Description

CRYSTAL OF 1,2-DIHYDROPYRIDINE COMPOUND AND METHOD FOR PRODUCING SAME

Technical Field

[0001] This invention relates to crystals of 1,2-dihydropyridine compound [3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one] which are provided with antagonistic action against AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptor and/or inhibitory action against kainate receptor and which are useful as a therapeutic or prophylactic agent for neurodegenerative diseases or others, as well as their production process.

Background Art

[0002] 1,2-Dihydropyridine compounds possess antagonistic action against AMPA receptor and/or inhibitory action against kainate receptor and are useful as therapeutic or prophylactic agents for neurodegenerative diseases and others. Particularly, 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one (hereafter referred to as compound (1)) shows significant antagonistic action against AMPA receptor (see Patent Document 1).

Although Example 7 in Patent Document 1 discloses a process for producing the compound (1), there is merely described, "the residue is purified by silica gel column chromatography (ethyl acetate/hexane=1:2)" and there is no disclosure of the form of the obtained compound.

[0003] [Patent Document 1] WO01/96308

Disclosure of Invention

Problem to be Solved by the Invention

[0004] When a compound existing in crystal polymorphism is used as a medicament, it is necessary to stably supply the compound having uniform crystal form so that the uniform quality and the consistent potency required for the medicament may be guaranteed. There is also a need for the crystal form capable of maintaining the

same quality during its storage and its formulation process (such as blending and granulation).

[0005] Since a drug substance is industrially used in a large amount, desirable crystal forms are those having high explosion concentration high limit and minimum ignition energy, index of explosiveness and dangerousness.

[0006] Generally, powders that tend to be charged have great adhesiveness to other objects; and there is concern about their adhesion to protective goods or the skin.

When a drug substance has chargeability, it happens that the production efficiency and workability lower if the compound adheres to a rotary blade at a milling stage in the manufacture of the compound, or adheres to and agglomerate on the production machines during the process of formulation. When a large quantity of powders having chargeability is processed on an industrial scale, there is the possibility that dust explosion will occur. It is, therefore, desired that a compound (crystal) having weak chargeability be used as the drug substance.

As for a compound having high pharmacological activity (such as the drug substance), the standpoint of the avoidance of exposure to the workers and the prevention of the facility contamination makes powders that do not tend to be charged desirable.

[0007] For the reasons above, when the active pharmaceutical ingredient of a medicament is obtained as a crystalline substance, it desirably comprises a homogeneous crystal form, has consistently preferable properties, and does not contain impurities such as metals. There has also been a need to develop a process for stably producing such crystals on an industrial scale.

Accordingly, it is an object of this invention to provide a crystal comprising a homogeneous crystal form of the compound (1) and a production process therefor.

Means for Solving the Problem

[0008] As a result of the intensive and diligent studies, the

present inventors discovered that certain crystallization solvents could be used in the crystallization of the compound (1) to produce the compound (1) comprising a homogeneous crystal form, upon which this invention has been completed.

Specifically, the present invention provides among others the following:

(1) A crystal of 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one hydrate having a diffraction peak at a diffraction angle (2θ ± 0.2°) of 8.7° in a powder X-ray diffraction (Hydrate).

(2) A crystal of 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one hydrate having a diffraction peak at a diffraction angle (2θ ± 0.2°) of 12.5° in a powder X-ray diffraction (Hydrate).

(3) A crystal of 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one hydrate having diffraction peaks at diffraction angles (2θ ± 0.2°) of 8.7° and 12.5° in a powder X-ray diffraction (Hydrate).

(4) A crystal of 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one hydrate having an absorption peak at a wavenumber of 1588 ± 1 cm^{-1} in an infrared absorption spectrum (KBr method) (Hydrate).

(5) A crystal of 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one hydrate having absorption peaks at wavenumbers of 1588 ± 1 cm^{-1} and 751 ± 1 cm^{-1} in an infrared absorption spectrum (KBr method) (Hydrate).

(5-2) The crystal according to any of Items (1) to (3) having an absorption peak at a wavenumber of 1588 ± 1 cm^{-1} in an infrared absorption spectrum (KBr method) (Hydrate).

(5-3) The crystal according to any of Items (1) to (3) having absorption peaks at wavenumbers of 1588 ± 1 cm^{-1} and 751 ± 1 cm^{-1} in an infrared absorption spectrum (KBr method) (Hydrate).

(5-4) The crystal according to any of Items (1) to (5), (5-2) and (5-3)

having a palladium content of 20 ppm or less, preferably 15 ppm or less (Hydrate).

(6) A crystal of 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one hydrate having peaks at chemical shifts of around 146.7 ppm and around 123.3 ppm in a ^{13}C Solid State Nuclear Magnetic Resonance spectrum (Hydrate).

(7) A process for producing a crystal of 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one hydrate according to any of Items (1) to (5), (5-1), (5-2), (5-3), (5-4) and (6), the process comprising the step of crystallizing 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one with an aid of one or two crystallization solvents selected from the group consisting of an alcoholic solvent, an alkylketone solvent, and water.

(8) The process according to Item (7), wherein the crystallization solvent is a mixed solvent of acetone and water.

(9) The process according to Item (7), wherein the crystallization solvent is a mixed solvent of acetone and water with a volume ratio of 37:3 to 24:16, preferably a mixed solvent of acetone and water with a volume ratio of 9:1 to 7:3, and more preferably a mixed solvent of acetone and water with a volume ratio of 8:2 formed by dissolving the crystals in a mixed solvent of acetone and water with a volume ratio of 9:1 and thereafter adding water to the mixed solvent.

(10) The process according to any of Items (7) to (9), wherein the crystallization is carried out at a temperature of 60 to -30 °C.

(11) The process according to any of Items (7) to (9) comprising the steps of heating a solution of 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one dissolved in the crystallization solvent at a temperature of 50 °C or more (preferably at a temperature of the reflux temperature of the crystallization solvent to 50 °C, more preferably at a temperature of 65 to 55 °C) and thereafter cooling the solution to a temperature of 10 to -20 °C (preferably to a temperature of 10 to 5 °C) at a cooling rate of 40 to 5 °C per hour (preferably at a cooling rate of 25 to 15 °C per hour).

(12) The process according to any of Items (7) to (11), wherein the crystallization solvent is used in a volume ratio of 10- to 50-fold (v/w) based on the weight of 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one.

The quantity of the crystallization solvent is preferably from 30- to 50-fold (v/w), more preferably about 40-fold (v/w) where acetone and water (9:1) is used as the crystallization solvent and about 45-fold (v/w) where acetone and water (8:2) is used as the crystallization solvent.

(13) The process according to any of Items (7) to (12), wherein seed crystals (a small amount of crystals of 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one hydrate) are added at a temperature of 60 °C or less (preferably at a temperature of 55 to 0 °C, more preferably 55 to 35 °C, and most preferably about 40 °C).

(14) The process according to any of Items (7) to (13), wherein the crystals are dried under reduced pressure after the crystallization.

(15) The process according to any of Items (7) to (14), wherein the crystals are allowed to stand in the atmosphere after the crystallization and the drying under reduced pressure.

(15-1) The process according to any of Items (7) to (13), wherein the crystals are allowed to stand in the atmosphere after the crystallization.

(15-2) The process according to Item (14), wherein the crystals are allowed to stand in the atmosphere after the drying under reduced pressure.

(16) An anhydrous crystal of 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one having a diffraction peak at a diffraction angle (2θ ± 0.2°) of 10.3° in a powder X-ray diffraction (Anhydrous form I).

(17) The crystal according to Item (16) further having a diffraction peak at a diffraction angle (2θ ± 0.2°) of 19.1° in a powder X-ray diffraction (Anhydrous form I).

(18) An anhydrous crystal of 3-(2-cyanophenyl)-5-(2-pyridyl)-1-

phenyl-1,2-dihydropyridin-2-one having peaks at chemical shifts of around 149.0 ppm and around 125.6 ppm in a ^{13}C Solid State Nuclear Magnetic Resonance spectrum (Anhydrous form I).

(19) An anhydrous crystal of 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one having a diffraction peak at a diffraction angle (2θ ± 0.2°) of 16.7° in a powder X-ray diffraction (Anhydrous form V).

(20) The crystal according to Item (19) further having diffraction peaks at diffraction angles (2θ ± 0.2°) of 12.9° and 24.9° in a powder X-ray diffraction (Anhydrous form V).

(21) An anhydrous crystal of 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one having an absorption peak at a wavenumber of 1658 ± 1 cm^{-1} in an infrared absorption spectrum (KBr method) (Anhydrous form V).

(22) The crystal according to Item (21) further having an absorption peak at a wavenumber of 501 ± 1 cm^{-1} in an infrared absorption spectrum (KBr method) (Anhydrous form V).

(23) An anhydrous crystal of 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one having peaks at chemical shifts of around 145.9 ppm and around 137.7 ppm in a ^{13}C Solid State Nuclear Magnetic Resonance spectrum (Anhydrous form V).

(24) An anhydrous crystal of 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one having diffraction peaks at diffraction angles (2θ ± 0.2°) of 23.7° and 25.0° in a powder X-ray diffraction (Anhydrous form III).

(25) The crystal according to (24) further having diffraction peaks at diffraction angles (2θ ± 0.2°) of 5.7° and 9.5° in a powder X-ray diffraction (Anhydrous form III).

(26) A medicament comprising the crystal according to Item (1).

(27) A pharmaceutical composition comprising the crystal according to Item (1).

(28) A therapeutic or prophylactic agent for an acute neurodegenerative disease comprising the crystal according to Item

(1).

(29) A therapeutic or prophylactic agent for neuropathy caused by acute phase of cerebrovascular disorder, head injury, spinal cord injury or hypoxia, or neuropathy caused by hypoglycemia, comprising the crystal according to Item (1).

(30) A therapeutic or prophylactic agent for a chronic neurodegenerative disease comprising the crystal according to Item (1).

(31) A therapeutic or prophylactic agent for Alzheimer's disease, Parkinson's disease, Huntington's chorea, amyotrophic lateral sclerosis or spinocerebellar degeneration, comprising the crystal according to Item (1).

(32) A therapeutic or prophylactic agent for epilepsy, hepatic encephalopathy, peripheral neuropathy, Parkinsonism, spastic paralysis, pain, neuralgia, schizophrenia, anxiety, drug-dependence, nausea, vomiting, dysuria, vision impairment caused by glaucoma, hearing impairment caused by antibiotics, or food poisoning, the agent comprising the crystal according to Item (1).

(33) A therapeutic or prophylactic agent for infectious encephalomyelitis, cerebrovascular dementia, or dementia or neurological symptom caused by meningitis, comprising the crystal according to Item (1).

(34) A therapeutic or prophylactic agent for a demyelinating disease comprising the crystal according to Item (1).

(35) The therapeutic or prophylactic agent according to Item (33), wherein the infectious encephalomyelitis is HIV encephalomyelitis.

(36) The therapeutic or prophylactic agent according to Item (34), wherein the demyelinating disease is encephalitis, acute sporadic encephalomyelitis, multiple sclerosis, acute polyradiculoneuropathy, Guillain-Barre syndrome, chronic inflammatory demyelinating polyradiculoneuropathy, Marchifava-Bignami disease, central pontomedullary myelinolysis, neuromyelitis optica, Devic's disease, Balo's disease, HIV-associated myelopathy, HTLV-associated

myelopathy, progressive multifocal leukoencephalitis or a secondary demyelinating disease.

(37) The therapeutic or prophylactic agent according to Item (36), wherein the secondary demyelinating disease is CNS lupus erythematosus, polyarteritis nodosa, Sjoegren's syndrome, sarcoidosis or dissociated cerebral vasculitis.

Effects of the Invention

[0009] According to the invention, it has become possible that the compound (1) is readily produced as a homogeneous crystal form on an industrial scale. The crystal forms of the invention have preferable properties such as no chargeability and are suitable for use as an active ingredient of therapeutic or prophylactic agents for neurodegenerative diseases or others.

Brief Description of Drawings

[0010] Fig. 1 shows an infrared spectrum (KBr method) of the crystals obtained in Example B1.

Fig. 2 shows an infrared spectrum (KBr method) of the crystals obtained in Example C1.

Fig. 3 shows a powder X-ray diffraction pattern of the crystals obtained in Reference Example A1.

Fig. 4 shows a powder X-ray diffraction pattern of the crystals obtained in Example B1.

Fig. 5 shows a powder X-ray diffraction pattern of the crystals obtained in Example C1.

Fig. 6 shows a powder X-ray diffraction pattern of the crystals obtained in Example D1.

Fig. 7 shows a powder X-ray diffraction pattern of the crystals as described in Example E1.

Fig. 8 shows a ^{13}C Solid State Nuclear Magnetic Resonance (NMR) spectrum of the crystals obtained in Example B1.

Fig. 9 shows a ^{13}C Solid State NMR spectrum of the crystals obtained in Example D1.

Fig. 10 shows a ^{13}C Solid State NMR spectrum of the crystals

obtained in Example C1.

Fig. 11 shows powder X-ray diffraction patterns of Hydrate at various temperatures.

Fig. 12 shows powder X-ray diffraction patterns of Hydrate under various relative humidities.

Best mode for carrying out the Invention

[0011] This invention will be described in detail hereafter.

In this Specification, "A crystal of 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one hydrate" is a crystal form of 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one containing water in the crystal, and as such, the amount of water contained in the crystal form is not particularly limited; it may be devoid of a portion of the water in the crystal. The term also encompasses the form wherein the water may coexist with adhesion water.

This "crystal of 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one hydrate" means such a crystal form that it has preferably 1/2 to one molecule of water per one molecule of 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one in the crystal, may further contain 0 to 1/4 molecules of adhesion water and may even be devoid of 0 to 1/2 molecules of water in the crystal.

Specifically, it means the following:

(1) A crystal of 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one 3/4 hydrate;

(2) A crystal of 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one monohydrate (devoid of 1/4 in the crystal);

(3) A crystal of 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one 1/2 hydrate coexisting with 1/4 adhesion water; and

(4) A crystal of 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one 1/2 hydrate; and

(5) A crystal of 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one monohydrate.

[0012] The crystal forms of the invention are crystal forms of the hydrate of the compound (1) with the characteristics described below. Although the respective measurement conditions for powder X-ray diffraction patterns and infrared absorption spectra (KBr method) are not particularly limited, the measurement should preferably be conducted under the measurement conditions for the powder X-ray diffraction patterns and the infrared absorption spectra (KBr method) as will be described below.

(1) A crystal having a diffraction peak at a diffraction angle (2θ ± 0.2°) of 8.7° in a powder X-ray diffraction;

(2) A crystal having a diffraction peak at a diffraction angle (2θ ± 0.2°) of 12.5° in a powder X-ray diffraction;

(3) A crystal having diffraction peaks at diffraction angles (2θ ± 0.2°) of 8.7° and 12.5° in a powder X-ray diffraction;

(4) A crystal having diffraction peaks at the diffraction angles (2θ ± 0.2°) shown in Fig. 4 or Table 5 below in a powder X-ray diffraction;

(5) A crystal having an absorption peak at a wavelength of 1588 ± 1 cm^{-1} in an infrared absorption spectrum (KBr method);

(6) A crystal having absorption peaks at wavelengths of 1588 ± 1 cm^{-1} and 751 ± 1 cm^{-1} in an infrared absorption spectrum (KBr method); and

(7) A crystal having absorption peaks at the wavelengths (cm^{-1}) shown in Fig. 1 or Table 2 below in an infrared absorption spectrum (KBr method).

[0013] These characteristic peaks in the powder X-ray diffraction are not observable in the crystal form obtained by the production process disclosed in Patent Document 1 (see Reference Example A1, Table 4 and Fig. 3 as described below).

As for a diffraction angle (2θ) in the powder X-ray diffraction analysis, errors in the diffraction angle, generally, may occur within the range of ±0.2°. It is, therefore, to be understood that the values of the diffraction angles may include numerals on the order of ± 0.2°. Accordingly, this invention encompasses not only crystal form

having completely matching diffraction angles of the peaks in powder X-ray diffraction, but also crystal form having matching diffraction angles of the peaks within the errors of about ± 0.2°.

[0014] [Hydrate]

In this Specification, "having a diffraction peak at a diffraction angle (2θ ± 0.2°) of 8.7°" means "having a diffraction peak at a diffraction angle (2θ) of 8.5° to 8.9°." The term "having a diffraction peak at a diffraction angle (2θ ± 0.2°) of 12.5°" means "having a diffraction peak at a diffraction angle (2θ) of 12.3° to 12.7°."

[0015] In this Specification, "having an absorption peak at a wavenumber of 1588 ± 1 cm^{-1}" means "having an absorption peak at a wavenumber of 1587 to 1589 cm^{-1}."

[0016] In this Specification, "having absorption peaks at wavenumbers of 1588 ± 1 cm^{-1} and 751 ± 1 cm^{-1}" means "having absorption peaks at wavenumbers of 1587 to 1589 cm^{-1} and of 750 to 752 cm^{-1}."

[0017] In this Specification, "having a peak at chemical shifts of around 146.7 ppm" means "having a peak substantially equivalent to 146.7 ppm when a ^{13}C Solid State NMR spectrum is measured under normal conditions or under the conditions substantially the same as those described in this Specification." In this Specification, "having a peak at chemical shifts of around 123.3 ppm" means "having a peak substantially equivalent to 123.3 ppm when a ^{13}C Solid State NMR spectrum is measured under normal conditions or under the conditions substantially the same as those described in this Specification."

[0018] [Anhydrous form I]

In this Specification, "having a diffraction peak at a diffraction angle (2θ ± 0.2°) of 10.3°" means "having a diffraction peak at a diffraction angle (2θ) of 10.1° to 10.5°." The term "having a diffraction peak at a diffraction angle (2θ ± 0.2°) of 19.1°" means "having a diffraction peak at a diffraction angle (2θ) of 18.9° to

19.3°."

[0019] In this Specification, "having a peak at chemical shifts of around 149.0 ppm" means "having a peak substantially equivalent to 149.0 ppm when a ^{13}C Solid State NMR spectrum is measured under normal conditions or under the conditions substantially the same as those described in this Specification." In this Specification, "having a peak at chemical shifts of around 125.6 ppm" means "having a peak substantially equivalent to 125.6 ppm when a ^{13}C Solid State NMR spectrum is measured under normal conditions or under the conditions substantially the same as those described in this Specification."

[0020] [Anhydrous form V]

In this Specification, "having a diffraction peak at a diffraction angle (2θ ± 0.2°) of 16.7°" means "having a diffraction peak at a diffraction angle (2θ) of 16.5° to 16.9°." The term "having a diffraction peak at a diffraction angle (2θ ± 0.2°) of 12.9°" means "having a diffraction peak at a diffraction angle (2θ) of 12.7° to 13.1°." The term "having a diffraction peak at a diffraction angle (2θ ± 0.2°) of 24.9°" means "having a diffraction peak at a diffraction angle (2θ) of 24.7° to 25.1°."

[0021] In this Specification, "having an absorption peak at a wavenumber of 1658 ± 1 cm^{-1}" means "having an absorption peak at a wavenumber of 1657 to 1659 cm^{-1}."

[0022] In this Specification, "having an absorption peak at a wavenumber of 501 ± 1 cm^{-1}" means "having an absorption peak at a wavenumber of 500 to 502 cm^{-1}."

[0023] In this Specification, "having a peak at chemical shifts of around 145.9 ppm" means "having a peak substantially equivalent to 145.9 ppm when a ^{13}C Solid State NMR spectrum is measured under normal conditions or under the conditions substantially the same as those described in this Specification." In this Specification, "having a peak at chemical shifts of around 137.7 ppm" means "having a peak substantially equivalent to 137.7 ppm when a ^{13}C

Solid State NMR spectrum is measured under normal conditions or under the conditions substantially the same as those described in this Specification."

[0024] [Anhydrous form III]

In this Specification, "having a diffraction peak at a diffraction angle (2θ ± 0.2°) of 23.7°" means "having a diffraction peak at a diffraction angle (2θ) of 23.5° to 23.9°." The term "having a diffraction peak at a diffraction angle (2θ ± 0.2°) of 25.0°" means "having a diffraction peak at a diffraction angle (2θ) of 24.8° to 25.2°." The term "having a diffraction peak at a diffraction angle (2θ ± 0.2°) of 5.7°" means "having a diffraction peak at a diffraction angle (2θ) of 5.5° to 5.9°." The term "having a diffraction peak at a diffraction angle (2θ ± 0.2°) of 9.5°" means "having a diffraction peak at a diffraction angle (2θ) of 9.3° to 9.7°."

[0025] In this Specification, "an alkyl ketone solvent" means an organic solvent of dialkyl ketone such as acetone and ethyl methyl ketone, and preferably acetone.

[0026] In this Specification, "an alcoholic solvent" means an organic solvent of C_{1-6} alcohol, such as methanol, ethanol, 1-propanol and 2-propanol, and preferably methanol or 1-propanol.

[0027] In this Specification, "under reduced pressure" is not particularly limited insofar as it is 760 mmHg or less; and it is preferably from 760 to 0.1 mmHg, more preferably from 50 to 0.1 mmHg, and most preferably from 30 to 5 mmHg.

[0028] [General production process for Hydrate]

The hydrate of this invention can be stably produced on an industrial scale by preparing the compound (1) according to Example 7 in Patent Document 1 (WO01/96308) or Production Example 3 (described below), dissolving this compound (1) in a specific solvent by heating, and crystallizing it by cooling at stirring.

[0029] The compound (1) to be used in the crystallization may be any form of hydrate, anhydrous, amorphous and crystalline forms (which includes plural crystal polymorphs), and may even be a

mixture of the foregoing.

[0030] The solvents to be used in the crystallization include one member or a mixed solvent of two members selected from the group consisting of an alcoholic solvent, an alkyl ketone solvent, and water. The solvent is preferably a mixed solvent of acetone and water.

When the mixed solvent of acetone and water is used, its mixing ratio (volume ratio) is preferably from 37:3 to 24:16, more preferably from 9:1 to 7:3, and further more preferably about 8:2. The most preferred is a mixed solvent formed by dissolving the crystals in a mixed solvent of acetone and water (9:1) and thereafter adding water to the mixed solvent to prepare a solution of acetone and water (8:2).

[0031] The amount of the solvent used may appropriately be selected between the lower limit and the upper limit, the lower limit being an amount to dissolve the compound (1) by heating and the upper limit being an amount so as not to significantly reduce the yield of the crystals. The amount of crystallization solvent is preferably from 10- to 50-fold (v/w) as a volume ratio based on the weight of the compound (1), more preferably from 30- to 50-fold (v/w). Further preferably, the amount is about 40-fold (v/w) if acetone-water (9:1) is used; and it is about 45-fold (v/w) if acetone-water (8:2) is used.

[0032] The temperature at which the compound (1) is dissolved by heating may appropriately be selected as the temperature to dissolve the compound (1) depending on the solvent. The temperature is preferably from the reflux temperature of the crystallization solvent to 50 °C, more preferably from 65 to 55 °C.

Any change in the cooling rate during crystallization may produce crystals with different forms (polymorphisms). It is, therefore, desired that the crystallization be performed by suitably adjusting the cooling rate in consideration of possible effects on the quality and the particle size of the crystals or the like. Cooling is preferably performed at a rate of 40 to 5 °C per hour and more

preferably at a rate of 25 to 15 °C per hour.

The final crystallization temperature may also appropriately be selected in consideration of the yield and the quality of the crystals, or the like; and it is preferably from 10 to -25 °C.

[0033] In the crystallization, seed crystals may or may not be added, which comprise a small amount of crystals of 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one hydrate. There is no particular limitation to the temperature at which the seed crystals are added. The temperature is preferably 60 °C or less, more preferably from 55 to 0 °C, further more preferably from 55 to 35 °C, and most preferably about 40 °C.

[0034] The precipitated crystals can be separated by usual filtration, washed with solvent if necessary, and then dried to produce the desired crystals. The solvent for use in washing the crystals is common to the crystallization solvent, and it is preferably a mixed solvent of acetone-water (9:1 to 1:1), more preferably a mixed solvent of acetone-water (about 1:1).

[0035] [Drying Method for Crystals]

The crystals separated by the filtration can be dried by allowing them to stand in the atmosphere, where appropriate, or by heating.

The time during which the residual solvent is removed below the prescribed amount may appropriately be selected as the drying time, depending on the production quantity, the drying apparatus, the drying temperature or the like. Drying can be performed either under aeration or under reduced pressure. The level of pressure reduction may appropriately be selected, depending on the production quantity, the drying apparatus, the drying temperature or the like. The obtained crystals may be allowed to stand in the atmosphere after drying if necessary.

[0036] The crystals produced by the above-mentioned process comprise a homogeneous crystal form. Being provided with the preferable properties such that it is stable, has no tendency to readily

transform into other crystal or amorphous forms, and is not hygroscopic, these crystals are suited to formulation.

The use of the compound (1) as a therapeutic agent for neurodegenerative diseases or others is fully disclosed in Patent Document 1. The crystal forms of the invention can be used as the active ingredient in the therapeutic agent for neurodegenerative diseases or others. The entire disclosure of Patent Document 1 is thus hereby incorporated in this Specification by reference.

[0037] When a compound of this invention is to be used as a medicament, it is normally compounded with suitable pharmaceutical ingredients to prepare pharmaceutical products for use. Notwithstanding, the use of a drug substance form of the compound of the invention as a medicament should not be negated.

The pharmaceutical ingredients may include excipients, binders, lubricants, disintegrating agents, coloring agents, taste correctives, emulsifiers, surfactants, dissolving aids, suspending agents, isotonizing agents, buffering agents, preservatives, antioxidants, stabilizers, absorption enhancers, and the like, all of which are generally used in medicaments. If desired, these agents may be combined for use.

[0038] The excipients may include, for example, lactose, white soft sugar, glucose, corn starch, mannitol, sorbitol, starch, alpha starch, dextrin, crystalline cellulose, light silicic anhydride, aluminum silicate, calcium silicate, magnesium aluminometasilicate, calcium hydrogenphosphate, and the like.

[0039] The binders may include, for example, polyvinyl alcohol, methylcellulose, ethylcellulose, gum Arabic, tragacanth, gelatin, shellac, hydroxypropylmethylcellulose, hydroxypropylcellulose, carboxymethylcellulose sodium, polyvinylpyrrolidone, macrogol, and the like.

[0040] The lubricants may include, for example, magnesium stearate, calcium stearate, sodium stearyl fumarate, talc, polyethylene glycol, colloidal silica, and the like.

[0041] The disintegrating agents may include, for example, crystalline cellulose, agar, gelatin, calcium carbonate, sodium hydrogencarbonate, calcium citrate, dextrin, pectin, low-substituted hydroxypropylcellulose, carboxymethylcellulose, carboxymethylcellulose calcium, croscarmellose sodium, carboxymethyl starch, carboxymethyl starch sodium, and the like.

[0042] The coloring agents may include iron sesquioxide, yellow iron sesquioxide, carmine, caramel, beta-carotene, titanium oxide, talc, riboflavin sodium phosphate, yellow aluminum lake, and the like, which have been approved as additives for medicaments.

[0043] The taste correctives agents may include cocoa powder, menthol, aromatic powder, mentha oil, borneol, powdered cinnamon bark, and the like

[0044] The emulsifiers or the surfactants may include stearyl triethanolamine, sodium lauryl sulfate, lauryl aminopropionic acid, lecithin, glycerin monostearate, sucrose fatty acid ester, glycerin fatty acid ester, and the like.

[0045] The dissolving aids may include polyethylene glycol, propylene glycol, benzyl benzoate, ethanol, cholesterol, triethanolamine, sodium carbonate, sodium citrate, Polysorbate 80, nicotinamide, and the like.

[0046] The suspending agents may include, in addition to the surfactants, hydrophilic polymers such as polyvinyl alcohol, polyvinylpyrrolidone, methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, and hydroxypropylcellulose.

[0047] The isotonizing agents may include glucose, sodium chloride, mannitol, sorbitol and the like.

[0048] The buffering agents may include the buffers of phosphate, acetate, carbonate, citrate and the like.

[0049] The preservatives may include methylparaben, propylparaben, chlorobutanol, benzyl alcohol, phenethyl alcohol, dehydroacetic acid, sorbic acid and the like.

[0050] The antioxidants may include sulfite, ascorbic acid,

alpha-tocopherol and the like.

[0051] The stabilizers may include those generally used in medicaments.

[0052] The absorption enhancers may include those generally used in medicaments.

[0053] The pharmaceutical products described above may include: oral agents such as tablets, powders, granules, capsules, syrups, troches, and inhalations; external preparations such as suppositories, ointments, ophthalmic ointments, tapes, ophthalmic solutions, nasal drops, ear drops, poultices, and lotions; and injections.

[0054] The oral agents may appropriately be combined with the auxiliaries described above to form preparations. In addition, the surfaces of the agents may be coated if necessary.

[0055] The external preparations may appropriately be combined with the auxiliaries, in particular, excipients, binders, taste correctives, emulsifiers, surfactants, dissolving aids, suspending agents, isotonizing agents, preservatives, antioxidants, stabilizers, or absorption enhancers to form the preparations.

[0056] The injections may appropriately be combined with the auxiliaries, in particular, emulsifiers, surfactants, dissolving aids, suspending agents, isotonizing agents, preservatives, antioxidants, stabilizers, or absorption enhancers to form the preparations.

[0057] When the compound of this invention is to be used as a medicament, its dosage level may differ depending on the symptoms, ages or others. The compound is normally given in a single administration or in divided administrations 2 to 6 times daily at the following doses: from 0.05 to 10 mg (preferably from 0.1 to 5 mg) in the case of an oral agent; from 0.01 to 10 mg (preferably from 0.05 to 5 mg) in the case of an external preparation; and 0.01 to 5 mg in the case of an injection. Here, the actual amounts to be administered are indicated with respect to the oral agent and the injection, while the amount to be absorbed by the body is indicated with respect to

the external preparation.

[0058] The preparations for therapeutic or prophylactic use in humans containing crystal of 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one hydrate (compound (1)) according to the invention may be obtained by the general methods that are accepted in manufacturing pharmacy. The specific formulation examples of preparations are shown below.

[0059] The compound of the invention [i.e., 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one], lactose, low-substituted hydroxypropylcellulose were blended. Polyvinylpyrrolidone dissolved in an appropriate amount of purified water was then used to wet granulate the blend. These granulates were dried and then size-controlled. Low-substituted Hydroxypropylcellulose and magnesium stearate were blended to the resulting granulates, after which they was tabletted. The obtained tablets were film-coated with an aqueous solution of the coating base (a mixture of hydroxypropylmethylcellulose, talc, Macrogol 6000, titanium oxide and yellow iron sesquioxide). The amounts of the respective materials to be used per tablet are shown in the table below.

[0060] [Table 1]

Material	Purpose	0.5mg tablet	1.0mg tablet	2.0mg tablet
compound of the invention*1	principle agent	0.5mg	1.0mg	2.0mg
lactose	excipient	80.0mg	79.5mg	78.5mg
low-substituted hydroxypropylcellulose	disintegrator	9.0mg	9.0mg	9.0mg
polyvinylpyrrolidone	binder	5.0mg	5.0mg	5.0mg
low-substituted hydroxypropylcellulose	disintegrator	5.0mg	5.0mg	5.0mg
magnesium stearate	lubricant	0.5mg	0.5mg	0.5mg
purified water	solvent	q.s.	q.s.	q.s.
coating base*2	coating agent	5.0mg	5.0mg	5.0mg
purified water	solvent	q.s.	q.s.	q.s.
total		105mg	105mg	105mg

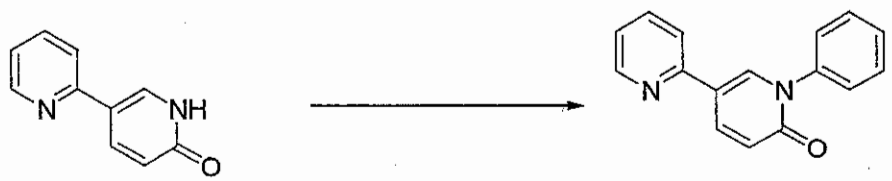
*1: 3-(2-Cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one (Hydrate)
*2: Mixture of hydroxypropylmethylcellulose, talc, Macrogol 6000, titanium oxide and yellow iron sesquioxide

Examples

[0061] This invention will be specifically described in detail by way of the following examples; however, the invention is not to be limited to these examples.

[0062] (Production Example 1)

Synthesis of 5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one



After a reactor was purged with nitrogen, a mixture of 5-(2-pyridyl)-1,2-dihydropyridin-2-one (7.33 kg: WO2004/009553), triphenylboroxine (9.0 kg), copper acetate (anhydrous) (0.80 kg), water (0.50 kg), pyridine (7.1 kg), and N,N-dimethylformamide (66.7 kg) was stirred in the reactor at an internal temperature of 28 °C for 1 hour.

While the air of which oxygen concentration was adjusted to

9% with nitrogen was blown into the reactor at a rate of 30 L/min, the reaction mixture was stirred at 39-40 °C (internal temperature) for 16 hours to yield reaction mixture 1A.

Water (191 kg) and 25% aqueous ammonia (85.8 kg) were charged in a separate reactor and cooled with cold water to 8.7 °C. The reaction mixture 1A was then added to the reactor over 3 minutes. The reaction mixture was stirred for 4 hours at cooling with cold water. The precipitates in the reaction mixture were collected by filtration with a centrifuge and the filtrated residue was washed with 65 kg of water.

The precipitates, water (97 kg), and 25% aqueous ammonia (43.5 kg) were poured in a reactor and stirred for 1 hour while the temperature was maintained with warm water (25 °C). The precipitates in the reaction mixture were collected by filtration with a centrifuge and the filtrated residue was washed with 32.6 kg of water. The precipitates were then dried under reduced pressure (60 °C; 18 hours) to give 9.6 kg of 5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one.

^{1}H NMR (400 MHz DMSO-d6): δ 8.61-8.50 (m, 1H), 8.36 (d, 1H), 8.29 (dd, 1H), 7.90 (d, 1H), 7.80 (ddd, 1H), 7.56-7.45 (m, 5H), 7.27 (dd, 1H), 6.62 (d, 1H).

[0063] (Production Example 2)

Synthesis of 3-bromo-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one



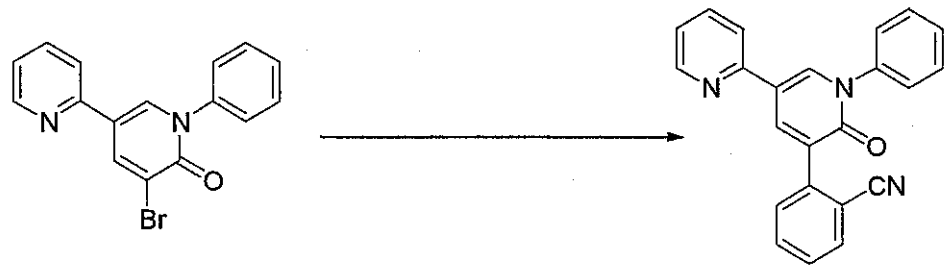
5-(2-Pyridyl)-1-phenyl-1,2-dihydropyridin-2-one (200 g), N-bromosuccinimide (157.7 g), and ethyl acetate (4 L) were added to a 10L-reactor and the reaction mixture was stirred under a nitrogen stream at 30 °C (external temperature) for 9 hours and 20 minutes. 3% Hydrosulfite solution (2 L) and toluene (2 L) were added to the

reaction mixture and then it was stirred at 55 °C (external temperature) for 30 minutes. After the completion of reaction, the aqueous layer (lower layer) in the reaction mixture was separated, and then, the organic layer was washed with water (2 L) four times. The solvent was evaporated at stirring under reduced pressure.

Subsequently, further addition of 1,2-dimethoxyethane (4 L) and concentration under reduced pressure gave a crude product of 3-bromo-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one.

[0064] (Production Example 3)

Synthesis of 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one



To the reactor containing the whole amount of the crude product of 3-bromo-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one obtained as the residue after concentration in Production Example 2 were added 2-(1,3,2-dioxaborinan-2-yl)benzonitrile (214.9 g), palladium acetate (3.44 g), triphenylphosphine (16.07 g), cuprous iodide (7.29 g), 1,2-dimethoxyethane (3.1 L) and potassium carbonate (158.8 g). Stirring at heating was carried out at 70 °C (external temperature) under a nitrogen atmosphere for 30 minutes and, then, at heating under reflux for 4 hours.

Subsequently, ethyl acetate (2.5 L) was added to the reaction mixture at 70 °C (external temperature) and the mixture was stirred for 10 minutes. The reaction mixture was filtrated and the filtrated residue was washed with ethyl acetate (2.5 L). This whole filtrate was transferred to a reactor, to which 12.5% aqueous ammonia (5 L) was further added. Stirring was carried out at 60 °C (external temperature) for 53 minutes. The lower layer (aqueous layer) in the

reaction mixture was separated. 5% Brine (2.5 L) and 25% aqueous ammonia (2.5 L) were added to the remaining organic layer. After stirring, the lower (aqueous layer) was separated. 5% Brine (5 L) was further added to the remaining organic layer. After stirring, the lower (aqueous layer) was separated. The remaining organic layer was concentrated under reduced pressure, and then, acetone (4 L) was added, followed by concentration under reduced pressure.

Acetone (7.2 L) and water (0.8 L) were added to this residue, and it was dissolved by stirring at 60 °C (external temperature) for 1 hour and 10 minutes. Next, cooling was carried out at 38 °C (external temperature) for 18 minutes while stirring. To the reaction mixture was added 1 g of seed crystals, crystals of 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one hydrate. Stirring was carried out at 35 °C (external temperature) for 30 minutes. Subsequently, the reaction mixture was stirred at an external temperature being lowered by 5 °C every 30 minutes, and stirred at an external temperature of 10 °C for 17 hours.

Water (2.29 L) was added dropwise to the reaction mixture at stirring over a period of 3 hours and 10 minutes. After the addition, stirring continued for additional 1 hour and 20 minutes. The reaction mixture was filtrated and the filtrated residue was washed with 2 L of 50% acetone-water to give 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one (526.28 g) as a wet cake, which corresponded to 168.3 g as dry weight.

[0065] Conversion of 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one in the wet cake to dried weight

The obtained wet cake (4.378 g) was weighed out and dried under reduced pressure at 50 °C for 4 hours to give 1.4005 g of a dried powder.

Converted value as dried weight = (1.4005/4.378) x 526.28 = 168.3 g

[0066] Determination of acetone and water weight contents in the wet cake of 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one

Gas chromatographic analysis of the obtained wet cake under the conditions described below ascertained that the wet cake obtained in Production Example 3 contained 168 mL of acetone and 186 mL of water.

[0067] Gas chromatographic analysis conditions:
Column: DB-WAX (30m x 0.53mm, 1μm); detector: TCD; oven temp.: 60 °C (8min), 60-180 °C (70 °C/min), 180 °C (5min); detector temp.: 210 °C; inlet temp.: 150 °C; column flow: 5.0 mL/min; split ratio:(1:4); injection vol.: 2 μL

[0068] (Example 1X)
Crystallization of 3-(2-cyano-phenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one (Hydrate)

A 10 L-flask was charged with 526.28 g of 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one obtained as the wet cake in Production Example 3. Out of an acetone-water prepared from 5890 mL of acetone and 490 mL of water, 5.5 L was added to the flask and heated. Filtration was carried out after dissolution. While the 10-L flask and the filtrated residue were washed with the remaining total of the acetone water, all the filtrate was transferred to a 10-L flask.

The mixture was stirred at an external temperature of 40 °C, and after the internal temperature reached 40 °C, the external temperature was adjusted to 35 °C. Next, 842 mg of 3-(2cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one hydrate was added to the mixture. After stirring the mixture for 30 minutes, the external temperature was changed to 30 °C, and then to 25 °C after 30 minutes. The external temperature was lowered by 5 °C every 30 minutes thereafter to as low as 15 °C. After stirring the mixture at an external temperature of 15 °C for 30 minutes, the external temperature was further lowered to 8 °C and stirring continued for 1 hour.

To the mixture was added dropwise 842 mL of water at 11 °C (internal temperature) over a period of 1 hour and 10 minutes. One

hour after the completion of addition, the external temperature was changed to 0 °C and the mixture was stirred for 40 minutes. The external temperature was then lowered to -20 °C and stirring continued for 15 hours.

The precipitates in the mixture were collected by filtration. After the precipitates were washed with 1700 mL of 50% acetone-water, they were dried under aeration for 50 minutes. Subsequently, these precipitates were dried with a vibration drier at 40 °C under reduced pressure for 11 hours and were additionally dried at 60 °C for 3 hours.

After the temperature of the drier was cooled to room temperature, the external atmosphere was aspirated into the drier at 950 hpa for 4 hours to give 172.4 g of 3-(2cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one (crystal form of the hydrate).

^{1}H NMR (400MHz, DMSO-d_6): δ 8.61-8.57 (m, 1H), 8.53-8.52 (d-like, 1H), 8.47 (d, 1H), 8.01 (d, 1H), 7.92 (d, 1H), 7.86-7.81 (t-like, 1H), 7.79-7.76 (t-like, 1H), 7.72(d, 1H), 7.61-7.48 (m, 6H), 7.31-7.28 (m, 1H).

Residual palladium: 15 ppm

[0069] (Reference Example A1)

Production anhydrous crystals of 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydopyridin-2-one (Anhydrous form II)

In the same manner as the procedure after reaction work-up that are described in Example 7 in WO01/96308, the production was carried out below. The synthetic method for 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one [alternative name: 2-(2-oxo-1-phenyl-5-(pyridin-2-yl)-1,2-dihydropyridin-3-yl)benzonitrile] is described in Example 7 in WO01/96308 as well as in Production Example 3 above.

Ethyl acetate (400 mL) was added to 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one (8g). The mixture was heated at 60 °C in a warm bath. Additional acetate (160 mL) was

added to the mixture and the solids were dissolved by heating at 70 °C in the warm bath. After n-hexane (80 mL) was added to this solution, the solvent was evaporated under reduced pressure to give 7.7 g of a pale yellow powder.

^{1}H NMR (400MHz, DMSO-d_6): δ 8.59-8.57 (m, 1H), 8.53 (d, 1H), 8.47 (d, 1H,), 8.01 (d, 1H), 7.92 (d, 1H), 7.83 (ddd, 1H), 7.80-7.76 (m,1H), 7.73-7.71 (d-like, 1H), 7.61-7.48 (m, 6H), 7.30 (dd, 1H).

[0070] (Example B1)

Production of crystals of 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one hydrate (Hydrate)

A 500 mL-egg plant vessel was charged with 7 g of 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one. To the vessel was added 280 mL of 90% acetone-water prepared from 252 mL of acetone and 28 mL of water. The mixture was stirred at heating in a water bath and dissolved under reflux (water bath; 65 °C). After the dissolution was confirmed, the water bath was cooled to 50 °C. After addition of 35 mL of water, 140 mg of seed crystals [a small amount of crystals of 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one hydrate] was added to the vessel at an internal temperature of 50 °C. A thermostat bath was used to cool the mixture to -20 °C at a cooling rate of about 35 °C/hour. After stirring the mixture at -20 °C for 1 hour, the precipitated solids were collected by filtration and dried under reduced pressure (at an external temperature of 30 °C for 1 hour and then at 60 °C for 2 hours). The obtained dried powders (6.3 g) were transferred to a Petri dish and were allowed to stand in the atmosphere for 17 hours (humidity before standing: 55.4%; humidity after overnight standing: 61.6%) to give 6.2 g of crystals of 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one hydrate.

^{1}H NMR (400MHz, DMSO-d_6): δ 8.61-8.57 (m, 1H), 8.53 (d, 1H), 8.47 (d, 1H,), 8.01 (d, 1H), 7.92 (d, 1H), 7.83 (ddd, 1H), 7.78 (ddd, 1H), 7.73-7.71 (d-like, 1H), 7.61-7.48 (m, 6H), 7.30 (dd, 1H).

[0071] (Example C1)

Production of anhydrous crystals of 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one (Anhydrous form V)

A 500 mL-vessel was charged with 9 g of 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one (crystal form of the hydrate). Acetone (360 mL) was added to the vessel and the mixture was stirred at heating under reflux (at 70 °C in a water bath).

After dissolution, the mixture was filtrated by suction and the filtrate was concentrated at 75 °C under normal pressure to solidify. After the solids were finely ground in a mortar, an acetone-water solution prepared from 216 mL of acetone and 54 mL of water was added to the solids.

The mixture was stirred at heating under reflux (at 75 °C in a water bath). After dissolution, the mixture was additional stirred at heating under reflux for 2 hours and 40 minutes. Subsequently, the temperature of the water bath for the mixture (external temperature) was cooled to room temperature at a cooling rate of 10 °C/hour, and it was stirred at room temperature for 16 hours.

The precipitates in the reaction mixture were suction-filtrated and then dried under reduced pressure (an external temperature of 20 °C for 40 minutes and then at 60 °C for 3 hours) to give 7.2 g of the anhydrous crystals of 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one.

^{1}H NMR (400MHz, DMSO-d_6): δ 8.61-8.57 (m, 1H), 8.53 (d, 1H), 8.47 (d, 1H,), 8.01 (d, 1H), 7.92 (dd, 1H), 7.83 (ddd, 1H), 7.78 (ddd, 1H), 7.72 (dd, 1H), 7.61-7.48 (m, 6H), 7.31-7.28 (m, 1H).

[0072] (Example D1)

Production of the anhydrous crystals of 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one (Anhydrous form I)

A 1-L vessel was charged with 8 g of 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one (Hydrate). Ethyl acetate (480 mL) was added to the vessel and the mixture was stirred at heating under reflux (in an oil bath) to effect dissolution. Heating

was stopped and the stirring was allowed to continue while the vessel was in the oil bath (under gradual cooling). At the point that the internal temperature reached 50.9 °C, 0.2 g of seed crystals [3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one (anhydrous crystal)] was added to the mixture. Subsequently, stirring continued until the internal temperature reached 31.3 °C. The mixture was stirred for additional 2 hours in an ice bath. The precipitated crystals were collected by filtration and dried under aeration (50 °C/18 hours) to give 5.8 g of anhydrous crystals of 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one.

^{1}H NMR (400MHz, DMSO-d_6): δ 8.58 (d, 1H), 8.53 (d, 1H), 8.47 (d, 1H,), 8.01 (d, 1H), 7.93 (d, 1H), 7.83 (ddd, 1H), 7.78 (d, 1H), 7.72 (d, 1H), 7.61-7.48 (m, 6H), 7.32-7.27 (m, 1H).

[0073] Physical stability in mixing operation in the presence of water or water-ethanol (1:1) mixed solution

(Operation Procedure)

About 150 mg of respective crystals are placed in an agate mortar, and the mixing operation is carried out at room temperature for a few minutes while the dropwise addition of water (or water-ethanol (1:1) mixed solution) continues. Subsequently, respective crystals are dried at about 60 °C for 2 to 3 hours.

(Results)

The powder X-ray diffraction analysis showed that the crystals obtained in Reference Example A1 underwent a change in crystal form during the mixing operation in the presence of water or a water-ethanol (1:1) mixed solution and the same crystal form as that obtained in Example D1 increased in quantity.

The powder X-ray diffraction analysis showed that the respective crystals obtained in Example B1, Example C1 and Example D1 displayed no change in crystal form and they were physically stable in the presence of water or a water-ethanol (1:1) mixed solution.

[0074] Influence of change in temperature and humidity on

Hydrate

(Apparatus)

Rigaku X-ray DTA system: RINT-2000 manufactured by Rigaku Corporation

(Operation Method)

Crystals obtained in Example B1 (Hydrate) were ground in a mortar and then sampled on a 13-mm diameter glass plate. Measurement was carried out under the conditions below.

X-ray in use: CuKα ray

Tube voltage: 40 kV

Tube current: 200 mA

Divergent slit: 1/2 deg

Receiving slit: 0.3 mm

Scattering slit: 1/2 deg

Scanning speed: 2°/min

Scanning step: 0.01°

Scanning range (2θ): 5 to 40°

[0075] Measurement temperature was changed as follows in turn and powder X-ray diffraction patterns were measured at the respective temperatures in sequence: 30, 40, 50, 60, 70, 80, 100, 70, 60, 50, 40 and 30 °C.

(Results)

Fig. 11 shows powder X-ray diffraction patterns of Hydrate at respective temperatures above. The changes in the powder X-ray diffraction patterns revealed that the crystals of Example B1 (Hydrate) transform to the same crystals as crystals of Example E1 (Anhydrous form III) at about 60 °C or more, and return again to Hydrate when the temperature was lowered.

[0076] Measurement humidity was changed as follows in turn and powder X-ray diffraction patterns were measured at the respective humidities in sequence: 4, 5, 10, 15, 20, 50, 90, 50, 15, and 5 %RH (relative humidity).

(Results)

Fig. 12 shows powder X-ray diffraction patterns of Hydrate at respective humidities above. From changes in the powder X-ray diffraction patterns, reversible patterns of Hydrate and Anhydrous form III were observed under the humidity of more and less of about 10% RH. It is confirmed that the crystals of Example B1 (Hydrate) change to Anhydrous form III under the humidity of about 10% RH or less, and stay Hydrate under the humidity of about 10% RH or more.

[0077] These experiments about the influence of changes in temperature and humidity on Hydrate, and Example 1X revealed that the state of the precipitates before the air drying was the same crystals as those of Example E1 (Anhydrous form III) or a mixture of Anhydrous form III and Hydrate, which is a useful intermediate for the production of Hydrate.

[0078] Minimum Ignition Energy and Lower Explosion Concentration Limit

(Operation Method)

An appropriate amount of Hydrate corresponding to a concentration was uniformly put on sample dish of blown-up type dust explosion test apparatus. 50 kPa of air was compressed in a 1.3 L pressure tank, and the air was introduced into a glass cylinder by opening of a solenoid operated valve to form dust clouds. A discharge electrode was supplied with energy after 0.1 seconds after the opening of the solenoid operated valve. The criterion of ignition is an arrival of flame at an ignition mark set 100 mm above the discharge electrode.

(Measurement Conditions for Lower Explosion Concentration Limit)

Temperature of the measurement room: 24 °C

Humidity: 49%

Popping pressure of compressed air: 50 kPa

Ignition start time: 0.1 sec

Repetition of ignition test: 5 times

Ignition discharge energy: 10 J

(Measurement Conditions for Minimum Ignition Energy)

Temperature of the measurement room: 24 °C
Humidity: 49%
Popping pressure of compressed air: 50 kPa
Ignition start time: 0.1 sec
Repetition of ignition test: 10 times
(Apparatus)
Blown-up type dust explosion test apparatus (Environmental Technology Co., Ltd. DES-10)
(Results)
Lower Explosion Concentration Limit: 160-170 g/m^3
Minimum Ignition Energy: 50-100 mJ
Dust concentration: 1250 g/m^3

[0079] Chargeability

(Operation Method)

About 1 g of respective compounds is weighed into a weighing bottle (diameter of 35 mm). A stirring bar [fluoroplastic (tetrafluoroethylene resin) coating; 20 mm] is placed in the bottle and after the lid is in place, the powders are stirred for 30 minutes. The lid is opened at the same time that stirring is stopped; and the static potential of the powder is measured using a static potential measuring instrument.

(Apparatus)
STATIRON-DZ3 manufactured by Shishido Electrostatic, Ltd.
(Results)
Crystals of Reference Example A1: 70-100 V
Crystals of Example B1: 0 V

[0080] Measurement of Infrared Spectra

Infrared spectrum of the crystals obtained in Example B1 was measured under the measurement conditions described below according to the potassium bromide disk method for infrared spectrum measurement as described in General Tests in the Japanese Pharmacopoeia.

(Apparatus)

FT/IR-620 manufactured by JASCO Corporation

Measuring range: 4000-400 cm^{-1}

Resolution: 4 cm^{-1}

Integration number: 36

Scanning speed: 2 mm/sec

[0081] Fig. 1 shows an infrared spectrum of the crystals obtained in Example B1 (KBr method) and Fig. 2 shows an infrared spectrum of the crystals obtained in Example C1 (KBr method).

Table 2 shows the wavenumbers (cm^{-1}) and transmittances (%) of the absorption peaks for the crystals obtained in Example B1. Table 3 shows the wavenumbers (cm^{-1}) and transmittances (%) of the absorption peaks for the crystals obtained in Example C1.

[0082] [Table 2]

PEAK NUMBER	WAVENUMBER (cm^{-1})	%T
1	3406.64	46.3391
2	2217.74	56.7481
3	1661.37	6.6427
4	1619.91	40.6542
5	1588.09	25.9365
6	1566.88	40.1575
7	1550.49	43.7805
8	1482.03	35.2300
9	1434.78	48.9801
10	1369.21	56.9666
11	1318.11	46.9775
12	1282.43	47.1779
13	1249.65	56.0844
14	1157.08	60.4468
15	1099.23	60.6605
16	899.63	68.4385
17	879.38	62.5325
18	784.89	24.6745
19	751.14	35.0064
20	730.89	57.4603
21	697.14	39.9667
22	606.50	56.3319
23	557.33	62.4188
24	505.26	58.3988

[0083] [Table 3]

PEAK NUMBER	WAVENUMBER (cm^{-1})	%T
1	3447.13	50.2836
2	3066.26	49.6530
3	2221.59	49.7414
4	1657.52	1.0035
5	1618.95	24.2890
6	1585.20	11.2133
7	1565.92	26.5039
8	1549.52	26.7864
9	1476.24	17.5093
10	1434.78	36.9734
11	1368.25	45.1127
12	1318.11	29.2805
13	1266.04	36.7269
14	1247.72	39.2277
15	1157.08	52.6189
16	1135.87	64.5032
17	1097.30	55.2787
18	933.38	66.5017
19	896.74	61.6446
20	879.38	55.0085
21	785.85	14.4121
22	753.07	24.8345
23	729.92	54.7682
24	694.25	30.5167
25	630.61	61.1148
26	603.61	46.5267
27	556.36	62.4971
28	501.40	51.0929
29	443.55	67.0781

[0084] Measurement of Powder X-ray Diffraction Pattern

Powder X-ray diffraction patterns of the crystals obtained in the respective Examples were measured under the measurement conditions described below according to the powder X-ray diffraction measurement method as described in General Tests in the Japanese Pharmacopoeia.

(Apparatus)

Rigaku X-ray DTA system: RINT-2000 manufactured by Rigaku Corporation

(Operation Method)

A sample was ground in a mortar and then sampled on a 13-mm diameter glass plate. Measurement was carried out under the conditions below.

X-ray in use: CuKα ray

Tube voltage: 40 kV

Tube current: 200 mA

Divergent slit: 1/2 deg

Receiving slit: 0.3 mm

Scattering slit: 1/2 deg

Scanning speed: 1°/min

Scanning step: 0.01°

Scanning range (2θ): 5 to 40°

[0085] Fig. 3 shows a powder X-ray diffraction pattern of the crystals obtained in Reference Example A1, Fig. 4 shows a powder X-ray diffraction pattern of the crystals obtained in Example B1, Fig. 5 shows a powder X-ray diffraction pattern of the crystals obtained in Example C1, and Fig. 6 shows a powder X-ray diffraction pattern of the crystals obtained in Example D1.

[0086] Table 4 shows the peaks and their intensities at diffraction angles (2θ) for the crystals obtained in Reference Example A1, Table 5 shows the peaks and their intensities at diffraction angles (2θ) for the crystals obtained in Example B1, Table 6 shows the peaks and their intensities at diffraction angles (2θ) for the crystals obtained in Example C1, and Table 7 shows the peaks and their intensities at diffraction angles (2θ) for the crystals obtained in Example D1.

[0087] Based on Fig. 4 and Table 5 that represent the powder X-ray diffraction pattern of the crystals obtained in Example B1, it can be found that the powder X-ray diffraction pattern of the crystals obtained in Example B1 provides a characteristic peak having a diffraction angle (2θ) of about 12.5°.

This suggests that the crystals obtained in Reference Example A1 do not contain the same crystal form as do the crystals obtained

in Example B1, since Fig. 3 and Table 4 that represent the powder X-ray diffraction pattern of the crystals obtained in Reference Example A1 does not provide the peak having a diffraction angle (2θ) of about 12.5.

[0088] Example E1 (Anhydrous form III)

With respect to the crystals of 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one hydrate, the powder X-ray diffraction pattern was measured under the conditions similar to those described above. However, the measurement was conducted at a scanning speed of 2°/min under heating conditions in the vicinity of 110 °C.

Fig. 7 shows the powder X-ray diffraction pattern, and Table 8 shows the peaks and the intensity of diffraction angles (2θ ± 0.2°) for the crystals.

[0089] [Table 4]

PEAK NUMBER	2 θ	HALF WIDTH	d-VALUE	INTENSITY	RELATIVE INTENSITY
1	9.010	0.588	9.8067	13370	100
2	15.850	0.682	5.5867	10137	76
3	24.390	0.847	3.6465	10672	80

[0090] [Table 5]

PEAK NUMBER	2 θ	HALF WIDTH	d-VALUE	INTENSITY	RELATIVE INTENSITY
1	7.780	0.259	11.3542	16328	100
2	8.700	0.247	10.1555	5298	32
3	9.520	0.282	9.2825	11203	69
4	12.450	0.365	7.1037	4845	30
5	14.590	0.282	6.0663	2872	18
6	15.240	0.329	5.8090	7037	43
7	15.600	0.188	5.6757	2162	13
8	16.180	0.282	5.4735	2358	14
9	17.540	0.341	5.0521	6268	38
10	19.980	0.318	4.4403	3823	23
11	21.040	0.247	4.2189	2430	15
12	21.420	0.271	4.1449	2708	17
13	23.260	0.282	3.8210	3838	24
14	24.190	0.294	3.6762	12030	74
15	25.440	0.282	3.4983	5205	32
16	25.820	0.188	3.4477	2953	18
17	26.430	0.294	3.3695	4488	27
18	27.310	0.259	3.2629	2295	14
19	27.860	0.341	3.1997	3567	22
20	28.870	0.294	3.0900	2645	16

[0091] [Table 6]

PEAK NUMBER	2 θ	HALF WIDTH	d-VALUE	INTENSITY	RELATIVE INTENSITY
1	8.000	0.259	11.0424	18318	76
2	9.160	0.259	9.6465	24045	100
3	10.000	0.294	8.8380	3002	12
4	12.870	0.259	6.8728	2838	12
5	15.140	0.247	5.8471	5210	22
6	15.950	0.282	5.5519	17707	74
7	16.720	0.306	5.2979	8272	34
8	18.370	0.271	4.8256	5460	23
9	18.820	0.235	4.7113	4523	19
10	20.650	0.259	4.2977	5878	24
11	22.150	0.318	4.0099	3967	16
12	23.100	0.224	3.8471	5378	22
13	24.320	0.365	3.6568	5333	22
14	24.930	0.306	3.5687	19343	80
15	26.280	0.271	3.3884	3737	16
16	26.860	0.282	3.3165	5103	21
17	28.010	0.306	3.1829	2182	9
18	28.660	0.294	3.1122	5767	24
19	30.410	0.259	2.9369	3333	14
20	30.900	0.282	2.8915	2363	10

[0092] [Table 7]

PEAK NUMBER	2 θ	HALF WIDTH	d-VALUE	INTENSITY	RELATIVE INTENSITY
1	7.780	0.235	11.3542	20997	100
2	9.450	0.259	9.3511	7993	38
3	10.270	0.247	8.6062	6090	29
4	14.240	0.247	6.2146	3092	15
5	15.060	0.353	5.8780	6283	30
6	16.070	0.271	5.5107	16920	81
7	19.080	0.294	4.6476	7162	34
8	20.450	0.259	4.3393	3658	17
9	22.440	0.259	3.9588	3212	15
10	23.300	0.176	3.8145	5342	25
11	24.150	0.094	3.6822	7478	36
12	27.310	0.106	3.2629	4648	22

[0093] [Table 8]

PEAK NUMBER	2 θ	HALF WIDTH	d-VALUE	INTENSITY	RELATIVE INTENSITY
1	5.700	0.235	15.4919	557	8
2	7.660	0.224	11.5318	6780	100
3	8.650	0.247	10.2141	1813	27
4	9.490	0.259	9.3118	3490	51
5	11.640	0.259	7.5962	1603	24
6	12.350	0.282	7.1610	1817	27
7	13.690	0.271	6.4630	1057	16
8	14.550	0.200	6.0828	1247	18
9	15.240	0.271	5.8090	1230	18
10	15.530	0.118	5.7011	717	11
11	16.110	0.141	5.4972	650	10
12	17.590	0.306	5.0378	1237	18
13	19.940	0.141	4.4491	417	6
14	21.450	0.141	4.1392	540	8
15	22.300	0.271	3.9833	750	11
16	23.700	0.247	3.7511	2560	38
17	24.960	0.235	3.5645	1783	26
18	25.420	0.106	3.5010	1173	17
19	26.150	0.259	3.4049	720	11
20	27.030	*****	3.2960	703	10
21	28.500	0.200	3.1293	670	10

[0094] Measurement of ^{13}C Solid State NMR spectrum

^{13}C Solid State NMR spectra were measured for the crystals obtained in Examples B1, C1 and D1 under the following conditions.

Measurement temperature: room temperature (~22 °C)

Standard compound: carbonyl carbon of glycine (external standard: 176.03 ppm)

Measurement nucleus: ^{13}C (100.6248425MHz)

Pulse-repetition time:

50 sec for Examples C1 and D1

5 sec for Example B1

Pulse mode: CP/TOSS measurement

[0095] Fig. 8 shows a ^{13}C Solid State NMR spectrum of the crystals obtained in Example B1, and the chemical shifts are summarized in Table 9. Fig. 9 shows a ^{13}C Solid State NMR spectrum of the crystals obtained in Example D1, and the chemical

shifts are summarized in Table 10. Fig. 10 shows a ^{13}C Solid State NMR spectrum of the crystals obtained in Example C1, and the chemical shifts are summarized in Table 11.

[0096] [Table 9]

Chemical Shift(ppm)	Chemical Shift(ppm)
159.8	127.8
150.8	126.5
146.7	125.8
139.4	123.3
136.6	120.8
134.9	118.4
132.7	114.6
129.0	108.8

[0097] [Table 10]

Chemical Shift(ppm)	Chemical Shift(ppm)
160.0	129.5
152.8	128.2
152.0	127.0
149.0	125.6
140.5	120.3
137.0	118.2
134.7	114.6
133.4	108.2
131.0	

[0098] [Table 11]

Chemical Shift(ppm)	Chemical Shift(ppm)
159.7	128.2
151.2	127.3
145.9	126.8
139.9	125.8
137.7	121.1
134.9	120.6
132.8	119.1
131.7	114.2
130.1	109.4
129.0	

Industrial Applicability

[0099] The crystal forms of the invention have preferable properties and are suitable for use as an active ingredient of therapeutic or prophylactic agents for neurodegenerative diseases or the like.

Claims

1. A crystal of 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one hydrate having a diffraction peak at a diffraction angle (2θ ± 0.2°) of 8.7° in a powder X-ray diffraction.

2. A crystal of 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one hydrate having a diffraction peak at a diffraction angle (2θ ± 0.2°) of 12.5° in a powder X-ray diffraction.

3. A crystal of 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one hydrate having diffraction peaks at diffraction angles (2θ ± 0.2°) of 8.7° and 12.5°in a powder X-ray diffraction.

4. A crystal of 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one hydrate having an absorption peak at a wavenumber of 1588 ± 1 cm^{-1} in an infrared absorption spectrum (KBr method).

5. A crystal of 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one hydrate having absorption peaks at wavenumbers of 1588 ± 1 cm^{-1} and 751 ± 1 cm^{-1} in an infrared absorption spectrum (KBr method).

6. A crystal of 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one hydrate having peaks at chemical shifts of around 146.7 ppm and around 123.3 ppm in a ^{13}C Solid State Nuclear Magnetic Resonance spectrum.

7. A process for producing a crystal of 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one hydrate according to any of claims 1 to 6, the process comprising the step of crystallizing 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one with an aid of one or two crystallization solvents selected from the group consisting of an alcoholic solvent, an alkylketone solvent, and water.

8. The process according to claim 7, wherein the crystallization solvent is a mixed solvent of acetone and water.

9. The process according to claim 7, wherein the crystallization solvent is a mixed solvent of acetone and water with a

volume ratio of 37:3 to 24:16.

10. The process according to any of claims 7 to 9, wherein the crystallization is carried out at a temperature of 60 to –30 °C.

11. The process according to any of claims 7 to 9 comprising the steps of heating a solution of 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one dissolved in the crystallization solvent at a temperature of 50 °C or more and thereafter cooling the solution to a temperature of 10 to -20 °C at a cooling rate of 40 to 5 °C per hour.

12. The process according to any of claims 7 to 11, wherein the crystallization solvent is used in a volume ratio of 10- to 50-fold (v/w) based on the weight of 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one.

13. The process according to any of claims 7 to 12, wherein seed crystals are added at 60 °C or less.

14. The process according to any of claims 7 to 13, wherein the crystals are dried under reduced pressure after the crystallization.

15. The process according to any of claims 7 to 14, wherein the crystals are allowed to stand in the atmosphere after the crystallization and the drying under reduced pressure.

16. An anhydrous crystal of 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one having a diffraction peak at a diffraction angle (2θ ± 0.2°) of 10.3° in a powder X-ray diffraction.

17. The crystal according to claim 16 further having a diffraction peak at a diffraction angle (2θ ± 0.2°) of 19.1° in a powder X-ray diffraction.

18. An anhydrous crystal of 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one having peaks at chemical shifts of around 149.0 ppm and around 125.6 ppm in a ^{13}C Solid State Nuclear Magnetic Resonance spectrum.

19. An anhydrous crystal of 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one having a diffraction peak at a diffraction angle (2θ ± 0.2°) of 16.7° in a powder X-ray diffraction.

20. The crystal according to claim 19 further having diffraction peaks at diffraction angles (2θ ± 0.2°) of 12.9° and 24.9° in a powder X-ray diffraction.

21. An anhydrous crystal of 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one having an absorption peak at a wavenumber of 1658 ± 1 cm^{-1} in an infrared absorption spectrum (KBr method).

22. The crystal according to claim 21 further having an absorption peak at a wavenumber of 501 ± 1 cm^{-1} in an infrared absorption spectrum (KBr method).

23. An anhydrous crystal of 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one having peaks at chemical shifts of around 145.9 ppm and around 137.7 ppm in a ^{13}C Solid State Nuclear Magnetic Resonance spectrum.

24. An anhydrous crystal of 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridin-2-one having diffraction peaks at diffraction angles (2θ ± 0.2°) of 23.7° and 25.0° in a powder X-ray diffraction.

25. The crystal according to claim 24 further having diffraction peaks at diffraction angles (2θ ± 0.2°) of 5.7° and 9.5° in a powder X-ray diffraction.