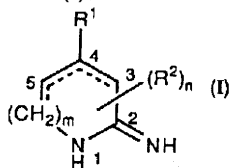


**(57) (Abstract)****(Construction)**

A compound represented by general formula (I), an acid addition salt thereof or hydrate thereof



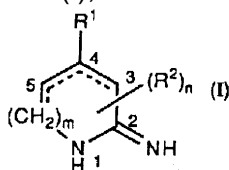
(wherein, R1 is hydrogen, C1-10 alkyl, C3-7 cycloalkyl, R2 denotes hydrogen, C1-10 alkyl, C2-10 alkenyl, C2-10 alkynyl, C3-7 cycloalkyl, C1-10 alkoxy or hydroxy group, amino, C1-10 alkyl substituted with C1-10 alkoxy, and furthermore two R2s and carbon atom on one or adjacent two rings bonded each other are linked together and may denote 3-7 membered saturated carbon ring, n is integer of 1-4 and m is integer of 1-2)

**(Effect)**

A compound of general formula (I) and a salt thereof have NOS inhibitory action and are useful in therapy and/or prevention of shock, hypotension, chronic rheumatism, ulcerative colitis, ischemic encephalopathy, tumour, insulin-dependent diabetes mellitus and the like.

**Patent Claims****Claim 1**

A compound represented by general formula (I), an acid addition salt thereof or hydrate thereof



(wherein, R1 is hydrogen, C1-10 alkyl or C3-7 cycloalkyl, R2 each independently denotes (i) hydrogen atom, (ii) C1-10 alkyl group, (iii) C2-10 alkenyl group, (iv) C2-10 alkynyl group, (v) C3-7 cycloalkyl group, (vi) C1-10 alkoxy group or (vii) hydroxy group, amino group or C1-10 alkyl group substituted with C1-10 alkoxy group, and furthermore two R2s and carbon atom on one or adjacent two rings bonded each other are linked together and may denote 3-7 membered saturated carbon ring, n is integer of 1-4, m is integer of 1-2 and

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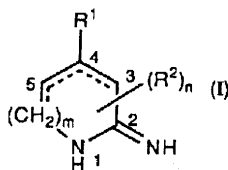
denotes any one of 3-4, 4-5 or 5-6 position is double bond. Wherein when R1 denotes hydrogen atom and also 3-4 position is double bond, n denotes an integer of 2 or more, two R2s among them denote groups other than hydrogen atom and the two R2s are substituted with 5 position.

### (Detailed Description of the Invention)

(0001)

This invention relates to a nitric monoxide synthase inhibitor. More particularly, it relates to a compound represented by general formula (I)

(0002)



(0003)

(wherein, all the symbols have the same following meanings),  
an acid addition salt thereof or hydrate thereof.

(0004)

#### Background of invention

The discovery that macrophage, one of immunocompetent cell produced a large quantity of nitrate, led to the discovery of the fact that nitric monoxide (NO) was formed in-vivo (Proc. Natl. Acad. Sci. USA, 82, 7738-7742 (1985); J. Immunol., 138, 550-565 (1987)). Moreover, a substance discharged from vascular endothelium cells, having relaxation action was discovered in the field of circulatory organ system, and it was named vascular endothelium derived relaxing factor (EDRF). Moreover, it was found out that the main body of this EDRF comprised NO (Nature, 327, 524-526 [1987]).

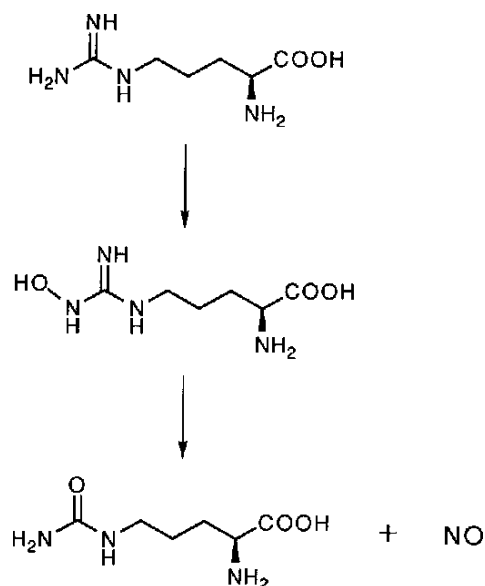
(0005)

The NO which thus became clear is produced in-vivo is formed by nitric monoxide synthase (NOS) using L-arginine as substrate by the following pathway.

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(0006)



(0007)

As far as NOS is concerned, there are at least non-inducible type (vascular endothelium type and nerve type) and inducible type isozymes present. Vascular endothelium type NOS is mainly present in vascular endothelium cells and the activity is controlled by intracellular calcium concentration. Nerve type NOS is present in central nerve cells, peripheral nerve cells or beta-cells of islet, gastrointestinal tract nerve, adrenal medulla, kidney macula densa and the like, and the activity is controlled by intracellular calcium concentration in the same way as vascular endothelium type NOS.

(0008)

Vascular endothelium type NOS and nerve type NOS (abbreviated to constitutive NOS, c-NOS) is constantly present in cells, and there is almost no change of enzyme quantity due to physiological change. Inducible type NOS (known as inducible NOS, abbreviated to i-NOS) is present in hepatocyte, neutrophil, macrophage, smooth muscle, fibroblast, kidney mesangial cell, gastrointestinal tract epithelium, beta-cells of islet, vascular smooth muscle cells, glial cell and the like. This is not usually observed intracellularly and it is induced by stimulation using endotoxin or various cytokine and the like.

(0009)

Action of NO produced by NOS varies and for example includes, vasodilation action, platelet aggregation inhibitory action, adhesion inhibition, leukocyte adhesion and migration inhibition, sympathetic nerve activity inhibition, hypotension due to endotoxin•cytokine, endotoxin shock, action as signal transduction substance between neurones, ischemic brain cell injury, antitumour, bactericidal action, autoimmune disease, insulin-dependent diabetes mellitus, arthritis, post-transplantation tissue disorder, rejection and the like.

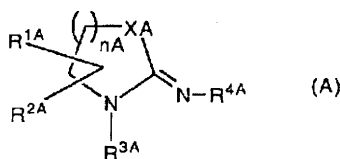
(0010)

When analysing in-vivo activity of NO, NO synthase inhibitor is useful, and also there is a possibility that it is used as a therapeutic drug, for example, for shock and ischemic diseases, therefore, recently the development of various kinds of NOS inhibitors has been carried out. For example, there are arginine analogues as substrate competing agent, and N omega-monomethyl-L-arginine (L-NMMA), N omega-nitro-L-arginine (L-NNA), N omega-amino-L-arginine (L-NAA), N omega-imino ethyl-ornithine (L-NIO) and the like belong to these. Moreover, there are diphenylene idonium (DPI), di-2-thienyl idonium (DTI), calcineurin and the like as cofactor competitive inhibition agent. Moreover, as species which inhibit induction of genetic transcription, there are corticosteroid, TGF beta, IL-4, IL-10 and the like.

(0011)

In WO95/11231 specification, there is description that a compound represented by general formula (A), salts thereof, pharmacologically permitted ester and prodrug are nitric monoxide synthase inhibitors.

(0012)

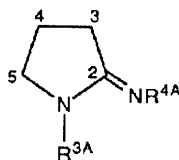


(0013)

[Wherein, XA is selected from the group comprising methylene, nitrogen atom, oxygen atom, S, SO or SO<sub>2</sub>. Among them, nitrogen atom and lower alkyl radical may be substituted with hydroxy group, lower alkyl, lower alkoxy, amino or haloalkyl; nA denotes 0 to about 7; R<sub>1A</sub> and R<sub>2A</sub> are each

independently denote hydrogen atom, hydroxy group, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, lower thio alkoxy, halogen, nitro, amino, carboxyl, cyano, sulfonyl, haloalkyl, carboalkoxy, carboaryloxy, carboalkyl aryloxy, alicyclic hydrocarbon, heterocycle, aromatic hydrocarbon, -CONR<sub>5</sub>AR<sub>6</sub>A, -SO<sub>2</sub>NR<sub>5</sub>AR<sub>6</sub>A, -COR<sub>5</sub>A, -SO<sub>2</sub>R<sub>5</sub>A, alkyl sulfoxide, aryl sulfoxide, alkyl sulfone, aryl sulfone, alkyl sulfate, aryl sulfate and sulfonamide. Among them, all aforesaid radicals may be substituted with one or more of following: hydroxy group, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, lower thio alkoxy, halogen, nitro, amino, carboxyl, cyano, sulfonyl, carbo alkoxy, carbo aryloxy, carboxyalkyl aryloxy, haloalkyl, -SO<sub>2</sub>NR<sub>5</sub>ANR<sub>6</sub>A and SO<sub>2</sub>R<sub>5</sub>A. Among them, all aforesaid substituent may be substituted with one or more of following: amino, carboxyl, carbo alkoxy, carbo aryloxy, carboxyalkyl aryloxy and lower alkoxy; and R<sub>1</sub>A and R<sub>2</sub>A may form together alicyclic hydrocarbon, heterocycle or aromatic hydrocarbon and aforesaid ring which is arbitrarily formed may be substituted with one or more of following: carboxyl, carbo alkoxy, carbo aryloxy, carboxyalkyl aryloxy and lower alkyl, lower alkenyl and lower alkynyl which may be substituted with lower alkoxy; R<sub>3</sub>A and R<sub>4</sub>A are each independently selected from the group comprising hydrogen atom, hydroxy group and alkoxy; R<sub>5</sub>A and R<sub>6</sub>A are each independently selected from the group comprising hydrogen atom, lower alkyl and aryl; wherein when nA denotes 1, namely

(0014)



(0015)

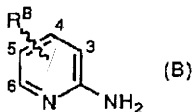
and also when R<sub>1</sub>A and/or R<sub>2</sub>A are substituted at 3 or 4 position, both R<sub>1</sub>A and R<sub>2</sub>A do not denote aryl]. Moreover, in gist collection of IBC's Fifth Annual Conference on NITRIC OXIDE academic society (28, 29 March, 1996), there is a description that a compound represented by Table 1 is nitric monoxide synthase inhibitor (some of compounds in Table 1 are extracted).

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(0016)

(Table 1)

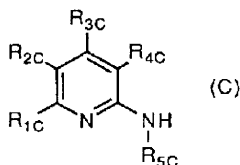


No.	R <sup>B</sup>
B1	4-methyl
B2	3-methyl
B3	hydrogen atom
B4	5-methyl
B5	6-methyl
B6	4,6-dimethyl

(0017)

Moreover, in WO96/18616 specification, there is description that a compound represented by general formula (C) and pharmacologically permitted salts thereof are nitric monoxide synthase inhibitors.

(0018)

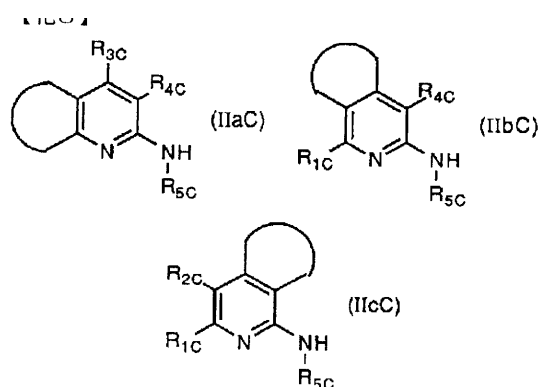


(0019)

[wherein, R1C, R2C, R3C and R4C are each independently selected from the group comprising (a) hydrogen atom, (b) hydroxy group, (c) amino, (d) carboxy, (e) aminocarbonyl, (f) cyano, (g) nitro, (h) halogen atom selected from fluorine atom, chloro atom, bromine atom and iodine atom, (i) trifluoromethyl, (j) C1-12 alkyl, (k) C2-12 alkenyl, (l) C2-12 alkynyl, (m) C1-12 alkoxy, (n) C1-12 alkyl carbonyl, (o) C1-12 alkoxy carbonyl, (p) C1-12 alkylamino carbonyl, (q) mono and di-C1-12 alkylamino, (r) C1-12 alkylthio, (s) aryl (among the groups aryl is selected from phenyl and naphthyl), (t) aryloxy (among the groups aryl is selected from phenyl and naphthyl), (u) arylthio (among the

groups aryl is selected from phenyl and naphthyl), (v) aryl C1-6 alkyl (among the groups aryl is selected from phenyl and naphthyl), (w) cycloalkyl (among the groups cycloalkyl denotes 5-10 membered monocycle and may contain one or two heteroatom selected from sulfur atom, oxygen atom and nitrogen atom), (x) heteroaryl (among the groups heteroaryl is selected from following groups; (1) pyridyl, (2) pyrrolyl, (3) furanyl, (4) thienyl, (5) iso thiazolyl, (6) imidazolyl, (7) benzimidazolyl, (8) tetrazolyl, (9) pyrazinyl, (10) pyrimidyl, (11) quinolyl, (12) isoquinolyl, (13) benzofuranyl, (14) iso benzofuryl, (15) benzothienyl, (16) pyrazolyl, (17) pyrazinyl, (18) indolyl, (19) iso indolyl, (20) pyrinyl, (21) carbazolyl, (22) isoxazolyl, (23) thiazolyl, (24) triazolyl, (25) oxazolyl, (26) oxadiazolyl, (27) thiadiazolyl, (28) benz thiazolyl and (29) benz oxazolyl), (y) heteroaryl C1-6 alkyl (among the groups heteroaryl is defined by aforesaid (x)). Moreover, each group represented by (j)-(y) may be mono- or di-substituted and substituents thereof are each independently selected from (1) hydroxy group, (2) C1-6 alkyl, (3) C1-6 alkoxy, (4) amino, (5) mono- and di-C1-6 alkylamino, (6) carboxy, (7) C1-6 alkylthio, (8) -S(O)<sub>k</sub>-C1-3 alkyl (among the groups k denotes 1 or 2), (9) C1-6 alkoxy carbonyl, (10) halogen atom selected from fluorine atom, chloro atom, bromine atom and iodine atom, (11) oxo, (12) amidino and (13) guanidino. R<sub>1C</sub> and R<sub>2C</sub>, R<sub>2C</sub> and R<sub>3C</sub> or R<sub>3C</sub> and R<sub>4C</sub> contain 0-2 heteroatoms together with atom bonded respectively and may form 5-10 membered saturated or unsaturated ring, and bicyclo ring is formed according to the general formula (IIaC-IIcC). Heteroatom is selected from the group comprising oxygen atom, sulfur atom and nitrogen atom.

(0020)



(0021)

R<sub>5C</sub> is selected from the group comprising (a) hydrogen atom, (b) C1-12 alkyl, (c) C2-12 alkenyl, (d) C2-12 alkynyl, (e) aryl (among the groups aryl is defined as above), (f) aryl C1-6 alkyl (among the groups aryl is defined as above), (g) heteroaryl (among the groups heteroaryl is defined as above),

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(h) heteroaryl C1-6 alkyl (among the groups heteroaryl is defined as above), (i) cycloalkyl (among the groups cycloalkyl denotes 5-10 membered monocycle and may contain one or two hetero atom selected from the group comprising sulfur atom, oxygen atom and nitrogen atom). Each group represented by (b)-(i) may be mono- or di-substituted. Substituent thereof are each independently selected from (1) hydroxy group, (2) C1-6 alkyl, (3) C1-6 alkoxy, (4) amino, (5) mono- and di-C1-6 alkylamino, (6) carboxy, (7) C1-6 alkylthio, (8) -S(O)<sub>k</sub>-C1-3 alkyl (among the groups k denotes 1 or 2), (9) C1-6 alkoxy carbonyl, (10) halogen atom selected from fluorine atom, chloro atom, bromine atom and iodine atom, (11) oxo, (12) amidino and (13) guanidino. Wherein R<sub>2</sub>C does not denote aryl, heteroaryl, aryl C1-4 alkyl or heteroaryl C1-4 alkyl].

(0022)

(Object of the invention).

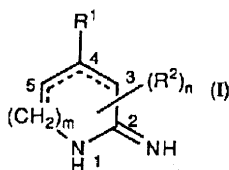
These inventors carried out assiduous investigation, as a result, discovered that the compound represented by general formula (I) hindered nitric monoxide synthase (in particular, inducible NOS). Moreover, it was discovered that some of the compound are almost unaffected in normal blood pressure. This invention was completed as a result of this.

(0023)

(Disclosure of the invention)

This invention is related to (1) a compound represented by general formula (I), acid addition salts thereof or hydrates thereof

(0024)



(0025)

(wherein, R<sub>1</sub> is hydrogen, C1-10 alkyl or C3-7 cycloalkyl, R<sub>2</sub> each independently denotes (i) hydrogen atom, (ii) C1-10 alkyl group, (iii) C2-10 alkenyl group, (iv) C2-10 alkynyl group, (v) C3-7 cycloalkyl group, (vi) C1-10 alkoxy group or (vii) hydroxy group, amino group or C1-10 alkyl group substituted with C1-10 alkoxy group, and furthermore two R<sub>2</sub>s and carbon atom on one or adjacent

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two rings bonded each other are linked together and may denote 3-7 membered saturated carbon ring, n is integer of 1-4, m is integer of 1-2 and

(0026)



(0027)

denotes any one of 3-4, 4-5 or 5-6 position is double bond. Wherein when R1 denotes hydrogen atom and also 3-4 position is double bond, n denotes an integer of 2 or more, two R2s among them denote groups other than hydrogen atom and the two R2s are substituted with 5 position), (2) a process for the production thereof and (3) nitric monoxide synthase inhibitor containing them as an effective component.

(0028)

In general formula (I), C1-10 alkyl group represented by R1 and R2 denotes methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl group and an isomer thereof. C3-7 cycloalkyl group represented by R1 and R2 in general formula (I) denotes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl group.

(0029)

In general formula (I), C2-10 alkenyl group represented by R2 denotes ethenyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, nonenyl, decenyl group and an isomer thereof. C2-10 alkynyl group represented by R2 in general formula (I) denotes ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, nonyl, decynyl group and an isomer thereof.

(0030)

In general formula (I), C1-10 alkoxy group represented by R2 denotes methoxy, ethoxy, propoxy, butoxy, pentyloxy, hexyloxy, octyloxy, nonyloxy, decyloxy group and an isomer thereof. Substituent represented by R2 is substituted from 3, 4, 5, 6 and 7 position, and does not form structurally impossible substitution pattern.

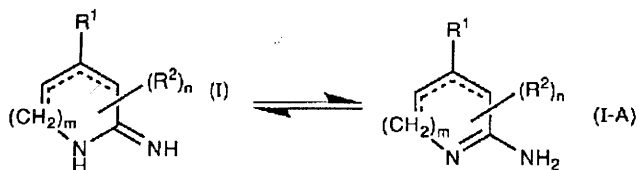
(0031)

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A compound represented by general formula (I) is equivalent to a compound represented by general formula (I-A)

(0032)



(0033)

(wherein, all the aforesaid symbols have the same aforesaid meaning). Moreover, in this invention unless specifically indicated to the contrary all isomers are also included. For example, branched chain types and straight chain types are included for the alkyl group. Moreover, isomers produced by the presence of asymmetric carbon atom such as the situation where a branched chain alkyl group is present are also include.

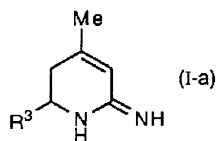
(0034)

The compounds described in the Examples and the compounds shown in the following Table 2 to Table 7 comprise particularly preferred compounds among the compounds represented by general formula (I).

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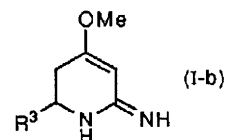
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(0035)  
(Table 2)



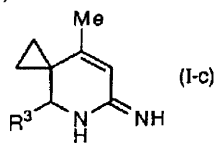
No.	R <sup>3</sup>
1	H
2	Me
3	n-Pr
4	i-Pr
5	n-Bu
6	i-Bu
7	
8	
9	
10	
11	
12	

(0036)  
(Table 3)



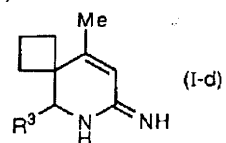
No.	R <sup>3</sup>
1	H
2	Me
3	n-Pr
4	i-Pr
5	n-Bu
6	i-Bu
7	
8	
9	
10	
11	
12	

(0037)  
(Table 4)



No.	R <sup>3</sup>
1	H
2	Me
3	n-Pr
4	i-Pr
5	n-Bu
6	i-Bu
7	
8	
9	
10	
11	
12	

(0038)  
(Table 5)

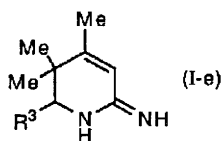


No.	R <sup>3</sup>
1	H
2	Me
3	n-Pr
4	i-Pr
5	n-Bu
6	i-Bu
7	
8	
9	
10	
11	
12	

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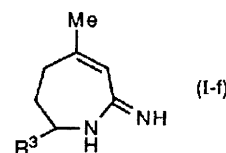
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(0039)  
(Table 6)



No.	R <sup>3</sup>
1	H
2	Me
3	n-Pr
4	i-Pr
5	n-Bu
6	i-Bu
7	
8	
9	
10	
11	
12	

(0040)  
(Table 7)



No.	R <sup>3</sup>
1	H
2	Me
3	n-Pr
4	i-Pr
5	n-Bu
6	i-Bu
7	
8	
9	
10	
11	
12	

(0041)

(In Tables, R<sub>3</sub> denotes (i) hydrogen atom, (ii) C<sub>1</sub>-10 alkyl group, (iii) C<sub>2</sub>-10 alkenyl group, (iv) C<sub>2</sub>-10 alkynyl group, (v) C<sub>3</sub>-7 cycloalkyl group, (vi) C<sub>1</sub>-10 alkoxy group or (vii) C<sub>1</sub>-10 alkyl group substituted with hydroxy group, amino group or C<sub>1</sub>-10 alkoxy group, Me denotes methyl group, n-Pr denotes normal propyl group, i-Pr denotes isopropyl group, n-Bu denotes normal butyl group and i-Bu denotes isobutyl group.)

The compound represented by general formula (I) is converted into acid addition salt by well known method.

(0042)

As acid addition salt, nontoxic water soluble species are preferred. As suitable acid addition salts, organic salts such as acetate, lactate, tartrate, oxalate, fumarate, maleate, citrate, benzoate, methanesulphonate, ethanesulphonic acid salt, benzenesulphonate, toluenesulphonate, isethionate, glucuronic acid salt and gluconate, and inorganic acid salts such as hydrochloride, hydrobromic acid salt, hydroiodic acid salt, sulphate, phosphate and nitrate are nominated.

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(0043)

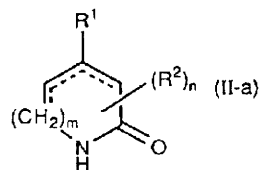
The compounds of this invention represented by general formula (I) and salts thereof may be converted into hydrates by well known method.

(0044)

(Process for the Production of the Compounds of this Invention).

It is possible that the compounds of this invention represented by general formula (I) can be produced by causing amidino formation of the compound represented by general formula (II-a)

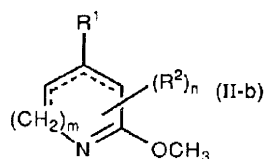
(0045)



(0046)

(wherein, all the aforesaid symbols have the same aforesaid meaning), by causing amidino formation of the compound represented by general formula (II-b)

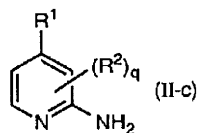
(0047)



(0048)

(wherein, all the aforesaid symbols have the same aforesaid meaning) or by subjecting to reductive reaction of the compound represented by general formula (II-c)

(0049)



(0050)

(wherein, q denotes an integer of 1-3 and other symbols have the same aforesaid meaning). As reaction to produce the compound represented by general formula (I) from the compound

represented by general formula (II-a), for example it can be carried out by the following process. In halogenated hydrocarbon series solvent (dichloromethane, chloroform, carbon tetrachloride and the like), the compound represented by formula (II-a) is reacted with alkylation reagent (dialkyl sulphate (dimethylsulfate, diethyl sulfate and the like) or trialkyl ester oxonium tetrafluoroborate (trimethyl oxonium tetrafluoroborate, triethyl oxonium tetrafluoroborate and the like)) at 0-150 degrees, thereafter the solvent is eliminated by distillation and thereafter alcohol system solvent (methanol, ethanol, isopropanol and the like) and ammonia or ammonium chloride are added and reaction is carried out at 0-150 degrees.

(0051)

Reaction to produce a compound represented by general formula (I) from a compound represented by general formula (II-b) can be carried out for example by the following process. It can be carried out by reacting a compound represented by formula (II-b) and ammonium chloride in an alcohol system solvent (methanol, ethanol, isopropanol and the like) at 0-150 degrees.

(0052)

Reaction to produce a compound represented by general formula (I) from a compound represented by general formula (II-c) can be carried out for example by the following process. It can be carried out by reacting a compound represented by general formula (II-c), liquid ammonia and metal reagent (alkali metal (lithium, sodium, potassium and the like), alkaline earth metal (calcium, magnesium and the like)) at -80 degrees to -34 degrees in inert organic solvent (diethyl ether, tetrahydrofuran, dimethoxyethane and the like) in the presence of proton source (methanol, ethanol, water, ammonium chloride and the like) for 1 minute to 3 hours.

(0053)

Compound represented by general formula (II-a) and (II-b) can be produced by using well known reaction. For example, it is possible to be produced by a process shown in the following reaction step equation 1 and process in accordance with Examples. Symbols in reaction step equation 1 denote following meanings or same meanings as above.

Me: methyl,

Py: pyridine,

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TFA: trifluoroacetic acid,

MeOH: methanol,

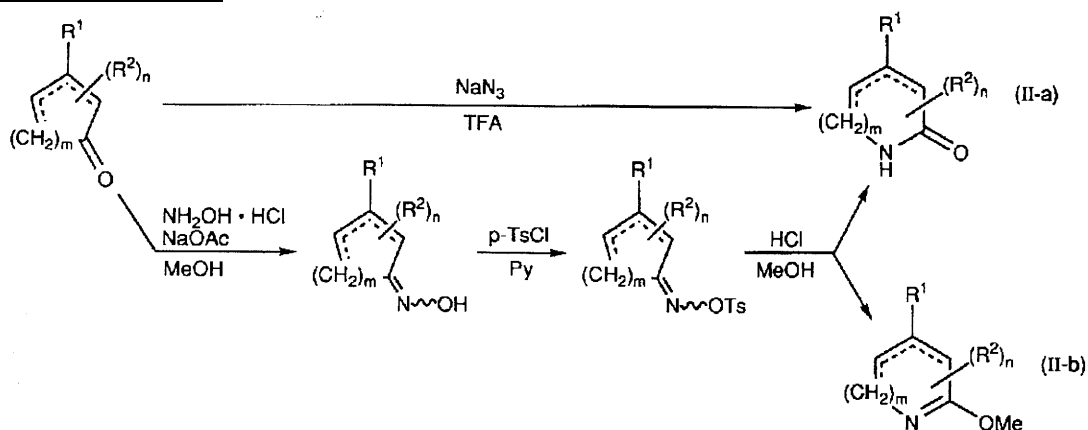
NaOAc: sodium acetate,

p-TsCl: para toluenesulfonyl chloride,

Ts: para toluene sulphonyl group.

(0054)

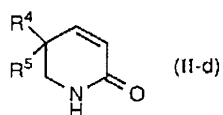
Reaction step equation 1



(0055)

Moreover, a compound represented by general formula (II-d)

(0056)



(0057)

(wherein,  $R^4$  and  $R^5$  each independently denote the same meaning as  $R^3$ ) can be produced by a process represented by reaction step equation 2. Symbols in reaction step equation 1 denote following meanings or same meanings as above.

DDQ: 2,3-dichloro-5,6-dicyano-1,4-benzoquinone,

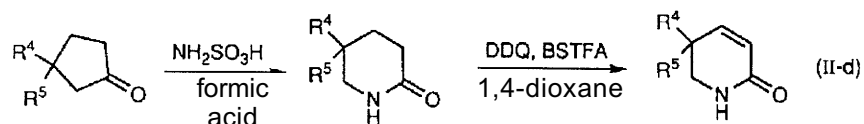
BSTFA: bis(trimethylsilyl) trifluoroacetamido.

(0058)

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(unexamined)

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Reaction step equation 2



(0059)

A compound used as starting material and a compound represented by general formula (II-c) in each reaction step equation are well known compounds respectively or can be readily produced by well known method from well known compounds. In each reaction in this specification, the reaction products can be refined by ordinary purifying techniques, for example, processes such as distillation at ambient pressure or under reduced pressure, high performance liquid chromatography using silica gel or magnesium silicate, thin layer chromatography, column chromatography, washing or recrystallisation and the like. Purification may be carried out at each reaction or may be carried out after completion of all the reactions.

(0060)

In this invention, the other starting materials and all the reagents are all well known in themselves or can be produced by well known methods.

(0061)

(Pharmacological Activity of the Compounds of this Invention).

An experiment which examined the inhibitory action of the compounds of this invention represented by general formula (I) with respect to inducible NOS (i-NOS) was carried out by the following process.

Inhibitory action on inducible NOS (i-NOS)

10 ng/ml of lipopolysaccharide (LPS) was added to cells RAW 264.7 derived from mouse macrophage, and after 24 hours, the cells were pulverised with ultrasound wave, and the 15,000 rpm centrifuge supernatant formed the i-NOS enzyme source.

(0062)

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**(unexamined)**

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14C labelled L-arginine was used as substrate, and the inhibition rate of the compounds of this invention was determined from the formed quantity of L-citrulline which was converted by NOS as follows. To 70  $\mu$ l solution containing 50 mM Hepes (N-2-hydroxyethyl piperazine-N'-2-ethanesulphonic acid) (pH 7.8), 1 mM DTT (dithiothreitol), 1 mM NADPH (reduced form nicotinamide adenine dinucleotide phosphosphate), 0.1 mM tetrahydrobiopterin (BH4) and 10  $\mu$ M FAD (flavin adenine dinucleotide), were added 1.55 mM L-[U-14C] arginine (10  $\mu$ l), cell homogenate supernatant liquid (10  $\mu$ l) and the compound of this invention (10  $\mu$ l), and the whole quantity was made up to 100  $\mu$ l. The solution was incubated at 37°C for ten minutes and thereafter introduced into Dowex 50WX (Na<sup>+</sup> type, vol 250  $\mu$ l). 100 mM Hepes and 10 mM EDTA (ethylenediamine tetraacetic acid) (500  $\mu$ l, pH 5.4) were passed through the Dowex 50WX, the unreacted L-arginine was eliminated, and the activity of NO synthase was measured with a liquid scintillation counter. The results are shown in Table 8.

(0063)

(Table 8)

Example No.	i-NOS (IC50, $\mu$ M)
1	0.02
1(1)	0.14
2	0.12
2(1)	0.11
2(2)	0.11
2(3)	0.10
2(4)	> 50
2(5)	0.95
2(6)	0.54
2(7)	6.50
2(8)	0.22
2(9)	0.18
2(10)	2.56
2(11)	0.14
2(12)	0.10
2(13)	0.03
2(14)	0.18
2(15)	0.50
2(16)	0.04
2(17)	0.20
2(18)	0.20
3	0.07
4	0.17

(0064)

Action of the compounds of this invention with respect to blood pressure

Rat was fixed on dorsal position under ether anaesthesia, and cannula for blood pressure measurement and drug administration were respectively inserted in right carotid artery and vein. After awaking from the anaesthesia, the blood pressure of rat was measured under restraint.

(1) Action on blood pressure of normal individual:

After the blood pressure was stabilised, the compound of this invention or comparative compound (0.003-0.1 mg/kg/min) was continuously administered (0.88 ml/hr) for 60 minutes, and the action with respect to blood pressure was observed.

(2) Action on blood pressure under lipopolysaccharide (LPS) induced hypotension:

After the blood pressure was stabilised, LPS (10 mg/kg) was administered intravenously. From 5 hours after LPS treatment, the compound of this invention and comparative compound were administered in the same way as in (1), and the action with respect to blood pressure was observed.

The difference between the value of blood pressure just before the start of administration of the compound of this invention or comparative compound and the value after 60 minutes from the start of administration was determined for both (1) and (2).

(0065)

As compounds of this invention, the compound produced in Example 1 was used. Moreover, as comparative compound, 2-imino-4-methylpiperidine (A-1) described in Example 6 of WO95/11231 specification and 2-amino-4-methylpyridine (B-1) described in gist collection of IBC's Fifth Annual Conference on NITRIC OXIDE (28th, 29th March, 1996) were used. The results are shown in Table 9.

Normal rat vasopressor value (mmHg) = [Blood pressure value of normal rat 60 minutes from the start of administration] - [Blood pressure value of normal rat just before the start of administration]

LPS administration rat vasopressor value (mmHg) = [Blood pressure value of LPS administration rat 60 minutes from the start of administration] - [Blood pressure value of LPS administration rat just before the start of administration]

(0066)

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(unexamined)

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(Table 9).

Example	Administration dose (mg/kg/min)	(1) Vasopressor value of normal rat (mmHg)	(2) Vasopressor value of LPS administration rat (mmHg)
1	0.01	5	34
	0.003	0	7
Comparative comp. (A-1)	0.01	12	27
	0.003	4	8
Comparative comp. (B-1)	0.01	12	20
	0.0003	3	5

(0067)

From the results of Table 9, the compound of this invention gave little influence to the blood pressure of normal rat, but showed stronger elevation of the blood pressure of LPS administration rat.

(0068)

(Toxicity)

Toxicity of the compounds of this invention was sufficiently low, and it was confirmed to be satisfactorily safe for the use as pharmaceutical.

(0069)

(Application in Drugs)

The compounds of this invention represented by general formula (I), acid addition salts thereof or hydrates thereof have an action to hinder nitric oxide synthase, therefore they are expected to be useful as therapy and/or prevention of septicaemia, endotoxin shock, cardiac failure, shock, tuberculosis, hypotension, rheumatic inflammation, chronic rheumatism, osteoarthritis, ulcerative colitis, stress-induced gastric ulcer, Crohn's disease, autoimmune disease, post-organ transplantation tissue damage, rejection, ischemic reperfusion disorder, acute coronary microvascular embolisation, shock-induced vascular embolisation (disseminated intravascular coagulation syndrome (DIC) and the like), ischemic encephalopathy, arteriosclerosis, pernicious anaemia, Fanconi's anaemia, sickle cell anaemia, pancreatitis, nephrotic syndrome, leishmaniasis,

glomerulonephritis, insulin-dependent diabetes mellitus, hepatic porphyria, alcoholism, Parkinson's disease, chronic leukaemia, acute leukaemia, tumour, myeloma, anticancer agent side effect reduction, infant and adult respiration distress syndrome, emphysema, Alzheimer's disease, multiple sclerosis, vitamin E deficiency, aging, sun burn, muscular dystrophy, cataract, influenza infection, malaria, AIDS, radiation damage, burn, in vitro fertilisation promotion.

(0070)

When each effective ingredient and salts thereof included this invention is used for aforesaid object, usually it is systemically or locally administered orally or aorally. The dosage is different depending on age, body weight, symptom, therapy effect, administration method, treatment time, however, it is usually orally administered per adult in a range of 1 mg-1000 mg per administration from once to several times per day or it is aorally administered in a rage of range of 100 µg-100 mg per administration from once to several times per day (preferably intravenous or intracerebroventricular administration). Of course, as described above, the dosage changes with various kinds of conditions, there is a situation wherein the quantity less than aforesaid dose is adequate, and there also is a situation wherein the administration above the range is required.

(0071)

When the compound of this invention is administered, it is used as solid composition, liquid composition or other composition for oral administration, or as injection, topical agent, suppository for aoral administration. Tablet, pill, encapsulated formulation, powder, granules are included in the solid composition for oral administration.

(0072)

In such solid composition, one or more active substances are used by mixing with at least one inert diluent (lactose, mannitol, dextrose, hydroxypropylcellulose, microcrystalline cellulose, starch, polyvinylpyrrolidone, magnesium metasilicate aluminate and the like). In accordance with normal methods, these compositions may contain additive other than inert diluent, for example lubricant (magnesium stearate and the like), disintegrating agent (fibrin glycolic acid calcium and the like), solubiliser (arginine, glutamic acid, aspartic acid and the like) and stabilising agent (human serum albumin, lactose and the like).

(0073)

Tablet or pill may be coated in accordance with requirements with film of stomach or intestine soluble substance (refined sugar, gelatine, hydroxypropylcellulose, hydroxypropyl methyl cellulose phthalate and the like). Hard capsule and soft capsule are included to capsule formulation. As liquid composition for oral administration, solution, emulsion, suspension, syrup, elixir agent are included.

(0074)

In such liquid composition, generally used inert diluent (purified water, ethanol and the like) is included. These compositions may contain adjuvant such as wetting agent, suspending agent, sweetener, flavours, aromatics and preservatives in addition to inert diluent. As other composition for oral administration, spray agent containing one or more active materials, which is formulated in accordance with conventional procedures is included. The spray agent may contain stabilising agent (sodium sulphite and the like) and buffer agent to impart isotonicity (sodium chloride, sodium citrate, citric acid and the like) besides inert diluent. For production of spray agent, for example processes described in US Patent No 2,868,691 and US Patent No 3,095,355 specification can be used.

(0075)

As injection agent for aoral administration, sterile aqueous or non-aqueous solution, suspension, emulsion are included. In such injection, one or more active substances are mixed with at least one member of inert aqueous diluent (distilled water for injection, physiological saline and the like) or inert non-aqueous diluent (propylene glycol, polyethyleneglycol, olive oil, ethanol, Polysolvate 80 (registered trade name)). These injections may further contain adjuvant such as preservative, wetting agent, emulsifier, dispersant, stabilising agent (human serum albumin, lactose and the like), solubiliser (arginine, glutamic acid, aspartic acid, polyvinylpyrrolidone and the like).

(0076)

These are usually sterilised by filtration using bacteria retaining filter and the like, formulation of fungicide or irradiation, or after these treatment were carried out, a solid composition is formed, and sterile water or sterile injectable diluent is added immediately before use, and it is used.

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(0077)

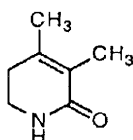
**(Examples).**

Hereinafter, this invention is explained in detail by Reference Examples and Examples. However, this invention is not restricted to these. Solvent in brackets shown in the separation section by chromatography shows eluting solvent or developing solvent used, and the proportion denotes the volume ratio.

**Reference Example 1**

**3,4-dimethyl-3,4-dehydro-piperidin-2-one**

(0078)



(0079)

Sodium azide (0.89 g) was added to trifluoroacetic acid solution (27 ml) of 2,3-dimethyl-2-cyclopentenone (1.03 g) and it was heated under reflux for 15 hours while adding sodium azide (0.44 g) every one hour 4 times in total. The reaction mixture solution was cooled to room temperature, concentrated under vacuum, and water was added, and it was extracted with chloroform. The organic layer was washed successively with saturated aqueous sodium bicarbonate solution, water and saturated aqueous sodium chloride solution, dried with anhydrous magnesium sulphate, and thereafter concentrated. The residue was purified by silica gel column chromatography (ethyl acetate), and the title compound (0.68 g) having the following physical property values was obtained in a yield of 60 %.

TLC: Rf 0.40 (chloroform : methanol = 10:1),

MS (APCI) m/z 126 (M+H)+,

NMR (CDCl<sub>3</sub>): delta 5.76 (1H, brs), 3.34 (2H, dt, J=2.8, 7.0 Hz), 2.31 (2H, t, J = 7.0 Hz), 1.89 (3H, q, J = 1.0 Hz), 1.87-1.83 (3H, m).

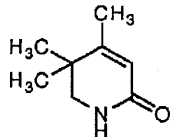
**Reference Example 1 (1)**

**4,5,5-trimethyl-3,4-dehydro-piperidin-2-one**

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(0080)



(0081)

The same operation as in Reference Example 1 was carried out using 3,4,4-trimethyl-2-cyclopentenone instead of 2,3-dimethyl-2-cyclopentenone, and the title compound having the following physical property values was obtained.

TLC: Rf 0.36 (chloroform : methanol = 10:1),

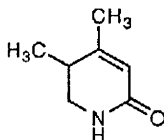
MS(APCI) m/z 140 (M+H)<sup>+</sup>, 124, 111, 98, 83,

NMR (CDCl<sub>3</sub>): delta 5.88 (1H, br), 5.63-5.60 (1H, m), 3.14 (2H, d, J = 2.8 Hz), 1.86 (3H, d, J = 1.4 Hz), 1.10 (6H, s).

### Reference Example 1 (2)

4,5-dimethyl-3,4-dehydro-piperidin-2-one.

(0082)



(0083)

The same operation as in Reference Example 1 was carried out using 3,4-dimethyl-2-cyclopentenone instead of 2,3-dimethyl-2-cyclopentenone, and the title compound having the following physical property values was obtained.

TLC: Rf 0.36 (chloroform : methanol = 10:1),

MS (APCI) m/z 126(M+H)<sup>+</sup>, 110, 96,

NMR (CDCl<sub>3</sub>): delta 6.17 (1H, br), 5.66 (1H, s), 3.54 (1H, ddd, J = 1.8, 5.3, 12.2 Hz), 3.11 (1H, ddd, J = 3.7, 4.9, 12.2 Hz), 2.41-2.23 (1H, m), 1.92 (3H, d, J = 1.4 Hz), 1.15 (3H, d, J = 7.0 Hz).

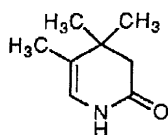
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**Reference Example 1 (3)**

**4,4,5-trimethyl-5,6-dehydro-piperidin-2-one**

(0084)



(0085)

The same operation as in Reference Example 1 was carried out using 3,4,4-trimethyl-2-cyclohexenone instead of 2,3-dimethyl-2-cyclohexenone, and the title compound having the following physical property values was obtained.

TLC: R<sub>f</sub> 0.45 (chloroform : methanol = 10:1),

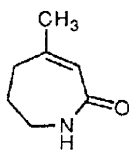
MS (APCI) m/z 140(M+H)<sup>+</sup>,

NMR (CDCl<sub>3</sub>): delta 7.10 (1H, brs), 5.74 (1H, dq, J = 3.6, 1.6 Hz), 2.31(2H, s), 1.65 (3H, d, J = 1.6 Hz), 1.04(6H, s).

**Reference Example 2**

**2H-4-methyl-1,5,6,7-tetrahydroazepin-2-one**

(0086)



(0087)

Sodium acetate (8.9 g, anhydrous) and hydroxyl ammonium chloride (7.6 g) were added to methanol (80 ml) solution of 3-methyl-2-cyclohexen-1-one (10 g), and the mixture was heated under reflux for two hours. It was allowed to cool, thereafter filtered, and the filtrate was concentrated. Water was added to the residue, and extraction was carried out with ethyl acetate. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, dried with anhydrous sodium sulphate, and thereafter concentrated. The obtained white powder (13.0 g, oxime body) was dissolved in 50 ml pyridine, and p-toluenesulfonyl chloride (20.7 g) was added, and,

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under argon gas atmosphere, it was stirred for one hour at room temperature. The reaction mixture solution was poured into iced water, and extraction was carried out with ethyl acetate. The organic layer was washed successively with 1 N hydrochloric acid, saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution, dried with anhydrous sodium sulphate, and thereafter concentrated. The obtained orange powder (22.8 g, tosyl body) was dissolved in 100 ml methanol and concentrated hydrochloric acid (6 ml) was added, and it was stirred at room temperature for 12 hours and at 50 degrees with for 6 hours. The reaction mixture solution was concentrated, thereafter it was refined by silica gel column chromatography (chloroform : methanol = 20:1), and the title compound having the following physical property values (3.9 g) was obtained by a yield of 34 % (three steps).

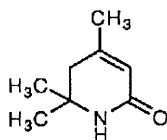
TLC: Rf 0.26 (chloroform : methanol = 20:1),

NMR (CDCl<sub>3</sub>): delta 6.8-6.4 (1H, br), 5.78 (1H, d, J = 1.0 Hz), 3.40-3.15 (2H, m), 2.36 (2H, t, J = 6.6 Hz), 2.05-1.85 (2H, m), 1.92 (3H, d, J = 1.0 Hz).

### **Reference Example 2 (1)**

4,6,6-trimethyl-3,4-dehydro-piperidin-2-one

(0088)



(0089)

The same operation as in Reference Example 2 was carried out using 3,5,5-trimethyl-2-cyclopentenone instead of 3-methyl-2-cyclohexen-1-one, and the title compound having the following physical property values was obtained.

TLC: Rf 0.26 (n-hexane : ethyl acetate = 2:1),

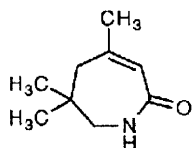
NMR (CDCl<sub>3</sub>): delta 5.19 (1H, d, J = 1.5 Hz), 2.51(2H, s), 2.00 (3H, d, J = 1.5 Hz), 1.26(6H, s).

### **Reference Example 2 (2)**

2H-4,6,6-trimethyl-1,5,6,7-tetrahydroazepin-2-one

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(unexamined)

(0090)



(0091)

The same operation as in Reference Example 2 was carried out using 3,5,5-trimethyl-2-cyclohexen-1-one instead of 3-methyl-2-cyclohexen-1-one, and the title compound having the following physical property values was obtained.

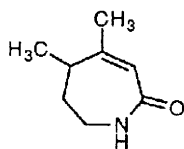
TLC: R<sub>f</sub> 0.29 (chloroform : methanol = 20:1),

MS (APCI) m/z 154(M+H)+,

NMR (CDCl<sub>3</sub>): delta 6.50 (1H, br), 5.79-5.74 (1H, m), 2.88 (2H, d, J = 5.8 Hz), 2.06(2H, s), 1.94(3H, s), 0.98 (6H, s).

**Reference Example 2 (3)****2H-4,5-dimethyl-1,5,6,7-tetrahydroazepin-2-one**

(0092)



(0093)

The same operation as in Reference Example 2 was carried out using 3,4-dimethyl-2-cyclohexen-1-one instead of 3-methyl-2-cyclohexen-1-one, and the title compound having the following physical property values was obtained.

TLC: R<sub>f</sub> 0.16 (chloroform : methanol = 20:1),

MS (APCI) m/z 140(M+H)+,

NMR (CDCl<sub>3</sub>): delta 6.6-6.4 (1H, br), 5.75 (1H, s), 3.28-3.10(2H, m), 2.65-2.42 (1H, m), 2.18-2.00 (1H, m), 1.91 (3H, s), 1.78-1.60 (1H, m), 1.14 (3H, d, J = 7.0 Hz).

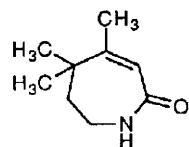
**Reference Example 2 (4)**

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2H-4,5,5-trimethyl-1,5,6,7-tetrahydroazepin-2-one

(0094)



(0095)

The same operation as in Reference Example 2 was carried out using 3,4,4-trimethyl-2-cyclohexen-1-one instead of 3-methyl-2-cyclohexen-1-one, and the title compound having the following physical property values was obtained.

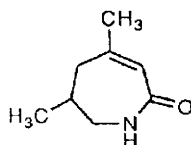
TLC: Rf 0.48 (chloroform : methanol = 10:1),

NMR (CDCl<sub>3</sub>): delta 6.55-6.05 (1H, br), 5.75 (1H, s), 3.22 (2H, dd, J = 10.0, 5.4 Hz), 1.90 (3H, s), 1.91-1.85 (1H, m), 1.14 (6H, s).

**Reference Example 2 (5)**

2H-4,6-dimethyl-1,5,6,7-tetrahydroazepin-2-one

(0096)



(0097)

The same operation as in Reference Example 2 was carried out using 3,5-dimethyl-2-cyclohexen-1-one instead of 3-methyl-2-cyclohexen-1-one, and the title compound having the following physical property values was obtained.

TLC: Rf 0.41 (chloroform : methanol : acetic acid = 10:1:1),

MS (APCI) m/z 140 (M+H)+,

NMR (CDCl<sub>3</sub>): delta 6.95-6.65 (1H, br), 5.76 (1H, s), 3.17 (1H, ddd, J = 14.2, 6.6, 4.0 Hz), 2.94 (1H, ddd, J = 14.2, 7.4, 5.0 Hz), 2.42 (1H, dd, J = 15.8, 5.5 Hz), 2.35-2.11 (1H, m), 2.01 (1H, dd, J = 15.8, 7.8 Hz), 1.92 (3H, s), 0.97 (3H, d, J = 6.7 Hz).

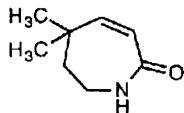
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**Reference Example 2 (6)**

2H-5,5-dimethyl-1,5,6,7-tetrahydroazepin-2-one

(0098)



(0099)

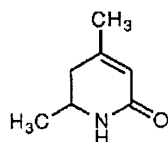
The same operation as in Reference Example 2 was carried out using 4,4-dimethyl-2-cyclohexen-1-one instead of 3-methyl-2-cyclohexen-1-one, and the title compound having the following physical property values was obtained.

TLC: Rf 0.71 (chloroform : methanol = 10:1).

**Reference Example 2 (7)**

4,6-dimethyl-3,4-dehydro-piperidin-2-one

(0100)



(0101)

The same operation as in Reference Example 2 was carried out using 3,5-dimethyl-2-cyclopenten-1-one instead of 3-methyl-2-cyclohexen-1-one, and the title compound having the following physical property values was obtained.

TLC: Rf 0.65 (chloroform : methanol = 10:1),

MS (APCI) m/z 126 (M+H)+,

NMR (CDCl<sub>3</sub>): delta 5.70 (1H, s), 5.68-5.35 (1H, br), 3.83-3.60 (1H, m), 2.33-2.00(2H, m), 1.91(3H, s), 1.24 (3H, d, J = 6.6 Hz).

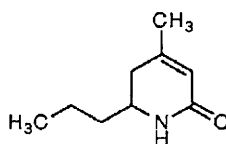
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**Reference Example 2 (8)**

4-methyl-6-propyl-3,4-dehydro-piperidin-2-one

(0102)



(0103)

The same operation as in Reference Example 2 was carried out using 3-methyl-5-propyl-2-cyclopenten-1-one instead of 3-methyl-2-cyclohexen-1-one, and the title compound having the following physical property values was obtained.

TLC: Rf 0.38 (chloroform : methanol = 20:1),

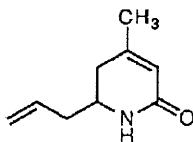
MS (APCI) m/z 154 (M+ + H),

NMR (CDCl<sub>3</sub>): delta 5.69 (1H, s), 5.50 (1H, br), 3.70-3.45 (1H, m), 2.35-2.00 (2H, m), 1.92 (3H, s), 1.63-1.20 (4H, m), 0.95 (3H, t, J = 7.0 Hz).

**Reference Example 2 (9)**

4-methyl-6-(2-propenyl)-3,4-dehydro-piperidin-2-one

(0104)



(0105)

The same operation as in Reference Example 2 was carried out using 3-methyl-5-(2-propenyl)-2-cyclopenten-1-one instead of 3-methyl-2-cyclohexen-1-one, and the title compound having the following physical property values was obtained.

TLC: Rf 0.25 (n-hexane : ethyl acetate = 2:1),

MS (APCI) m/z 152 (M+H)+,

JP10-120654  
(unexamined)

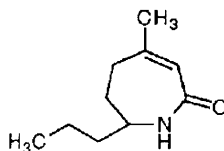
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NMR (CDCl<sub>3</sub>): delta 5.90-5.55 (3H, m), 5.21 (1H, brs), 5.15-5.10 (1H, m), 3.70-3.55 (1H, m), 3.00-1.70 (4H, m), 1.92 (3H, s).

**Reference Example 2 (10)**

2H-4-methyl-7-propyl-1,5,6,7-tetrahydroazepin-2-one

(0106)



(0107)

The same operation as in Reference Example 2 was carried out using 3-methyl-6-propyl-2-cyclohexen-1-one instead of 3-methyl-2-cyclohexen-1-one, and the title compound having the following physical property values was obtained.

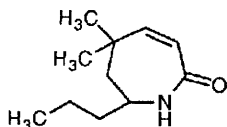
TLC: R<sub>f</sub> 0.46 (chloroform : methanol = 20:1),

NMR (CDCl<sub>3</sub>): delta 5.78 (1H, s), 5.65 (1H, brs), 3.32 (1H, m), 2.45 (1H, m), 2.23 (1H, m), 1.90 (3H, s), 2.0-1.7 (2H, m), 1.5-1.2 (4H, m), 0.93 (3H, t, J = 7.2 Hz).

**Reference Example 2 (11)**

2H-5,5-dimethyl-7-propyl-1,5,6,7-tetrahydroazepin-2-one

(0108)



(0109)

The same operation as in Reference Example 2 was carried out using 4,4-dimethyl-6-propyl-2-cyclohexen-1-one instead of 3-methyl-2-cyclohexen-1-one, and the title compound having the following physical property values was obtained.

TLC: R<sub>f</sub> 0.50 (chloroform : methanol = 10:1),

JP10-120654  
(unexamined)

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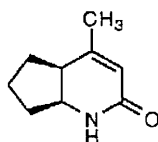
MS (APCI) m/z 182 (M+H)+,

NMR (CDCl<sub>3</sub>): delta 5.95 (1H, d, J = 10.4 Hz), 5.90-5.70 (1H, br), 5.73 (1H, dd, J = 10.4, 0.8 Hz), 3.50-3.32 (1H, m), 1.90-1.50 (6H, m), 1.10 (3H, s), 1.08 (3H, s), 0.95 (3H, t, J = 6.6 Hz).

**Reference Example 2 (12)**

dl-cis-4-methyl-2-oxo-1,4a,5,6,7,7a-hexahydro-2H-pyridine

(0110)



(0111)

The same operation as in Reference Example 2 was carried out using dl-cis-2-methyl-4-oxo-bicyclo (3.3.0) oct-2-ene instead of 3-methyl-2-cyclohexen-1-one, and the title compound having the following physical property values was obtained.

TLC: R<sub>f</sub> 0.48 (chloroform : methanol = 10:1),

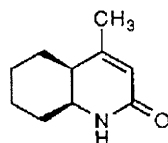
MS (APCI) m/z 152 (M+H)+,

NMR (CDCl<sub>3</sub>): delta 5.79 (1H, brs), 5.62-5.57 (1H, m), 4.08-3.98 (1H, m), 2.43 (1H, q, J = 7.8 Hz), 2.20-1.52 (6H, m), 1.92 (3H, s).

**Reference Example 2 (13)**

dl-cis-4-methyl-2-oxo-1,2,4a,5,6,7,8,8a-octahydro-quinoline

(0112)



(0113)

JP10-120654  
(unexamined)

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The same operation as in Reference Example 2 was carried out using dl-cis-7-methyl-9-oxo-bicyclo (4.3.0) non-7-ene instead of 3-methyl-2-cyclohexen-1-one, and the title compound having the following physical property values was obtained.

TLC: Rf 0.48 (chloroform : methanol = 10:1),

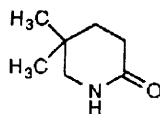
MS (APCI) m/z 166 (M+H)+,

NMR (CDCl<sub>3</sub>): delta 5.69-5.63 (1H, m), 5.23 (1H, brs), 3.77-3.72 (1H, m), 2.07-1.95 (1H, m), 1.92 (3H, d, J = 1.6 Hz), 1.80-1.11(8H, m).

### Reference Example 3

#### 5,5-dimethyl-piperidin-2-one

(0114)



(0115)

A formic acid (76 ml) suspension of 3,3-dimethylcyclopentenone (8.50 g) and hydroxyamine-O-sulfonic acid (12.8 g) was heated under reflux for 12 hours and thereafter it was cooled to room temperature. The reaction mixture solution was poured into ice, it was neutralised with 5 N sodium hydroxide solution, and thereafter the extraction was carried out with chloroform. The organic layer was washed with saturated aqueous sodium chloride solution, dried with anhydrous sodium sulphate, thereafter concentrated, and a mixture of 5,5-dimethyl-piperidin-2-one and 4,4-dimethyl-piperidin-2-one was obtained. Recrystallisation of mixture was carried out using ethyl acetate, and the title compound (5.04 g) having the following physical property values was obtained in a yield of 54 %.

TLC: Rf 0.40 (chloroform : methanol = 10:1),

MS (APCI) m/z 128 (M+H)+,

NMR (CDCl<sub>3</sub>): delta 5.88 (1H, br), 3.02 (2H, d, J = 2.5 Hz), 2.38 (2H, t, J = 7.0 Hz), 1.61 (2H, t, J = 7.0 Hz), 1.05 (6H, s).

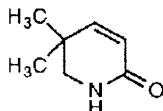
### Reference Example 4

JP10-120654  
(unexamined)

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5,5-dimethyl-3,4-dehydro-piperidin-2-one

(0116)



(0117)

2,3-dichloro-5,6-dicyano-1,4-benzoquinone (4.68 g) and bis (trimethylsilyl) trifluoroacetamide (21 ml) were added to 1,4-dioxane (65 ml) solution of the compound produced in Reference Example 3 (2.50 g) and the mixture was stirred at room temperature for four hours and next heated under reflux for 16 hours. The reaction mixture solution was cooled to room temperature, it was discharged into mixture of dichloromethane (100 ml) and 1 % sodium bisulfite solution (30 ml) and was stirred for 15 minutes. Filtration was carried out, hydroquinone was eliminated, and next the organic layer and the aqueous layer were separated. The organic layer was washed successively with 2 N hydrochloric acid and saturated aqueous sodium chloride solution, dried with anhydrous sodium sulphate, and thereafter concentrated. The residue was purified by silica gel column chromatography (ethyl acetate then to chloroform : methanol = 10:1), and the title compound (1.72 g) having the following physical property values was obtained in a yield of 70 %.

TLC: Rf 0.36 (chloroform : methanol = 10:1),

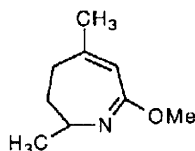
MS (APCI) m/z 126 (M+H)+,

NMR (CDCl<sub>3</sub>): delta 6.37 (1H, d, J = 10.0 Hz), 5.76 (1H, dd, J = 1.8, 10.0 Hz), 5.58 (1H, br), 3.22-3.17(2H, m), 1.14(6H, s).

**Reference Example 5**

2H-2,5-dimethyl-7-methoxy-3,4-dihydroazepin.

(0118)



JP10-120654  
(unexamined)

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(0119)

Hydroxylamine • hydrochloride (2.47 g) and anhydrous sodium acetate (3.00 g) were added to methanol (50 ml) solution of 3,6-dimethyl-2-cyclohexen-1-one (4.13 g) and were heated under reflux for one hour. It was cooled to room temperature, and next filtration was carried out, and the filtrate was concentrated under reduced pressure. The residue (oxime body, 4.60 g) was dissolved in 15 ml pyridine, and p-tosyl chloride (6.62 g) was added under ice cooling and was stirred for 30 minutes. The reaction mixture solution was poured into iced water, and extraction was carried out with ethyl acetate. The organic layer was washed successively with 1 N hydrochloric acid, water and saturated aqueous sodium chloride solution, dried with anhydrous sodium sulphate, and thereafter concentrated. The residue (tosyl body, 5.90 g) was dissolved in 50 ml methanol, and concentrated hydrochloric acid (3 ml) was added and was stirred at 50 degrees at room temperature for three hours for 12 hours. It was cooled to room temperature, and next the reaction mixed solution was neutralised with 2 N sodium hydroxide solution, and it was concentrated. The residue was dissolved in chloroform, washed with water and saturated aqueous sodium chloride solution, dried with anhydrous sodium sulphate, and thereafter concentrated. The residue was purified by silica gel column chromatography (chloroform : methanol = 50:1), and the title compound (0.98 g) having the following physical property values was obtained.

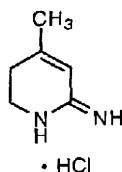
TLC: R<sub>f</sub> 0.63 (ethyl acetate : n-hexane = 10:1),

NMR (CDCl<sub>3</sub>): delta 5.63 (1H, s), 3.58 (3H, s), 3.55 (1H, m), 2.31 (2H, t, J = 7 Hz), 1.86 (2H, m), 1.24 (3H, d, J = 7.0 Hz).

### **Example 1**

4-methyl-3,4-dehydro-2-iminopiperidine • hydrochloride

(0120)



(0121)

JP10-120654  
(unexamined)

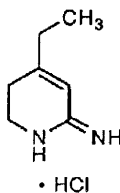
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A mixture of 4-methyl-2-aminopyridine (2.00 g), tetrahydrofuran (6.2 ml) and ethanol (2.2 ml) was cooled to -78 degrees, and liquid ammonia (62 ml) was added, furthermore, metallic lithium (321 mg) was added, and it was stirred for one hour. Ammonium chloride (2.5 g) was added to the reaction mixture, it was gradually warmed to room temperature, saturated ammonium chloride solution was added, and it was extracted with chloroform. The organic layer was dried with anhydrous sodium sulphate, and thereafter it was concentrated. The residue was dissolved in 30 ml ethanol, and hydrochloric acid solution (4 N, 8 ml) of ethyl acetate was added at 0 degrees, it was stirred at room temperature for 30 minutes, and thereafter it was concentrated. The residue was purified by silica gel column chromatography (chloroform : methanol = 200:1 to 10:1 to 6:1), and the compounds of this invention having the following physical property values (1.79 g) was obtained in a yield of 66 %.  
TLC: Rf 0.28 (chloroform : methanol : acetic acid = 10:2:1),  
MS (EI) m/z 110(M)+, 95, 92, 81,  
NMR (CDCl<sub>3</sub>): delta 9.08 (1H, brs), 8.46 (1H, brs), 8.41 (1H, brs), 6.24 (1H, s), 3.50 (2H, dt, J = 2.6, 7.6 Hz) 2.43 (2H, t, J = 7.6 Hz), 2.06 (3H, s).

### **Example 1 (1)**

4-ethyl-3,4-dehydro-2-iminopiperidine • hydrochloride

(0122)



(0123)

The same operation as in Example 1 was carried out using 4-ethyl-2-aminopyridine instead of 4-methyl-2-aminopyridine, and the compounds of this invention having the following physical property values was obtained.

TLC: Rf 0.45 (chloroform : methanol : acetic acid = 10:1:1),

MS (APCI) m/z 125 (M+H)+,

NMR (CDCl<sub>3</sub>): delta 9.33 (1H, brs), 8.82 (1H, brs), 8.64 (1H, brs), 6.30 (1H, s), 3.49 (2H, t, J = 7.2 Hz), 2.42 (2H, t, J = 7.2 Hz), 2.32 (2H, q, J = 7.4 Hz), 1.14 (3H, t, J = 7.4 Hz).

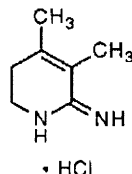
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### Example 2

3,4-dimethyl-3,4-dehydro-2-iminopiperidine • hydrochloride

(0124)



(0125)

2 M triethyl tetrafluoroborate (2.9 ml, dichloromethane solution) was added to dichloromethane (5 ml) solution of compound produced in Reference Example 1 (663 mg) under argon gas atmosphere and it was stirred at room temperature for four hours. The reaction mixture solution was concentrated, absolute ethanol (5 ml) was added, thereafter saturated ammonia solution (15 ml) of absolute ethanol was added and it was stirred at room temperature for 15 hours. Chloroform was added to the reaction mixed solution, it was filtered, and the filtrate was concentrated. The residue was purified by silica gel column chromatography (chloroform : methanol = 10:1 to chloroform : methanol : acetic acid = 10:2:1), and a straw-coloured oily substance was obtained. An oily substance was dissolved in chloroform, washed successively with 1 N sodium hydroxide solution and saturated aqueous sodium chloride solution, thereafter dried with anhydrous sodium sulphate, and 4 N hydrochloric acid solution of dioxane was added, and it was concentrated. The residue was purified by silica gel column chromatography (chloroform : methanol = 10:1 to 5:1), and the compounds of this invention (614 mg) having the following physical property values was obtained in a yield of 72 %.

TLC: Rf 0.51 (chloroform : methanol : acetic acid = 10:2:1),

MS (EI) m/z 124(M)+, 109, 106, 94,

NMR (CDCl<sub>3</sub>): delta 9.41 (1H, brs), 8.90 (1H, brs), 8.44 (1H, brs), 3.29 (2H, dt, J = 2.8, 7.6 Hz), 2.38 (2H, t, J = 7.6 Hz), 1.97 (3H, s), 1.86 (3H, s)

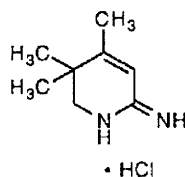
### Example 2 (1)

4,5,5-trimethyl-3,4 -dehydro-2-iminopiperidine • hydrochloride

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(unexamined)

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(0126)



(0127)

In Example 2, same operation was carried out using compound produced in Reference Example 1 (1) instead of compound produced with Reference Example 1, and the compounds of this invention having the following physical property values was obtained.

TLC: Rf 0.43 (chloroform : methanol : acetic acid = 10:2:1),

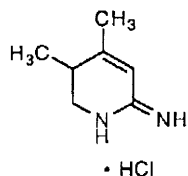
MS (APCI) m/z 139 (M+H)<sup>+</sup>, 124,

NMR (d6-DMSO): delta 9.30 (1H, brs), 8.98 (1H, brs), 8.60 (1H, brs), 5.95-5.90 (1H, m), 3.15 (2H, d, J = 3.0 Hz), 1.96 (3H, d, J = 1.2 Hz), 1.05 (6H, s).

### Example 2 (2)

4,5-dimethyl-3,4-dehydro-2-iminopiperidine • hydrochloride

(0128)



(0129)

The same operation as in Example 2 was carried out using compound produced in Reference Example 1 (2) instead of compound produced in Reference Example 1, and the compounds of this invention having the following physical property values was obtained.

TLC: Rf 0.50 (chloroform : methanol : acetic acid = 10:2:1),

MS (EI) m/z (M)<sup>+</sup>, 109, 106, 94, 92,

JP10-120654  
(unexamined)

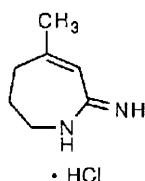
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NMR (d6-DMSO): delta 9.13 (1H, brs), 8.92 (1H, brs), 8.53 (1H, brs), 5.97-5.92 (1H, m), 3.43 (1H, ddd, J = 1.8, 6.0, 13.2 Hz), 3.17 (1H, ddd, J = 4.4, 5.0, 13.2 Hz), 2.51-2.40 (1H, m), 2.01 (3H, s), 1.05 (3H, d, J = 7.2 Hz).

**Example 2 (3)**

2H-4-methyl-2-imino-1,5,6,7-tetrahydroazepin • hydrochloride

(0130)



(0131)

The same operation as in Example 2 was carried out using compound produced in Reference Example 2 instead of compound produced in Reference Example 1, and the compounds of this invention having the following physical property values was obtained.

TLC: Rf 0.25 (chloroform : methanol : acetic acid = 10:1:1),

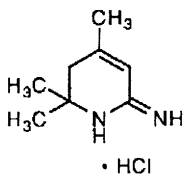
MS (FAB) m/z 125 (M+H)+,

NMR (d6-DMSO): delta 9.48-9.32 (1H, brs), 8.67-8.46 (1H, brs), 8.26-8.13 (1H, brs), 5.88 (1H, s), 3.32-3.24 (2H, m), 2.52-2.43 (2H, m), 1.98 (3H, s), 1.95-1.78 (2H, m).

**Example 2 (4)**

4,6,6-trimethyl-3,4-dehydro-2-iminopiperidine • hydrochloride

(0132)



(0133)

JP10-120654  
(unexamined)

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The same operation as in Example 2 was carried out using compound produced in Reference Example 2 (1) instead of compound produced in Reference Example 1, and the compounds of this invention having the following physical property values was obtained.

TLC: Rf 0.19 (chloroform : methanol : acetic acid = 10:1:1),

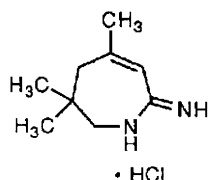
MS (EI) m/z 139 (M+H)+,

NMR (d6-DMSO): delta 11.40-10.65(2H, br), 6.37 (1H, s), 2.70 (2H, s), 2.09 (3H, s), 1.43 (6H, s).

### Example 2 (5)

2H-4, 6, 6-trimethyl-2-imino-1,5,6,7-tetrahydroazepin • hydrochloride

(0134)



(0135)

The same operation as in Example 2 was carried out using compound produced in Reference Example 2 (2) instead of compound produced in Reference Example 1, and the compounds of this invention having the following physical property values was obtained.

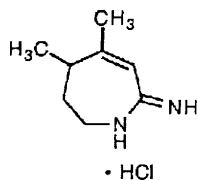
TLC: Rf 0.40 (chloroform : methanol : acetic acid = 20:2:1), MS(FAB) m/z153 (M+H)+,

NMR (d6-DMSO): delta 9.68 (1H, brs), 8.77 (1H, brs), 8.51 (1H, brs), 5.94 (1H, s), 2.98 (2H, d, J = 5.2 Hz), 2.17(2H, s), 2.02(3H, s), 0.95(6H, s).

### Example 2 (6)

2H-4,5-dimethyl-2-imino-1,5,6,7-tetrahydroazepin • hydrochloride

(0136)



JP10-120654  
(unexamined)

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(0137)

The same operation as in Example 2 was carried out using compound produced in Reference Example 2 (3) instead of compound produced in Reference Example 1, and the compounds of this invention having the following physical property values was obtained.

TLC: Rf 0.36 (chloroform : methanol : acetic acid = 10:1:1),

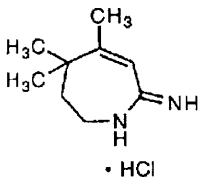
MS (APCI) m/z 139 (M+H)+,

NMR (d6-DMSO): delta 9.42-9.20 (1H, brs), 8.62-8.46 (1H, brs), 8.20-8.07 (1H, brs), 5.84 (1H, s), 3.40-3.20 (2H, m), 2.68-2.53 (1H, m), 2.05-1.97 (1H, m), 1.99 (3H, s), 1.78-1.62 (1H, m), 1.10 (3H, d, J = 7.2 Hz).

### Example 2 (7)

2H-4, 5, 5-trimethyl-2-imino-1,5,6,7-tetrahydroazepin • hydrochloride

(0138)



(0139)

The same operation as in Example 2 was carried out using compound produced in Reference Example 2 (4) instead of compound produced in Reference Example 1, and the compounds of this invention having the following physical property values was obtained.

TLC: Rf 0.31 (chloroform : methanol : acetic acid = 10:1:1),

MS (APCI) m/z 153 (M+H)+, 85,

NMR (d6-DMSO): delta 9.98-9.85 (1H, brs), 8.93-8.74, (1H, brs), 8.58-8.42 (1H, brs), 5.89 (1H, s), 3.34-3.27 (2H, m), 1.97(3H, s), 1.78 (1H, d, J = 8.8 Hz), 1.78 (1H, t, J = 4.4 Hz), 1.11 (6H, s).

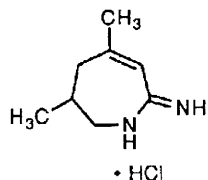
### Example 2 (8)

2H-4,6-dimethyl-2-imino-1,5,6,7-tetrahydroazepin • hydrochloride

(0140)

JP10-120654  
(unexamined)

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(0141)

The same operation as in Example 2 was carried out using compound produced in Reference Example 2 (5) instead of compound produced in Reference Example 1, and the compounds of this invention having the following physical property values was obtained.

TLC: Rf 0.38 (chloroform : methanol : acetic acid = 10:1:1),

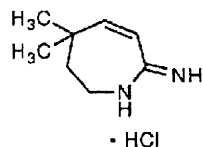
MS (APCI) m/z 139 (M+H)+, 128,

NMR (d6-DMSO): delta 9.64-9.54 (1H, brs), 8.78-8.63 (1H, brs), 8.49-8.37 (1H, brs), 5.91 (1H, s), 3.40-2.49 (2H, m), 2.62-2.42 (1H, m), 2.25-2.06 (2H, m), 1.98(3H, s), 0.91 (3H, d, J = 6.6 Hz).

### Example 2 (9)

2H-5,5-dimethyl-2-imino-1,5,6,7-tetrahydroazepin • hydrochloride

(0142)



(0143)

The same operation as in Example 2 was carried out using compound produced in Reference Example 2 (6) instead of compound produced in Reference Example 1, and the compounds of this invention having the following physical property values was obtained.

TLC: Rf 0.40 (chloroform : methanol : acetic acid = 10:1:1),

MS (APCI) m/z 139 (M+H)+,

NMR (d6-DMSO): delta 10.07-9.89 (1H, brs), 9.13-8.94 (1H, brs), 8.70-8.53 (1H, brs), 6.45 (1H, d, J = 12.8 Hz), 5.90 (1H, d, J = 12.8 Hz), 3.38-3.20 (2H, m), 1.77-1.72 (2H, m), 1.07(6H, s).

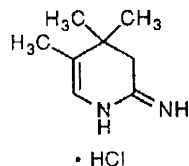
### Example 2 (10)

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4,4,5-trimethyl-5,6-dehydro-2-iminopiperidine • hydrochloride

(0144)



(0145)

The same operation as in Example 2 was carried out using compound produced in Reference Example 1 (3) instead of compound produced in Reference Example 1, and the compounds of this invention having the following physical property values was obtained.

TLC: Rf 0.45 (chloroform : methanol : acetic acid = 10:1:1),

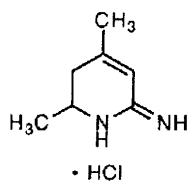
MS (EI) m/z 138(M)+, 123,106,

NMR (d6-DMSO): delta 10.72 (1H, brs), 9.51 (1H, brs), 9.09 (1H, brs), 6.02-5.95 (1H, m), 2.57(2H, s), 1.67 (3H, d, J = 1.4 Hz), 1.00 (6H, s).

**Example 2 (11)**

4,6-dimethyl-3,4-dehydro-2-iminopiperidine • hydrochloride

(0146)



(0147)

The same operation as in Example 2 was carried out using compound produced in Reference Example 2 (7) instead of compound produced in Reference Example 1, and the compounds of this invention having the following physical property values was obtained.

TLC: Rf 0.15 (chloroform : methanol : acetic acid = 10:1:1),

MS (APCI) m/z 125 (M+H)+,

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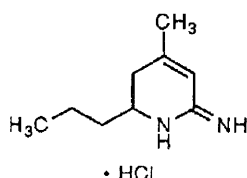
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NMR (d6-DMSO): delta 8.98-8.82 (1H, brs), 8.80-8.64 (1H, brs), 8.08-7.92 (1H, brs), 5.91 (1H, s), 3.80-3.58 (1H, m), 2.58-2.40 (1H, m), 2.18 (1H, dd, J = 18.0, 10.0 Hz), 1.98(3H, s), 1.18 (3H, d, J = 6.6 Hz).

**Example 2 (12)**

4-methyl-6-propyl-3,4-dehydro-2-iminopiperidine • hydrochloride

(0148)



(0149)

The same operation as in Example 2 was carried out using compound produced in Reference Example 2 (8) instead of compound produced in Reference Example 1, and the compounds of this invention having the following physical property values was obtained.

TLC: Rf 0.30 (chloroform : methanol : acetic acid = 20:1:1),

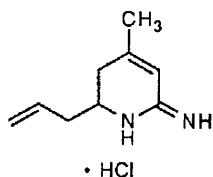
MS (EI) m/z 152(M)+, 109, 92,

NMR (d6-DMSO): delta 9.39 (1H, br), 8.98 (1H, br), 8.42 (1H, br), 5.97 (1H, s), 3.68-3.45 (1H, m), 2.60-2.40 (1H, m), 2.21 (1H, dd, J = 18.0, 10.0 Hz), 1.98 (3H, s), 1.70-1.10 (4H, m), 0.88 (3H, t, J = 7.0 Hz).

**Example 2 (13)**

4-methyl-6-(2-propenyl)-3,4-dehydro-2-iminopiperidine • hydrochloride

(0150)



(0151)

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(unexamined)

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The same operation as in Example 2 was carried out using compound produced in Reference Example 2 (9) instead of compound produced in Reference Example 1, and the compounds of this invention having the following physical property values was obtained.

TLC: R<sub>f</sub> 0.49 (chloroform : methanol : acetic acid = 15:2:1),

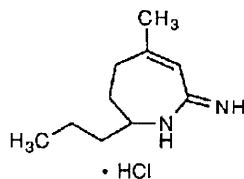
MS (APCI) m/z 151 (M+H)<sup>+</sup>, 109,

NMR (CDCl<sub>3</sub>): delta 9.40-9.20 (1H, br), 9.00-8.85 (1H, br), 8.85-8.65 (1H, br), 6.31 (1H, s), 5.88-5.68 (1H, m), 5.24-5.16 (2H, m), 3.77-3.62 (1H, m), 2.47-2.27 (4H, m), 2.02 (3H, s).

### **Example 2 (14)**

2H-4-methyl-7-propyl-2-imino-1,5,6,7-tetrahydroazepin • hydrochloride

(0152)



(0153)

The same operation as in Example 2 was carried out using compound produced in Reference Example 2 (10) instead of compound produced in Reference Example 1, and the compounds of this invention having the following physical property values was obtained.

TLC: R<sub>f</sub> 0.58 (chloroform : methanol : acetic acid = 15:2:1),

MS (APCI) m/z 167 (M+H)<sup>+</sup>,

NMR (CDCl<sub>3</sub>): delta 9.82 (1H, brs), 8.91 (1H, brs), 7.82 (1H, brs), 6.08 (1H, s), 3.44 (1H, m), 2.48 (2H, m), 2.04 (3H, s), 2.1-1.4 (6H, m), 0.95 (3H, t, J = 7 Hz).

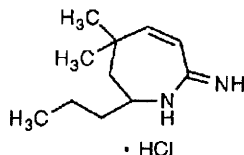
### **Example 2 (15)**

2H-5,5-dimethyl-7-propyl-2-imino-1,5,6,7-tetrahydroazepin • hydrochloride

(0154)

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(unexamined)

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(0155)

The same operation as in Example 2 was carried out using compound produced with Reference Example 2 (11) instead of compound produced in Reference Example 1, and the compounds of this invention having the following physical property values was obtained.

TLC: Rf 0.25 (chloroform : methanol : acetic acid = 10:1:1),

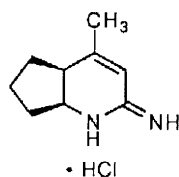
MS (APCI) m/z 181 (M+H)+,

NMR (CDCl<sub>3</sub>): delta 9.65-9.20 (1H, br), 8.75-8.43 (1H, br), 8.40-8.00 (1H, br), 6.33 (1H, d, J = 12.8 Hz), 6.08 (1H, d, J = 12.8 Hz), 3.52-3.33 (1H, m), 2.00-1.38 (6H, m), 1.14 (3H, s), 1.13 (3H, s), 0.97 (3H, t, J = 6.4 Hz).

### **Example 2 (16)**

dl-cis-2-imino-4-methyl-1,4a,5,6,7,8-hexahydro-2H-pyridine • hydrochloride

(0156)



(0157)

The same operation as in Example 2 was carried out using compound produced in Reference Example 2 (12) instead of compound produced in Reference Example 1, and the compounds of this invention having the following physical property values was obtained.

TLC: Rf 0.44 (chloroform : methanol : acetic acid = 10:1:1),

MS (FAB) m/z 337 (2M+HCl+H)+, 151 (M+H)+, 122, 109,

NMR (d<sub>6</sub>-DMSO): delta 9.41 (1H, brs), 9.00 (1H, brs), 8.37 (1H, brs), 5.92 (1H, s), 4.05-3.92 (1H, m), 2.70 (1H, dt, J = 8.6, 8.6 Hz), 2.25-1.90 (2H, m), 2.01 (3H, s), 1.87-1.34 (4H, m).

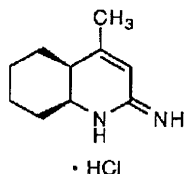
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**Example 2 (17)**

dl-cis-2-imino-4-methyl-1,2,4a,5,6,7,8,8a-octahydroquinoline • hydrochloride

(0158)



(0159)

The same operation as in Example 2 was carried out using compound produced in Reference Example 2 (13) instead of compound produced in Reference Example 1, and the compounds of this invention having the following physical property values was obtained.

TLC: Rf 0.36 (chloroform : methanol : acetic acid = 10:1:1),

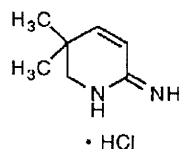
MS (EI) m/z 164(M)<sup>+</sup>, 149(M-CH<sub>3</sub>)<sup>+</sup>, 135, 121, 109,

NMR (d<sub>6</sub>-DMSO): delta 9.26 (1H, brs), 8.90 (1H, brs), 8.13 (1H, brs), 5.96-5.92 (1H, m), 3.70-3.61 (1H, m), 2.35-2.21 (1H, m), 2.02 (3H, s), 1.95-0.95 (8H, m).

**Example 2 (18)**

5,5-dimethyl-3,4-dehydro-2-iminopiperidine • hydrochloride

(0160)



(0161)

The same operation as in Example 2 was carried out using compound produced in Reference Example 4 instead of compound produced in Reference Example 1, and the compounds of this invention having the following physical property values was obtained.

TLC: Rf 0.44 (chloroform : methanol : acetic acid = 10:1:1),

MS (EI) m/z 124(M)<sup>+</sup>, 123 (M-H)<sup>+</sup>, 109 (M-CH<sub>3</sub>)<sup>+</sup>, 94 (M-2CH<sub>3</sub>)<sup>+</sup>,

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(unexamined)

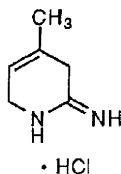
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NMR (d6-DMSO): delta 9.28 (1H, brs), 9.12 (1H, brs), 8.73 (1H, brs), 6.80 (1H, d, J = 9.8 Hz), 6.11 (1H, dd, J = 2.0, 9.8 Hz), 3.19 (2H, d, J = 2.6 Hz), 1.07 (6H, s).

### **Example 3**

4-methyl-4,5-dehydro-2-iminopiperidine • hydrochloride

(0162)



(0163)

A mixture of 4-methyl-2-aminopyridine (1 g), tetrahydrofuran (3.1 ml) and ethanol (1.1 ml) was cooled to -78 degrees, and liquid ammonia (31 ml) was added, furthermore, metallic lithium (210 mg) was added, and it was stirred for one hour. Ethanol (2 ml), and thereafter water (4 ml) were added to the reaction mixed solution, and ammonia was eliminated while gradually warming to room temperature. Water was added, and extraction with chloroform was carried out. The organic layer was dried with anhydrous sodium sulphate, and thereafter it was concentrated. The residue was dissolved in 15 ml ethanol, and next it was cooled to 0 degrees, hydrochloric acid solution (4 N, 4 ml) of ethyl acetate was added, it was stirred with room temperature for 30 minutes, and it was concentrated. The residue was purified by silica gel column chromatography (chloroform : methanol = 200:1 to 10:1 to 6:1), and the compounds of this invention having the following physical property values (840 mg) was obtained in a yield of 66 %.

TLC: Rf 0.38 (chloroform : methanol : acetic acid = 10:1:1),

MS (APCI) m/z 111 (M+H)+,

NMR (CDCl3): delta 10.15-9.95 (1H, brs), 9.05-8.95 (1H, brs), 8.95-8.65 (1H, brs), 5.55 (1H, s), 4.05-3.90 (2H, m), 3.22 (2H, t, J = 5.1 Hz), 1.80 (3H, s).

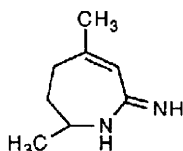
### **Example 4**

2H-4,7-dimethyl-2-imino-1,5,6,7-tetrahydroazepin • hydrochloride

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(0164)



(0165)

Ammonium chloride (2 g) was added to absolute ethanol (10 ml) solution of compound produced in Reference Example 5 (0.98 g) and was heated under reflux for two hours. It was cooled to room temperature, and next filtration was carried out, and the filtrate was concentrated. The residue was purified by silica gel column chromatography (chloroform : methanol : acetic acid = 15:2:1). The purified material was dissolved in 20 ml chloroform, and 4 N hydrochloric acid-ethyl acetate solution (2 ml) was added and it was stirred at room temperature for ten minutes. The reaction mixture solution was concentrated, and the compounds of this invention (496 mg) having the following physical property values was obtained in a yield of 44 %.

TLC: Rf 0.37 (chloroform : methanol : acetic acid = 15:2:1),

MS (APCI) m/z 139 (M+H)+,

NMR (CDCl<sub>3</sub>): delta 9.71 (1H, brs), 8.53 (1H, brs), 8.35 (1H, brs), 6.17 (1H, s), 3.63 (1H, m), 2.49 (2H, m), 2.04 (3H, s), 1.99-1.91 (2H, m), 1.38 (3H, d, J = 6.8 Hz).

#### **Formulation Example 1: Production of tablet.**

The following compounds were mixed in accordance with conventional procedures, tabletted, and 100 tablets containing 100 mg active ingredient per tablet were obtained.

- |  |        |
|--|--------|
| • 4-methyl-3,4-dehydro-2-iminopiperidine                 | 10 g   |
| • calcium carboxymethyl cellulose (disintegrating agent) | 200 mg |
| • magnesium stearate (lubricant)                         | 100 mg |
| • microcrystalline cellulose                             | 9.7 g. |

#### **Formulation Example 2: Production of injection.**

Each of the following components were mixed in accordance with conventional procedures, thereafter the solution was sterilised in accordance with conventional procedures, packed into

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ampoule by 5 ml each, freeze-dried in accordance with conventional procedures, and thereby 100 ampoules containing active ingredient 20 mg per ampoule were obtained.

4-methyl-3,4-dehydro-2-iminopiperidine	2 g
• mannite	5 g
• distilled water	1000 ml.

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