H, m)

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Preparation 2

The following compound was obtained according to a similar manner to that of Preparation 1.

5 1-(3-Chlorophenyl)-2-benzyl-3,4-dihydroisoquinolinium
iodide

mp : 191-192°C

IR (Nujol) : 1615, 1595, 1560 cm^{-1}

10 NMR (CDCl_3 , δ) : 3.33 (2H, t, $J=7\text{Hz}$), 4.25 (2H, t,
 $J=7\text{Hz}$), 5.12 (2H, s), 7.06-8.02 (14H, m)

Preparation 3

To a suspension of 1-phenyl-2-benzyl-3,4-
15 dihydroisoquinolinium iodide (1.0 g) in diethyl ether (10
ml) was added 3 M diethyl ether solution of
methylmagnesium bromide (4.5 ml). The mixture was
refluxed for 30 minutes with stirring and then poured into
saturated ammonium chloride aqueous solution and extracted
20 with ethyl acetate. The separated organic layer was
washed with water, sodium chloride aqueous solution and
dried over magnesium sulfate and evaporated in vacuo. The
residue was crystallized from n-hexane to give
1-methyl-1-phenyl-2-benzyl-1,2,3,4-tetrahydroisoquinoline
(0.64 g).

25 mp : 102-103°C

IR (Nujol) : 1600, 1580, 1485 cm^{-1}

NMR (CDCl_3 , δ) : 1.78 (3H, s), 2.58-3.10 (4H, m),
3.22 (1H, d, $J=14\text{Hz}$), 3.56 (1H, d, $J=14\text{Hz}$),
6.60-7.65 (14H, m)

30 Mass : 313 (M^+)

The following compounds (Preparations 4 and 5) were
obtained according to a similar manner to that of
Preparation 3.

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Preparation 4

1-Ethyl-1-phenyl-2-benzyl-1,2,3,4-tetrahydroisoquinoline

mp : 96-97°C (recrystallized from n-hexane)

IR (Nujol) : 1600, 1490 cm^{-1}

NMR (CDCl_3 , δ) : 0.85 (3H, t, $J=7\text{Hz}$), 2.12 (1H, dd, $J=7\text{Hz}$ and 14Hz), 2.46-3.05 (5H, m), 3.88 (1H, d, $J=14\text{Hz}$), 6.70-7.30 (14H, m)

Mass : 327 (M^+)

Preparation 5

1-Methyl-1-(3-chlorophenyl)-2-benzyl-1,2,3,4-tetrahydroisoquinoline

NMR (CDCl_3 , δ) : 1.81 (3H, s), 2.78-3.75 (6H, m), 6.62-7.70 (14H, m)

Mass : 347 (M^+)

Example 1

A mixture of 1-methyl-1-phenyl-2-benzyl-1,2,3,4-tetrahydroisoquinoline (0.5 g) and 10% palladium on carbon (50% wet 0.1 g) in acetic acid (15 ml) was hydrogenated under one atmospheric pressure of hydrogen at room temperature for 9 hours. Insoluble material was filtered off and the filtrate was concentrated in vacuo. The residue was dissolved in ethyl acetate and washed with saturated sodium bicarbonate aqueous solution, water, sodium chloride aqueous solution and dried over magnesium sulfate and evaporated in vacuo. The residue was dissolved in ethanol and to the solution was added 7 M ethanol solution of hydrogen chloride. The precipitate was collected by filtration, washed with ethanol and diethyl ether and dried in vacuo to give 1-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline hydrochloride (0.4 g).

mp : 274-276°C (decomp.)

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IR (Nujol) : 1585, 1490 cm^{-1}

NMR (DMSO- d_6 , δ) : 2.10 (3H, s), 2.80-3.50 (4H, m),
7.05-7.45 (9H, m), 9.80 (1H, s), 10.40 (1H, s)

Mass : 222 ($\text{M}^+ - 1$)

Elemental Analysis for $\text{C}_{16}\text{H}_{17}\text{N} \cdot \text{HCl}$

Calcd. : C 73.98, H 6.98, N 5.45

Found : C 73.55, H 6.98, N 5.28

The following compounds (Examples 2 and 3) were
obtained according to a similar manner to that of Example
1.

Example 2

1-Ethyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline
hydrochloride

mp : 288-290°C

IR (Nujol) : 1580, 1495 cm^{-1}

NMR (DMSO- d_6 , δ) : 0.98 (3H, t, $J=7\text{Hz}$), 2.56-3.36
(6H, m), 7.16-7.36 (9H, m), 9.65-10.26 (2H,
broad)

Mass : 236 ($\text{M}^+ - 1$)

Elemental Analysis

Calcd. : C 74.58, H 7.36, N 5.12

Found : C 74.57, H 7.42, N 5.08

Example 3

1-Methyl-1-(3-chlorophenyl)-1,2,3,4-tetrahydro-
isoquinoline hydrochloride

mp : 265-267°C

IR (Nujol) : 1580, 1495 cm^{-1}

NMR (DMSO- d_6 , δ) : 2.13 (3H, s), 2.90-3.55 (4H, m),
7.05-7.50 (8H, m)

Mass : 257 (M^+)

Elemental Analysis

Calcd. : C 65.32, H 5.82, N 4.76

Found : C 65.10, H 5.65, N 4.78

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Example 4

(1) 1-Methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline (racemic mixture) (10.2 g) and (+)-di-p-toluoyl-D-tartaric acid (17.65 g) was dissolved in ethanol (270 ml) at about 50°C, then left to stand for 2 days at room temperature. The precipitate was collected by filtration and dissolved in ethanol (180 ml), then left to stand overnight at room temperature. The precipitate was collected by filtration and washed with ethanol, then dried to give (+)-di-p-toluoyl-D-tartaric acid salt of 1-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline (4.42 g).

While, the filtrate was evaporated in vacuo and the residue was dissolved in ethyl acetate. The solution was adjusted to pH 8.0 with K_2CO_3 aqueous solution and organic layer was separated and washed with water and sodium chloride aqueous solution, dried over magnesium sulfate and evaporated in vacuo. The residue (6.0 g) and (-)-di-p-toluoyl-D-tartaric acid monohydrate (10.86 g) was dissolved in ethanol (170 ml), then left to stand overnight at room temperature. The precipitate was collected by filtration and washed with ethanol, then dried to give (-)-di-p-toluoyl-D-tartaric acid salt of 1-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline (10.0 g).

(2) (+)-Di-p-toluoyl-D-tartaric acid salt of 1-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline (3.0 g) was dissolved in ethyl acetate and the solution was adjusted to pH 8.0 with saturated K_2CO_3 aqueous solution. The organic layer was separated and washed with water and sodium chloride aqueous solution, dried over magnesium sulfate and evaporated in vacuo. The residue was dissolved in ethanol and added 7M ethanol solution of hydrogen chloride. The precipitate was collected by filtration, washed with ethanol and diethyl ether, then dried to give (+)-1-methyl-1-phenyl-1,2,3,4-

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tetrahydroisoquinoline hydrochloride (1.20 g).

(-)-1-Methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline hydrochloride (1.70 g) was obtained according to a similar manner to that of (+) isomer from (-)-di-p-toluoyl-D-tartaric acid salt of 1-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline.

Physicochemical Properties of Obtained Compounds

(+)-Di-p-toluoyl-D-tartaric acid salt of 1-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline

mp : 183-184°C

$[\alpha]_D^{20} = -19.5^\circ$ (C=1, EtOH) (optical rotation was measured after this tartaric acid salt was converted to free form)

(-)-Di-p-toluoyl-D-tartaric acid salt of 1-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline

mp : 184-185°C

$[\alpha]_D^{20} = +17.9^\circ$ (C=1, EtOH) (optical rotation was measured after this tartaric acid salt was converted to free form)

(+)-1-Methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline hydrochloride

mp : 302-303°C

$[\alpha]_D^{20} = +10.9^\circ$ (C=1, EtOH)

IR (Nujol) : 1585, 1500, 1260 cm^{-1}

NMR (DMSO- d_6 , δ) : 2.20 (3H, s), 2.90-3.70 (4H, m), 7.15-7.50 (9H, m)

Mass : 222 ($M^+ - 1$)

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(-)-1-Methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline
hydrochloride

mp : 300-301°C

$[\alpha]_D^{20} = -13.30^\circ$ (C=1, EtOH)

5 IR (Nujol) : 1585, 1500, 1260 cm^{-1}

NMR (DMSO- d_6 , δ) : 2.20 (3H, s), 2.90-3.70 (4H, m),
7.15-7.50 (9H, m)

Mass : 222 ($M^+ - 1$)

Elemental Analysis for $\text{C}_{16}\text{H}_{17}\text{N} \cdot \text{HCl}$

10 Calcd. : C 73.98, H 6.98, N 5.39

Found : C 74.06, H 6.95, N 5.37

(to be continued to the next page)

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The following compounds (Preparations 6 to 20) were obtained according to a similar manner to that of Preparation 1.

5 Preparation 6

1-(p-Tolyl)-2-benzyl-3,4-dihydroisoquinolinium iodide

mp : 203-204°C

IR (Nujol) : 1620, 1610, 1560 cm⁻¹

10 NMR (DMSO-d₆, δ) : 2.45 (3H, s), 3.28 (2H, d, J=7Hz), 4.15 (2H, d, J=7Hz), 5.10 (2H, s), 7.04-7.86 (13H, m)

Preparation 7

15 1-(4-Methoxyphenyl)-2-benzyl-3,4-dihydro-isoquinolinium iodide

mp : 76-78°C

IR (Nujol) : 1600, 1560, 1510 cm⁻¹

20 NMR (DMSO-d₆, δ) : 3.24 (2H, t, J=7Hz), 3.88 (3H, s), 4.13 (2H, t, J=7Hz), 5.14 (2H, s), 7.08-7.86 (13H, m)

Preparation 8

25 1-(3-Fluorophenyl)-2-benzyl-3,4-dihydroisoquinolinium iodide

mp : 178-180°C

IR (Nujol) : 1615, 1600, 1580, 1560 cm⁻¹

NMR (DMSO-d₆, δ) : 3.32 (2H, t, J=7Hz), 4.17 (2H, t, J=7Hz), 5.09 (2H, s), 7.07-7.88 (13H, m)

30 Preparation 9

1-(4-Fluorophenyl)-2-benzyl-3,4-dihydroisoquinolinium iodide

mp : 195-196°C

35 NMR (DMSO-d₆, δ) : 3.40 (2H, t, J=9Hz), 4.28 (2H, t, J=9Hz), 5.21 (2H, s), 7.08-8.14 (13H, m)

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Preparation 10

1-(2-Chlorophenyl)-2-benzyl-3,4-dihydroisoquinolinium
iodide

mp : 181-182°C

5 IR (Nujol) : 1620, 1600, 1565 cm⁻¹

NMR (DMSO-d₆, δ) : 3.256-3.46 (2H, m), 4.14-4.44
(2H, m), 5.04 (1H, d, J=15Hz), 5.25 (1H, d,
J=15Hz), 7.04-8.10 (13H, m)

10 Preparation 11

1-(4-Chlorophenyl)-2-benzyl-3,4-dihydroisoquinolinium
iodide

mp : 188-189°C

IR (Nujol) : 1615, 1600, 1565, 1480 cm⁻¹

15 NMR (DMSO-d₆, δ) : 3.32 (2H, t, J=7Hz), 4.17 (2H, t,
J=7Hz), 5.09 (2H, s), 7.06-7.88 (13H, m)

Preparation 12

20 1-Phenyl-2-benzyl-4-methyl-3,4-dihydroisoquinolinium
iodide

mp : 195-197°C

IR (Nujol) : 1610, 1600, 1565, 1480 cm⁻¹

25 NMR (DMSO-d₆, δ) : 1.13 and 1.16 (total 3H, each s),
3.35-3.59 (1H, m), 4.00 (1H, dd, J=7Hz and
14Hz), 4.25 (1H, dd, J=6Hz and 14Hz), 5.03 (1H,
d, J=15Hz), 5.16 (1H, d, J=15Hz), 7.03-7.92
(14H, m)

Preparation 13

30 1-Phenyl-2-benzyl-7-methyl-3,4-dihydroisoquinolinium
iodide

mp : 211-212°C

IR (Nujol) : 1620, 1560 cm⁻¹

35 NMR (DMSO-d₆, δ) : 2.25 (3H, s), 3.26 (2H, t,
J=7Hz), 4.15 (2H, t, J=7Hz), 5.06 (2H, s), 6.82

(1H, s), 7.40-7.81 (12H, m)

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Preparation 14

1-Phenyl-2-benzyl-3-acetoxymethyl-3,4-dihydro-
isoquinolinium iodide

mp : 176-177°C

IR (Nujol) : 1740, 1600, 1560 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.79 (3H, s), 3.35 (1H, s),
3.59-3.71 (1H, m), 4.37-4.58 (3H, m), 5.25 (2H,
s), 6.99-7.91 (14H, m)

Preparation 15

1-Phenyl-2-benzyl-5-chloro-3,4-dihydroisoquinolinium
iodide

mp : 244-246°C

IR (Nujol) : 1620, 1585, 1560, 1495 cm^{-1}

NMR (DMSO- d_6 , δ) : 3.53 (2H, t, $J=8\text{Hz}$), 4.22 (2H, t,
 $J=8\text{Hz}$), 5.11 (2H, s), 7.01-8.02 (13H, m)

Preparation 16

1-Phenyl-2-benzyl-7-chloro-3,4-dihydroisoquinolinium
iodide

mp : 236-237°C

NMR (DMSO- d_6 , δ) : 3.37 (2H, t, $J=8\text{Hz}$), 4.29 (2H, t,
 $J=8\text{Hz}$), 5.16 (2H, s), 6.98-8.08 (13H, m)

Preparation 17

1-Phenyl-2-benzyl-6-ethoxycarbonylamino-3,4-
dihydroisoquinolinium bromide

mp : 218-219°C (dec.)

IR (Nujol) : 3400, 3200, 3140, 1740, 1600 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.27 (3H, t, $J=7\text{Hz}$), 3.23 (2H, t,
 $J=7\text{Hz}$), 4.09 (2H, t, $J=7\text{Hz}$), 4.18 (2H, t,
 $J=7\text{Hz}$), 4.98 (2H, s), 6.95-7.71 (13H, m)

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Preparation 18

1-Cyclohexyl-2-benzyl-3,4-dihydroisoquinolinium
iodide

mp : 162-164°C

IR (Nujol) : 1600, 1560, 1495 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.09-2.08 (10H, m), 3.10 (2H, t, $J=7\text{Hz}$), 3.35-3.44 (1H, m), 3.85 and 4.00 (total 2H, each t, $J=7\text{Hz}$), 5.50 (2H, s), 7.48-8.37 (9H, m)

Preparation 19

1-(2-Thienyl)-2-(4-methoxybenzyl)-3,4-dihydro-
isoquinolinium iodide

IR (Film) : 1610, 1255 cm^{-1}

NMR (DMSO- d_6 , δ) : 3.20 (2H, t, $J=7\text{Hz}$), 3.75 (3H, s), 4.08 (2H, t, $J=7\text{Hz}$), 5.17 (2H, s), 6.87-8.23 (11H, m)

Preparation 20

1-Phenyl-2-benzyl-4,5-dihydro-3H-2-benzazepinium
bromide

mp : 236-238°C

IR (Nujol) : 1610, 1595, 1565 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.96 (2H, t, $J=7\text{Hz}$), 2.90 (2H, t, $J=7\text{Hz}$), 3.89 (2H, t, $J=7\text{Hz}$), 5.35 (2H, s), 6.99-7.84 (14H, m)

The following compounds (Preparations 21 to 36) were
obtained according to a similar manner to that of
Preparation 3.

Preparation 21

1-Methyl-1-(p-tolyl)-2-benzyl-1,2,3,4-tetrahydro-
isoquinoline

mp : 139-140°C

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IR (Nu ϕ l) : 1600, 1510, 1490 cm^{-1}
 NMR (CDCl $_3$, δ) : 1.78 (3H, s), 2.60 (3H, s),
 2.60-3.16 (4H, m), 3.27 (1H, d, $J=14\text{Hz}$), 3.57
 (1H, d, $J=14\text{Hz}$), 6.67-7.49 (13H, m)

5

Preparation 22

1-Methyl-1-(4-methoxyphenyl)-2-benzyl-1,2,3,4-

tetrahydroisoquinoline

mp : 113-114°C

IR (Nu ϕ l) : 1600, 1505, 1490 cm^{-1}

NMR (CDCl $_3$, δ) : 1.76 (3H, s), 2.63-3.15 (4H, m),
 3.25 (1H, d, $J=14\text{Hz}$), 3.59 (1H, d, $J=14\text{Hz}$), 3.73
 (3H, s), 6.67-7.52 (13H, m)

10

Preparation 23

1-Methyl-1-(3-fluorophenyl)-2-benzyl-1,2,3,4-

tetrahydroisoquinoline

mp : 83-85°C

IR (Nu ϕ l) : 1605, 1590, 1485 cm^{-1}

20

Preparation 24

1-Methyl-1-(4-fluorophenyl)-2-benzyl-1,2,3,4-

tetrahydroisoquinoline

mp : 154-155°C

NMR (CDCl $_3$, δ) : 1.86 (3H, s), 2.65-3.06 (4H, m),
 3.33 (1H, d, $J=14\text{Hz}$), 3.70 (1H, d, $J=14\text{Hz}$),
 6.68-7.78 (13H, m)

25

Preparation 25

1-Methyl-1-(2-chlorophenyl)-2-benzyl-1,2,3,4-

tetrahydroisoquinoline hydrochloride

NMR (DMSO- d_6 , δ) : 2.10 (3H, s), 3.00-4.20 (6H, m),
 7.15-8.00 (13H, m)

35

Mass (M/Z) : 347 (M $^+$)

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Preparation 26

1-Methyl-1-(4-chlorophenyl)-2-benzyl-1,2,3,4-tetrahydroisoquinoline

mp : 134-135°C

5 NMR (CDCl₃, δ) : 1.82 (3H, s), 2.60-3.05 (4H, m),
3.28 (1H, d, J=14Hz), 3.65 (1H, d, J=14Hz),
6.58-7.68 (13H, m)

Mass (M/Z) : 347 (M⁺)

10 Preparation 27

1-Methyl-1-phenyl-2-benzyl-4-methyl-1,2,3,4-tetrahydroisoquinoline

mp : 125-126°C

IR (Nujol) : 1600, 1580, 1490 cm⁻¹

15 NMR (CDCl₃, δ) : 1.21 and 1.24 (total 3H, each s),
1.76 (3H, s), 2.50-3.05 (3H, m), 3.19 (1H, d,
J=13Hz), 3.63 (1H, d, J=13Hz), 6.63-7.67 (14H,
m)

20 Preparation 28

1-Methyl-1-phenyl-2-benzyl-7-methyl-1,2,3,4-tetrahydroisoquinoline

mp : 94-95°C

IR (Nujol) : 1600, 1490, 1420 cm⁻¹

25 NMR (DMSO-d₆, δ) : 1.79 (3H, s), 2.12 (3H, s),
2.44-3.12 (4H, m), 3.17 (2H, d, J=14Hz), 3.54
(2H, d, J=14Hz), 6.49 (1H, s), 6.83-7.62 (12H,
m)

30 Preparation 29

1-Methyl-1-phenyl-2-benzyl-3-hydroxymethyl-1,2,3,4-tetrahydroisoquinoline

IR (Film) : 3550, 3400, 1600, 1495, 1450 cm⁻¹

35 NMR (CDCl₃, δ) : 1.76 and 1.82 (total 3H, s),
2.70-4.02 (6H, m), 6.62-7.52 (14H, m)

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Mass (M/Z) : 342 ($M^+ - 1$)

Preparation 30

1-Methyl-1-phenyl-2-benzyl-5-chloro-1,2,3,4-
tetrahydroisoquinoline

mp : 98-100°C

IR (Nujol) : 1565, 1490 cm^{-1}

NMR (CDCl_3 , δ) : 1.80 (3H, s), 2.73-2.95 (4H, m),
3.26 (1H, d, $J=14\text{Hz}$), 3.55 (1H, d, $J=14\text{Hz}$),

5.58-7.59 (13H, m)

Preparation 31

1-Methyl-1-phenyl-2-benzyl-7-chloro-1,2,3,4-
tetrahydroisoquinoline

mp : 96-97°C

NMR (CDCl_3 , δ) : 1.85 (3H, s), 2.60-3.15 (4H, m),
3.30 (1H, d, $J=14\text{Hz}$), 3.62 (1H, d, $J=14\text{Hz}$),

6.70-7.72 (13H, m)

Mass (M/Z) : 347 (M^+)

Preparation 32

1-Methyl-1-phenyl-2-benzyl-6-ethoxycarbonylamino-
1,2,3,4-tetrahydroisoquinoline

IR (Film) : 3420, 1720 cm^{-1}

NMR (CDCl_3 , δ) : 12.5 (3H, t, $J=7\text{Hz}$), 1.75 (3H, s),
2.55-3.06 (4H, m), 3.24 (1H, d, $J=14\text{Hz}$), 3.53
(1H, d, $J=14\text{Hz}$), 4.18 (2H, d, $J=7\text{Hz}$), 6.52-7.62
(14H, m)

Mass (M/Z) : 385 ($M^+ - 15$)

Preparation 33

1-Methyl-1-cyclohexyl-2-benzyl-1,2,3,4-
tetrahydroisoquinoline

IR (Film) : 2940, 1600, 1490, 1450 cm^{-1}

NMR (CDCl_3 , δ) : 1.15-2.10 (14H, m), 2.56-3.08 (4H,

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m), 3.40 (1H, d, J=15Hz), 4.22 (1H, d, J=15Hz),
7.12-7.54 (9H, m)

Mass (M/Z) : 302 (M^+ + 1)

5 Preparation 34

1-Methyl-1-(2-furyl)-2-benzyl-1,2,3,4-tetrahydro-
isoquinoline

NMR(CDCl₃, δ) : 1.88 (3H, s), 2.94 (4H, s), 3.48
(1H, d, J=14Hz), 3.75 (1H, d, J=14Hz), 6.44 (2H,
10 s), 7.05-7.54 (10H, m)

Mass (M/Z) : 303 (M^+)

Preparation 35

15 1-Methyl-1-(2-thienyl)-2-(4-methoxybenzyl)-1,2,3,4-
tetrahydroisoquinoline

mp : 80-82°C

IR (Nujol) : 1610, 1240, 1035, 700 cm⁻¹

NMR (CDCl₃, δ) : 1.81 (3H, s), 2.5-3.2 (4H, m), 3.30
(1H, d, J=14Hz), 3.68 (1H, d, J=14Hz), 3.72 (3H,
20 s), 6.7-7.4 (11H, m)

Preparation 36

1-Methyl-1-phenyl-2-benzyl-2,3,4,5-tetrahydro-1H-2-
benzazepine

25 mp : 134-135°C

IR (Nujol) : 1600, 1485 cm⁻¹

NMR (CDCl₃, δ) : 1.11-1.29 (1H, m), 1.73-1.79 (1H,
m), 1.89 (3H, s), 2.56-2.84 (3H, m), 3.35-3.46
(1H, m), 3.35 (1H, d, J=7Hz), 3.80 (1H, d,
30 J=7Hz), 7.15-7.44 (14H, m)

Mass (M/Z) : 312 (M^+ - 15)

Preparation 37

35 1-Methyl-1-(3-thienyl)-2-(4-methoxybenzyl)-1,2,3,4-
tetrahydroisoquinoline was prepared by reacting

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1-(3-thienyl)-3,4-dihydroisoquinoline with 4-methoxybenzyl
bromide according to a similar manner to that of
Preparation 1, and then by reacting the obtained
1-(3-thienyl)-2-(4-methoxybenzyl)-3,4-
5 dihydroisoquinolinium bromide with 3 M diethyl ether
solution of methylmagnesium bromide according to a similar
manner to that of Preparation 3.

IR (Film) : 1610, 1040 cm^{-1}

10 NMR (CDCl_3 , δ) : 1.78 (3H, s), 2.8-3.1 (4H, m), 3.20
(1H, d, $J=13.5\text{Hz}$), 3.28 (1H, d, $J=13.5\text{Hz}$), 3.78
(3H, s), 6.9-7.2 (11H, m)

Preparation 38

15 The mixture of 1-phenyl-3,4-dihydroisoquinoline
(292.0 g) and benzyl bromide (176 ml) in acetonitrile (3
l) was refluxed for 1 hour. After cooling the mixture to
room temperature, the solvent was evaporated in vacuo.
The residue was triturated with diethyl ether (1 l) to
give 1-phenyl-2-benzyl-3,4-dihydroisoquinolinium bromide
20 (471.2 g).

mp : 181-183°C

IR (Nujol) : 1620, 1600 cm^{-1}

25 NMR ($\text{DMSO}-d_6$, δ) : 3.24 (2H, t, $J=5\text{Hz}$), 4.14 (2H, t,
 $J=5\text{Hz}$), 5.02 (2H, s), 6.88-7.86 (14H, m)

Preparation 39

30 To a suspension of 1-phenyl-2-benzyl-3,4-
dihydroisoquinolinium bromide (353.1 g) in tetrahydrofuran
(3.5 l) was added 2.0 M tetrahydrofuran solution of
methylmagnesium bromide (700 ml) for 1.5 hours with
stirring at room temperature. After additional stirring
for 1.5 hours, the mixture was poured into a solution of
ammonium chloride (300 g) in water (650 ml) under ice
cooling. After separation, the aqueous layer was
35 extracted with ethyl acetate (3.5 l). The combined

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organic layers were washed with water (1 l), sodium chloride aqueous solution (1 l) and dried over magnesium sulfate (125 g) and evaporated in vacuo. The residue was crystallized from ethanol (500 ml) to give 1-methyl-1-phenyl-2-benzyl-1,2,3,4-tetrahydroisoquinoline (254.0 g).

mp : 102-103°C

IR (Nujol) : 1600, 1580, 1485 cm^{-1}

NMR (CDCl_3 , δ) : 1.78 (3H, s), 2.58-3.10 (4H, m),
3.22 (1H, d, $J=14\text{Hz}$), 3.56 (1H, d, $J=14\text{Hz}$),
6.60-7.65 (14H, m)

Mass : 313 (M^+)

The following compounds (Preparations 40 to 42) were obtained according to a similar manner to that of Preparation 1.

Preparation 40

1-Phenyl-2-ethyl-3,4-dihydroisoquinolinium iodide

mp : 165-166°C (dec.)

IR (Nujol) : 1620, 1600, 1560 cm^{-1}

NMR ($\text{DMSO}-d_6$, δ) : 1.35 (3H, t, $J=7\text{Hz}$), 3.35-3.45
(2H, m), 3.78 (2H, t, $J=7\text{Hz}$)

Preparation 41

1-(2-Thienyl)-2-methyl-3,4-dihydroisoquinolinium iodide

mp : 180-181°C (dec.)

IR (Nujol) : 1590, 720 cm^{-1}

NMR ($\text{DMSO}-d_6$, δ) : 3.25-3.6 (2H, m), 3.75 (3H, s),
4.2-4.55 (2H, m), 7.2-8.0 (7H, m)

Preparation 42

1-(2-Thienyl)-2-ethyl-3,4-dihydroisoquinolinium iodide

mp : 194-195°C

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IR (Nujol) : 1600, 800, 740 cm^{-1}

NMR (DMSO-d_6 , δ) : 1.43 (3H, t, $J=8\text{Hz}$), 3.2-3.5 (2H, m), 3.7-4.2 (2H, m), 4.25 (2H, t, $J=8\text{Hz}$), 7.0-8.3 (7H, m)

5

The following compounds (Examples 5 to 18) were obtained according to a similar manner to that of Example 1.

10

Example 5

1-Methyl-1-(p-tolyl)-1,2,3,4-tetrahydroisoquinoline hydrochloride

mp : 294-295°C

IR (Nujol) : 1575, 1510, 1490 cm^{-1}

15

NMR (DMSO-d_6 , δ) : 2.12 (3H, s), 2.32 (3H, s), 2.80-3.85 (4H, m), 7.12-7.40 (8H, m), 10.00 (1H, s), 10.55 (1H, s)

Mass (M/Z) : 236 ($\text{M}^+ - 1$)

20

Example 6

1-Methyl-1-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline hydrochloride

mp : 251-253°C

IR (Nujol) : 1610, 1585, 1535 cm^{-1}

25

NMR (DMSO-d_6 , δ) : 2.15 (3H, s), 2.85-3.50 (4H, m), 3.80 (3H, s), 6.90-7.50 (8H, m)

Mass (M/Z) : 252 ($\text{M}^+ - 1$)

Elemental analysis for $\text{C}_{17}\text{H}_{19}\text{NO} \cdot \text{HCl}$

Calcd. : C 70.46, H 6.96, N 4.83

30

Found : C 70.06, H 7.00, N 4.80

Example 7

1-Methyl-1-(3-fluorophenyl)-1,2,3,4-tetrahydroisoquinoline hydrochloride

35

mp : 285-287°C

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IR (Nujol) : 1605, 1585, 1490 cm^{-1}

NMR (DMSO-d_6 , δ) : 2.06 (3H, s), 2.80-3.40 (4H, m),
6.95-7.48 (8H, m), 10.00 (1H, broad), 10.42 (1H,
broad)

5 Mass (M/Z) : 240 ($\text{M}^+ - 1$)

Elemental Analysis for $\text{C}_{16}\text{H}_{16}\text{FN}\cdot\text{HCl}$

Calcd. : C 69.19, H 6.17, N 5.04

Found : C 68.79, H 6.45, N 4.97

10 Example 8

1-Methyl-1-(4-fluorophenyl)-1,2,3,4-tetrahydro-
isoquinoline hydrochloride

mp : 254-256°C

IR (Nujol) : 1600, 1585, 1510, 1490 cm^{-1}

15 NMR (DMSO-d_6 , δ) : 2.18 (3H, s), 2.70-3.55 (4H, m),
7.10-7.60 (8H, m), 9.80-10.80 (2H, broad)

Mass (M/Z) : 240 ($\text{M}^+ - 1$)

Elemental Analysis for $\text{C}_{16}\text{H}_{16}\text{FN}\cdot\text{HCl}$

Calcd. : C 69.19, H 6.17, N 5.04

20 Found : C 68.84, H 6.09, N 4.96

Example 9

1-Methyl-1-(2-chlorophenyl)-1,2,3,4-
tetrahydroisoquinoline hydrochloride

25 mp : 264-265°C (dec.)

IR (Nujol) : 1580, 1490, 1435 cm^{-1}

NMR (DMSO-d_6 , δ) : 2.26 (3H, s), 3.00-3.70 (4H, m),
6.58-8.10 (8H, m)

Mass (M/Z) : 257 (M^+)

30 Elemental Analysis for $\text{C}_{16}\text{H}_{16}\text{ClN}\cdot\text{HCl}\cdot 1/2\text{H}_2\text{O}$

Calcd. : C 63.38, H 5.98, N 4.62

Found : C 63.78, H 6.14, N 4.37

Example 10

35 1-Methyl-1-(4-chlorophenyl)-1,2,3,4-

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tetrahydroisoquinoline hydrochloride

mp : 286-287°C (dec.)

IR (Nujol) : 1580, 1490, 1420, 1400 cm^{-1}

NMR (DMSO- d_6 , δ) : 2.12 (3H, s), 2.80-3.50 (4H, m),
7.00-7.53 (8H, m), 10.12 (1H, broad), 10.55
(1H, broad)

Mass (M/Z) : 256 ($\text{M}^+ - 1$)

Example 11

1-Methyl-1-phenyl-4-methyl-1,2,3,4-
tetrahydroisoquinoline hydrochloride

mp : 245°C (dec.)

IR (Nujol) : 1585, 1490 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.25 (3H, d, $J=7\text{Hz}$), 2.22 (3H,
s), 3.20-3.78 (3H, m), 7.26-7.62 (9H, m),
10.00-10.70 (2H, broad)

Mass (M/Z) : 236 ($\text{M}^+ - 1$)

Elemental Analysis for $\text{C}_{17}\text{H}_{19}\text{N}\cdot\text{HCl}$

Calcd. : C 74.58, H 7.36, N 5.12

Found : C 74.37, H 7.12, N 5.15

Example 12

1-Methyl-1-phenyl-7-methyl-1,2,3,4-
tetrahydroisoquinoline hydrochloride

mp : 304-305°C (dec.)

IR (Nujol) : 1590, 1500 cm^{-1}

NMR (DMSO- d_6 , δ) : 2.20 (3H, s), 2.32 (3H, s),
3.05-3.35 (4H, m), 7.02 (1H, s), 7.24 (2H, s),
7.45 (5H, s), 10.04 (1H, s), 10.55 (1H, s)

Mass (M/Z) : 236 ($\text{M}^+ - 1$)

Elemental Analysis for $\text{C}_{17}\text{H}_{19}\text{N}\cdot\text{HCl}\cdot 1/4\text{H}_2\text{O}$

Calcd. : C 73.37, H 7.42, N 5.03

Found : C 73.53, H 7.47, N 5.00

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Example 13

1-Methyl-1-phenyl-3-hydroxymethyl-1,2,3,4-tetrahydroisoquinoline

mp : 125-127°C

5 IR (Nujol) : 3250, 1595, 1585, 1490 cm^{-1}

NMR (CDCl_3 , δ) : 1.85 (3H, s), 2.58-3.00 (3H, m),
3.30-3.98 (2H, m), 7.12-7.22 (9H, m)

Mass (M/Z) : 252 (M^+ - 1)

Elemental Analysis for $\text{C}_{17}\text{H}_{19}\text{NO}$

10 Calcd. : C 80.57, H 7.56, N 5.53

Found : C 80.21, H 7.35, N 5.41

Example 14

15 1-Methyl-1-phenyl-5-chloro-1,2,3,4-tetrahydroisoquinoline hydrochloride

mp : 315°C (dec.)

IR (Nujol) : 1575, 1490 cm^{-1}

NMR (DMSO-d_6 , δ) : 2.16 (3H, s), 2.90-3.40 (4H, m),
7.05-7.56 (8H, m)

20 Elemental Analysis for $\text{C}_{16}\text{H}_{16}\text{ClN}\cdot\text{HCl}$

Calcd. : C 65.32, H 5.82, N 4.76

Found : C 65.18, H 5.80, N 4.56

Example 15

25 1-Methyl-1-phenyl-7-chloro-1,2,3,4-tetrahydroisoquinoline hydrochloride

mp : 319-320°C (dec.)

IR (Nujol) : 1585, 1480 cm^{-1}

30 NMR (DMSO-d_6 , δ) : 2.24 (3H, s), 3.10-3.40 (4H, m),
7.38-7.62 (8H, m)

Elemental Analysis for $\text{C}_{16}\text{H}_{16}\text{ClN}\cdot\text{HCl}\cdot 1/3\text{H}_2\text{O}$

Calcd. : C 64.01, H 5.93, N 4.67

Found : C 64.05, H 5.99, N 4.50

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Example 16

1-Methyl-1-phenyl-6-ethoxycarbonylamino-1,2,3,4-tetrahydroisoquinoline hydrochloride

mp : 260-261°C (dec.)

IR (Nujol) : 3260, 1730, 1600, 1585 cm⁻¹

NMR (DMSO-d₆, δ) : 1.35 (3H, t, J=7Hz), 2.28 (3H, s), 2.95-3.40 (4H, m), 4.25 (2H, q, J=7Hz), 7.10-7.65 (8H, m), 9.82 (1H, s)

Mass (M/Z) : 311 (M⁺ + 1)

Example 17

1-Methyl-1-cyclohexyl-1,2,3,4-tetrahydroisoquinoline hydrochloride

mp : 280-281°C

IR (Nujol) : 1590, 1495, 1415 cm⁻¹

NMR (DMSO-d₆, δ) : 1.00-2.35 (14H, m), 2.80-3.55 (4H, m), 7.22-7.40 (4H, m)

Mass (M/Z) : 228 (M⁺ - 1)

Example 18

1-Methyl-1-(2-furyl)-1,2,3,4-tetrahydroisoquinoline hydrochloride

mp : 223-225°C

IR (Nujol) : 1580, 1485, 1425 cm⁻¹

NMR (DMSO-d₆, δ) : 2.12 (3H, s), 3.16-3.58 (4H, m), 6.40-6.58 (2H, m), 7.18-7.36 (4H, m), 7.75 (1H, broad), 10.08 (1H, broad), 10.82 (1H, broad)

Mass (M/Z) : 212 (M⁺ - 1)

Elemental Analysis for C₁₄H₁₅NO·HCl

Calcd. : C 67.33, H 6.46, N 5.61

Found : C 66.60, H 6.27, N 5.45

Example 19

To a solution of ceric ammonium nitrate (7 g) in a mixture of acetonitrile (30 ml) and water (15 ml) was

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added 1-methyl-1-(2-thienyl)-2-(4-methoxybenzyl)-
1,2,3,4-tetrahydroisoquinoline (1.5 g). After stirring
for 1.5 hours at room temperature, the mixture was poured
into a mixture of n-hexane (50 ml) and water (50 ml) with
stirring. The separated aqueous layer was adjusted to pH
10 with saturated potassium carbonate aqueous solution and
extracted with ethyl acetate (50 ml x 2). The organic
layer was washed with sodium chloride aqueous solution,
dried over magnesium sulfate and extracted in vacuo. The
residue was recrystallized from 6N-hydrogen chloride
ethanol solution (1 ml) and diethyl ether (10 ml) to give
1-methyl-1-(2-thienyl)-1,2,3,4-tetrahydroisoquinoline
hydrochloride (0.51 g).

mp : 264-265°C (dec.)

IR (Nujol) : 1580, 1260 cm^{-1}

NMR (DMSO- d_6 , δ) : 2.18 (3H, s), 2.8-3.5 (4H, m),
6.9-7.6 (7H, m), 9.8-10.7 (2H, broad)

Elemental Analysis for $\text{C}_{14}\text{H}_{15}\text{NS}\cdot\text{HCl}$

Calcd. : C 63.26, H 6.07, N 5.27

Found : C 62.68, H 5.96, N 5.07

Example 20

1-Methyl-1-(3-thienyl)-1,2,3,4-tetrahydroisoquinoline
hydrochloride was obtained according to a similar manner
to that of Example 19.

mp : 280-281°C (dec.)

IR (Nujol) : 1580, 1165, 800 cm^{-1}

NMR (DMSO- d_6 , δ) : 2.12 (3H, s), 2.8-3.3 (4H, m),
7.1-7.3 (6H, m), 7.5-7.7 (1H, m), 10.05 (1H,
broad), 10.33 (1H, broad)

Elemental Analysis for $\text{C}_{14}\text{H}_{15}\text{NS}\cdot\text{HCl}$

Calcd. : C 63.26, H 6.06, N 5.26

Found : C 63.06, H 5.64, N 5.08

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Example 21

1-Methyl-1-(2-thienyl)-1,2,3,4-tetrahydroisoquinoline hydrochloride was subjected to optical resolution according to a similar manner to that of Example 4 to give the following pair of enantiomers.

- i) (+)-1-Methyl-1-(2-thienyl)-1,2,3,4-tetrahydroisoquinoline hydrochloride

mp : 292-293°C

$[\alpha]_D^{25} = +8.9^\circ$ (c=1, MeOH)

IR (Nujol) : 2700, 1580, 1260 cm^{-1}

NMR (DMSO- d_6 , δ) : 2.22 (3H, s), 2.8-3.4 (4H, m), 7.0-7.7 (7H, m), 9.8-10.9 (2H, broad)

- ii) (-)-1-Methyl-1-(2-thienyl)-1,2,3,4-tetrahydroisoquinoline hydrochloride

mp : 289-290°C (dec.)

$[\alpha]_D^{25} = -10.00^\circ$ (c=1, EtOH)

IR (Nujol) : 2700, 1580, 1260 cm^{-1}

NMR (DMSO- d_6 , δ) : 2.27 (3H, s), 3.0-3.4 (4H, m), 7.0-7.7 (7H, m), 9.8-10.9 (2H, broad)

Elemental Analysis for $\text{C}_{14}\text{H}_{16}\text{ClNS} \cdot 1/4\text{H}_2\text{O}$

Calcd. : C 62.21, H 6.15, N 5.18

Found : C 62.58, H 6.26, N 5.13

Example 22

To a suspension of 1-phenyl-2-methyl-3,4-dihydroisoquinolinium iodide (1.0 g) in tetrahydrofuran (15 ml) was added 3M diethyl ether solution of methyl magnesium bromide (1.9 ml) with stirring at room temperature. After stirring for 30 minutes, the mixture was poured into saturated ammonium chloride aqueous solution and ethyl acetate. The organic layer was washed with water, sodium chloride aqueous solution and dried over magnesium sulfate, and evaporated in vacuo. The

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residue was recrystallized from n-hexane to give
1,2-dimethyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline (0.6
g).

mp : 39-40°C

IR (Nujol) : 1600, 1590, 1490 cm^{-1}

NMR (CDCl_3 , δ) : 1.70 (3H, s), 2.15 (3H, s),
2.68-3.25 (4H, m), 6.62-7.50 (9H, m)

Mass (M/Z) : 237 (M^+)

The following compounds (Examples 23 to 25) were
obtained according to a similar manner to that of Example
22.

Example 23

1-Methyl-1-phenyl-2-ethyl-1,2,3,4-
tetrahydroisoquinoline hydrochloride

mp : 193-194°C

IR (Nujol) : 1490, 1420, 1400 cm^{-1}

NMR ($\text{DMSO}-d_6$, δ) : 1.24-1.34 (3H, m), 2.02-2.35
(total 3H, s), 2.90-3.70 (6H, m), 6.62-7.64 (9H,
m), 10.50-10.80 (1H, broad), 11.30-11.60 (1H,
broad)

Mass (M/Z) : 251 (M^+)

Elemental Analysis for $\text{C}_{18}\text{H}_{21}\text{N} \cdot \text{HCl} \cdot 1/4\text{H}_2\text{O}$

Calcd. : C 73.95, H 7.75, N 4.79

Found : C 74.21, H 7.44, N 4.80

Example 24

1,2-Dimethyl-1-(2-thienyl)-1,2,3,4-
tetrahydroisoquinoline hydrochloride

mp : 220-222°C

IR (Nujol) : 2320, 1260, 725 cm^{-1}

NMR (D_2O , δ) : 2.27 (3H, s), 2.89 (3H, s),
3.2-3.8 (4H, m), 7.0-7.7 (7H, m)

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Elemental Analysis for $C_{15}H_{18}ClNS$

Calcd. : C 64.38, H 6.48, N 5.01

Found : C 63.83, H 6.44, N 4.94

5 Example 25

1-Methyl-1-(2-thienyl)-2-ethyl-1,2,3,4-tetrahydroisoquinoline hydrochloride

mp : 198-200°C

IR (Nujol) : 1175, 740 cm^{-1}

10 NMR (DMSO- d_6 , δ) : 1.34 (3H, t, $J=7.5Hz$), 2.22 (3H, s), 3.0-3.9 (6H, m), 6.9-7.7 (7H, m)

Example 26

15 A solution of 1-phenyl-3,4-dihydroisoquinoline (1.0 g) and allyl bromide (0.44 ml) in acetonitrile (10 ml) was refluxed for 2 hours. After cooling it to room temperature, the solvent was evaporated in vacuo and then the residue was stirred in diethyl ether (15 ml) at room temperature. To the mixture was added 3 M diethyl ether
20 solution of methylmagnesium bromide (2.0 ml). After 1 hour, the mixture was poured into aqueous ammonium chloride solution. The organic layer was washed with water, sodium chloride aqueous solution and dried over magnesium sulfate, and evaporated in vacuo to give
25 1-methyl-1-phenyl-2-allyl-1,2,3,4-tetrahydroisoquinoline (0.7 g).

IR (Film) : 1640, 1600, 1490, 1450 cm^{-1}

NMR ($CDCl_3$, δ) : 1.69 (3H, s), 2.70-3.15 (6H, m), 4.98-5.19 (2H, m), 5.54-5.78 (1H, m), 6.64-7.54
30 (9H, m)

Mass (M/Z) : 263 (M^+)

Example 27

35 1-Methyl-1-phenyl-2-phenethyl-1,2,3,4-tetrahydroisoquinoline hydrochloride was prepared by

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reacting 1-phenyl-3,4-dihydroisoquinoline with phenethyl
bromide, then 3 M diethyl ether solution of
methylmagnesium bromide according to a similar manner to
that of Example 26, and then converting the resultant
5 compound to its hydrochloride according to a conventional
manner.

mp : 255-256°C

IR (Nujol) : 1600, 1580, 1490, 1420 cm^{-1}

NMR (DMSO- d_6 , δ) : 2.15 and 2.48 (total 3H, s),

10 3.05-3.50 (4H, m), 3.55-4.20 (4H, m),

7.10-8.00 (14H, m)

Mass (M/Z) : 325 (M^+ - 15)

Elemental Analysis for $\text{C}_{24}\text{H}_{25}\text{N} \cdot \text{HCl} \cdot 0.1\text{H}_2\text{O}$

Calcd. : C 78.81, H 7.22, N 3.82

15 Found : C 78.77, H 7.30, N 3.79

Example 28

To a solution of (+)-1-methyl-1-phenyl-1,2,3,4-
tetrahydroisoquinoline (1.0 g) in N,N-dimethylformamide
20 (10 ml) was added sodium hydride (0.19 g) in ice-bath with
stirring. After stirring for 30 minutes at room
temperature, to the mixture was added methyl iodide (0.31
ml). And after stirring for an hour at room temperature,
the mixture was poured into ice-water and extracted with
25 ethyl acetate. The organic layer was washed with water,
sodium chloride aqueous solution, dried over magnesium
sulfate and evaporated in vacuo to give (+)-1,2-dimethyl-
1-phenyl-1,2,3,4-tetrahydroisoquinoline (0.6 g).

$[\alpha]_{\text{D}}^{20} = +105.6^\circ$ (c=1.3 EtOH)

30 IR (Film) : 1600, 1585, 1495, 1450 cm^{-1}

NMR (CDCl_3 , δ) : 1.64 (3H, s), 2.11 (3H, s),

2.72-3.30 (4H, m), 6.62-7.44 (9H, m)

Mass (M/Z) : 237 (M^+)

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Example 29

To a solution of 1-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline (1.0 g) in methylene chloride (10 ml) was added chloroacetic anhydride (2.9 g) and the mixture was stirred overnight at room temperature. The solvent was evaporated in vacuo. The residue was poured into saturated aqueous solution of sodium bicarbonate and extracted with ethyl acetate. The organic layer was washed with water, sodium chloride aqueous solution and dried over magnesium sulfate, evaporated in vacuo. The resultant precipitate was recrystallized from diethyl ether and dried in vacuo to give 1-methyl-1-phenyl-2-(2-chloroacetyl)-1,2,3,4-tetrahydroisoquinoline (0.77 g).

mp : 150-152°C

IR (Nujol) : 1665, 1640 cm^{-1}

NMR (CDCl_3 , δ) : 2.03 (3H, s), 3.04 (1H, d, $J=11\text{Hz}$),
3.06 (1H, d, $J=11\text{Hz}$), 3.75-4.12 (4H, m),
6.62-7.34 (9H, m)

Mass (M/Z) : 299 (M^+)

Example 30

To a solution of 1-methyl-1-phenyl-2-(2-chloroacetyl)-1,2,3,4-tetrahydroisoquinoline (1.0 g) in methylene chloride (10 ml) was added piperidine (0.82 ml) under ice-cooling, and the mixture was stirred for 3 hours at room temperature. The reaction mixture was poured into water and extracted with methylene chloride. The organic layer was washed with saturated aqueous solution of sodium bicarbonate, sodium chloride aqueous solution and dried over magnesium sulfate, evaporated in vacuo. The residue was dissolved in ethanol (5 ml) and to the solution was added 6 M ethanol solution of hydrogen chloride (1 ml). The mixture was evaporated in vacuo and the residue was recrystallized from isopropyl alcohol and diisopropyl ether. The crystal was washed with diethyl ether and

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dried in vacuo to give 1-methyl-1-phenyl-2-(2-piperidinoacetyl)-1,2,3,4-tetrahydroisoquinoline hydrochloride (0.4 g).

mp : 146-147°C (dec.)

IR (Nujol) : 3340, 1660 cm^{-1}

NMR (DMSO-d_6 , δ) : 1.60-1.72 (6H, m), 2.05 (3H, s),
2.95-3.34 (4H, m), 3.64-3.84 (2H, m), 4.34-4.57
(2H, m), 6.73-7.38 (9H, m), 9.30 (1H, s)

Mass (M/Z) : 348 (M^+)

Elemental Analysis for $\text{C}_{23}\text{H}_{28}\text{N}_2\text{O}$ (free)

Calcd. : C 79.27, H 8.09, N 8.03

Found : C 79.20, H 7.37, N 8.01

Example 31

A solution of 1-methyl-1-phenyl-2-(2-piperidinoacetyl)-1,2,3,4-tetrahydroisoquinoline (1.0 g) in tetrahydrofuran (5 ml) was dropped into a suspension of lithium aluminum hydride (0.16 g) in tetrahydrofuran (15 ml) over a period of 30 minutes under refluxing. The reaction mixture was heated under refluxing for an additional 1 hour. After cooling it in an ice-bath, to the reaction mixture was added ethyl acetate (5 ml), water (1 ml), 4N aqueous solution of sodium hydroxide (1 ml) and magnesium sulfate (2 g), then the mixture was filtrated and evaporated in vacuo. The residue was dissolved in ethanol (10 ml) and to the solution was added 6 M ethanol solution of hydrogen chloride (2 ml). The precipitate was collected by filtration and washed with diethyl ether, and dried in vacuo to give 1-methyl-1-phenyl-2-(2-piperidinoethyl)-1,2,3,4-tetrahydroisoquinoline dihydrochloride (0.4 g).

mp : 130°C (dec.)

IR (Nujol) : 3380, 1590 cm^{-1}

NMR ($\text{DMSO-d}_6 + \text{D}_2\text{O}$, δ) : 1.40-1.70 (6H, broad), 2.13
(3H, s), 2.68-2.86 (4H, broad), 3.22-3.63 (8H,

broad), 6.70-7.56 (9H, m)

Mass (M/Z) : 334 (M^+)

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Elemental Analysis for $C_{23}H_{30}N_2 \cdot 2HCl$

Calcd. : C 67.80, H 7.91, N 6.87, Cl 17.40

Found : C 67.44, H 7.71, N 6.46, Cl 17.32

Example 32

1-Methyl-1-phenyl-2,3,4,5-tetrahydro-1H-2-benzazepine hydrochloride was obtained according to a similar manner to that of Example 1.

mp : 275-277°C

IR (Nujol) : 1580, 1480 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.58-1.85 (2H, m), 2.12 (3H, s),
2.38-3.25 (4H, m), 7.20-7.55 (9H, m)

Mass (M/Z) : 236 ($M^+ - 1$)

Elemental Analysis for $C_{17}H_{19}N \cdot HCl \cdot 1/5H_2O$

Calcd. : C 73.60, H 7.41, N 5.04

Found : C 74.05, H 7.82, N 5.05

The following compounds (Examples 33 to 37) were obtained according to a similar manner to that of Example 28.

Example 33

1-Methyl-1-phenyl-2-ethyl-1,2,3,4-tetrahydroisoquinoline hydrochloride

IR (Nujol) : 1490, 1420, 1400 cm^{-1}

Example 34

1,2-Dimethyl-1-(2-thienyl)-1,2,3,4-tetrahydroisoquinoline hydrochloride

IR (Nujol) : 2320, 1260, 725 cm^{-1}

Example 35

1-Methyl-1-(2-thienyl)-2-ethyl-1,2,3,4-

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tetrahydroisoquinoline hydrochloride

IR (Nujol) : 1175, 740 cm^{-1}

Example 36

5 1-Methyl-1-phenyl-2-allyl-1,2,3,4-
tetrahydroisoquinoline

IR (Film) : 1640, 1600, 1490, 1450 cm^{-1}

Example 37

10 1-Methyl-1-phenyl-2-phenethyl-1,2,3,4-
tetrahydroisoquinoline hydrochloride

IR (Nujol) : 1600, 1580, 1490, 1420 cm^{-1}

15 The following compounds (Examples 38 and 39) were
obtained according to a similar manner to that of Example
22.

Example 38

20 1-Methyl-1-phenyl-2-(2-piperidinoacetyl)-1,2,3,4-
tetrahydroisoquinoline hydrochloride

IR (Nujol) : 3340, 1660 cm^{-1}

Example 39

25 1-Methyl-1-phenyl-2-(2-piperidinoethyl)-1,2,3,4-
tetrahydroisoquinoline dihydrochloride

IR (Nujol) : 3380, 1590 cm^{-1}

Example 40

30 1-Methyl-1-phenyl-2-(2-piperidinoacetyl)-1,2,3,4-
tetrahydroisoquinoline hydrochloride was obtained
according to a similar manner to that of Example 29.

IR (Nujol) : 3340, 1660 cm^{-1}

Example 41

35 1-Methyl-1-phenyl-2-(2-piperidinoethyl)-1,2,3,4-

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tetrahydroisoquinoline dihydrochloride was obtained according to a similar manner to that of Example 28.

IR (Nujol) : 3380, 1590 cm^{-1}

5

10

15

20

25

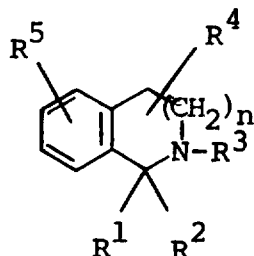
30

35

What we claim is :

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1. A bicyclic amine compound of the formula :



wherein R¹ is lower alkyl,

R² is aryl which may have one or more
suitable substituent(s),
cyclo(lower)alkyl or
heterocyclic group,

R³ is hydrogen, lower alkyl which may have
one or more suitable substituent(s),
lower alkenyl, or acyl which may have
one or more suitable substituent(s),

R⁴ is hydrogen, lower alkyl, or
hydroxy(lower)alkyl,

R⁵ is hydrogen, lower alkyl, halogen,
or protected amino, and

n is an integer of 1 or 2,

and a pharmaceutically acceptable salt thereof.

2. A compound of claim 1, wherein

R² is aryl which may have 1 to 3 suitable
substituent(s) selected from a group consisting
of lower alkyl, lower alkoxy and halogen;
cyclo(lower)alkyl or unsaturated 5- or
6-membered heterocyclic group having 1 to 3
oxygen or sulfur atom(s),

R³ is hydrogen, lower alkyl which may have 1 to 3
suitable substituent(s) selected from a group

consisting of aryl and cyclic amino; lower alkenyl or acyl which may have 1 to 3 suitable substituent(s) selected from a group consisting of halogen and cyclic amino.

- 5
3. A compound of claim 2, wherein
- 10 R^2 is phenyl which may have 1 to 3 suitable substituent(s) selected from a group consisting of lower alkyl, lower alkoxy and halogen, cyclo(lower)alkyl or unsaturated 5-membered heterocyclic group having 1 to 2 oxygen or sulfur atom(s),
- 15 R^3 is hydrogen, lower alkyl which may have 1 to 3 suitable substituent(s) selected from a group consisting of phenyl and 6-membered cyclic amino; lower alkenyl or lower alkanoyl which may have 1 to 3 suitable substituent(s) selected from a group consisting of halogen and 6-membered cyclic amino.

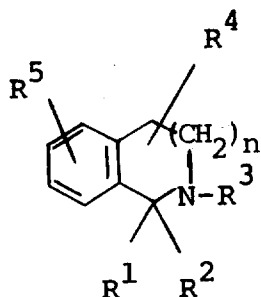
- 20
4. A compound of claim 3, wherein
- 25 R^2 is phenyl, phenyl having lower alkyl, phenyl having lower alkoxy, phenyl having halogen, cyclo(lower)alkyl, furyl or thienyl,
- R^3 is hydrogen, lower alkyl, lower alkyl having phenyl, lower alkyl having piperidino, lower alkenyl, lower alkanoyl having halogen or lower alkanoyl having piperidino,
- 30 and
- R^5 is hydrogen, lower alkyl, halogen or lower alkoxycarbonylamino.

- 35
5. A compound of claim 4, wherein
- n is an integer of 1.

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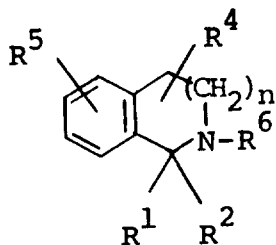
6. A compound of claim 5, wherein
R³ is hydrogen.
- 5 7. A compound of claim 6, wherein
R¹ is methyl,
R² is phenyl, furyl or thienyl, and
R³, R⁴ and R⁵ are each hydrogen.
- 10 8. A compound of claim 7, which is 1-methyl-1-phenyl-
1,2,3,4-tetrahydroisoquinoline or its hydrochloride.
- 15 9. A compound of claim 5, wherein
R² is phenyl or thienyl,
R³ is lower alkyl,
R⁴ and R⁵ are each hydrogen.
- 20 10. A compound of claim 5, wherein
R² is phenyl,
R³ is lower alkyl having phenyl, lower alkyl having
piperidino, lower alkenyl, lower alkanoyl
having halogen or lower alkanoyl having
piperidino,
and
R⁴ and R⁵ are each hydrogen.
- 25 11. A compound of claim 4,
wherein n is an integer of 2.
- 30 12. A compound of claim 11, wherein
R¹ is lower alkyl,
R² is phenyl,
R³, R⁴ and R⁵ are each hydrogen.
- 35 13. A process for preparing a bicyclic amine compound of
the formula :

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wherein R^1 is lower alkyl,
 R^2 is aryl which may have one or more
suitable substituent(s),
cyclo(lower)alkyl or heterocyclic
group,
 R^3 is hydrogen, lower alkyl which may have
one or more suitable substituent(s),
lower alkenyl, or acyl which may have
one or more suitable substituent(s),
 R^4 is hydrogen, lower alkyl, or
hydroxy(lower)alkyl,
 R^5 is hydrogen, lower alkyl, halogen, or
protected amino, and
n is an integer of 1 or 2,
or a salt thereof, which comprises

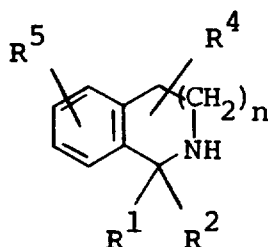
i) subjecting a compound of the formula :



wherein R^1 , R^2 , R^4 , R^5 and n are each as defined
above, and
 R^6 is amino protective group,
or a salt thereof, to elimination reaction of the

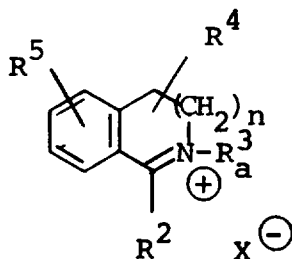
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amino protective group, to give a compound of the formula :



wherein R^1 , R^2 , R^4 , R^5 and n are each as defined above,
or a salt thereof, or

ii) reacting a compound of the formula :

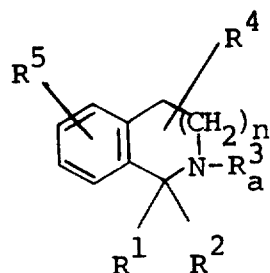


wherein R^2 , R^4 , R^5 and n are each as defined above,

R_a^3 is lower alkyl which may have one or more suitable substituent(s), lower alkenyl or acyl which may have one or more suitable substituent(s), and X^- is an anion,

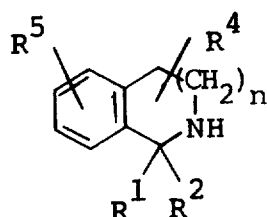
or a salt thereof, with a lower alkylating agent, to give a compound of the formula :

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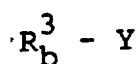


wherein R^1 , R^2 , R_a^3 , R^4 , R^5 and n are each as defined above,
or a salt thereof, or

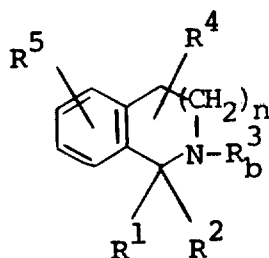
iii) reacting a compound of the formula :



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



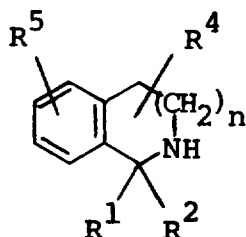
wherein R_b^3 is lower alkyl which may have one or more suitable substituent(s) or lower alkenyl, and
 Y is a leaving group,
or a salt thereof, to give a compound of the formula :



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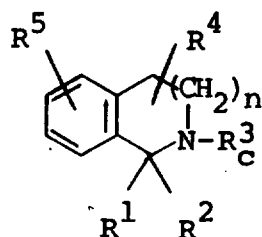
wherein R^1 , R^2 , R^3 , R^4 , R^5 and n are each as defined above,
or a salt thereof, or

iv) subjecting a compound of the formula :



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

or a salt thereof, to introduction reaction of acyl which may have one or more suitable substituent(s), to give a compound of the formula:



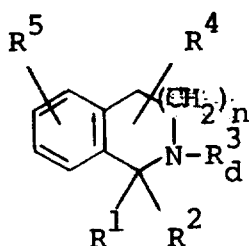
wherein R^1 , R^2 , R^4 , R^5 and n are each as defined above, and

R^3_C is acyl which may have one or more suitable substituent(s),

or a salt thereof, or

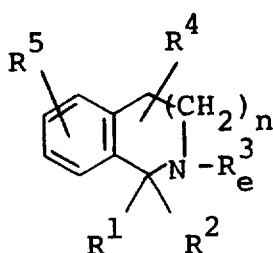
v) reacting a compound of the formula :

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

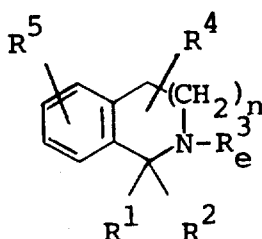
R_d^3 is lower alkanoyl having halogen, or a salt thereof, with cyclic amine or a salt thereof, to give a compound of the formula :



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

R_e^3 is lower alkanoyl having cyclic amino, or a salt thereof, or

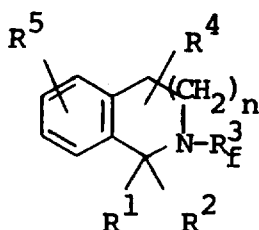
vi) subjecting a compound of the formula :



wherein R^1 , R^2 , R_e^3 , R^4 , R^5 and n are each as defined above,

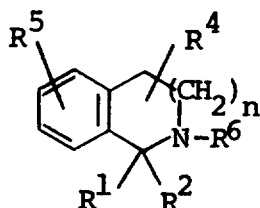
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or a salt thereof, to reduction, to give a compound of the formula :



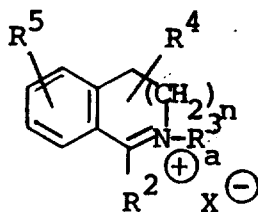
wherein R^1 , R^2 , R^4 , R^5 and n are each as defined above, and R^3_f is lower alkyl having cyclic amino, or a salt thereof.

14. A compound of the formula :



wherein R^1 , R^2 , R^4 , R^5 and n are each as defined in claim 1, and R^6 is amino protective group, and a salt thereof.

15. A compound of the formula :



wherein R^2 , R^4 , R^5 and n are each as defined in claim 1,

R^3_a is lower alkyl which may have one or more

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suitable substituent(s), lower alkyl
or acyl which may have one or more
suitable substituent(s), and

$X^{\ominus}$ is an anion,
and a salt thereof.

16. A pharmaceutical composition comprising a compound of claim 1, as an active ingredient, in association with a pharmaceutically acceptable, substantially nontoxic carrier or excipient.
17. A compound of claim 1 for use as a medicament.
18. A method for the therapeutic treatment of convulsion and delayed neuronal death which comprises administering a compound of claim 1 in human being or animals.

Hisashi Takasegi

Atsushi Kuno

Mitsuru Okubo

END ORIGINAL