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## Īsziņas

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⑤④ Virsraksts: **Kristalisks mononātrijs 4-amino-1-hidroksibutilidīn-1,1-difosfāta trihidrāts**

⑤⑦ Kopsavilkums: Pieteikta jauna viela 4-amino-1-hidroksibutilidīn-1,1-difosfāta trihidrāts, ko var izmantot kā farmaceitisko līdzekli. Aprakstīts paņēmieni šīs vielas iegūšanai, izmantojot 4-aminofosforskābes reakciju ar fosforskābes un  $PCl_3$  maisījumu un reakcijas maisījuma hidrolīzi ar nātrijs sārmu.

\* pieteikums pieņemts ievērojot LR Patentu likuma Pārejas noteikumu 1. punktu  
(Eiropas pat publ. Nr. 0402152, reģistrācijas diena 02.11.1995  
Eiropas pat. piet. Nr. 90306236.8, iesniegšanas datums 08.06.1990)

### Izgudrojuma formula

1. Kristalisks mononātrijs 4-amino-1-hidroksibutilidīn-1,1-difosfāta trihidrāts.
2. Savienojums pēc 1. punkta birstoša pulvera veidā.
3. Savienojums pēc 1. vai 2. punkta, kas paredzēts pielietojumam farmaceutiskās kompozīcijās.
4. Farmaceutiskā kompozīcija, kas satur savienojumu pēc 1. vai 2. punkta.
5. Paņēmiens savienojuma pēc 1. vai 2. punkta iegūšanai, kas **atšķiras** ar to, ka tas paredz:
  - (a) 4-aminosviestskābes apstrādāšanu ar fosforskābes un  $\text{PCl}_3$  maisījumu metānsulfoskābes klātbūtnē pie temperatūras, zemākas par  $85\text{ }^\circ\text{C}$ ;
  - (b) apstrādi ar ūdeni;
  - (c) nātrija hidroksīda pievienošanu līdz vides pH 4,3 pie temperatūras  $20 \div 25\text{ }^\circ\text{C}$ ;
  - (d) atdzesēšanu līdz temperatūrai  $0 \div 5\text{ }^\circ\text{C}$ ;
  - (e) vajadzīgā produkta atdalīšanu filtrējot, mazgāšanu ar ūdeni un 95 % etanolu un žāvēšanu gaisā.
6. Paņēmiens pēc 5. punkta, kas **atšķiras** ar to, ka posmu (a) veic bez šķīdinātāja.
7. Paņēmiens pēc 5. vai 6. punkta, kas **atšķiras** ar to, ka posmu (a) veic pie apmēram  $65\text{ }^\circ\text{C}$  un posmu (e) pie  $40\text{ }^\circ\text{C}$ .
8. Paņēmiens pēc jebkura no 5. - 7. punktam, kas **atšķiras** ar to, ka uz molu 4-aminosviestskābes ņem 1,5 molus  $\text{H}_3\text{PO}_4$  un 2,4 molus  $\text{PCl}_3$ .
9. Paņēmiens pēc jebkura no 5. - 8. punktam, kas **atšķiras** ar to, ka posmā (c) izmanto 50 % nātrija hidroksīdu.
10. Paņēmiens pēc jebkura no 5. - 9. punktam, kas **atšķiras** ar to, ka posmā (b) iegūto šķīdumu iztur pie  $95 \div 100\text{ }^\circ\text{C}$  pirms apstrādes posmā (c).

## Description

This invention relates to crystalline 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt trihydrate and a process therefor, where the end product is obtained in particularly pure form and at high yields in a one-pot procedure, and compositions containing said salt and its use in their manufacture.

GB-A-2166741 discloses the preparation of 4-amino-1-hydroxybutylidene-1,1-diphosphonic acid and described its potentiometric titration in solution. EP-A-0039033 discloses a process for the preparation of omega amino-1-hydroxyalkylidene-1-bisphosphonic acids but did not describe any salt of 4-amino-1-hydroxybutylidene-1,1-diphosphonic acid. Analytical methods for the determination of 4-amino-1-hydroxybutylidene-1,1-diphosphonic acid monosodium salt were described before 9 June 1989.

It is known according to U.S. Patent 4,407,761 to prepare 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid by reacting an aminocarboxylic acid with a phosphonating reactant and then hydrolyzing the reaction mixture by addition of concentrated hydrochloric acid with heating. Problems result from this reaction whereby it does not remain homogeneous and local solidification occurs. This solidification causes variable yields, which in part results from the exothermic nature of the reactions with development of hot spots.

Our new process allows the reaction to remain fluid and homogeneous and makes manufacturing of crystalline 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt trihydrate possible. It also has the advantage of requiring only one process step and provides a yield of 85-90%.

It has been found that pure crystalline 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt trihydrate can surprisingly be obtained (in high yields) by the reaction of 4-aminobutyric acid with phosphonating reactants in the presence of methanesulfonic acid at a temperature of less than 85 °C to yield a reaction mixture containing 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid; the crystalline monosodium salt trihydrate is crystallized directly from the reaction mixture in about 90% yield after quenching, hydrolysis, and pH adjustment to about 4.3 with no further purification necessary.

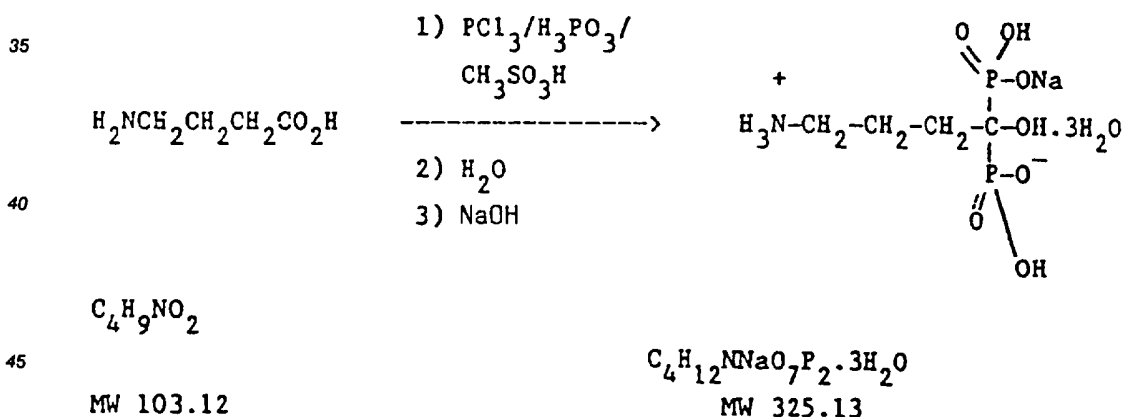
The phosphorylation reaction generally takes place at temperatures of about 65 °C.

Preferably 1 to 2, particularly 1.5 moles of  $H_3PO_3$  and 1 to 2.5, particularly 2.4 mols of  $PCl_3$  are used per mol of aminobutyric acid.

It is not necessary to use a diluent when methanesulfonic acid is used in the reaction.

In general, the hydrolysis is completed after about 3 hours boiling under reflux, as is shown by the chromatographic test of the reaction solution.

The reaction is schematically represented as follows:



Crystalline 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt trihydrate described here is useful as a pharmaceutical composition and for the treatment or prevention of diseases involving bone resorption. Such diseases as hypercalcemia of malignancy, Paget's disease, and osteoporosis are advantageously treated with crystalline 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt trihydrate made according to the process of the present invention.

The following examples are illustrative of the practice of the invention without being limiting in any way.

## EXAMPLE 1

### Preparation of crystalline 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt trihydrate

5 A 250 mL flask was fitted with a mechanical stirrer, a thermocouple, an addition funnel and a reflux condenser through which is circulated -20 °C brine. The system was connected to a caustic scrubber which places a back pressure of (4.8 - 6.9)10<sup>4</sup> Pa (7-10psi) on the system. The system was flushed with nitrogen and charged with 20 g (0.19 mol) of aminobutyric acid, 80 mL of methanesulfonic acid, and 24 g (0.29 mol) of phosphorous acid. For larger scale operations, the methanesulfonic acid can be charged first, followed by  
10 the 4-aminobutyric acid and phosphorus acid. Upon mixing, the heat of neutralization and solution increased the reaction temperature to 75 °C. The suspension was aged for 15 minutes at 70-75 °C resulting in a clear colorless solution. The solution was cooled to 35 °C and phosphorus trichloride (PCl<sub>3</sub>), 40 mL (0.46 mol) was added cautiously over 20 minutes. The reaction was then heated to 65 °C and aged at that temperature for 20 hours. The reaction should not be allowed to get much above 65 °C. The reaction becomes self-  
15 heating above 85 °C and under adiabatic conditions the temperature will increase steadily. At about 150 degrees an exotherm accompanied by a large pressure release occurs. It is therefore recommended that the reaction be immediately quenched into cold water if the temperature reaches 85 °C. The reaction was then cooled to 25 °C and added to 200 mL of deionized water over 5 minutes. The flask was rinsed with an additional 100 mL of water and the combined solution aged at 95-100 °C for 5 hours. The reaction was  
20 cooled to 20 °C and maintained at 20-25 °C while the pH was adjusted to 4.3 with ca. 80 mL of 50% NaOH. The resulting white suspension was then cooled to 0-5 °C and aged for 1 hour. The pH was readjusted to 4.3 if necessary and the suspension aged at 0-5 °C for an additional 2 hours. The product was collected by filtration, then washed with 2 x 50 mL of cold (0-5 °C) water and 100 mL of 95% EtOH. The yield after air drying at 40 °C to constant weight was 56.4 g (90%).

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## EXAMPLE 2

### Analysis of crystalline 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt trihydrate

30 The reaction product of Example 1 was analysed with the results as follows:-

Tests	Results
color,form,appearance	fine white free flowing crystalline powder
Particle size	10-100 μ, average <50
Melting point	inserted at 245, starts to melt at 257, decomposes at 262.5
Assay (NaOH titration)	99.7%
Assay (complexometric titration)	99.9%
HPLC	99.5%
Karl Fisher	16.6% (theory 16.6%)
Loss on drying	16.7%
GC-residual ethanol	<0.01%
TLC for other acids	<0.01% (not detected)
Heavy metals	<20 ppm
pH of 0.5% H <sub>2</sub> O solution	4.36
IR	conforms
X-ray	conforms
Flame test for Na	conforms

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Microchemical analysis		
	Theory	Found
Carbon	14.77	14.67
Hydrogen	5.54	5.58
Nitrogen	4.31	4.22
Sodium*	7.08	7.00
Phosphorous	19.08	19.00
Residual chloride		<0.05

\*Determined by AA.

### Claims

Claims for the following Contracting States : AT, BE, DK, FR, DE, GB, NL, IT, LU, CH, LI, SE

1. Crystalline 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt trihydrate.
2. The compound according to claim 1 in the form of a free flowing powder.
3. A compound according to claim 1 or claim 2 for use in the manufacture of a pharmaceutical composition.
4. A pharmaceutical composition comprising a compound according to claim 1 or claim 2.
5. A process for the preparation of a compound according to claim 1 or claim 2 which comprises:
  - (a) reacting 4-aminobutyric acid with a mixture of phosphorous acid and  $\text{PCl}_3$  in the presence of methanesulphonic acid at a temperature of less than  $85^\circ\text{C}$ ;
  - (b) treating with water,
  - (c) bringing the pH to 4.3 with sodium hydroxide solution at a temperature of  $20\text{-}25^\circ\text{C}$ ,
  - (d) cooling to  $0\text{-}5^\circ\text{C}$  and
  - (e) collecting the desired compound by filtration, washing with water and 95% ethanol and air drying.
6. A process according to claim 5 wherein step (a) is performed in the absence of a diluent.
7. A process according to claim 5 or claim 6 wherein step (a) is performed at about  $65^\circ\text{C}$  and step (e) at  $40^\circ\text{C}$ .
8. A process according to any of claims 5 to 7 wherein 1.5 moles of  $\text{H}_3\text{PO}_3$  and 2.4 moles of  $\text{PCl}_3$  are used per mol of 4-aminobutyric acid.
9. A process according to any of claims 5 to 8 wherein step (c) employs 50% sodium hydroxide solution.
10. A process according to any of claims 5 to 9 wherein the solution obtained in stage (b) is aged at  $95\text{-}100^\circ\text{C}$  prior to commencement of step (c).

### Abstract

A method for preparation of crystalline 4-amino-1-hydroxybutyridine-1,1-bisphosphonic acid monosodium trihydrate, based on reaction 4-aminobutyric acid with a mixture of phosphorous acid and  $\text{PCl}_3$  and following hydrolysis of reaction mixture with sodium hydroxide is disclosed.