[0004] It is disclosed in Patent Document 2 that crude crystal of the compound A can be obtained by reacting 2-aminomalonamide with triethyl orthoformate in the presence of sulfuric acid. However, this production method has disadvantageous in that a large amount of triethyl orthoformate is required and also a large amount of activated charcoal is required. Thus, it is difficult to say that the production method is indeed an industrially favorable production method. It is also described in Patent Document 2 that, by reacting crude crystal of the compound A with an acid and neutralizing it with ammonia, the compound A can be obtained. However, there is no concrete description regarding the stability.

[0005] For formulation production of the compound A, it is known that coloration with blue color can be prevented by containing an acidic material (see, Patent Document 3, for example). It is described in Patent Document 3 that "the present compound has a property of exhibiting color either by itself or caused by oxygen, heat, or light, and in a case in which the present compound is applied as an oral agent, for example, a tendency of showing more significant coloration based on more complex reaction pathways resulting from an interaction with co-existing excipients is observed."

Patent Document

[0006] Patent Document 1: International Publication No. 2009/035168

Patent Document 2: Japanese Patent Application Laid-Open (JP-A) No. 58-24569

Patent Document 3: JP-A No. 60-185727

Non-Patent Document

[0007] Non-Patent Document 1: Journal of American Chemical Society (J. Am. Chem. Soc.), vol. 74, pages 2892 to 2894, 1952.

SUMMARY ~~OF INVENTION~~

Technical Problem

[0008] Until now, it is believed that the compound A has a problem in terms of storage stability due to coloration with blue color. It is also believed that, to obtain the compound A having excellent storage stability, the followings are required: (1) producing an acid salt of the compound A, (2) having co-presence of an acidic material, or (3) containing a trace amount of an acidic material. Further, the compound A having excellent storage stability without using additives in combination is hardly known until now. Meanwhile, the original compound used for medicines is strongly required to be a single compound with stability instead of a mixture.

[0009] An object of the ~~invention~~ present disclosure is to provide crystal of the compound A which is excellent in storage stability. Another object of the ~~invention~~ present disclosure is to provide crystal of the compound A

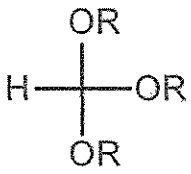
having little impurities, having a small color difference between the crystal before storage and the crystal after storage, and excellent in storage stability, and a method for producing the same.

Solution to Problem

[0010] Under the circumstances, the inventors of the present ~~invention~~ disclosure conducted intensive studies, and as a result, found the following [1] to [24]. The ~~invention~~ present disclosure was completed accordingly.

In one aspect, there is provided a method for producing 5-hydroxy-1H-imidazole-4-carboxamide·3/4 hydrate, comprising:

reacting 2-aminomalonamide with a compound represented by the following formula [1] in the presence of a carboxylic acid to obtain 5-hydroxy-1H-imidazole-4-carboxamide:



[1]

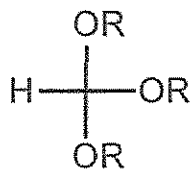
wherein, in formula [1], each R independently represents a C_{1-3} alkyl group;

reacting the resulting 5-hydroxy-1H-imidazole-4-carboxamide with an acidic compound to obtain a 5-hydroxy-1H-imidazole-4-carboxamide acid salt or a hydrate thereof; and

reacting the resulting 5-hydroxy-1H-imidazole-4-carboxamide acid salt or hydrate thereof with a salt in the presence of an acidic solvent to obtain the 5-hydroxy-1H-imidazole-4-carboxamide·3/4 hydrate.

In another aspect, there is provided a method for producing 5-hydroxy-1H-imidazole-4-carboxamide·3/4 hydrate, comprising:

reacting 2-aminomalonamide with a compound represented by the following formula [1] in the absence of mineral acid and in the absence of sulfonic acid to obtain 5-hydroxy-1H-imidazole-4-carboxamide:



[1]

wherein, in formula [1], each R independently represents a C_{1-3} alkyl group;

reacting the resulting 5-hydroxy-1H-imidazole-4-carboxamide with an acidic compound to obtain a 5-hydroxy-1H-imidazole-4-carboxamide acid salt or a hydrate thereof;

and

reacting the resulting 5-hydroxy-1H-imidazole-4-carboxamide acid salt or hydrate thereof with a salt in the presence of an acidic solvent to obtain the 5-hydroxy-1H-imidazole-4-carboxamide·3/4 hydrate.

In yet another aspect, there is provided a crystal of 5-hydroxy-1H-imidazole-4-carboxamide·3/4 hydrate having an acidic compound content of 0.1% by mass or less, wherein, in a case in which the crystal is stored in conditions of a temperature of 40°C and a relative humidity of 75% for 2 weeks, the crystal exhibits a color difference (ΔE) of 6 or less between before the storage and after the storage.

In yet another aspect, there is provided 5-hydroxy-1H-imidazole-4-carboxamide·3/4 hydrate obtained by the production method as disclosed herein.

In yet another aspect, there is provided a crystal of 5-hydroxy-1H-imidazole-4-carboxamide·3/4 hydrate which is obtained by the production method as disclosed herein and has an acidic compound content of 0.1% by mass or less, wherein, in a case in which the crystal is stored in conditions of a temperature of 40°C and a relative humidity of 75% for 2 weeks, the crystal exhibits a color difference (ΔE) of 6 or less between before the storage and after the storage.

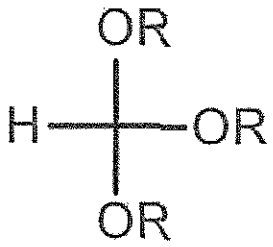
In yet another aspect, there is provided a crystal of 5-hydroxy-1H-imidazole-4-carboxamide hydrate, wherein the crystal has diffraction peaks at diffraction angles of 8.1, 12.6, 17.1, 19.3, 20.3 and 21.6°, represented by 2θ in a powder X-ray diffraction pattern.

In yet another aspect, there is provided a pharmaceutical composition containing a crystal of 5-hydroxy-1H-imidazole-4-carboxamide hydrate, wherein the crystal has diffraction peaks at diffraction angles of 8.1, 12.6, 17.1, 19.3, 20.3 and 21.6°, represented by 2θ in a powder X-ray diffraction pattern.

Specific means for solving the problem is as follows.

[0011] [1] A method for producing a hydrate of the compound A including reacting 2-aminomalonamide with a compound represented by the following formula [1] in the presence of a carboxylic acid to obtain the compound A,

[0012]

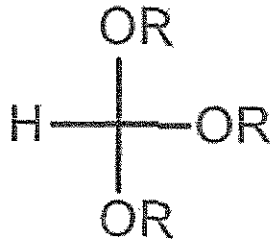


[1]

[0013] (in formula [1], each R independently represents a C_{1-3} alkyl group), reacting the resulting compound A with an acidic compound to obtain an acid salt of the compound A or a hydrate thereof, and reacting the resulting acid salt of the compound A or the hydrate thereof with a salt in the presence of an acidic solvent to obtain a hydrate of the compound A.

[0014] [2] A method for producing a hydrate of the compound A including reacting 2-aminomalonamide with a compound represented by the following formula [1] in the absence of mineral acid and in the absence of sulfonic acid to obtain the compound A,

[0015]



[1]

[0016] (in the formula, each R independently represents a C_{1-3} alkyl group), reacting the resulting compound A with an acidic compound to obtain an acid salt of the compound A or a hydrate thereof, and reacting the resulting acid salt of the compound A or

[0030] [16] The crystal of the hydrate of the compound A according to [14], wherein the color difference (ΔE) is 3 or less and the acidic compound content is 0.05% by mass or less.

[0031] [17] The crystal of the hydrate of the compound A according to any one of [14] to [16], wherein the crystal is colorless, pale yellow or yellow before the crystal is stored in conditions of a temperature of 40°C and a relative humidity of 75% for 2 weeks.

[0032] [18] The crystal of the hydrate of the compound A according to any one of [14] to [16], wherein the crystal is colorless, or has a hue (H) in the Munsell color system of from 1Y to 6Y before the crystal is stored in conditions of a temperature of 40°C and a relative humidity of 75% for 2 weeks.

[0033] [19] A hydrate of the compound A obtained by the production method according to any one of [1] to [13].

[0034] [20] A crystal of the hydrate of the compound A which is obtained by the production method according to any one of [1] to [13], and has an acidic compound content of 0.1% by mass or less, wherein, in a case in which the crystal is stored in conditions of a temperature of 40°C and a relative humidity of 75% for 2 weeks, the crystal exhibits a color difference (ΔE) of 6 or less between before the storage and after the storage.

[0035] [21] The crystal of the hydrate of the compound A according to [20], wherein the color difference (ΔE) is 3 or less.

[0036] [22] The crystal of the hydrate of the compound A according to [20], wherein the color difference (ΔE) is 3 or less and the acidic compound content is 0.05% by mass or less.

[0037] [23] A crystal (hereinbelow, also referred to as "β type crystal") of a hydrate of the compound A, wherein the crystal has diffraction peaks at diffraction angles of 8.1, 12.6, 17.1, 19.3, 20.3 and 21.6°, represented by 2θ in a powder X-ray diffraction pattern.

[0038] [24] A pharmaceutical composition containing a crystal of a hydrate of the compound A, wherein the crystal has diffraction peaks at diffraction angles of 8.1, 12.6, 17.1, 19.3, 20.3 and 21.6°, represented by 2θ in a powder X-ray diffraction pattern.

Advantageous Effects of Invention

[0039] According to the present ~~invention~~disclosure, crystal of the compound A having an excellent storage stability can be provided. According to the present ~~invention~~disclosure, crystal of the compound A having little impurities, having a small color difference between the crystal before storage and the crystal after storage, and having an excellent storage stability and a method for producing the same can be further provided.