Description

This invention relates to a process for purification of 1,2-bis(nicotinamido)propane which has been known to have a therapeutic effect on blood and blood vessel disorders such as arteriosclerosis or thrombosis through 1,2-bis(nicotinamido)propane dinitrate.

A process for purifying crude 1,2-bis(nicotinamido)propane by forming 1,2-bis(nicotinamido)propane oxalate and dissociating free 1,2-bis(nicotinamido)propane from the oxalate in an aqueous solution of potassium carbonate is known from JP-A-56-75474. The thus-formed free 1,2-bis(nicotinamido)propane is then crystallized, and recrystallized or purified with the use of silica gel column chromatography .

However, this purification process through the oxalate salt of 1,2-bis(nicotinamido)propane as described above has a problem in that the oxalate salt is very difficult to be recrystallized, and, thus, the desired 1,2-bis(nicotinamido)propane can only be obtained with a low purity, since free 1,2-bis(nicotinamido)propane is obtained from a mixture containing various impurities such as nicotinic acid, N-(2-ethoxycarbonylamino)-propylnicotinamide and N-(2-ethoxycarbonylamino-1-methyl)ethyl-nicotinamide. The desired product thus obtained generally contains such impurities at a proportion of 0.4 to 1.0% (ratio of area) as determined in the high performance liquid chromatography (HPLC). Further, it is very difficult to completely remove the impurities by recrystallization of 1,2-bis(nicotinamido)propane, and the recrystallized product generally contains such impurities at a proportion of 0.1 to 0.3 (ratio of area) as determined by HPLC. It is therefore necessary to subject the product to further purification by silica gel chromatography, but such a purification procedure is disadvantageous from the standpoint of production cost and operation in the production of a large quantity of 1,2-bis(nicotinamido)propane.

An object of the present invention is therefore to provide an efficient process for purification of 1,2-bis-(nicotinamido)propane through the dinitrate salt thereof.

The above object of the present invention can be attained by a process for purifying crude 1,2-bis-(nicotinamido)propane obtained by the reaction of nicotinic acid with 1,2-propanediamine, which comprises forming 1,2-bis(nicotinamido)propane dinitrate from the crude 1,2-bis(nicotinamido)propane, suspending the dinitrate salt in an organic solvent, extracting the free 1,2-bis(nicotinamido)propane dissociated by adding an alkali or a solution of alkali to the suspension with a solvent, and removing the solvent from the extract.

According to the present invention, 1,2-bis(nicotinamido)propane can be obtained by suspending nicotinic acid in an inert organic solvent and reacting nicotinic acid with an organic base and a condensing agent, and further with 1,2-propanediamine. The solvent is then removed from the resulting reaction solution to obtain crude 1,2-bis(nicotinamido)propane. The crude product is then reacted with a lower alcohol such as methanol and nitric acid to produce 1,2-bis(nicotinamido)propane dinitrate, and the resulting dinitrate salt is recrystallized from a mixture of water and a lower alcohol. The 1,2-bis(nicotinamido)propane dinitrate thus obtained was suspended in an organic solvent, and an alkali or a solution of alkali is added to the suspension. The organic layer containing the dissociated 1,2-bis(nicotinamido)propane was separated, the solvent is distilled off under reduced pressure, and the product is crystallized from a solvent and then purified by recrystallization to obtain 1,2-bis(nicotinamido)propane having a high purity.

Preferred examples of the organic solvent used for suspending nicotinic acid include methylene chloride, acetonitrile, acetone, ethyl acetate and tetrahydrofuran and methylene chloride and ethyl acetate are particularly preferred.

Preferred examples of the organic base include triethylamine, N-methylmorpholine and N-methyl-piperidine with triethylamine being particularly preferred. The organic base can be generally used in an amount of from 1 to 3 mols per mol of nicotinic acid.

Preferred examples of the condensing agent include a chloride of carbonic acid ester such as ethyl chlorocarbonate and isobutyl chlorocarbonate, a chloride of carboxylic acid such as pivalic acid chloride, an organophosphoric acid chloride and an organosulfonic acid chloride with ethyl chlorocarbonate being particularly preferred. The condensing agent can be generally used in an amount of from 1 to 1.5 mols per mol of nicotinic acid.

The reaction between nicotinic acid and the condensing agent can be carried out in an inert organic solvent in the presence of the organic base at a temperature of from -20 °C to 40 °C, preferably from -10 °C to 30 °C, for a period of from 10 to 60 minutes, preferably from 20 to 30 minutes.

To the resulting reaction solution was then added 1,2-propanediamine in an amount of from 0.45 to 0.6 mol per mol of nicotinic acid, and the mixture is reacted at a temperature of from -20 °C to 40 °C, preferably from -10 °C to 35 °C, for a period of from 30 to 60 minutes, preferably 60 minutes. Then, a lower alcohol, e.g., methanol, was added to the reaction mixture containing the produced 1,2-bis(nicotinamido)-propane or, preferably, to the reaction mixture from which the solvent has been distilled off as completely as possible, and further nitric acid is added to the mixture in an amount of from 0.7 to 2 mols, preferably

from 1.0 to 1.9 mol, per mol of nicotinic acid, and the resulting mixture was allowed to stand at a temperature of from -20 °C to 20 °C, preferably at -10 °C, for a period of from 1 to 5 hours, preferably for 5 hours, to precipitate crystals thereby obtaining 1,2-bis(nicotinamido)propane dinitrate. The thus-obtained dinitrate salt can be recrystallized from a mixed solvent of water and a lower alcohol, e.g., methanol, ethanol or propanol, preferably methanol. The resulting dinitrate salt is a novel compound which has not been disclosed in literature references.

Preferred examples of the organic solvent for suspending the dinitrate salt include methylene chloride, ethyl acetate, and a lower alcohol, e.g., methanol, ethanol or propanol.

Examples of an alkali or a solution of alkali include an inorganic base such as sodium carbonate, potassium carbonate, sodium hydroxide and potassium hydroxide with an aqueous solution of sodium hydroxide being preferred.

Examples of the organic solvent used for recrystallization of 1,2-bis(nicotinamido)propane include acetone, a mixed solvent of acetone and ethanol, or toluene, with the mixed solvent of acetone and ethanol being preferred.

Thus, according to the process as described above, 1,2-bis(nicotinamido)propane having a high purity can be obtained.

The process for purification of 1,2-bis(nicotinamido)propane according to the present invention overcomes the disadvantages of the conventional purification process through 1,2-bis(nicotinamido)propane oxalate and using silica gel column chromatography, and is an excellent and efficient purification process for 1,2-bis(nicotinamido)propane having the following advantages.

(1) 1,2-Bis(nicotinamido)propane oxalate is very difficult to be recrystallized, whereas 1,2-bis-(nicotinamido)propane dinitrate can be easily recrystallized from a solvent system of water and a lower alcohol whereby contamination with impurities can be prevented, as proved by a single peak observed in HPLC of the product.

(2) In removal of the salt formed after dissociation of free 1,2-bis(nicotinamido)propane, the conventional process using 1,2-bis(nicotinamido)propane oxalate should involve removal of potassium oxalate and then extraction of the free compound, whereas, in the process according to the present invention, substantially whole amount of the dinitrate salt is dissolved in an aqueous layer and thus a time-consuming purification procedure can be eliminated.

(3) The conventional process requires a purification step using silica gel chromatography which is apparently disadvantageous from the standpoint of production cost and operation, whereas the present invention does not require such a step and therefore is very efficient.

The present invention is further illustrated in greater detail by the following examples, but the present invention is not to be construed as being limited thereto.

Example 1 Preparation of 1,2-Bis(nicotinamido)propane Dinitrate

10.7 g (0.087 mol) of nicotinic acid was suspended in 140 ml of methylene chloride, and 9.2 g (0.091 mol) of triethylamine and 9.9 g (0.091 mol) of ethyl chlorocarbonate were added to the suspension. The resulting mixture was reacted for 30 minutes at -10 °C to produce a mixed acid anhydrides. Then, 3.2 g (0.043 mol) of 1,2-propanediamine was added thereto, and the mixture was reacted for 60 minutes at 30 °C. Thereafter, 15.5 g (0.148 mol) of a 60% aqueous nitric acid solution and 7 ml of purified water were added to the reaction mixture, and the aqueous layer was separated. 130 ml of methanol was added to the aqueous layer, and the resulting methanolic solution was allowed to stand for 5 hours at -10 °C to precipitate crystals. The crystals were filtered and recrystallized from a mixed solvent of 10 ml of water and 100 ml of methanol to obtain 9.4 g (0.023 mol) of 1,2-bis(nicotinamido)propane dinitrate having a melting point of 189.5 °C.

Elementary Analysis for $C_{15}H_{18}N_6O_8$:			
Calc'd(%)	C, 43.91;	H, 4.42;	N, 20.48
Found (%)	C, 44.03;	H, 4.44;	N, 20.26

$IR\nu_{max}^{KBr}$ cm^{-1}:

3300 (N-H), 1650 (C=0), 1350, 830 (NO_3^-)

Example 2 Preparation of 1,2-Bis(nicotinamido)propane Dinitrate

10.7 g (0.087 mol) of nicotinic acid was suspended in 140 ml of ethyl acetate, and 9.2 g (0.091 mol) of triethylamine and 9.9 g (0.091 mol) of ethyl chlorocarbonate were added to the suspension. The resulting mixture was reacted for 30 minutes at -10 °C to produce a mixed acid anhydrides. Then, 3.2 g (0.043 mol) of 1,2-propanediamine was added thereto, and the mixture was reacted for 60 minutes at 30 °C. Thereafter, 15.5 g (0.148 mol) of a 60% aqueous nitric acid solution and 7 ml of purified water were added to the reaction mixture, and the aqueous layer was separated. 130 ml of methanol was added to the aqueous layer, and the resulting methanolic solution was allowed to stand for 5 hours at -10 °C to precipitate crystals. The crystals were filtered and recrystallized from a mixed solvent of 10 ml of water and 100 ml of methanol to obtain 9.4 g (0.023 mol) of 1,2-bis(nicotinamido)propane dinitrate. The melting point, elementary analysis values and infrared absorption spectrum of the resulting product were found to be substantially identical to those of the product obtained in Example 1.

Example 3 Preparation of 1,2-Bis(nicotinamido)propane

28.7 g (0.070 mol) of 1,2-bis(nicotinamido)propane dinitrate obtained in Example 1 or 2 was suspended in 165 ml of methylene chloride, and 30 ml of a 5N aqueous sodium carbonate solution was added to the suspension. The methylene chloride layer containing the dissociated 1,2-bis(nicotinamido)propane was separated, and the solvent was distilled off under reduced pressure. Then, 60 ml of acetone was added to the residue to crystallize the product which was then separated by filtration and recrystallized from a mixed solvent of 24 ml of ethanol and 80 ml of acetone to obtain 11.6 g (0.041) mol of 1,2-bis(nicotinamido)-propane having a melting point of 156 - 157 °C.

Elementary Analysis for $C_{15}H_{16}N_4O_2$:			
Calc'd(%)	C, 63.4;	H, 5.7;	N, 19.7
Found (%)	C, 63.2;	H, 5.9;	N, 19.5

$IR\nu_{max}^{KBr}$ cm^{-1}:

3280 (N-H), 1660 (C=O),

Example 4 Preparation of 1,2-Bis(nicotinamido)propane

28.7 g (0.070 mol) of 1,2-bis(nicotinamido)propane dinitrate obtained in Example 1 or 2 was suspended in 165 ml of ethyl acetate, and 30 ml of a 20% aqueous sodium hydroxide solution and 33 ml of n-propanol were added to the suspension. The ethyl acetate layer containing the dissociated 1,2-bis(nicotinamido)-propane was separated, and the solvent was distilled off under reduced pressure. Then, 60 ml of acetone was added to the residue to crystallize the product which was then separated by filtration and recrystallized from a mixed solvent of 24 ml of ethanol and 80 ml of acetone to obtain 11.6 g (0.041 mol) of 1,2-bis-(nicotinamido)propane. The melting point, elementary analysis values and infrared absorption spectrum of the resulting product were found to be substantially identical to those of the product obtained in Example 3.

Example 5 Preparation of 1,2-Bis(nicotinamido)propane

28.7 g (0.070 mol) of 1,2-bis(nicotinamido)propane dinitrate was suspended in 60 ml of ethanol, and 9.2 g of potassium hydroxide was added to the suspension. The resulting ethanol layer containing the dissociated free 1,2-bis(nicotinamido)propane was separated, and the precipitated potassium nitrate was removed by filtration. After distilling off the solvent under reduced pressure, 60 ml of acetone was added to the residue to crystallize the product which was then separated by filtration and recrystallized from a mixed solvent of 24 ml of ethanol and 80 ml of acetone to obtain 11.6 g (0.041 mol) of 1,2-bis(nicotinamido)-propane. The melting point, elementary analysis values and infrared absorption spectrum of the resulting product were found to be substantially identical to those of the product obtained in Example 3.

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Claims

1. A process for purifying crude 1,2-bis(nicotinamido)propane obtained by the reaction of nicotinic acid with 1,2-propanediamine, which comprises forming 1,2-bis(nicotinamido)propane dinitrate from the crude 1,2-bis(nicotinamido)propane, suspending the dinitrate salt in an organic solvent, extracting the free 1,2-bis(nicotinamido)propane dissociated by adding an alkali or a solution of alkali to the suspension with a solvent, removing the solvent from the extract, and purifying the thus-obtained 1,2-bis(nicotinamido)propane.

2. A process as claimed in Claim 1, wherein said organic solvent for suspending the dinitrate salt is methylene chloride, ethyl acetate or a lower alcohol.

3. A process as claimed in Claim 1, wherein said alkali or the solution of alkali is sodium carbonate, potassium carbonate, sodium hydroxide or potassium hydroxide, or an aqueous solution thereof.

4. A process as claimed in Claim 1, wherein said purification is carried out by recrystallization from acetone, toluene or a mixed solvent of acetone and ethanol.

5. 1,2-Bis(nicotinamido)propane dinitrate.

6. Process for producing 1,2-bis(nicotinamido)propane dinitrate according to claim 5 by reacting crude 1,2-bis(nicotinamido)propane with a lower alcohol and nitric acid and recrystallizing the resulting dinitrate salt.

Patentansprüche

1. Reinigungsverfahren für rohes, durch Umsetzung von Nicotinsäure mit 1,2-Propandiamin erhaltenes 1,2-Bis(nicotinamido)propan, das die Bildung von 1,2-Bis(nicotinamido)propandinitrat aus dem rohen 1,2-Bis(nicotinamido)propan, Suspendieren des Dinitratsalzes in einem organischen Lösungsmittel, Extrahieren des freien 1,2-Bis(nicotinamido)propan, das durch Zugabe von einem Alkali oder einer Alkalilösung zur Suspension in einem organischen Lösungsmittel dissoziiert wurde, Entfernen des Lösungsmittels aus dem Extrakt und Reinigung des so erhaltenen 1,2-Bis(nicotinamido)propans umfaßt.

2. Verfahren gemäß Anspruch 1, bei dem das organische Lösungsmittel zur Suspension des Dinitratsalzes Methylenchlorid, Essigsäureethylester oder ein niederer Alkohol ist.

3. Verfahren gemäß Anspruch 1, bei dem das Alkali oder die Alkalilösung Natriumcarbonat, Kaliumcarbonat, Natriumhydroxid oder Kaliumhydroxid oder eine wäßrige Lösung davon ist.

4. Verfahren gemäß Anspruch 1, bei dem die Reinigung durch Umkristallisieren aus Aceton, Toluol oder einem Lösungsmittelgemisch aus Aceton und Ethanol erfolgt.

5. 1,2-Bis(nicotinamido)propandinitrat.

6. Verfahren zur Herstellung von 1,2-Bis(nicotinamido)propandinitrat gemäß Anspruch 5 durch Umsetzen von rohem 1,2-Bis(nicotinamido)propan mit einem niederen Alkohol und Salpetersäure und Umkristallisation des entstandenen Salzes.

Revendications

1. Procédé de purification du 1,2-bis(nicotinamide)propane brut obtenu par la réaction de l'acide nicotinique avec la 1,2-propanediamine, qui comprend la formation du dinitrate de 1,2-bis(nicotinamide)-propane à partir du 1,2-bis(nicotinamide)propane brut, la mise en suspension du dinitrate dans un solvant organique, l'extraction du 1,2-bis(nicotinamide) propane libre, dissocié par addition d'un alcali ou d'une solution alcaline à la suspension avec un solvant, l'élimination du solvant de l'extrait, et la purification du 1,2-bis(nicotinamide)propane ainsi obtenu.

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2. Procédé suivant la revendication 1, dans lequel ledit solvant organique pour la mise en suspension du dinitrate est le chlorure de méthylène, l'acétate d'éthyle ou un alcool inférieur.

3. Procédé suivant la revendication 1, dans lequel ledit alcali ou ladite solution alcaline est le carbonate de sodium, le carbonate de potassium, l'hydroxyde de sodium ou l'hydroxyde de potassium, ou une solution aqueuse de ceux-ci.

4. Procédé suivant la revendication 1, dans lequel ladite purification est effectuée par recristallisation dans l'acétone, le toluène ou un mélange de solvant d'acétone et d'éthanol.

5. Dinitrate de 1,2-bis(nicotinamide)propane.

6. Procédé de production du dinitrate de 1,2-bis(nicotinamide)propane conformément à la revendication 5, par réaction du 1,2-bis(nicotinamide)propane brut avec un alcool inférieur et l'acide nitrique et la recristallisation du dinitrate résultant.