IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

MERCK & CO., INC., Plaintiff, v. TEVA PHARMACEUTICALS USA, INC., Defendants.	C.A. NO. 06-2484 (WHW)(MF)

FIRST AMENDED COMPLAINT FOR PATENT INFRINGEMENT

For its Complaint, Plaintiff Merck & Co., Inc. ("Merck") alleges as follows:

1. This is a declaratory judgment action for a declaration that defendant Teva Pharmaceuticals USA, Inc. ("Teva") will infringe valid and enforceable claims of plaintiff Merck & Co., Inc.'s ("Merck") United States patents for processes for the manufacture of alendronate sodium. The term alendronate sodium is used herein to refer both to alendronate and to alendronate sodium, a salt of alendronate that is the commercial form of the drug. Alendronate sodium is a medicinal drug compound.

PARTIES

2. Merck is incorporated under the laws of New Jersey with its principal place of business at One Merck Drive, Whitehouse Station, New Jersey 08889.

3. On information and belief, Teva is incorporated under the laws of Delaware, with its principal place of business at 650 Cathill Drive, Sellers, Pennsylvania.

4. On information and belief, Teva is in the business of making and selling generic drug products.

5. On information and belief, Teva owns and operates manufacturing facilities in New Jersey.

6. On information and belief, Teva has submitted to the jurisdiction of the United States District Court for the District of New Jersey.

7. On information and belief, Teva employs numerous people within New Jersey.

JURISDICTION AND VENUE

8. This action arises under the patent laws of the United States of America, Title 35, United States Code and jurisdiction is founded on Title 28, United States Code §§ 1331, 1338, 2201, and 2202.

9. Venue is proper in this Court under Title 28, United States §§ 1391(c) and 1400(b), because Teva employs individuals in this judicial district and has offices and manufacturing facilities in this judicial district and thus purposefully avails itself of the privilege of conducting activities within New Jersey.

BACKGROUND

10. On May 1, 1990, United States Letters Patent No. 4,922,007 (the "'007 patent") issued to inventors Gerard R. Kieczykowski, David G. Melillo, and Ronald B. Jobson, entitled PROCESS FOR PREPARING 4-AMINO-1-HYDROXYBUTYLIDENE-1,1-BISPHOSPHONIC ACID OR SALTS THEREOF. A copy of the '007 patent is attached as Exhibit 1.

11. On May 28, 1991, United States Letters Patent No. 5,019,651 (the "'651 patent") issued to inventor Gerard R. Kieczykowski, entitled PROCESS FOR PREPARING 4-AMINO-1-HYDROXYBUTYLIDENE-1,1-BISPHOSPHONIC ACID (ABP) OR SALTS THEREOF. A copy of the '651 patent is attached as Exhibit 2.

12. On April 23, 1996, United States Letters Patent No. 5,510,517 (the "'517 patent") issued to inventors Richard R. Dauer, Lisa DiMichele, Mauricio Futran, and Gerard R. Kieczykowski, entitled PROCESS FOR PRODUCING N-AMINO-1-HYDROXY-ALKYLIDENE-1,1-BISPHOSPHONIC ACIDS. A copy of the '517 patent is attached as Exhibit 3.

13. On July 15, 1997, United States Letters Patent No. 5,648,491 (the "'491 patent") issued to inventors Richard R. Dauer, Lisa DiMichele, Mauricio Futran, and Gerard R. Kieczykowski, entitled PROCESS FOR PRODUCING N-AMINO-1-HYDROXY-ALKYLIDENE-1,1-BISPHOSPHONIC ACIDS. A copy of the '491 patent is attached as Exhibit 4.

14. On August 13, 1991, United States Letters Patent No. 5,039,819 (the "'819 patent") issued to inventor Gerard R. Kieczykowski, entitled DIPHOSPHONATE INTERMEDIATE FOR PREPARING AN ANTIHYPERCALCEMIC AGENT. A copy of the '819 patent is attached as Exhibit 5.

15. On October 27, 1992, United States Letters Patent No. 5,159,108 (the "'108 patent") issued to inventor Gerard R. Kieczykowski, entitled PROCESS FOR PREPARING AN ANTIHYPERCALCEMIC AGENT. A copy of the '108 patent is attached as Exhibit 6.

16. Merck is the owner through assignment of the '007, '651, '517, '491, '819, and '108 patents. Merck is the holder of an approved New Drug Application (NDA 20-560) for alendronate sodium tablets that are sold under its trademark FOSAMAX®.

17. Alendronate is an extremely successful drug that is widely used in the United States and throughout the world to treat osteoporosis and other bone diseases.

18. On information and belief, Defendant Teva has filed Abbreviated New Drug Application ("ANDA") No. 75-710 with the Food and Drug Administration ("FDA"), for tablets containing 5 milligrams, 10 milligrams, 35 milligrams, 40 milligrams and 70 milligrams of alendronate sodium.

19. On information and belief, Teva filed its ANDA for alendronate sodium tablets because Teva seeks to enter the alendronate sodium market that FOSAMAX® pharmaceutical products have created due to their benefits and advantages.

20. On information and belief, Merck is not aware of any proven commercially viable process to manufacture alendronate sodium, or its active ingredient, alendronate monosodium trihydrate, that is not covered by the processes claimed in the '007, '651, '517, '491, '819, and/or '108 patents.

21. Merck made a reasonable effort to determine the process actually used in the production of the alendronate sodium tablets that are the subject of Teva's ANDA prior to the filing of its Original Complaint (Dkt. No. 1).

22. Specifically, May 22, 2006, Merck sent a letter to Teva's representatives seeking information about Teva's process for preparing alendronate sodium. At the time Merck filed its Original Complaint (Dkt. No. 1) in this case, Merck had received no substantive response to its letter to Teva, and thus, pursuant to 35 U.S.C. § 295, the alendronate sodium tablets that are the subject of Teva's ANDA were presumed to have been made by one or more of the processes for the manufacture of alendronate sodium patented under the '007, '651, '517, '491, '819 and/or '108 patents.

23. On February 12, 2007, Teva provided Merck with information purportedly disclosing the method of manufacture of the alendronate sodium that will be used in the formulation of the alendronate sodium tablets that are the subject of Teva's ANDA No. 75-710. Based on its initial review of the information provided by Teva, Merck believes that the process for the manufacture of the alendronate sodium that will be used in the formulation of the alendronate sodium tablets that are the subject of Teva's ANDA No. 75-710 will infringe the '007 and '651 patents.

24. Should Merck learn, discover, and/or be informed that the disclosure provided by Teva on February 12, 2007, is not accurate, real, and/or sufficient, Merck, regardless of the state of its infringement assertions as to the '007 and '651 patents, may reassert that Teva infringes the '517, '491, '819 and/or '108 patents.

25. Merck previously brought declaratory judgment action against Teva in the United States District Court for the District of Delaware, C.A. No. 02-1377 ("the prior Teva litigation"), for a declaration of infringement of the '007 and '651 patents. The prior Teva litigation was voluntarily dismissed without prejudice on May 19, 2004.

COUNT I

26. Each of the preceding paragraphs 1-25 is incorporated as if fully set forth herein.

27. Teva has submitted ANDA No. 75-710 for alendronate sodium tablets in order to obtain approval under the Federal Food, Drug and Cosmetic Act to engage in the commercial manufacture, use, or sale of alendronate sodium drug products prepared using a process claimed in the '007 patent, before the expiration of the '007 patent, thus infringing the '007 patent.

28. A real, immediate and justiciable controversy exists with respect to Teva's anticipated future infringement of the '007 patent.

29. This litigation constitutes a substantial and continuing controversy between Merck and Teva. Based on Teva's filing of ANDA No. 75-710, Teva will manufacture alendronate sodium using one or more of Merck's patented processes and enter the alendronate sodium market. An imminent threat of injury to Merck exists because Teva's actions will infringe valid and enforceable claims of Merck's '007 patent.

COUNT II

30. Each of the preceding paragraphs 1-29 is incorporated as if fully set forth herein.

31. Teva has submitted ANDA No. 75-710 for alendronate sodium tablets in order to obtain approval under the Federal Food, Drug and Cosmetic Act to engage in the commercial manufacture, use, or sale of alendronate sodium drug products prepared using a process claimed in the '651 patent, before the expiration of the '651 patent, thus infringing the '651 patent.

32. A real, immediate and justiciable controversy exists with respect to Teva's anticipated future infringement of the '651 patent.

33. This litigation constitutes a substantial and continuing controversy between Merck and Teva. Based on Teva's filing of ANDA No. 75-710, Teva will manufacture alendronate sodium using one or more of Merck's patented processes and enter the alendronate sodium market. An imminent threat of injury to Merck exists because Teva's actions will infringe valid and enforceable claims of Merck's '651 patent.

REQUESTED RELIEF

WHEREFORE, Plaintiff MERCK respectfully seeks the following relief:

a. That judgment be entered that Defendant Teva's manufacture, use, importation, offer for sale and/or sale of alendronate sodium tablets that are the subject of Defendant Teva's ANDA will infringe the '007 and '651 patents;

b. That judgment be entered that the process by which the alendronate sodium tablets that are the subject of Defendant Teva's ANDA are made infringes the '007 and '651 patents;

c. That a preliminary and permanent injunction be issued under 35 U.S.C. §271(e) restraining or enjoining Defendant Teva, its officers, agents, or attorneys and employees, and those acting in privity or in concert with them, from engaging in the commercial manufacture, use, offer to sell, or sale within the United States, or importation into the United States, of any composition covered by either or both of the '007 and '651 patents, and any composition made by a process covered by either or both of the '007 and '651 patents, for the full term thereof;

d. That judgment be entered that Defendant Teva's manufacture, use, importation, offer for sale and/or sale of alendronate sodium tablets that are the subject of Defendant Teva's ANDA will be willful and deliberate infringement of the '007 and '651 patents;

e. That this is an exceptional case under 35 U.S.C. § 285, and that judgment be entered for costs and reasonable attorneys fees to be awarded to Merck; and;

f. That this Court award such other and further relief as the Court may deem proper under the circumstances.

Dated: June 13, 2007
Newark, New Jersey

Respectfully submitted,

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Exhibit 1

United States Patent [19]

Kieczykowski et al.

[11] **Patent Number: 4,922,007**

[45] **Date of Patent: May 1, 1990**

[54] **PROCESS FOR PREPARING 4-AMINO-1-HYDROXYBUTYLIDENE-1,1-BISPHOSPHONIC ACID OR SALTS THEREOF**

[75] Inventors: **Gerard R. Kieczykowski**, Westfield; **David G. Melillo**, Scotch Plains; **Ronald B. Jobson**, East Brunswick, all of N.J.

[73] Assignee: **Merck & Co., Inc.**, Rahway, N.J.

[21] Appl. No.: **363,820**

[22] Filed: **Jun. 9, 1989**

[51] **Int. Cl.**[5] **C07F 9/38**

[52] **U.S. Cl.** **562/13**

[58] **Field of Search** 562/13

[56] **References Cited**

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4,621,077	11/1986	Rosini .	
4,639,338	1/1987	Stahl et al.	562/13

Primary Examiner—J. E. Evans

Attorney, Agent, or Firm—Charles M. Caruso; Hesna J. Pfeiffer

[57] **ABSTRACT**

A process for the preparation of 4-amino-1-hydroxybutylidene-1, 1-bisphosphonic acid or salts thereof which comprises:

(a) reacting 4-aminobutyric acid with a mixture of phosphorous acid and PCl_3 in the presence of methanesulfonic acid; and

(b) recovering said 4-amino-1-hydroxybutylidene-1, 1-bisphosphonic acid or salts thereof.

5 Claims, No Drawings

PROCESS FOR PREPARING 4-AMINO-1-HYDROXYBUTYLIDENE-1,1-BIS-PHOSPHONIC ACID OR SALTS THEREOF

BACKGROUND OF THE INVENTION

This invention relates to an improved process for making 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid or salts thereof, where the end product is obtained in particularly pure form and at high yields in a one-pot procedure.

It is known according to U.S. Pat. No. 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 solidificaiton causes variable yields, which in part results from the exothermic nature of the reaction with development of hot spots. Morever, to make the sodium salt utilizing the prior art processes required isolation of 4-amino-1-hydroxybutylidine-1,1-bisphonic acid and an additional step to convert to the monosodium salt.

The present invention solves there problems by allowing the reaction to remain fluid and homogeneous making commerical manufacturing possible, reducing the number of process steps and providing a large improvement in isolated yield of from about 45–50% to about 85–90%.

SUMMARY OF THE INVENTION

The present invention provides a process for the preparation of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid or salts thereof which comprises:

(a) reacting 4-aminobutyric acid with a mixture of phosphorous acid and PCl_3 in the presence of methanesulfonic acid; and

(b) recovering said 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid or salts thereof.

The reaction can be conducted, if desired, in the presence of an inert organic diluent which does not solubilize the reaction product and at a temperature of from about 45° C. to 125° C., although this is not necessary when methanesulfonic acid is used.

DETAILED DESCRIPTION OF THE INVENTION

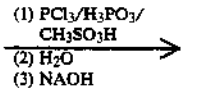
It has been found that pure crystallize 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid or salts thereof can surprisingly be obtained in high yields when using the procedure of the invention. The invention involves the reaction of an aminoalkane carboxylic acid with phosphonating reactants in the presence of methanesulfonic acid and recovering 4-amino-1-hyroxyutylidene-1,1-bisphosphonic acid or salts thereof. The compound 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 aminoalkane carboxylic acids which can be used is 4-aminobutyric acid. The phosphonylation reaction generally takes place at temperatures of from 45° to 125° C., preferably at about 65° C.

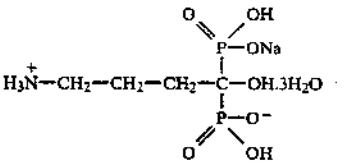
Preferably 1 to 2, particularly 1.5 moles of H_3PO_3 and 1 to 2.5, particularly 2.4 mols of PCl_3 are used per mol of aminocarboxylic acid. If desired, inert organic diluents, which do not solublize the reaction product, particularly hexane or chlorinated hydrocarbons, such as chlorobenzene, tetrachloroethane, tetrachloroethylene and trichloroethylene can be used in the reaction. 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 reactin solution.

The reaction is schematically represented as follows:



$C_4H_9NO_2$
MW 103.12



$C_4H_{12}NNaO_7P_2.3H_2O$
MW 325.13

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 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt trihydrate made according to the process of the present invention.

Other pharmaceutically acceptable salts, such as for example the calcium, potassium salts, can be prepared according to the processes of the present invention and are included within the scope thereof.

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

EXAMPLE 1

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

A 250 mL flask was fitted with a mechanical stirrer, a thermcouple, 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 7–10 psi 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 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 clear colorless solution. The solution was cooled to 35° C. and phosphorus trichloride (PCl_3), 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-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 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 2×50 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%).

EXAMPLE 2

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

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	10–100μ, average <50
Melting point	inserted at 245, starts to melt at 257, decomposes at 262.5
Assay (NaOH titration)	99.7%
Assay (complexometric tritration)	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_2O solution	4.36
IR	conforms
X-ray	conforms
Flame test for Na	conforms
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.

EXAMPLE 3

Preparation of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid

To isolate the bisphosphonic acid, the pH was adjusted to 1.8 rather than 4.32 as follows: The reaction was cooled to 20 degrees C. and maintained at 20–25 degrees C. while the pH was adjusted to 1.0 with about 80 mL of 50% NaOH. The resulting white suspension was then cooled to 0–5 degrees C. and aged for 1 hour. The pH was adjusted to 1.8 and the suspension aged at 0–5 degrees C. for an additional 2 hours. The product was collected by filtration and washed with 100 mL of 20 degrees C. deionized water, then air dried at 40 degrees C. yielding 44.0 g (86% yield) of white crystalline product.

EXAMPLE 4

Analysis of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid

The reaction product of Example 3 was analysed with the results as follows:

Tests	Results
Color,form,appearance	Clean, crystalline, white powder
NaOH titration	99.5%
Complexometric titration	99.8%
Loss on drying	6.79% (theory 6.74)
pH of 0.5% solution	2.15%
Microchemical analysis $C_4H_{13}NO_7P_2.H_2O$	

	Theory	Found
Carbon	17.97	17.84
Hydrogen	5.62	5.55
Nitrogen	5.24	5.16
Sodium*	—	.05*
Phosphorous	23.21	23.02

*By atomic absorbtion spectroscopy. The other elements are determined by combustion analysis.

The preceding specific embodiments are illustrative of the practice of the invention. It is to be understood, however, that other expedients known to those skilled in the art or disclosed herein, may be employed without departing from the spirit of the invention or the scope of the appended claims.

What is claimed is:

1. A process for the preparation of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid or salts thereof which comprises:

(a) reacting 4-aminobutyric acid with a mixture of phosphorous acid and PCl_3 in the presence of methanesulfonic acid; and

(b) recovering said 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid or salts thereof.

2. The process of claim 1 wherein said reaction is conducted at a temperature of from 45° C. to 125° C.

3. The process of claim 2 wherein said reaction is conducted at a temperature of about 65° C.

4. The process of claim 3 wherein sufficient sodium hydroxide is added to the reaction mixture and 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt trihydrate is recovered.

5. The process of claim 3 wherein 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid is recovered.

* * * * *

Exhibit 2

United States Patent [19]

Kieczykowski

[11] **Patent Number: 5,019,651**

[45] **Date of Patent: May 28, 1991**

[54] **PROCESS FOR PREPARING 4-AMINO-1-HYDROXYBUTYLIDENE-1,1-BISPHOSPHONIC ACID (ABP) OR SALTS THEREOF**

[75] Inventor: **Gerard R. Kieczykowski, Westfield, N.J.**

[73] Assignee: **Merck & Co., Inc., Rahway, N.J.**

[21] Appl. No.: **540,997**

[22] Filed: **Jun. 20, 1990**

[51] **Int. Cl.**[5] **C07F 9/38**

[52] **U.S. Cl.** **562/13**

[58] **Field of Search** 562/13

[56] **References Cited**

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Lancet, Apr. 14, 1979, pp. 803–805.

Primary Examiner—J. E. Evans

Attorney, Agent, or Firm—Robert J. North; Charles M. Caruso

[57] **ABSTRACT**

An improved process is described for the preparation of 4-amino-1-hydroxybutylidene-1,1-bisophosphonic acid (ABP) or salts thereof which comprises:

(a) reacting 4-aminobutyric acid with a mixture of phosphorous acid and PCl_3 in the presence of methanesulfonic acid;

(b) contacting the mixture from Step (a) with an aqueous hydrolysis mixture, wherein the pH is maintained in the range of 4 to 10 during the contacting; and

(c) recovering said 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid or salts thereof.

10 Claims, No Drawings

PROCESS FOR PREPARING 4-AMINO-1-HYDROXYBUTYLIDENE-1,1-BIS-PHOSPHONIC ACID (ABP) OR SALTS THEREOF

BACKGROUND OF THE INVENTION

This invention relates to an improved process for making 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid (ABP) or salts thereof, where the end product is obtained in pure form and high yield, and which avoids the use of a strongly-acidic hydrolysis medium.

It is known according to U.S. Pat. No. 4,407,761 to Henkel Kommanditgesellschaft to prepare 4-amino-1-hydroxy-butylidene-1,1-bisphosphonic acid by bisphosponating an aminocarboxylic acid with phosphonating reactants and then quenching the reaction mixture by addition of a strong non-oxidizing acid, preferably concentrated hydrochloric acid, with heating, to hydrolyze the formed phosphorous intermediates to final product. However, problems result from this reaction because the bisphosphonation reaction mixture does not remain homogeneous and local solidification occurs. This solidification causes variable yields, which in part results from the exothermic nature of the reaction due to the development of "hot spots". Moreover, to make the sodium salt, utilizing the prior art processes, requires isolation of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid and an additional step to convert this to the monosodium salt. Further, the use of concentrated hydrochloric acid in the quench, whose fumes present an environmental problem, is also required.

Furthermore, U.S. Pat. No. 4,922,007 to G. R. Kieczykowski, et al. (assigned to Merck & Co., Inc.) discloses the use of methanesulfonic acid to overcome the non-homogeneity and solidification problems associated with the bisphosphonation phase, but utilizes a non-pH controlled water quench which leads to the presence of a strongly acidic and corrosive hydrolysis mixture which requires the use of expensive glass reaction vessels with their inherent pressure limitations.

The present invention solves these problems by the use of methanesulfonic acid to allow the bisphosphonation reaction to remain fluid and homogeneous, and using a pH-controlled aqueous quench in the range of 4 to 10, followed by hydrolysis, which eliminates the need for concentrated hydrochloric acid in the quench. The present invention also eliminates the need to handle a corrosive acidic product hydrolysis mixture, such that stainless steel hydrolysis equipment rather than glass equipment can be utilized. Glass equipment has inherent pressure limitations not possessed by stainless steel. This is a big advantage in the instant process since it has been found that, by conducting the hydrolysis under pressure, the hydrolysis rate can be significantly increased.

It has been found that, in the quench, a pH above 10 leads to lower yields due to formed intermediates which resist hydrolysis, and a pH below 4 leads to much longer hydrolysis times. Further, it has been found that ABP is unstable at a pH above 8, thus limiting the reaction times and hydrolysis times at higher pHs.

SUMMARY OF THE INVENTION

By this invention, there is provided a process for the preparation of 4-amino-1-hydroxy-butylidene-1,1-bisphosphonic acid or salts thereof which comprises:

(a) reacting 4-aminobutyric acid with a mixture of phosphorous acid and PCl_3 in the presence of methanesulfonic acid;

(b) contacting the resulting mixture from Step (a) with an aqueous hydrolysis mixture, wherein the pH is maintained in the range of 4 to 10 during the contacting; and

(c) recovering said 4-amino-1-hydroxybutyl-idene-1,1-bisphosphonic acid or salts thereof.

The reaction can further be conducted by controlling the pH during the aqueous quench in a narrow range, i.e. 6–8, maintaining the temperature between 0°–20° C., and then heating the hydrolysis mixture at 50° C. - reflux, or under pressure for a sufficient time to insure complete hydrolysis to the titled product.

DETAILED DESCRIPTION OF THE INVENTION

The present invention process provides pure crystallized 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid, or salts thereof, which can surprisingly be obtained in high yields. The invention involves the bisphosphonation of an aminoalkane carboxylic acid with phosphonating reactants in the presence of methanesulfonic acid, quenching the reaction mixture with an aqueous hydrolysis mixture, maintaining the pH at 4 to 10, hydrolyzing the phosphorus intermediates, formed in the quench procedure, and recovering 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid or salts thereof. The compound can be crystallized directly from the reaction mixture in about 90% yield after the pH controlled hydrolysis, and pH adjustment to about 4.3 with no further purification necessary.

The aminoalkane carboxylic acids which can be used is 4-aminobutyric acid. The bisphosphonation reaction generally takes place at temperatures of from 45° to 125° C., preferably at about 65° C.

Generally 1 to 3, preferably 2.0 moles of H_3PO_3 and generally 1 to 5.0, preferably 4.0 mols of PCl_3 are used per mol of aminocarboxylic acid. Smaller amounts of 4-aminobutyric acid can be used which limits the formation of ABP dimers and decreases the necessary hydrolysis times. If desired, inert organic diluents, which do not solubilize the reaction product, particularly helped or chlorinated hydrocarbons, such as chlorobenzene, tetrachloroethane, tetrachloroethylene and trichloroethylene can be used in the reaction with methanesulfonic acid.

Following the reaction to form the product, the reaction is quenched, i.e. drowned into an aqueous hydrolysis mixture. The conditions of the quench are such that pH is controlled in the range of pH 4 to 10, and preferably the pH is controlled in a narrow pH region, i.e. 6–8. By controlling the pH in this manner, it has been found that the yield of ABP can be maximized.

The aqueous hydrolysis mixture can contain basic or acidic materials or buffering agents.

Representative examples include sodium, potassium and lithium hydroxides, carbonates, bicarbonates, dihydrogen phosphates, hydrogen phosphates, borates, oxalates, tartrates, phthalates, phosphorous acid salts, and the like, and mixtures thereof.

Preferred is where the hydrolysis mixture is a buffered solution, preferrably a phosphate or bicarbonate buffered solution in the range pH 6–8.

The pH of the resulting quench mixture can also be controlled during the hydrolysis drown by the simulta-

neous addition of a basic reagent, e.g. sodium hydroxide.

The temperature of the quench is carried out in the range of 0°–90° C., and preferably 0°–20° C.

The required time of the quench drowning procedure will vary according to the volumes used.

Following the pH-controlled, temperature-controlled quench, the resulting mixture is stirred and heated in the temperature range of 50° C. to reflux and preferably at the reflux temperature of about 105°–110° C. to complete and insure complete hydrolysis.

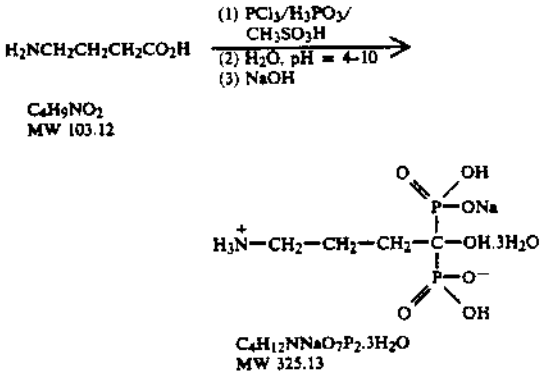
The volume ratio of the reaction mixture from the phosphonation Step (a) to the volume of the aqueous hydrolysis mixture in the quench Step (b) is about 1 to 5.

Alternatively, the hydrolysis mixture can be partially concentrated to about half the original volume, by distillation at atmospheric or reduced pressure, diluted with water to about the original volume and then refluxed. This procedure substantially reduces the hydrolysis time.

As a further alternative, the hydrolysis mixture can be heated at 110°–165° C. in a closed vessel under pressure. This also substantially reduces the hydrolysis times.

It should be noted that a pH above about 7–8, the product ABP starts to undergo degradation with resultant yield loss, and thus preferably the desired hydrolysis workup procedure should be carried out in the pH range 6–8.

The reaction is schematically represented as follows:



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 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt trihydrate made according to the process of the present invention.

Other pharmaceutically acceptable salts, such as for example the calcium, potassium salts, can be prepared according to the processes of the present invention and are included within the scope thereof.

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

EXAMPLE 1

Non-pH-Controlled Hydrolysis

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

Bisphosphonation Reaction Phase

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 0.5–1 psig 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 the 4-aminobutyric acid and phosphorous 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_3), 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-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.

Quench; Hydrolysis

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 strongly-acid solution (pH less than zero) aged at 95°–100° C. for 5 hours. The reaction was 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 2×50 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%).

EXAMPLE 2

Use of pH-Controlled Hydrolysis

4-aminobutyric acid: 20 g
methanesulfonic acid: 160 ml
phosphorous acid: 32 g
phosphorus trichloride: 80 ml

Bisphosphonation Reaction Phase

The above reagents were mixed and heated at 65° C. for 5 hours analogously according to the procedure of Example 1.

Quench; Hydrolysis

The reaction mixture was quenched over 35 minutes by adding dropwise to a solution of 10 g Na_2HPO_4 in one liter of water, at pH=7.0. The pH of the quench was maintained between 6.0 and 7.0 by simultaneously adding 25% sodium hydroxide and maintained below 25° C. by cooling with ice. Once the quench was complete, the pH was adjusted to 7.0 and the solution con-

centrated to 1080 ml by atmospheric distillation (100°–104° C.) over 3 hours. At this point, the reaction was subdivided into 2 parts, A and B.

A, being 630 ml, was concentrated further to 450 ml after adjusting the pH to 4.3. The solution was aged overnight at ambient temperature during which time the product crystallized. The suspension was aged at 0° C. for 2 hours then filtered, washed with 100 ml of cold water, 100 ml of 1:1 water/ethanol, and 100 ml of 100% ethanol and dried, yielding 20.5 g (56% yield).

B, being 450 ml, was treated by refluxing an additional 16 hours before adjusting the pH to 4.3 and concentrating to 300 ml. The product was isolated as above providing 16.5 g. (63% yield) of ABP.

This Example illustrates that the above bisphosphonation reaction, in conjunction with a buffered quench, minimized the ABP dimers and phosphonates which are more difficult to hydrolyze, thus reducing the required hydrolysis times.

EXAMPLE 3

4-aminobutyric acid: 60 g
methanesulfonic acid: 240 ml
phosphorous acid: 48 g
phosphorus trichloride: 120 ml

Bisphosphonation

The reaction was run analogously using the procedure described in Example 1 (65° C. overnight) with the above quantity of reagents. The total reaction volume was 430 ml. The reaction was subdivided into aliquots prior to quenching.

Quench; Hydrolysis

Aliquots were quenched into 100 ml of water while simultaneously adding 20% sodium hydroxide to maintain a pH of 6–10. The pH was adjusted to different values between 4–10 and the reaction refluxed for an appropriate amount of time to produce and isolate product (see below). The pH was then adjusted to 7 and the solution filtered. The pH was then adjusted to 4.3 and the solution aged overnight during which time the product crystallized. The suspension was then aged at 0° C. for 2 hours and filtered. The cake was washed with water then ethanol and dried.

Aliquot	pH	Time Refluxed[1]	Yield
50 ml	11	1 day	9.6 g (44%)
46 ml	10	2 days	11.4 g (56%)
20 ml	9	2 days	5.0 g (54%)
23 ml	8	6 days	6.8 g (66%)
21 ml	7	10 days	6.6 g (72%)
21 ml	7	10 days	7.2 g (78%)[2]
21 ml	7	5 days	7.0 g (75%)[3]
21 ml	7	42 hrs.[4]	2.4 g (65%)
21 ml	6	11 days	6.8 g (74%)
ml	5	days[5]	g (%)
ml	4	days[5]	g (%)

-continued

Aliquot	pH	Time Refluxed[1]	Yield
ml	3	days[5]	g (%)

[1]Temperature between 105–110° C. at 1 atmosphere.
[2]Used an equal volume of ethanol in the crystallization.
[3]Partially concentrated by atmospheric distillation to about half the volume, diluted with an equal volume of water and then refluxed.
[4]After quenching, refluxed at 140° C. in a closed pressure vessel.
[5]After 12 days, the hydrolysis mixture was analyzed by phosphorus NMR. The pH = 5 and pH = 4 reactions indicated incomplete hydrolysis mixtures. The pH = 3 reaction indicated incomplete hydrolysis mixture and significantly longer hydrolysis times projected for its completion.

This Example illustrates that the product can be quenched and hydrolyzed under neutral and basic conditions in good yield, but that at the higher pH values, the yields are lower due to competing degradation of the product.

What is claimed is:

1. A process for the preparation of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid or salts thereof which comprises:
   (a) reacting 4-aminobutyric acid with a mixture of phosphorous acid and PCl_3 in the presence of methanesulfonic acid;
   (b) contacting the resulting mixture from Step (a) with an aqueous hydrolysis mixture, wherein the pH is maintained the range at 4 to 10 during the contacting; and
   (c) recovering said 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid or salts thereof.

2. The process of claim 1 wherein the pH is maintained in Step (b) in the range of 6–8.

3. The process of claim 1 further comprising step (b-2), heating said resulting mixture from Step (b) in the range of 50° C. to the boiling point.

4. The process of claim 1 wherein said Step (b) is conducted at a temperature of from 0° C. to 90° C.

5. The process of claim 4 wherein said temperature is 0°–20° C.

6. The process of claim 1 wherein said aqueous hydrolysis mixture in Step (b) is a phosphate buffer.

7. The process of claim 6 wherein said buffer comprises monosodium dihydrogen phosphate and disodium monohydrogen phosphate.

8. The process of claim 1 wherein 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt trihydrate is recovered.

9. The process of claim 1 wherein 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid is recovered.

10. A process for the preparation of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid or salts thereof which comprises:
   (a) reacting 4-aminobutyric acid with a mixture of phosphorous acid and PCl_3 in the presence of methanesulfonic acid at a temperature of about 65° C.;
   (b) contacting the resulting mixture from Step (a) with an aqueous phosphate buffer at a temperature in the range of 0°–20° C., and maintaining the pH between 6–8 during the contacting;
   (b-2) heating the resulting mixture from Step (b) at the boiling point; and
   (c) recovering said 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid or salts thereof.

* * * * *

Exhibit 3

US005510517A

United States Patent [19]

Dauer et al.

[11] **Patent Number: 5,510,517**

[45] **Date of Patent: Apr. 23, 1996**

[54] **PROCESS FOR PRODUCING N-AMINO-1-HYDROXY-ALKYLIDENE-1,1-BISPHOSPHONIC ACIDS**

[75] Inventors: **Richard R. Dauer**, Longmont, Colo.; **Lisa DiMichele**, North Plainfield, N.J.; **Mauricio Futran**; **Gerard R. Kieczykowski**, both of Westfield, N.J.

[73] Assignee: **Merck & Co., Inc.**, Rahway, N.J.

[21] Appl. No.: **286,151**

[22] Filed: **Aug. 4, 1994**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 239,640, May 9, 1994, abandoned, which is a continuation of Ser. No. 111,751, Aug. 25, 1993, abandoned.

[51] **Int. Cl.**[6] **C07F 9/28**

[52] **U.S. Cl.** **562/13**

[58] **Field of Search** 562/13

[56] **References Cited**

U.S. PATENT DOCUMENTS

5,019,651 5/1991 Kieczykowski 562/13

Primary Examiner—José G. Dees
Assistant Examiner—Joseph M. Conrad, III
Attorney, Agent, or Firm—Joanne M. Giesser; Melvin Winokur

[57] **ABSTRACT**

A process for continuously producing alkylpyrophosphonate, alkylpyrophosphate and multimers thereof and for producing 4-amino-1-hydroxyalkylidene-1,1-bisphosphonic acids or salts thereof.

5 Claims, No Drawings

PROCESS FOR PRODUCING N-AMINO-1-HYDROXY-ALKYLIDENE-1,1-BISPHOSPHONIC ACIDS

BACKGROUND OF THE INVENTION

This application is a continuation-in-part of U.S. patent application Ser. No. 08/239,640, filed May 9, 1994 now abandoned, which is a continuation of U.S. patent application Ser. No. 08/111,751, filed Aug. 25, 1993, now abandoned.

This invention relates to a process for continuously producing alkylpyrophosphonates, alkylpyrophosphates and multimers thereof and in particular for producing 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid and salts thereof, where the end product is obtained in particularly pure form and at high yields in a continuous reaction.

It is known according to U.S. Pat. No. 4,407,761 to Henkel Kommanditgesellschaft to prepare 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid with phosphonating reactants and then quenching the reaction mixture by the addition of a strong non-oxidizing agent, preferably concentrated hydrochloric acid, with heating, to hydrolyze the formed phosphorous intermediates to final product. However, this phosphonation reaction does not remain homogeneous, thereby producing heterogeneous solidification of the reaction mixture. This solidification causes variable yields and leads to the development of "hot spots" which in part result from the exothermic nature of the reaction. Moreover, to make the sodium salt, using the prior art processes, requires isolation of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid and an additional step to convert this to the monosodium salt. Further, the use of concentrated hydrochloric acid in the quench, whose fumes present an environmental problem, is also required.

U.S. Pat. No. 4,922,007 to G. R. Kieczykowski, et al., (assigned to Merck & Co., Inc.) discloses the use of methanesulfonic acid to overcome the non-homogeneity and solidification problems associated with the formation of intermediates during the bisphosphonation phase. However, this process utilizes a non-pH controlled water quench that leads to the presence of a strongly acidic and corrosive hydrolysis mixture which requires specialized equipment.

U.S. Pat. No. 5,019,651 to G. R. Kieczykowski, et al., (assigned to Merck & Co., Inc.), discloses using a pH controlled quench step in the range of 4 to 10, followed by hydrolysis, that eliminates the concentrated hydrochloric acid formed in the quench step and the need to handle a corrosive acidic product hydrolysis mixture.

Prior methods teach the requirement that the reaction be completed at temperatures above the boiling point of PCl_3, for instance 90° C. However, this temperature is known to be in the adiabatic self-heat range that is an unsafe operating range as batch volumes increase and available cooling capacity decreases. In addition, control of stoichiometric ratio is important to achieving useful intermediates. However, control of stoichiometric ratios at constant temperature, typically 90° C., is impossible using prior batch methods because stoichiometric quantities of PCl_3 may only be added at sub reflux temperatures. For example, in U.S. Pat. No. 5,019,65 1, stoichiometric ratios were achieved by use of temperature programming whereby the stoichiometric amount of PCl_3 could be added at sub-reflux temperatures. Alternatively, in U.S. Pat. No. 4,407,761, PCl_3 was added slowly at isothermal reaction temperatures above PCl_3's boiling point. Thus, it is desirable to control both stoichiometry and reaction temperature at the same time to provide consistent distribution of useful intermediates and to ensure a safe operating environment. The prior batch modes of operation made control of stoichiometric ratios impossible while maintaining a constant temperature.

The present invention solves both of these problems through operation of the reaction in a continuous stirred tank reactor that allows greater heat transfer for temperature control while maintaining constant stoichiometric ratios of reactants. The more favorable surface to volume ratio of the present invention allows greater heat transfer for temperature control. Further, continuous steady operation results in fixed ratios of products and intermediates in a small controllable environment by controlling both reaction temperature and stoichiometric ratio at all times. The smaller reacting mixture reduces severity of an unexpected thermal event and allows the entire reacting mixture to be quenched.

SUMMARY OF THE INVENTION

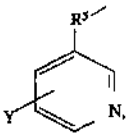
By this invention, there is provided a process for the continuous preparation of compounds of the structural Formula I

I

wherein Z is selected from the group consisting of:

a) $H_2N—C_{2-5}alkyl—$;

b)



wherein $R^5—$ is $C_{1-5}alkyl$, and Y is selected from

(i) hydrogen;

(ii) $C_{1-5}alkyl$;

(iii) R^6O;

(iv) R^6S;

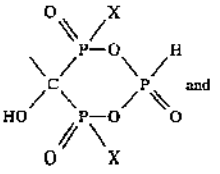
(v) R^6R^6N;

(vi) halogen;

R^6 is H or $C_{1-5}alkyl$; and

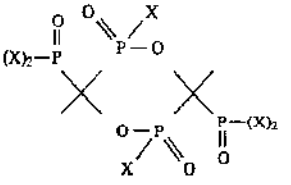
c) $C_{2-6}alkyl—(N—CH_3)C_2H_4—$; and R_1 is a member selected from the group consisting of:

a)



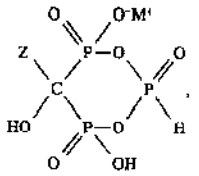
and

b)

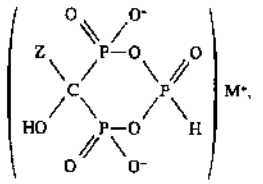


wherein X is OH or Cl. This invention also provides a process for the continuous production of intermediate com-

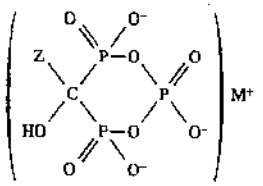
pounds of Formula IIA, IIB and IIC



IIA

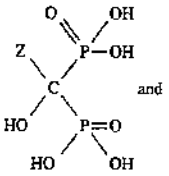


IIB



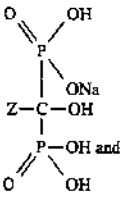
IIC

wherein Z is defined as above, and M is a monovalent, divalent or trivalent cation such as Na^+, K^+, Ca^{2+}, Mg^{2+}. It should be noted that all ionic forms of these intermediate compounds are encompassed by this invention. This invention further includes a process for the continuous production of compounds of Formula IIIA, IIIB, and IIIC

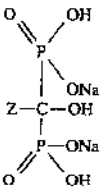


IIIA

and



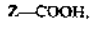
IIIB



IIIC

that comprises:

a) continuously mixing an aminoalkane carboxyiic acid of formula



wherein Z is as defined previously, with H_3PO_3 and PCl_3 in methanesulfonic acid (MSA), or optionally PCl_3 in MSA; and

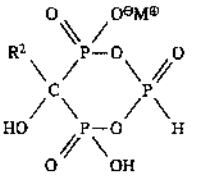
b) continuously adding aqueous base to the overflow mixture containing the compound of Formula I to produce the compounds of Formula II; and

c) hydrolyzing the overflow mixture containing the compounds of Formula II to produce the compounds of Formula III; and

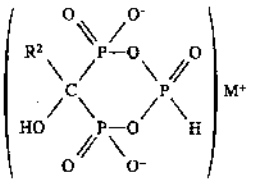
d) recovery of the products of Formula III and salts thereof.

It is noted that all possible hydrated forms are contemplated by this invention. For compounds of Formula IIIB, a trihydrate is a preferred embodiment.

In a preferred embodiment, the compound is of the Formula Ia, Z—R_1 wherein Z is group a) H_2N—C_{2-5}alkyl. Preferred intermediate compounds of the Formula IIa include compounds of the Formulas IIa(i) and IIa(ii):



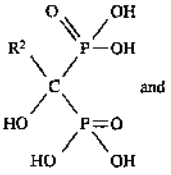
IIa(i)



IIb(i)

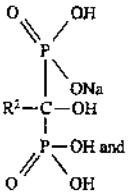
wherein R^2 is C_{2-5}alkyl substituted with a terminal amine or a protonated terminal amine.

This invention preferably includes a process for the continuous production of compounds of the Formula IIIa(i), IIIa(ii), and IIIa(iii).

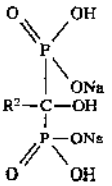


IIIa(i)

and



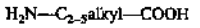
IIIa(ii)



IIIa(iii)

wherein R^2 is C_{2-5}alkyl substituted with a terminal amine, and the compounds may be in any hydrated state or a protonated terminal amine, said process comprising:

a) continuously mixing an aminoalkane carboxylic acid of the formula



with H_3PO_3 and PCl_3 in methanesulfonic acid (MSA), or optionally PCl_3 in MSA; and

b) continuously adding aqueous base to the overflow mixture containing the compound of Formula Ia to produce the compounds of Formula IIa; and

c) hydrolyzing the overflow mixture containing the compounds of Formula IIa to produce the compounds of Formula IIIa: and

d) recovery of the products of Formula IIIa and salts thereof.

DETAILED DESCRIPTION OF THE INVENTION

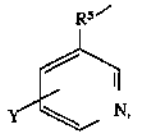
This invention relates to compounds of the structural Formula I

I

wherein Z is selected from the group consisting of:

a) H_2N—C_{2-5}alkyl—;

b)



wherein R^5— is C_{1-5}alkyl, and Y is selected from

(i) hydrogen

(ii) C_{1-5}alkyl;

(iii) R^6O;

(iv) R^6S;

(v) R^6R^6N;

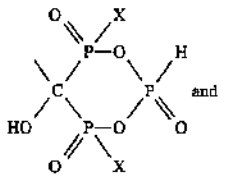
(vi) halogen;

R^6 is H or C_{1-5}alkyl; and

c) C_{2-6}alkyl—(N—CH_3)C_2H_4—; and

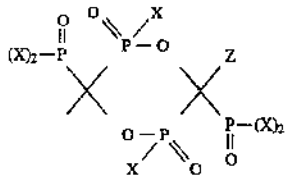
wherein R_1 is a member selected from the group consisting of:

a)



and

b)



wherein X is ⁻OH or ⁻Cl. The present invention is also directed to a process for producing said compounds and the bisphosphonate products thereof including 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid (ABP) and salts thereof. Specifically, this process may consist of five operations: continuous bisphosphonation reaction, continuous or batch pH controlled quench, continuous or batch hydrolysis, crude crystallization, and pure crystallization.

More specifically, the continuous bisphosphonation reaction consists of producing an carboxylic acid feed and reacting this feed with PCl_3 in a continuous stirred tank reactor.

The carboxylic acid feed is assembled by dissolving solid carboxylic acid and solid phosphorous acid (H_3PO_3) in methanesulfonic acid (MSA). Generally, 1 to 3, preferably 2 moles of H_3PO_3 and generally 6.3 to 6.4, preferably about 6.38 moles of MSA are used per mole of carboxylic acid. To facilitate complete dissolution of the solid components in the liquid MSA, the mixture can be heated from 40° C. to 90° C., preferably 70° C. Once the solid components of the carboxylic acid feed are dissolved, this feed may be maintained from 10° C. to 90° C., preferably 70° C. using an external heat source. Alternately, the H_3PO_3 addition may be eliminated in the carboxylic acid feed preparation. If this alternate procedure is chosen, then H_3PO_3 may be formed in situ from PCl_3 in methanesulfonic acid (MSA), PCl_3 and γ-amino butyric acid (GABA) in MSA, or H_2O in MSA.

The carboxylic acid feed is added to the cold reaction vessel to a point below the overflow level. During this fill, a heating medium is placed in the jacket and the vessel agitator tuned on. Temperature control is used to bring the temperature up to about 45°–100° C., preferably 90° C. The liquid PCl_3 feed is then initiated to the reactor vessel until the weight of PCl_3 fed to the reactor (adjusted for vapor loss) divided by the weight of carboxylic acid feed is from 0.22–0.33, preferably 0.32. At this point, the carboxylic acid feed is resumed at a flowrate sufficient to provide a residence time in the reactor from about 1.5–2.5 hours, preferably 1.8 hours. The residence time is expressed as the volume of the reactor overflow conditions divided by the flowrate (vol/min) of carboxylic acid feed. Shortly after the carboxylic acid feed is resumed, the reactor will overflow into the quench vessel which can initially be filled with either water or dilute aqueous base. The carboxylic acid and liquid PCl_3 are added simultaneously at their respective flowrates until the desired amount of material is produced.

Three residence times for the bisphosphonation reaction are undertaken before steady state synthesis occurs. Prior batch processes result in the uncontrollable formation of unwanted intermediates. The present invention overcomes this problem through stoichiometrically controlling the reaction components thereby minimizing the formation of unwanted intermediates.

The overflowing batch is neutralized in an attached quench vessel by the addition of aqueous base. The aqueous base may be any aqueous base of the formula MOH such as sodium hydroxide, or of the formula $MHCO_2$ or MCO_2 such as sodium carbonate or sodium bicarbonate, wherein M is any ion. Separate deionized (DI) water and base feeds are utilized to maintain an effective concentration of base in the quench solution from about 15–50%, preferably about 20%. Aqueous base is added to maintain pH in response to fluctuations in the pH of the quench solution. The pH in the quench vessel is maintained between 4.0 and 7.0, preferably about 5.0. The temperature of the quench mixture may be maintained from 0° C. to 100° C., preferably <50° C.

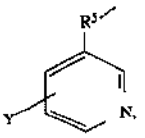
The bisphosphonation mixture produces compound of Formula I.

I

wherein Z is selected from the group consisting of:

a) H_2N—C_{2-5}alkyl—;

b)



wherein R^5— is C_{1-5}alkyl, and Y is selected from

(i) hydrogen;

(ii) C_{1-5}alkyl;

(iii) R^6O;

(iv) R^6S;

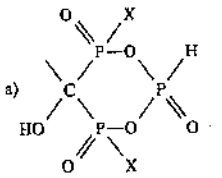
(v) R^6R^6N;

(vi) halogen;

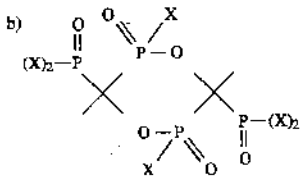
R^6 is H or C_{1-5}alkyl; and

c) C_{2-6}alkyl—$(N—CH_3)C_2H_4$—; and

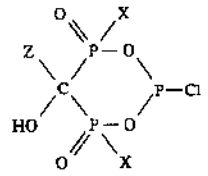
wherein R_1 is a member selected from the group consisting of:



and



wherein X is ⁻OH or Cl. It is likely that the compound of the following formula



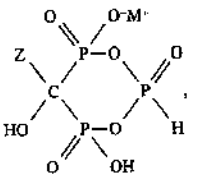
is also formed prior to quenching. Preferred compounds according to this invention are as follows. For compounds of the formula Z—R_1, where Z is a) $H_2N—C_{2-5}$alkyl—, Z is preferably a $H_2N—C_4$alkyl and the resulting compound may be used as an intermediate for the production of alendronate (4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid, sodium salt trihydrate.)

For compounds where Z=b), the preferred compound is where R^5 is CH_2, and the resulting compound may be used as an intermediate for the production of risedronate (1-hydroxy-2-(3-pyridinyl)ethylidene bisphosphonic acid.

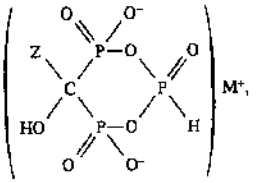
For compounds where Z=c) a preferred compound is where Z=C_4alkyl—$(N—CH_3)C_2H_4$—. This can be used as an intermediate for the production of the compound designated BM210955. (1-hydroxy-3-(methylpentylamino)propylidenebisphosphonate).

This reaction and/or the bisphosphonation mixture itself exhibits significant exothermic characteristics. Therefore sufficient safety precautions must be undertaken to assure the reaction proceeds safely. To this end, for a given productivity, the smaller reaction volume of the continuous reaction provides faster quench time in the event of reaction runaway than a batch system of similar productivity. The vessel that receives the normal overflow from the bisphosphonation reaction is also employed for the emergency quench. The minimum volume of the emergency quench is about twice the reaction volume of the reactor vessel. This enables the entire reaction volume to be quickly quenched in the event of an undesired thermal event.

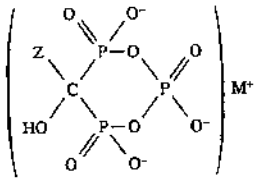
The compound of Formula IIA, IIB; or IIC:



IIA

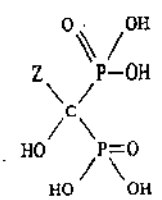


IIB



IIC

wherein Z is as defined previously, and preferably a C_{2-5} alkyl substituted with a terminal amine or a protonated terminal amine and M^+ is a monovalent or a divalent cation such as Na+, K+, Ca^{2+}, Mg^{2+}, may be accumulated or may be continuously removed from the quenching vessel via overflow into a new reactor for hydrolysis. It should be appreciated that other anionic forms of compounds of Formula II, for example tri-ionic, are formed under appropriate pH conditions: (structures throughout this specification should be understood as including all possible ionic forms dependent on the pH of the environment). The pH of the quenched material is checked and adjusted, if necessary, to between about 3.3 to 12.3, preferably to about 4.6 and 5.0. The batch is heated in a vessel composed of thick walled PYREX™, or if vessel degradation is a problem, then in a vessel lined with Hastelloy™ C-276, to about 100°–175° C., preferably 140° C. at 60 psig and aged for about 20 hours to breakdown Compounds IIA and IIB into product III.



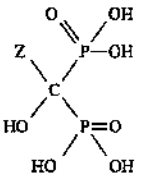
III

wherein Z is as defined previously and is preferably a C_{2-5} alkyl substituted with a terminal amine and salts thereof, particularly the monosodium and disodium salts.

The batch is then cooled to 85° C. and a sample is taken to confirm pH and completion of hydrolysis. However, hydrolysis of the pyrophosphonate may be carded out at

room temperature and recovery of the desired end product is possible. The batch volume may be adjusted before or after the hydrolysis by either distillation or the addition of water. Pure mother liquors may be returned to the batch before hydrolysis and the excess volume taken off by distillation to ensure the total solids specification for the crude crystallization is met.

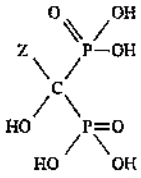
The pH of the warm solution is corrected if needed by the addition of an appropriate acid or base. After the pH adjustment at 85° C., the hydrolyzed batch may be seeded with crude or pure compound of Formula III or its mono or di- salt forms which may be present at the appropriate pH.



III

The batch is cooled to 0°-25° C. This crude solution is aged for >6 hours and the crystal slurry is isolated by filtration. The resulting cake may be washed with cold, deionized water. The crude cake may be dried or charged directly into the purification step.

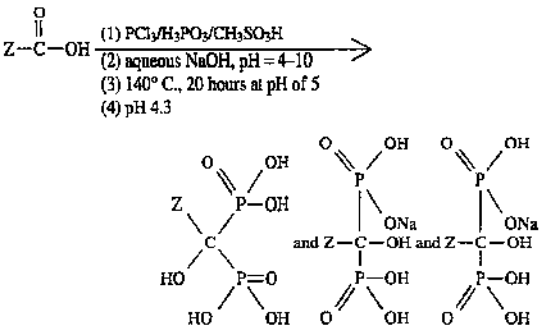
The crude undried mixture and deionized water are added to the purification vessel. The vessel temperature is taken up to from about 40° C. to about 100° C., preferably 50° C. and the solution aged until dissolution is complete. The recovery of end product is pH dependent, from about pH 3.0 to about pH 12.0. Preferably, the pH is adjusted to 4.3 to obtain the mono salt. The batch is filtered and then concentrated by distillation. The resulting slurry is cooled to from about 0° C. to about 5° C. and aged for longer than two hours. The chilled slurry is filtered and the wetcake washed with cold deionized water (0°–5° C.) and then dried in vacuo. The compound of Formula III



III

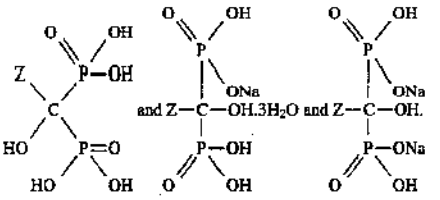
wherein Z is as defined previously and is preferably a C_{2-5} alkyl substituted with a terminal amine and salts thereof, particularly the monosodium and disodium salts, is obtained by this process.

The reaction is schematically represented as follows when the base is NaOH:



wherein Z is defined previously and is preferably a C_{2-5} alkyl substituted with a terminal amine.

A particular illustration of this reaction wherein Z is $NH_2—CH_2—CH_2—CH_2$ leads to



The bisphosphonic acids described here are useful because of their sequestering power for polyvalent metal ions and for complex formation with alkaline earth ions, preferably calcium ions. Therefore, substituted bisphosphonic acids may be useful in water softening, water purification, and in the preparation of non-toxic pharmaceutical medicaments.

Specifically, 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 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt trihydrate made according to the process of the present invention.

Other pharmaceutically acceptable salts, such as for example potassium salts, can be prepared according to the processes of the present invention and are included within the scope thereof. Other bisphosphonates that may be prepared by this continuous process include (a) 2-amino1-hydroxyisobutylidene-1,1-bisphosphonic acid, (b) 3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid, (c) 5-amino-1-hydroxypentylidene-1,1-bisphosphonic acid (d) 6-amino-1-hydroxy-hexylidene-1,1-bisphosphonic acid, (e) risedronate, (1-hydroxy-2-(3-pyridinyl)ethylene-1,1-bisphosphonic acid, and (f) BM210955 N-butyl-N-methyl-3-amino-1-hydroxypropylidine-1,1-bisphosphonic acid.

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

EXAMPLE 1

Continuous preparation of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid

2.6 kgs of MSA was charged to a reactor flask. 0.545 kg of GABA was charged into the flask with stirring followed by a charge of 0.865 kg H_3PO_3. This mixture of MSA, GABA and H_3PO_3 shall hereinafter be referred to as the GABA Feed. The mixture was maintained at 70° C. during dissolution. The remaining 0.645 kg of MSA was added as a rinse and the solution stirred at 70° C. until GABA and H_3PO_3 were dissolved.

The bisphosphonation reactor was jacketed and fitted with a mechanical agitator, feed ports, temperature probe, and a reflux-condenser and a bottom outlet. A standard hydrogenation mixing configuration was used to design the reactor. The reactor includes four half baffles set 90° C. apart extending from the bottom of the reactor. A Rushton turbine type agitator is located at the bottom of the impeller shaft. Also attached to the impeller shaft and located above the Rushton turbine was a propeller type agitator. The propeller type agitator had a larger diameter than the Rushton type

turbine. The jacket surrounding the reactor was located beneath the wetted wall. The bath used to heat the jacket medium was set between 97°–105° C. depending on the heat load requirements of the reaction mass to maintain a batch temperature of 90° C. The condenser and medium were set to achieve an off-gas temperature of −10° C.

Before the continuous bisphosphonation reaction reached steady state a semi-batch start up was employed. The reactor bath was set to 97° C. to maintain temperature of reaction mass at 90° C. The reactor jacket was not circulated until the GABA feed was charged to the reactor. The bath temperature was continuously adjusted as needed to maintain batch temperature of 90° C. The PCl_3 reservoir was filled and refilled as needed. The GABA feed reservoir was filled and refilled as needed. The reactor vessel was filled with 400 ml of the warm GABA feed. At this time agitation and bath circulation of the reactor jacket commenced. The GABA feed in the reactor was heated to 90° C. 50 ml of GABA feed was drained from the reactor. PCl_3 flow was initiated into the reactor at 0.95 ml/min. After 95 minutes, the flow of the GABA feed was initiated at 3.7 ml/min. This time corresponds to 90 ml of PCl_3 entering the reactor and a ratio of PCl_3/GABA feed of 0.33 (g/g). At this stage, the semi-batch start-up procedure was completed and the continuous operation mode was established.

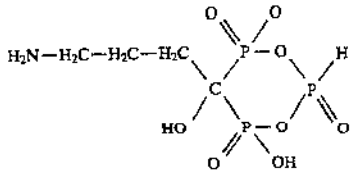
PCl_3 and GABA feeds were continued at 0.95 ml/min. and 3.7 ml/min., respectively, for the desired run time. The flowrates were chosen to give a residence time of 1.8 hours based on the flow rate of GABA feed. During the entire process, the reactor was overflowing into the quench vessel. The yield to intermediates that will subsequently be available after hydrolysis for recovery is about 60–72%, typically 70% at steady state. This is 10% above the yield expected from a direct change from batch to continuous mode.

The amount of material needed was the limiting factor in the length of the run. At the end of the run, the PCl_3 and GABA feeds were turned off. The reactor was drained once PCl_3 was no longer refluxing.

Continuous quenching took place in a 500 ml cylindrical, jacketed reaction flask with an attached overflow leg and a teflon paddle stirring mechanism. The pH probe for the quench was calibrated with buffer solutions of pH 4.0 and 7.0. The lower limit was set at 5.0. The 47% NaOH reservoir was filled and maintained. The deionized (DI) water or the pure mother liquor reservoir was filled and maintained. During the semi-batch start-up, the flow rate of the aqueous NaOH solution was calibrated to 12.3 ml/min. The DI water or the pure mother liquor reservoir flow rate was calibrated to 18.75 ml/min. An initial charge of 700 ml of DI water was placed in the quench vessel. As reaction mass from the bisphosphonation reaction reactor overflowed into the quench vessel, a pH of 5.0 was established by activating the NaOH pump via the pH controller. Once sufficient batch mixture and NaOH were charged to result in >550 g/l total solids, the DI water or pure mother liquor pump was turned on. At this time, the quench vessel overflowed via the overflow leg and the semi-batch start-up was completed.

For continuous operation, the quench vessel was operated with pH control and overflow until the desired mass of material was collected. At reaction shut down, supra, the quench vessel remained on pH control until the entire mass was quenched. 30 minutes after completion of the mass quenching, the pumps and the pH controller were tuned off and the quench vessel was drained.

The compound of the formula



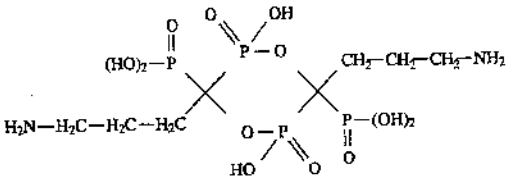
was produced and had the following characteristics:

a) Molecular weight=295; and

b) ^{31}P NMR at 161.98 MHz using H_3PO_4 (δ0.0) as an external reference standard δ3.8, (t, J_{PP}=13.5, J_{PH}=669.4) and δ15.9, (d, J_{PP}=13.5); and

c) ^{13}C NMR at 100.61 MHz using dioxane (δ67.4) as an external reference standard δ83.2, (td, J_{CP}=134.9, 10.4), δ41.2, δ31.8 (d, J_{CP}=3.2), δ23.8 (t, J_{CP}=6.4).

The compound of the formula



was also produced and had the following characteristics

a) Molecular weight=462; and

b) ^{31}P NMR at 161.98 MHz using H_3PO_4(δ0.0) as an external reference standard δ12.9 (t, J_{PP}=17.1), 8.0 (t, J_{PP}=17.1); and

c) ^{13}C NMR at 100.61 MHz using dioxane (δ67.4) as an external standard δ86.4 (ddd, J_{CP}=139.7,129.3,15.3), δ41.0, δ33.3, δ23.0(m).

Hydrolysis was carried out in a 250 ml Ace glass heavy walled safety coated storage bottle equipped with a Teflon™ coated magnetic stir bar and a modified Teflon™ cap to include a Teflon™ coated thermocouple that allowed in situ temperature monitoring. The vessel was suspended in a heated Silicon™ oil bath. 200 ml of quench material was charged to the hydrolysis vessel. The pH of the quench material was measured and adjusted accordingly to insure that the pH was between 4.6–5.5. The contents of the hydrolysis vessel were heated to 140° C. Once the proper temperature was reached the hydrolysis was aged for 20 hours at 140° C. After the aging was completed, the contents of the vessel were allowed to cool to 85° C. and the pH was checked and adjusted to 4.3 by addition of 50% NaOH or 37% HCl.

Crude crystallization was carried out in a 3-neck 250 ml round bottom flask equipped with a teflon paddle. 200 ml of 85° C. solution from the hydrolysis vessel were charged to the 250 ml 3-neck round bottom flask with stirring. The pH of the solution was measured and adjusted accordingly. However, if the pH was below 4.0, the solution was discarded and a new hydrolysis was done. The solution was allowed to cool to 20°–25° C. during which time the batch crystallized. The slurry was aged for >15 hours at room temperature with stirring and filtered with vacuum. The crystals were washed with 2×15 ml 0°–5° C. DI water. The product was dried overnight in vacuo at 45°–50° C.

The purification was carried out in a 3-neck 250 ml round bottom flask equipped with a teflon paddle. 10 g of dry crude material was charged into the 3-neck flask. 150 ml of DI

water was charged to the flask. The flask was heated to 50° C. and held at that temperature until all the solids were dissolved. The flask was removed from the heat and the contents were filtered by vacuum. The filtrate was charged to the 3-neck flask and atmospherically distilled to 44 ml. The flask was removed from the heat and allowed to cool to room temperature. The contents of the flask were allowed to age for two hours. The slurry was cooled to 0°–5° C., aged for two hours and filtered with vacuum. The crystals were washed with 2×15 ml 0°–5° C. water.

EXAMPLE 2

Continuous preparation of (a) 2-amino-1-hydroxyisobutylidene-1,1-bisphosphonic acid, (b) 3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid, (c) 5-amino-1-hydroxypentylidene-1,1-bisphosphonic acid or (d) 6-amino-1-hydroxyhexylidene-1,1-bisphosphonic acid

Using the appropriate aminocarboxylic acid in equivalent amounts to 4-aminobutyric acid it is possible to produce the title bisphosphonic acids using the method of Example 1. The appropriate aminocarboxylic acid include but are not limited to: 2-aminoisobutyric acid, 3-aminopropionic acid, 5-aminovaleric acid and 6-aminocaproic acid.

EXAMPLE 3

Continuous preparation of (a)risedronate, and (b) BM210955

Using the appropriate starting materials, it is possible to produce the title compounds using the method of Example 1. Starting materials include: but are not limited to: 3-pyridylacetic acid, and N-butyl-N-methyl-3-amino propionic acid.

What is claimed is:

1. A compound of the structural Formula I

$$Z—R_1$$

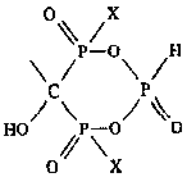
I

wherein Z is selected from the group consisting of:

a) $H_2N—C_{2-5}alkyl—$;

R_1 is:

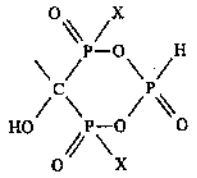
a)



wherein X is —OH or Cl.

2. A compound according to claim 1, having the formula $H_2N—C_{2-5}alkyl—R_1$ wherein R_1 is:

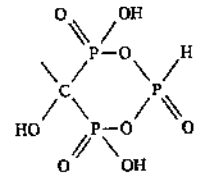
a)



wherein X is OH or Cl.

3. The compound of claim 2 of the formula $H_2N—CH_2—CH_2—CH_2—R_1$.

4. The compound of claim 3 wherein R_1 is



and is characterized by

a) Molecular weight=295; and

b) ^{31}P NMR at 161.98 MHz using H_3PO_4 (δ0.0) as an external reference standard δ3.8, (t, J_{PP}=13.5, J_{PH}=669.4) and δ15.9, (d, J_{PP}=13.5); and

c) ^{13}C NMR at 100.61 MHz using dioxane (δ67.4) as an external reference standard δ83.2, (td, J_{CP}=134.9, 10.4), δ41.2, δ31.8 (d, J_{CP}=3.2), δ23.8 (t, J_{CP}=6.4).

5. A compound according to claim 1 having the formula

$C_{2-6}alkyl—(N—CH_3)C_2H_4N(CH_3)—R_1$.

* * * * *

Exhibit 4

US005648491A

United States Patent [19]

Dauer et al.

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[54] **PROCESS FOR PRODUCING N-AMINO-1-HYDROXY-ALKYL-IDENE-1,1-BISPHOSPHONIC ACIDS**

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[73] Assignee: **Merck & Co., Inc.**, Rahway, N.J.

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PCT Pub. Date: **Mar. 2, 1995**

[51] **Int. Cl.**[6] **C07D 405/06**

[52] **U.S. Cl.** **546/22**; 546/24; 558/83; 558/84; 558/86

[58] **Field of Search** 546/22, 24; 558/83, 558/84, 86

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,407,761	10/1983	Blum et al.	260/502.5 C
4,922,007	5/1990	Kieczykowski et al.	562/13
5,019,651	5/1991	Kieczykowski et al.	562/13

FOREIGN PATENT DOCUMENTS

0039033	11/1981	European Pat. Off. .
216465	7/1983	Germany .

OTHER PUBLICATIONS

Z. anorg. allg. Chem. 576, 272–280, Schülke et al., 1989.
Z. anorg. allg. Chem., 247–259, Blaser et al., 1971.
J. Liquid Chromatography, 17(11), 2511–2531, Thompson et al., 1994.

Primary Examiner—Joseph McKane
Attorney, Agent, or Firm—Joanne M. Giesser; Melvin Winokur

[57] **ABSTRACT**

A process for continuously producing alkylpyrophosphonate, alkylpyrophosphate and multimers thereof and for producing 4-amino-1-hydroxyalkylidene-1,1-bisphosphonic acids or salts thereof.

14 Claims, No Drawings

PROCESS FOR PRODUCING N-AMINO-1-HYDROXY-ALKYL-IDENE-1,1-BISPHOSPHONIC ACIDS

This applicatin is a 371 of PCT/US94/09620 filed Aug. 24, 1994.

BACKGROUND OF THE INVENTION

This invention relates to a process for continuously producing alkylpyrophosphonates, alkylpyrophosphates and multimers thereof and in particular for producing 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid and salts thereof, where the end product is obtained in particularly pure form and at high yields in a continuous reaction.

It is known according to U.S. Pat. No. 4,407,761 to Henkel Kommanditgesellschaft to prepare 4-amino-1-hydroxy-butylidene-1,1-bisphosphonic acid with phosphonating reactants and then quenching the reaction mixture by the addition of a strong non-oxidizing agent, preferably concentrated hydrochloric acid, with heating, to hydrolyze the formed phosphorous intermediates to final product. However, this phosphonation reaction does not remain homogeneous, thereby producing heterogeneous solidification of the reaction mixture. This solidification causes variable yields and leads to the development "hot spots" which in part result from the exothermic nature of the reaction. Moreover, to make the sodium salt, using the prior art processes, requires isolation of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid and an additional step to convert this to the monosodium salt. Further, the use of concentrated hydrochloric acid in the quench, whose fumes present an environmental problem, is also required.

U.S. Pat. No. 4,922,007 to G. R. Kieczykowski, et al., (assigned to Merck & Co., Inc.) discloses the use of methanesulfonic acid to overcome the non-homogeneity and solidification problems associated with the formation of intermediates during the bisphosphonation phase. However, this process utilizes a non-pH controlled water quench that leads to the presence of a strongly acidic and corrosive hydrolysis mixture which requires specialized equipment.

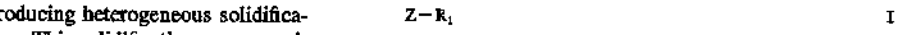
U.S. Pat. No. 5,019,651 to G. R. Kieczykowski, et al., (assigned to Merck & Co., Inc.), discloses using a pH controlled quench step in the range of 4 to 10, followed by hydrolysis, that eliminates the concentrated hydrochloric acid formed in the quench step and the need to handle a corrosive acidic product hydrolysis mixture.

Prior methods teach the requirement that the reaction be completed at temperatures above the boiling point of PCl_3, for instance 90° C. However, this temperature is known to be in the adiabatic self-heat range that is an unsafe operating range as batch volumes increase and available cooling capacity decreases. In addition, control of stoichiometric ratio is important to achieving useful intermediates. However, control of stoichiometric ratios at constant temperature, typically 90° C., is impossible using prior batch methods because stoichiometric quantities of PCl_3 may only be added at sub reflux temperatures. For example, in U.S. Pat. No. 5,019,651, stoichiometric ratios were achieved by use of temperature programming whereby the stoichiometric amount of PCl_3 could be added at sub-reflux temperatures. Alternatively, in U.S. Pat. No. 4,407,761, PCl_3 was added slowly at isothermal reaction temperatures above PCl_3's boiling point. Thus, it is desirable to control both stoichiometry and reaction temperature at the same time to provide consistent distribution of useful intermediates and to ensure a safe operating environment. The prior batch modes of operation made control of stoichiometric ratios impossible while maintaining a constant temperature.

The present invention solves both of these problems through operation of the reaction in a continuous stirred tank reactor that allows greater heat transfer for temperature control while maintaining constant stoichiometric ratios of reactants. The more favorable surface to volume ratio of the present invention allows greater heat transfer for temperature control. Further, continuous steady operation results in fixed ratios of products and intermediates in a small controllable environment by controlling both reaction temperature and stoichiometric ratio at all times. The smaller reacting mixture reduces severity of an unexpected thermal event and allows the entire reacting mixture to be quenched.

SUMMARY OF THE INVENTION

By this invention, there is provided a process for the continuous preparation of compounds of the structural Formula I

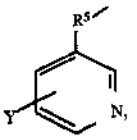


I

wherein Z is selected from the group consisting of:

a) $H_2N—C_{2-5}alkyl—$;

b)



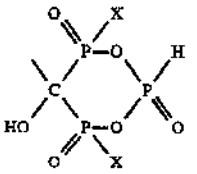
wherein R^5— is C_{1-5}alkyl, and Y is selected from

(i) hydrogen;
(ii) C_{1-5}alkyl;
(iii) R^6O;
(iv) R^6S;
(v) R^6R^6N;
(vi) halogen; R^6 is H or C_{1-5}alkyl; and

c) $C_{2-6}alkyl-(N—CH_3)C_2H_4—$; and

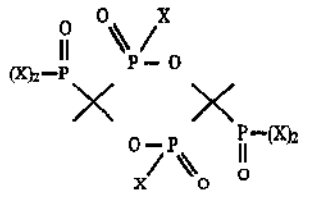
R_1 is a member selected from the group consisting of:

a)

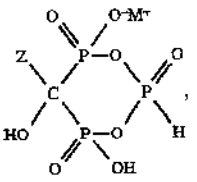


and

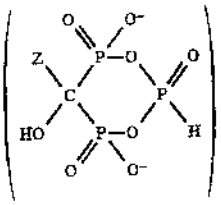
b)



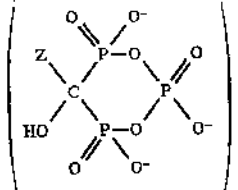
wherein X is OH or Cl. This invention also provides a process for the continuous production of intermediate compounds of Formula IIA, IIB and IIC



IIA

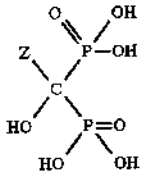


IIB



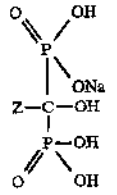
IIC

wherein Z is defined as above, and M is a monovalent, divalent or trivalent cation such as Na^+, K^+, Ca^{2+}, Mg^{2+}. It should be noted that all ionic forms of these intermediate compounds are encompassed by this invention. This invention further includes a process for the continuous production of compounds of Formula IIIA, IIIB, and IIIC



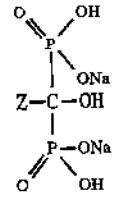
IIIA

and



IIIB

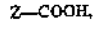
and



IIIC

that comprises:

a) continuously mixing an aminoalkane carboxylic acid of formula



wherein Z is as defined previously, with H_3PO_3 and PCl_3 in methanesulfonic acid (MSA), or optionally PCl_3 in MSA; and

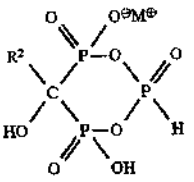
b) continuously adding aqueous base to the overflow mixture containing the compound of Formula I to produce the compounds of Formula II; and

c) hydrolyzing the overflow mixture containing the compounds of Formula II to produce the compounds of Formula III; and

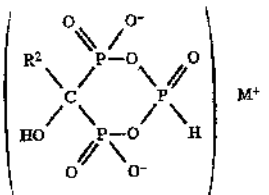
d) recovery of the products of Formula III and salts thereof.

It is noted that all possible hydrated forms are contemplated by this invention. For compounds of Formula IIIB, a trihydrate is a preferred embodiment.

In a preferred embodiment, the compound is of the Formula Ia, Z—R_1 wherein Z is group a) H_2N—C_{2-5}alkyl. Preferred intermediate compounds of the Formula IIa include compounds of the Formulas IIa(i) and IIa(ii):



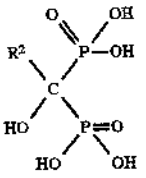
IIa(i)



IIa(ii)

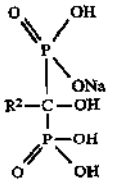
wherein R^2 is C_{2-5}alkyl substituted with a terminal amine or a protonated terminal amine.

This invention preferably includes a process for the continuous production of compounds of the Formula IIIa(i), IIIa(ii), and IIIa(iii).



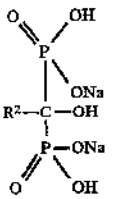
IIIa(i)

and



IIIa(ii)

and



IIIa(iii)

wherein R^2 is C_{2-5}alkyl substituted with a terminal amine, and the compounds may be in any hydrated state or a protonated terminal amine, said process comprising:

a) continuously mixing an aminoalkane carboxylic acid of the formula

$H_2N—C_{2-5}alkyl—COOH$

with H_3PO_3 and PCl_3 in methanesulfonic acid (MSA), or optionally PCl_3 in MSA; and

b) continuously adding aqueous base to the overflow mixture containing the compound of Formula Ia to produce the compounds of Formula IIa; and

c) hydrolyzing the overflow mixture containing the compounds of Formula IIa to produce the compounds of Formula IIIa; and

d) recovery of the products of Formula IIIa and salts thereof.

DETAILED DESCRIPTION OF THE INVENTION

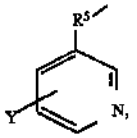
This invention relates to compounds of the structural Formula I

$$Z—R_1 \qquad I$$

wherein Z is selected from the group consisting of:

a) $H_2N—C_{2-5}alkyl—$;

b)



wherein R^5— is $C_{1-5}alkyl$, and Y is selected from

(i) hydrogen

(ii) $C_{1-5}alkyl$;

(iii) R^6O;

(iv) R^6S;

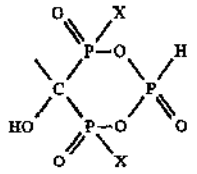
(v) R^6R^6N;

(vi) halogen; R^6 is H or $C_{1-5}alkyl$; and

c) $C_{2-6}alkyl$-$(N—CH_3)C_2H_4$—; and

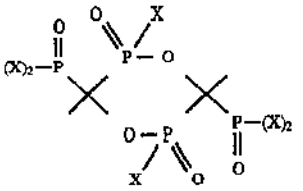
wherein R_1 is a member selected from the group consisting of:

a)



and

b)



wherein X is —OH or —Cl. The present invention is also directed to a process for producing said compounds and the bisphosphonate products thereof including 4-amino-1-hydroxybutylidene-1.1-bisphosphonic acid (ABP) and salts thereof. Specifically, this process may consist of five operations: continuous bisphosphonation reaction, continuous or batch pH controlled quench, continuous or batch hydrolysis, crude crystallization, and pure crystallization.

More specifically, the continuous bisphosphonation reaction consists of producing an carboxylic acid feed and reacting this feed with PCl_3 in a continuous stirred tank reactor.

The carboxylic acid feed is assembled by dissolving solid carboxylic acid and solid phosphorous acid (H_3PO_3) in methanesulfonic acid (MSA). Generally, 1 to 3, preferably 2 moles of H_3PO_3 and generally 6.3 to 6.4, preferably about 6.38 moles of MSA are used per mole of carboxylic acid. To facilitate complete dissolution of the solid components in the liquid MSA, the mixture can be heated from 40° C. to 90° C., preferably 70° C. Once the solid components of the carboxylic acid feed are dissolved, this feed may be maintained from 10° C. to 90° C., preferably 70° C. using an external heat source. Alternately, the H_3PO_3 addition may be eliminated in the carboxylic acid feed preparation. If this alternate procedure is chosen, then H_3PO_3 may be formed in situ from PCl_3 in methanesulfonic acid (MSA), PCl_3 and γ-amino butyric acid (GABA) in MSA, or H_2O in MSA.

The carboxylic acid feed is added to the cold reaction vessel to a point below the overflow level. During this fill, a heating medium is placed in the jacket and the vessel agitator turned on. Temperature control is used to bring the temperature up to about 45°–100° C., preferably 90° C. The liquid PCl_3 feed is then initiated to the reactor vessel until the weight of PCl_3 fed to the reactor (adjusted for vapor loss) divided by the weight of carboxylic acid feed is from 0.22–0.33, preferably 0.32. At this point, the carboxylic acid feed is resumed at a flowrate sufficient to provide a residence time in the reactor from about 1.5–2.5 hours, preferably 1.8 hours. The residence time is expressed as the volume of the reactor overflow conditions divided by the flowrate (vol/min) of carboxylic acid feed. Shortly after the carboxylic acid feed is resumed, the reactor will overflow into the quench vessel which can initially be filled with either water or dilute aqueous base. The carboxylic acid and liquid PCl_3 are added simultaneously at their respective flowrates until the desired amount of material is produced.

Three residence times for the bisphosphonation reaction are undertaken before steady state synthesis occurs. Prior batch processes result in the uncontrollable formation of unwanted intermediates. The present invention overcomes this problem through stoichiometrically controlling the reaction components thereby minimizing the formation of unwanted intermediates.

The overflowing batch is neutralized in an attached quench vessel by the addition of aqueous base. The aqueous base may be any aqueous base of the formula MOH such as sodium hydroxide, or of the formula $MHCO_2$ or MCO_2 such as sodium carbonate or sodium bicarbonate, wherein M is any ion. Separate deionized (DI) water and base feeds are utilized to maintain an effective concentration of base in the quench solution from about 15–50%, preferably about 20%. Aqueous base is added to maintain pH in response to fluctuations in the pH of the quench solution. The pH in the quench vessel is maintained between 4.0 and 7.0, preferably about 5.0. The temperature of the quench mixture may be maintained from 0° C. to 100° C., preferably <50° C.

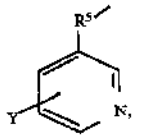
The bisphosphonation mixture produces compound of Formula I.

$$Z—R_1 \qquad I$$

wherein Z is selected from the group consisting of:

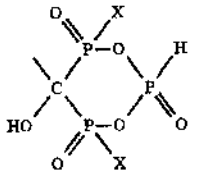
a) $H_2N—C_{2-5}alkyl—$;

b)



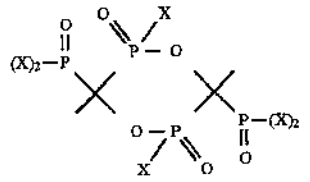
wherein R^5— is C_{1-5}alkyl, and Y is selected from
(i) hydrogen;
(ii) C_{1-5}alkyl;
(iii) R^6O;
(iv) R^6S;
(v) R^6R^6N;
(vi) halogen; R^6 is H or C_{1-5}alkyl; and
c) C_{2-6}alkyl—(N—CH_3)C_2H_4—; and wherein R_1 is a member selected from the group consisting of: a)

a)

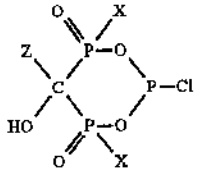


and

b)



wherein X is —OH or Cl. It is likely that the compound of the following formula



is also formed prior to quenching. Preferred compounds according to this invention are as follows. For compounds of the formula Z—R_1, where Z is a) H_2N—C_{2-5}alkyl—, Z is preferably a H_2N—C_4alkyl and the resulting compound may be used as an intermediate for the production of alendronate (4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid, sodium salt trihydrate.)

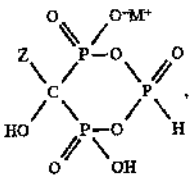
For compounds where Z=b), the preferred compound is where R^5 is CH_2, and the resulting compound may be used as an intermediate for the production of risedronate (1-hydroxy-2-(3-pyridinyl)ethylidene bisphosphonic acid.

For compounds where Z=c) a preferred compound is where Z=C_4alkyl-(N—CH_3)C_2H_4—. This can be used as an intermediate for the production of the compound designated BM210955. (1-hydroxy-3-(methylpentylamino) propylidenebisphosphonate).

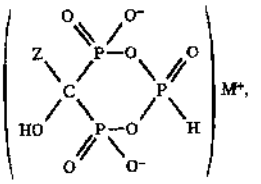
This reaction and/or the bisphosphonation mixture itself exhibits significant exothermic characteristics. Therefore sufficient safety precautions must be undertaken to assure the reaction proceeds safely. To this end, for a given productivity, the smaller reaction volume of the continuous reaction provides faster quench time in the event of reaction runaway than a batch system of similar productivity. The vessel that receives the normal overflow from the bisphosphonation reaction is also employed for the emergency quench. The minimum volume of the emergency quench is about twice the reaction volume of the reactor vessel. This enables the entire reaction volume to be quickly quenched in the event of an undesired thermal event.

The compound of Formula IIA, IIB; or IIC:

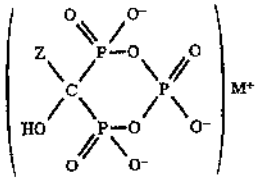
IIA



IIB

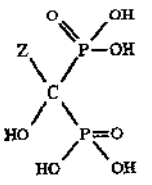


IIC



wherein Z is as defined previously, and preferably a C_{2-5} alkyl substituted with a terminal amine or a protonated terminal amine and M^+ is a monovalent or a divalent cation such as Na+, K+, Ca^{2+}, Mg^{2+}, may be accumulated or may be continuously removed from the quenching vessel via overflow into a new reactor for hydrolysis. It should be appreciated that other anionic forms of compounds of Formula II, for example tri-ionic, are formed under appropriate pH conditions: (structures throughout this specification should be understood as including all possible ionic forms dependent on the pH of the environment). The pH of the quenched material is checked and adjusted, if necessary, to between about 3.3 to 12.3, preferably to about 4.6 and 5.0. The batch is heated in a vessel composed of thick walled PYREX™, or if vessel degradation is a problem, then in a vessel lined with Hastealloy™ C-276, to about 100°–175° C., preferably 140° C. at 60 psig and aged for about 20 hours to breakdown Compounds IIA and IIB into product III.

III

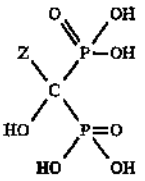


wherein Z is as defined previously and is preferably a C_{2-5} alkyl substituted with a terminal amine and salts thereof, particularly the monosodium and disodium salts.

The batch is then cooled to 85° C. and a sample is taken to confirm pH and completion of hydrolysis. However, hydrolysis of the pyrophosphonate may be carried out at room temperature and recovery of the desired end product is possible. The batch volume may be adjusted before or after

the hydrolysis by either distillation or the addition of water. Pure mother liquors may be returned to the batch before hydrolysis and the excess volume taken off by distillation to ensure the total solids specification for the crude crystallization is met.

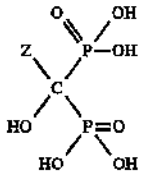
The pH of the warm solution is corrected if needed by the addition of an appropriate acid or base. After the pH adjustment at 85° C., the hydrolyzed batch may be seeded with crude or pure compound of Formula III or its mono or di-salt forms which may be present at the appropriate pH.



III

The batch is cooled to 0°–25° C. This crude solution is aged for >6 hours and the crystal slurry is isolated by filtration. The resulting cake may be washed with cold, deionized water. The crude cake may be dried or charged directly into the purification step.

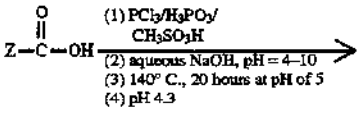
The crude undried mixture and deionized water are added to the purification vessel. The vessel temperature is taken up to from about 40° C. to about 100° C., preferably 50° C. and the solution aged until dissolution is complete. The recovery of end product is pH dependent, from about pH 3.0 to about pH 12.0. Preferably, the pH is adjusted to 4.3 to obtain the mono salt. The batch is filtered and then concentrated by distillation. The resulting slurry is cooled to from about 0° C. to about 5° C. and aged for longer than two hours. The chilled slurry is filtered and the wetcake washed with cold deionized water (0°–5° C.) and then dried in vacuo. The compound of Formula III

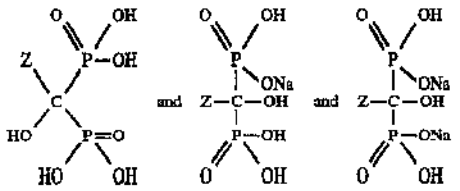


III

wherein Z is as defined previously and is preferably a C_{2-5} alkyl substituted with a terminal amine and salts thereof, particularly the monosodium and disodium salts, is obtained by this process.

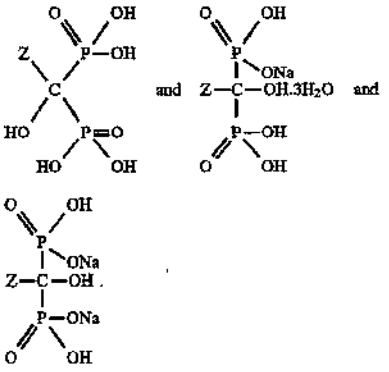
The reaction is schematically represented as follows when the base is NaOH:





wherein Z is defined previously and is preferably a C_{2-5}alkyl substituted with a terminal amine.

A particular illustration of this reaction wherein Z is $NH_2—CH_2—CH_2—CH_2$ leads to



The bisphosphonic acids described here are useful because of their sequestering power for polyvalent metal ions and for complex formation with alkaline earth ions, preferably calcium ions. Therefore, substituted bisphosphonic acids may be useful in water softening, water purification, and in the preparation of non-toxic pharmaceutical medicaments.

Specifically, 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 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt trihydrate made according to the process of the present invention.

Other pharmaceutically acceptable salts, such as for example potassium salts, can be prepared according to the processes of the present invention and are included within the scope thereof. Other bisphosphonates that may be prepared by this continuous process include (a) 2-amino-1-hydroxyisobutylidene-1,1-bisphosphonic acid, (b) 3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid, (c) 5-amino-1-hydroxypentylidene-1,1-bisphosphonic acid (d) 6-amino-1-hydroxyhexylidene-1,1-bisphosphonic acid, (e) risedronate, (1-hydroxy-2-(3-pyridinyl)ethylene-1,1-bisphosphonic acid, and (f) BM210955 N-butyl-N-methyl-3-amino-1-hydroxypropylidine-1,1-bisphosphonic acid.

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

EXAMPLE 1

Continuous Preparation of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic Acid

2.6 kgs of MSA was charged to a reactor flask. 0.545 kg of GABA was charged into the flask with stirring followed by a charge of 0.865 kg H_3PO_3. This mixture of MSA, GABA and H_3PO_3 shall hereinafter be referred to as the GABA Feed. The mixture was maintained at 70° C. during dissolution. The remaining 0.645 kg of MSA was added as a rinse and the solution stirred at 70° C. until GABA and H_3PO_3 were dissolved.

The bisphosphonation reactor was jacketed and fitted with a mechanical agitator, feed ports, temperature probe, and a reflux-condenser and a bottom outlet. A standard hydrogenation mixing configuration was used to design the reactor. The reactor includes four half baffles set 90° C. apart extending from the bottom of the reactor. A Rushton turbine type agitator is located at the bottom of the impeller shaft.

Also attached to the impeller shaft and located above the Rushton turbine was a propeller type agitator. The propeller type agitator had a larger diameter than the Rushton type turbine. The jacket surrounding the reactor was located beneath the wetted wall. The bath used to heat the jacket medium was set between 97°–105° C. depending on the heat load requirements of the reaction mass to maintain a batch temperature of 90° C. The condenser and medium were set to achieve an off-gas temperature of −10° C.

Before the continuous bisphosphonation reaction reached steady state a semi-batch start up was employed. The reaction bath was set to 97° C. to maintain temperature of reaction mass at 90° C. The reactor jacket was not circulated until the GABA feed was charged to the reactor. The bath temperature was continuously adjusted as needed to maintain batch temperature of 90° C. The PCl_3 reservoir was filled and refilled as needed. The GABA feed reservoir was filled and refilled as needed. The reactor vessel was filled with 400 ml of the warm GABA feed. At this time agitation and bath circulation of the reactor jacket commenced. The GABA feed in the reactor was heated to 90° C. 50 ml of GABA feed was drained from the reactor. PCl_3 flow was initiated into the reactor at 0.95 ml/min. After 95 minutes, the flow of the GABA feed was initiated at 3.7 ml/min. This time corresponds to 90 ml of PCl_3 entering the reactor and a ratio of PCl_3/GABA feed of 0.33 (g/g). At this stage, the semi-batch start-up procedure was completed and the continuous operation mode was established.

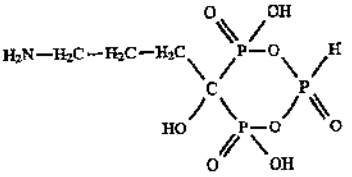
PCl_3 and GABA feeds were continued at 0.95 ml/min. and 3.7 ml/min., respectively, for the desired run time. The flowrates were chosen to give a residence time of 1.8 hours based on the flow rate of GABA feed. During the entire process, the reactor was overflowing into the quench vessel. The yield to intermediates that will subsequently be available after hydrolysis for recovery is about 60–72%, typically 70% at steady state. This is 10% above the yield expected from a direct change from batch to continuous mode.

The amount of material needed was the limiting factor in the length of the run. At the end of the run, the PCl_3 and GABA feeds were turned off. The reactor was drained once PCl_3 was no longer refluxing.

Continuous quenching took place in a 500 ml cylindrical, jacketed reaction flask with an attached overflow leg and a teflon paddle stirring mechanism. The pH probe for the quench was calibrated with buffer solutions of pH 4.0 and 7.0. The lower limit was set at 5.0. The 47% NaOH reservoir was filled and maintained. The deionized (DI) water or the pure mother liquor reservoir was filled and maintained. During the semi-batch start-up, the flow rate of the aqueous NaOH solution was calibrated to 12.3 ml/min. The DI water or the pure mother liquor reservoir flow rate was calibrated to 18.75 ml/min. An initial charge of 700 ml of DI water was placed in the quench vessel. As reaction mass from the bisphosphonation reaction reactor overflowed into the quench vessel, a pH of 5.0 was established by activating the NaOH pump via the pH controller. Once sufficient batch mixture and NaOH were charged to result in >550 g/l total solids, the DI water or pure mother liquor pump was turned on. At this time, the quench vessel overflowed via the overflow leg and the semi-batch start-up was completed.

For continuous operation, the quench vessel was operated with pH control and overflow until the desired mass of material was collected. At reaction shut down, supra, the quench vessel remained on pH control until the entire mass was quenched. 30 minutes after completion of the mass quenching, the pumps and the pH controller were turned off and the quench vessel was drained.

The compound of the formula



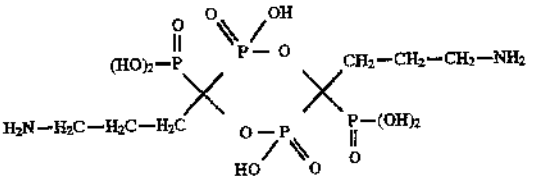
was produced and had the following characteristics:

a) Molecular weight=295; and

b) ^{31}P NMR at 161.98 MHz using H_3PO_4 (δ0.0) as an external reference standard δ3.8, (t, J_{PP}=13.5, J_{PH}=669.4) and δ15.9, (d, J_{PP}=13.5); and

c) ^{13}C NMR at 100.61 MHz using dioxane (δ67.4) as an external reference standard δ83.2, (td, J_{CP}=134.9, 10.4), δ41.2, δ31.8 (d, J_{CP}=3.2), δ23.8 (t, J_{CP}=6.4).

The compound of the formula



was also produced and had the following characteristics

a) Molecular weight=462; and

b) ^{31}P NMR at 161.98 MHz using H_3PO_4 (δ0.0) as an external reference standard δ12.9 (t, J_{PP}=17.1), 8.0 (t, J_{PP}=17.1); and

c) ^{13}C NMR at 100.61 MHz using dioxane (δ67.4) as an external standard δ86.4 (ddd, J_{CP}=139.7,129.3,15.3), δ41.0, δ33.3, δ23.0(m).

Hydrolysis was carried out in a 250 ml Ace glass heavy walled safety coated storage bottle equipped with a Teflon™ coated magnetic stir bar and a modified Teflon™ cap to include a Teflon™ coated thermocouple that allowed in situ temperature monitoring. The vessel was suspended in a heated Silicon™ oil bath. 200 ml of quench material was charged to the hydrolysis vessel. The pH of the quench material was measured and adjusted accordingly to insure that the pH was between 4.6–5.5. The contents of the hydrolysis vessel were heated to 140° C. Once the proper temperature was reached the hydrolysis was aged for 20 hours at 140° C. After the aging was completed, the contents of the vessel were allowed to cool to 85° C. and the pH was checked and adjusted to 4.3 by addition of 50% NaOH or 37% HCl.

Crude crystallization was carried out in a 3-neck 250 ml round bottom flask equipped with a teflon paddle. 200 ml of 85° C. solution from the hydrolysis vessel were charged to the 250 ml 3-neck round bottom flask with stirring. The pH of the solution was measured and adjusted accordingly. However, if the pH was below 4.0, the solution was discarded and a new hydrolysis was done. The solution was allowed to cool to 20°–25° C. during which time the batch crystallized. The slurry was aged for >15 hours at room temperature with stirring and filtered with vacuum. The crystals were washed with 2×15 ml 0°–5° C. DI water. The product was dried overnight in vacuo at 45°–50° C.

The purification was carried out in a 3-neck 250 ml round bottom flask equipped with a teflon paddle. 10 g of dry crude material was charged into the 3-neck flask. 150 ml of DI

water was charged to the flask. The flask was heated to 50° C. and held at that temperature until all the solids were dissolved. The flask was removed from the heat and the contents were filtered by vacuum. The filtrate was charged to the 3-neck flask and atmospherically distilled to 44 ml. The flask was removed from the heat and allowed to cool to room temperature. The contents of the flask were allowed to age for two hours. The slurry was cooled to 0°–5° C., aged for two hours and filtered with vacuum. The crystals were washed with 2×15 ml 0°–5° C. water.

EXAMPLE 2

Continuous Preparation of (a) 2-amino-1-hydroxyisobutylidene-1,1-bisphosphonic Acid, (b) 3-amino-1-hydroxypropylidene-1,1-bisphosphonic Acid, (c) 5-amino-1-hydroxypentylidene-1,1-bisphosphonic Acid

Using the appropriate aminocarboxylic acid in equivalent mounts to 4-aminobutyric acid it is possible to produce the title bisphosphonic acids using the method of Example 1. The appropriate aminocarboxylic acid include but are not limited to: 2-aminoisobutyric acid, 3-aminopropionic acid, 5-aminovaleric acid and 6-aminocaproic acid.

EXAMPLE 3

Continuous Preparation of (a) Risedronate, and (b) BM210955

Using the appropriate starting materials, it is possible to produce the title compounds using the method of Example 1. Starting materials include: but are not limited to: 3-pyridylacetic acid, and N-butyl-N-methyl-3-amino propionic acid.

What is claimed is:

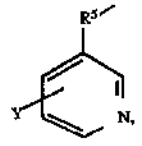
1. A process for the continuous preparation of compounds of the structural Formula I

$$Z-R_1 \quad \text{I}$$

wherein Z is selected from the group consisting of:

a) H_2N-C_{2-5}alkyl—;

b)



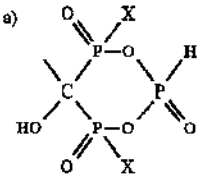
wherein R^5— is C_{1-5}alkyl, and Y is selected from

(i) hydrogen;
(ii) C_{1-5}alkyl;
(iii) R^6O;
(iv) R^6S;
(v) R^6R^6N;
(vi) halogen; R^6 is H or C_{1-5}alkyl; and

c) C_{2-6}alkyl-(N—CH_3)C_2H_4—; and

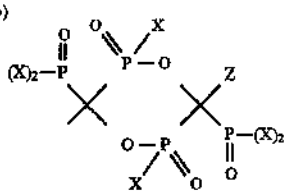
R_1 is a member selected from the group consisting of:

a)



and

b)



and wherein X is —OH or Cl;

that comprises:

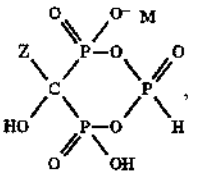
a) continuously mixing a carboxylic acid of formula

Z—COOH,

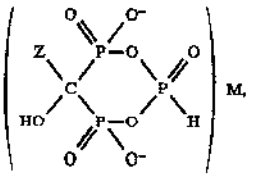
wherein Z is as defined previously, with H_3PO_3 and PCl_3 in methanesulfonic acid (MSA), or optionally PCl_3 in MSA; and

b) continuously adding aqueous base to the overflow mixture containing the compound of Formula I to produce the compounds Of Formula IIa, IIb or IIc; and

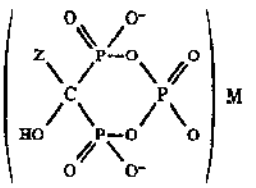
IIA



IIB

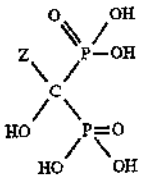


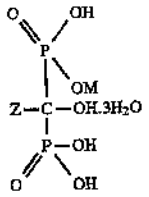
IIC

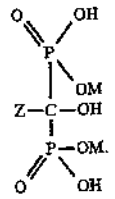


wherein Z is as defined above and M is a monovalent, divalent, or trivalent cation;

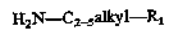
c) hydrolyzing the Compounds of IIa, IIb or IIc to produce the compounds of Formula IIA, IIB and IIC

IIIA 

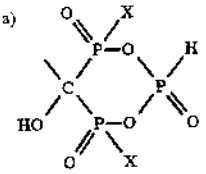
IIIB 

IIIC 

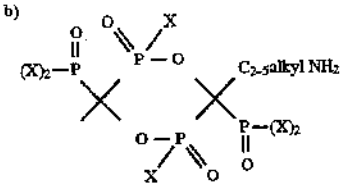
2. A process of claim 1 for the continuous production of a compound of Formula I:



wherein R_1 is a member selected from the group consisting of:

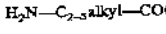
a) 

and

b) 

wherein X is —OH or Cl comprising:

a) continuously mixing an aminoalkane carboxylic acid of formula

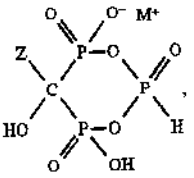


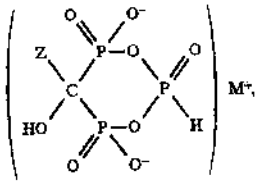
with PCl_3 and H_3PO_3 in the presence of methanesulfonic acid (MSA) or optionally PCl_3 in the presence of MSA; and

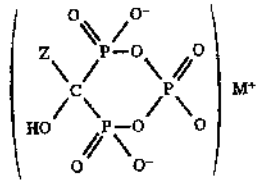
b) continuously removing the mixture containing the compound of Formula I.

3. The process of claim 2 further comprising:

a) continuously adding aqueous base of formula MOH, $MHCO_2$ or MCO_2 to a mixture containing the compound of Formula I to produce the compound of Formula IIa and IIb or IIc:

IIA 

IIB 

IIC 

wherein R_2 is a C_{2-5} alkyl substituted with a terminal amine or a protonated terminal amine and M is a monovalent, divalent or trivalent cation of the base; and

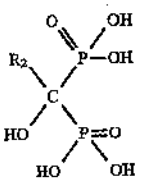
b) continuously removing the mixture containing the compound of Formula IIa, IIb or IIc.

4. The process of claim 3 wherein the aqueous base has a concentration of about 5% to about 50%.

5. The process of claim 4 wherein the aqueous base has a concentration of about 50%.

6. The process of claim 3 wherein the aqueous base is NaOH.

7. The process of claim 3 further comprising hydrolyzing the removed mixture containing the compound of Formula II to produce the compound of Formula III:

III 

or salt thereof.

8. The process of claim 7 wherein hydrolysis is carried out at a pH from about 3.0 to 12.0.

9. The process of claim 8 wherein hydrolysis is carried out at a pH of about 5.

10. The process of claim 9 wherein hydrolysis is carried out at a temperature of 110° C. to about 175° C.

11. The process of claim 10 wherein the temperature is about 140° C.

12. The process of claim 1 wherein the carboxylic acid is a member selected from the group consisting of:

a) 2-Aminoisobutyric acid;

b) 3-Aminopropanoic acid;

c) 4-Aminobutyric acid;

d) 5-Aminovaleric acid;

e) 6-Aminocaproic acid;

f) 3-Pyridylacetic acid; and

g) N-butyl-N-methyl-3-amino propionic acid.

13. The process of claim **5** carried out at a temperature of 45° C. to about 100° C.

14. The process of claim **6** carried out at the temperature of about 90° C.

* * * * *

Exhibit 5

United States Patent [19]

Kieczykowski

[11] **Patent Number: 5,039,819**

[45] **Date of Patent: Aug. 13, 1991**

[54] **DIPHOSPHONATE INTERMEDIATE FOR PREPARING AN ANTIHYPERCALCEMIC AGENT**

[75] Inventor: **Gerard R. Kieczykowski**, Westfield, N.J.

[73] Assignee: **Merck & Co., Inc.**, Rahway, N.J.

[21] Appl. No.: **584,322**

[22] Filed: **Sep. 18, 1990**

[51] Int. Cl.[5] **C07F 9/40**

[52] U.S. Cl. **548/415**

[58] Field of Search 548/415

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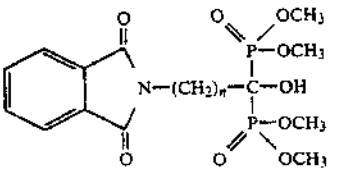
Primary Examiner—Mary C. Lee
Assistant Examiner—Michael G. Ambrose
Attorney, Agent, or Firm—Salvatore C. Mitri; Robert J. North; Charles M. Carusso

[57] **ABSTRACT**

Described is a new diphosphonate intermediate useful in a new process for producing 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid (ABP), a new antihypercalcemic agent. The process involves a 3-step sequence starting with 4-phthalimidobutanoyl chloride which can be practiced as a "one-pot" reaction sequence, without employing PCl_3 or H_3PO_3. The new intermediate has the structure:



IV

where n=1–5.

2 Claims, No Drawings

DIPHOSPHONATE INTERMEDIATE FOR PREPARING AN ANTIHYPERCALCEMIC AGENT

BACKGROUND OF THE INVENTION

4-Amino-1-hydroxybutylidene-1,1-bisphosphonic-acid (ABP), and salts thereof, is a new antihypercalcemic agent effective in the treatment or prevention of diseases involving hypercalcemia of pregnancy, Paget's disease and osteoporosis.

Methods for preparing ABP are known in the art and are disclosed in U.S. Pat. No. 4,407,761 to Henkel and U.S. Pat. No. 4,922,007 to G. R. Kieczykowski et al. (assigned to Merck & Co., Inc.). However, these methods employ the use of toxic and environmentally dangerous phosphorus trichloride and phosphorous acid in their procedures. Newer methods which do not employ these particularly hazardous and toxic reagents are constantly being searched for.

The articles, *J. Org. Chem.* Vol. 36, No. 24, pp 3843-45 (1971) and *J. Med. Chem.* 1987, Vol. 30, pp. 1426-1433, describe general methods of preparation of tetramethylalkyl-1-hydroxy-1,1-diphosphonates but do not specifically describe the preparation of omega-amino-1-hydroxyalkyl diphosphonates.

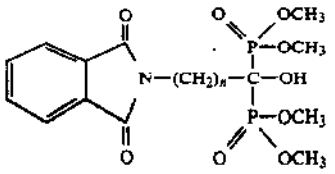
The use of the phthaloyl protecting group in amino acid chemistry is well known, e.g., J. Med. Chem. 1979, vol. 22, No. 11, pp. 1399-1402, but there is no specific teaching as to their possible use in preparing omega-amino-1-hydroalkyl diphsophonates.

SUMMARY OF THE INVENTION

It has been found that ABP can be produced in good yield via a novel process that does not employ PCl_3 or H_3PO_3. The process involves reacting 4-phthalimidobutanoyl chloride with a tri C_1-C_4 alkylphosphite, e.g., trimethyl phosphite, and then with a di C_1-C_4 alkylphosphite, e.g., dimethyl phosphite, to form the new disphosphonate tetraalkyl ester, e.g., tetramethyl bisphosphonate, which is then acid hydrolyzed to form ABP in good yield and purity.

In addition, the process is applicable to the preparation of other omega-amino-1-hydroxy-C_2-C_6 alkyl disphosphonates as well.

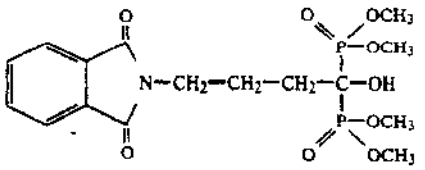
By this invention there is provided a compound of the formula:



IV

where n=1-5.

Specifically, there is further provided a compound of the formula:



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The claimed diphosphonate intermediate is useful in a new process for producing omega-amino-1-hydroxy-C_2-C_6 alkylidene-bisphosphonic acid comprising the steps of:

(a) contacting omega-phthalimido C_2-C_6 alkanoyl chloride with a tri C_1-C_4 alkyl trimethyl phosphite in a dry inert organic solvent at a temperature in the range of 0° to 60° C. to form di C_1-C_4 alkyl omega-phthalimido-C_2-C_6 alkanoyl phosphonate;

(b) contacting di C_1-C_4 alkyl omega-phthalimido-C_2-C_6 alkanoyl phosphonate from Step (a) with di C_1-C_4 alkyl phosphite in a dry inert organic solvent in the temperature range of 0° to 60° C. to form tetra C_1-C_4 alkyl omega-phthalimido-1-hydroxy-C_2-C_6 alkylidene-bisphosphonate;

(c) contacting tetra C_1-C_4 alkyl omega-phthalimido-1-hydroxy-C_2-C_6 alkylidene-bisphosphonate; from Step (b) with aqueous strong acid at a temperature in the range of 90° C. to reflux to form omega-amino-1-hydroxy-C_2-C_6 alkylidene-bisphosphonic acid.

Specifically there is provided a process for producing 4-amino-1-hydroxybutylidene-bisphosphonic acid comprising the steps of:

(a) contacting 4-phthalimidobutanoyl chloride with trimethyl phosphite in a dry inert organic solvent at a temperature in the range of 0° to 60° C. to form dimethyl 4-phthalimidobutanoyl phosphonate;

(b) contacting dimethyl 4-phthalimidobutanoyl phosphonate from Step (a) with dimethyl phosphite in a dry inert organic solvent in the temperature range of 0° to 60° C. to form tetramethyl phthalimido-1-hydroxy butylidene-bisphosphonate;

(c) contacting tetramethyl phthalimido-1-hydroxybutylidene-bisphosphonate from Step (b) with aqueous hydrochloric acid at a temperature range of 80° C. to reflux to. form 4-amino-1-hydroxybutylidene-bisphosphonic acid.

BRIEF DESCRIPTION OF PREFERRED EMBODIMENTS

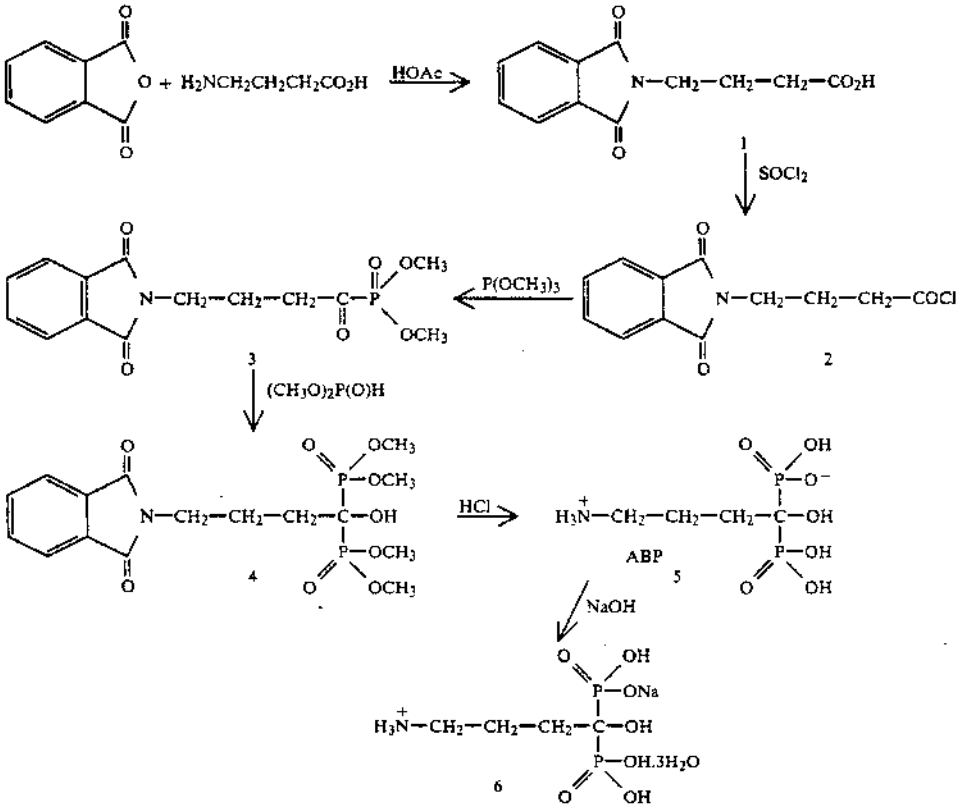
The invention process can be more readily seen and appreciated by referring to the following Flow Chart 1. This new process for the preparation of ABP can proceed in good overall yield from gamma-4-aminobutyric acid (GABA). As depicted in the flow chart, phthalic anhydride is reacted with GABA, e.g. in acetic acid, to form the known 4-phthalimido-butyric acid 1 which can be isolated by e.g., crystallization from acetic acid-water. It is converted into the known acid chloride 2 by reaction with about 1.2 equivalents of thionyl chloride in, e.g. toluene, and without isolation can be converted to the acyl phosphonate 3 with about 1.05 equivalents of trimethyl phosphite. The acyl phosphonate 3 can then be in turn converted, without isolation, into the bisphosphonate 4 by reacting with dimethyl phosphite (in e.g. toluene) in the presence of an amine base, e.g., triethylamine. The bisphosphonate can crystallize as it is formed and can be isolated by filtration in good overall yield. Hydrolysis of the bisphosphonate with a strong aqueous acid, e.g., 6N HCl, provides ABP which can then be converted into the monosodium salt, which is the preferred pharmaceutical dosage form, with sodium hydroxide at about a pH of 4.3, in which the sodium aqueous salt can easily be isolated.

In addition to utilizing 4-aminobutanoic acid, also operable are glycine, 3-aminopropanoic acid, 5-aminopentanoic acid and 6-aminohexanoic acid, which yield the corresponding omega-amino-1-hydroxy

C_2–C_6 alkylbisphosphonates in the invention process, e.g., 2-amino-1-hydroxyethylidene-1,1-bisphosphonic acid, 3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid, 5-amino-1-hydroxypentylidene-1,1-bisphosphonic acid, 6-amino-1-hydroxy-hexylidene-1,1-bisphosphonic acid.

More detail concerning the individual steps is as follows:

FLOW CHART



The 4-phthalimidobutanoic acid is known in the art. The compound can be easily made in our process by for example, reacting phthalic anhydride and aqueous aminobutyric acid in a 1:1 mole ratio in a liquid alkanoic acid, e.g. acetic acid, at about a 40% concentration, at a temperature in the range of 60° to reflux, preferably 110° C., for about 1–4 hours at 1 atmosphere pressure, under anhydrous conditions and then quenching the reaction mixture with water to isolate the resulting acid (1).

The acid chloride (2) also known in the art can easily be made by heating a mixture of the acid (1) with thionyl chloride in a 1:1.2 molar ratio in a dry inert solvent, including C_6–C_{10} aromatic hydrocarbons, chlorinated C_6–C_{10} aromatic hydrocarbons, chlorinated alkyl hydrocarbons, C_2–C_3 alkylnitriles, C_4–C_6 linear or cyclic ethers. Representative examples are: toluene, xylene, methylene chloride, chloroform, chlorobenzene, acetonitrile, ethylene dichloride, dichlorobenzene, THF, dioxane, dimethoxyethane, and the like, at a temperature of about 40° C.-reflux, preferably 45° C., at atmospheric pressure, under a dry atmosphere, e.g. under nitrogen, for 1–2 hours. The resulting acid chloride does not need to be isolated at this point but can be used directly in the next step by evaporating off the excess thionyl chloride and concentrating the solvent toluene to about one-half its original volume.

Step (a) in the process is conducted by reacting the acid chloride (2) with a tri C_1–C_4 alkyl-phosphite, wherein C1–C4 alkyl includes methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, e.g., trimethyl phosphite. In general, a 1:1.05 molar ratio of acid chloride/trimethylphosphite is used, in which a slight excess of phosphite is employed. The solvent used can be the same as that described above used in forming the acid chloride, e.g. toluene, et al., and preferably the same reaction vessel is employed. The concentration of the reactants is about 5–50% and the reaction is carried out at a temperature of 0°–60° C., preferably 20°–25° C., in the solvent in a dry atmosphere, e.g. under nitrogen, for 4–20 hours at atmospheric pressure. The resulting mono-phosphonate (3) does not need to be isolated but can be directly reacted without isolation with dimethylphosphite in Step (b).

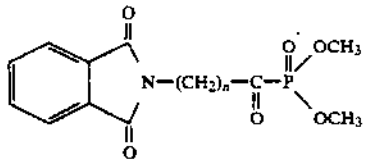
The acylphosphonate (3) is next reacted in Step (b) with or without prior isolation, preferably without isolation, with a di C_1–C_4 alkyl phosphite, wherein "C_1–C_4 alkyl" is defined above, and preferably dimethylphosphite, in a 1:1.1 molar ratio, the dimethylphosphite being in slight excess, also in the presence of a hydrogen acceptor, e.g. tertiary nitrogen amine. Large amounts of the phosphite can also be used but are not necessary. The amine, preferably a tertiary nitrogen amine, e.g. trimethylamine, triethylamine, phenyldimethylamine, and the like, is used in a 0.25–1:1 molar ratio of amine/acylphosphonate (3). The inert solvent used in

this step can be the same as used for Step (a), e.g. toluene, methylene chloride, chloroform, and the like, preferably toluene. The temperature for the step is carried out at 0°–60° C., preferably 20°–25° C., wherein higher temperatures may cause degradation. The pressure is atmospheric, and the reaction is conducted under a dry atmosphere, e.g. nitrogen, for 1–2 hours and then cooled and filtered to isolate the product. Alternatively, the product can be directly treated in Step (c) with aqueous strong acid in the hydrolysis, but preferably for purity consideration, at this point, the tetramethyl ester (4) is isolated by filtration.

Step (c), the strong acid hydrolysis, is conducted by treating the bisphosphonate (4) with aqueous strong acid at a temperature in the range of 85°–100° C. to reflux, and preferably at reflux. Strong acids operable in the process are: HCl, H_2SO_4, benzenesulfonic acid, p-toluenesulfonic acid, methanesulfonic acid, HBr, trichloroacetic acid, and the like. Preferably, 6N HCl is used. Generally the reaction is conducted from 4–24 hours at reflux at atmospheric pressure. The product can be isolated by the addition of e.g. ethanol, to precipitate the product and the solution. Or preferably, the monosodium salt can be formed in-situ by the addition of aqueous sodium hydroxide to the cooled hydrolysis reaction mixture, sufficient caustic being added to dissolve the acid and produce a pH of about 4.3, allowing the reaction mixture to age for 1 hour, then filtering the monosodium salt. The obtained salt can be used directly or purified by conventional purposes, e.g. recrystallization from water to form suitable material for pharmaceutical purposes.

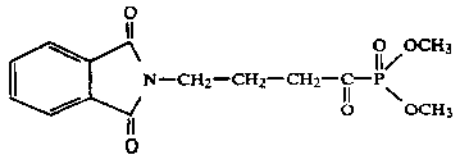
Apparatus for carrying out the above procedures is conventional in the art.

Also disclosed is the novel general process intermediate compound (III)



III

where n=1–5, and the specific intermediate (3),



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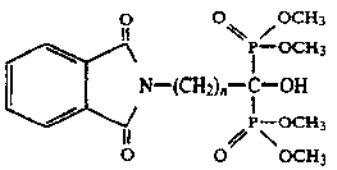
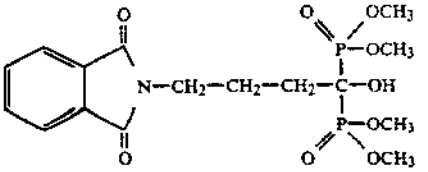
made by the above process and having the following physical properties described below in the Examples.

Claimed is the novel general process intermediate compound (IV)



IV

where n=1–5, and the specific intermediate (4):



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made by the above process and having the above physical properties described below in the Examples.

The following Examples are illustrative of carrying out Applicant's novel process and should not be construed to limit the scope or spirit of Applicant's invention.

EXAMPLE

Step 1

Preparation of 4-Phthalimidobutanoic Acid (1)

A 2 liter nitrogen flushed flask fitted with a mechanical stirrer and a reflux condenser was charged with 103 g (1 mole) of 4-aminobutyric acid (GABA), 148 g (1 mole) of phthalic anhydride and 250 ml of glacial acetic acid.

The suspension was heated to reflux (120° C.) and the resulting clear solution was maintained at reflux for 2 hr. The solution was cooled to 25° C. over 1 hr during which time the product crystallized out. Water (1.5 liters) was added over 15 min. and the resulting suspension aged at 5°–10° C. for 2 hours. The product was collected by filtration and washed with an additional 0.5 l of water. The product was vacuum dried (house vac) at 60° C. to constant weight yielding 214 g (91.8%, 93% corrected for GABA purity), MP 114°–117° C.

Anal. Calcd. For $C_{12}H_{11}NO$: C, 61.80; H, 4.72; N, 6.00; Found: C, 61.78; H, 4.65; N, 5.98.

Step 2

Preparation of 4-Phthalimidobutanoyl Chloride (2)

A 250 ml flask flushed and blanketed with nitrogen and fitted with a mechanical stirrer was charged with 23.3 g of 4-phthalimidobutyric acid from Step 1, 100 ml of toluene, 9.0 ml of thionyl chloride and 0.1 ml of DMF. The slurry was agitated gently and warmed to 45°–50° C. resulting in a clear, colorless solution.

During the age, gentle gas evolution was observed and ceased approximately 1 hour into the age. The excess thionyl chloride was removed by distillation. The volume of the reaction was reduced to 50 ml by distillation under house vacuum (100 mm Hg) and a jacket temperature of 80° C. An additional 100 ml of toluene was added and distilled. The clear, colorless solution was used without purification.

The acid chloride was isolated for characterization as a crystalline solid by concentrating the solution to an oil, adding diethyl ether and filtering, MP 65°–68° C.

Anal. Calcd. For $C_{12}H_{10}NO_3Cl$: C, 57.26; H, 3.97; N, 5.56; Cl, 14.09; Found: C, 57.48; H, 4.07; N, 5.52; Cl, 14.05.

Step 3

Preparation of Dimethyl 4-Phthalimidobutanoyl Phosphonate (3)

The toluene solution from Step 2 containing a theoretical 25.1 g (0.1 mole) of acid chloride was stirred at

20°–25° C. under nitrogen. To this solution was charged 13.0 g (0.105 mole) of trimethyl phosphite in one portion. The reaction temperature increased slightly from 25° C. to 27° C. The clear colorless solution was aged at 20°–25° C. for 18 hours.

Once the formation of the acyl phosphonate was complete, the solution was used without purification for the next reaction in the sequence, formation of the tetraalkyl bisphophonate ester. The acyl phosphonate was isolated as a crystalline solid by concentrating in vacuo to almost dryness, adding hexanes and filtering, MP 60°–63° C.

Anal. Calcd. For $C_{14}H_{16}NO_6P$: C, 51.69; H, 4.92; N, 4.30; P, 9.53; Found: C, 51.27; H, 4.93; N, 4.25; P, 9.31.

Step 4

Preparation of Tetramethyl Phthalimido-1-Hydroxybutylidene)Bisphosphonate (4)

The toluene solution from Step 3 containing a theoretical 32.5 g (0.1 mole) of the acyl phosphonate was used without purification for formation of the tetraalkyl bisphophonate ester. To the solution stirred at 20°–25° C. under nitrogen was added dimethyl phosphite, 11.6 g (0.105 mole) in one portion. Triethylamine, 10.0 g (0.1 mole) was added dropwise over 15 minutes while maintaining a reaction temperature of 20°–25° C. with external cooling. During the addition of the triethylamine there was a rapid crystallization of the bisphosphonate resulting in a thick slurry. The slurry was stirred at 20°–25° C. for an additional 1 hour.

The reaction mixture was cooled to 0°–5° C., aged for 1 hour then filtered. The cake was washed with 50 ml of toluene and the product dried in vacuo (house vacuum) at 40° C. to constant weight yielding 40.0 g (92%) of white crystalline bisphosphonate, MP 140°–143° C.

Anal. Calcd. For $C_{16}H_{23}NO_9P_2$: C, 44.14; H, 5.28; N, 3.21; P, 14.24; Found: C, 44.10; H, 5.23; N, 3.09; P, 14.20.

Step 5

Preparation of (4-Amino-1-Hydroxybutylidene)-Bisphosphonic Acid (ABP) (5)

Tetramethyl-1,1-bisphosphono-1-hydroxy-4-phthalimidobutane 40 g (0.091 mole) from *Step* 4 was dissolved in 200 ml of 6N HCl and the solution refluxed for 18 hours.

The resulting suspension was cooled to 0°–5° C. and the phthalic acid was removed by filtration. The phthalic acid cake was washed with 50 ml of 6N HCl and the combined filtrate concentrated to 25 ml then flushed with an additional 50 ml of water. The solution was cooled to 20°–25° C. during which time the ABP crystallizes. The crystallization was completed by adding 75 ml of 95% ethanol.

The suspension was cooled to 0°–5° C. and aged at that temperature for 2 hours. The titled product was collected by filtration and washed with 25 ml of 95% ethanol. The yield was 24.0 g (97.8%, but 89.8% based on starting GABA) after air drying to constant weight.

Step 6

Preparation of (4-Amino-1-Hydroxybutylidene)-Bisphosphonic Acid Monosodium Salt Trihydrate (6)

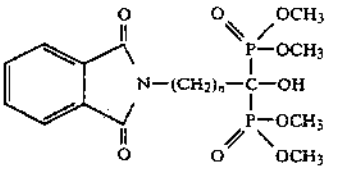
Ten grams (37.4 mmol) of (4-amino-1-hydroxybutylidene)biphosphonic acid, (ABP) was suspended in 300 mL of distilled deionized water with vigorous stirring at 25° C. The pH was 2.27 and was titrated to pH 4.3 to 4.4 by the gradual addition of 7.5 ml (37.4 mmol) 5N sodium hydroxide solution, resulting in a clear solution.

The clear solution was filtered through a medium sintered-glass funnel to remove any insoluble material. Twenty percent of the filtrate (~60 mL) was addedover 5 minutes to 400 mL of 95% ethanol at 20°–25° C. with vigorus stirring and aged for one hour.

The remaining 240 mL of aqueous solution was added over 15 minutes and the mixture aged for 2 hours at 20°–25° C. The white sodium salt was collected by filtration, washed with 100 ml of 2:1 EtOH:H_2O and air dried at 40° C. to yield 11.25 g (93%) of mono sodium salt trihydrate.

What is claimed is:

1. A compound of the formula:



IV

where n=1–5.

2. The compound of claim 1 of the formula:

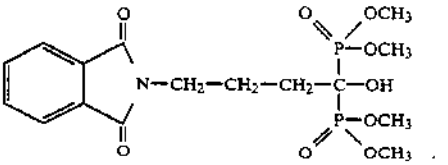


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Exhibit 6

US005159108A

United States Patent [19]

Kieczykowski

[11] Patent Number: 5,159,108

[45] Date of Patent: Oct. 27, 1992

[54] **PROCESS FOR PREPARING AN ANTIHYPERCALCEMIC AGENT**

[75] Inventor: **Gerard R. Kieczykowski**, Westfield, N.J.

[73] Assignee: **Merck & Co., Inc.**, Rahway, N.J.

[21] Appl. No.: **742,142**

[22] Filed: **Aug. 1, 1991**

Related U.S. Application Data

[63] Continuation of Ser. No. 584,318, Sep. 18, 1990, abandoned.

[51] **Int. Cl.**[5] **C07F 9/38**

[52] **U.S. Cl.** **562/13**; 548/415

[58] **Field of Search** 562/13; 548/415

[56] **References Cited**

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Primary Examiner—Jose G. Dees

Assistant Examiner—B. Frazier

Attorney, Agent, or Firm—Robert J. North; Charles C. Caruso

[57] **ABSTRACT**

Described is a new process for producing 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid (ABP), a new antihypercalcemic agent. The process involves a 3-step sequence starting with 4-phthalimidobutanoyl chloride which can be practiced as a "one-pot" reaction sequence, without employing PCl_3 or H_3PO_3.

10 Claims, No Drawings

PROCESS FOR PREPARING AN ANTIHYPERCALCEMIC AGENT

This is a continuation of application Ser. No. 07/584,318, filed on Sep. 18, 1990 now abandoned.

BACKGROUND OF THE INVENTION

4-Amino-1-hydroxybutylidene-1,1-bisphosphonic acid (ABP), and salts thereof, is a new antihypercalcemic agent effective in the treatment or prevention of diseases involving hypercalcemia of pregnancy, Paget's disease and osteoporosis.

Methods for preparing ABP are known in the art and are disclosed in U.S. Pat. No. 4,407,761 to Henkel and U.S. Pat. No. 4,922,007 to G. R. Kiecykowski et al (assigned to Merck & Co., Inc.). However, these methods employ the use of toxic and environmentally dangerous phosphorus trichloride and phosphorous acid in their procedures. Newer methods which do not employ these particularly hazardous and toxic reagents are constantly being searched for.

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The use of the phthaloyl protecting group in amino acid chemistry is well known, e.g., *J. Med. Chem.* 1979, vol. 22, No. 11, pp. 1399–1402, but there is no specific teaching as to their possible use in preparing omega-amino-1-hydroalkyl diphosphonates.

SUMMARY OF THE INVENTION

It has been found that ABP can be produced in good yield via a novel process that does not employ PCl_3 or H_3PO_3. The process involves reacting 4-phthalimidobutanoyl chloride with a tri C_1–C_4 alkylphosphite, e.g., trimethyl phosphite, and then with a di C_1–C_4 alkylphosphite, e.g., dimethyl phosphite, to form the tetraalkyl ester, e.g., tetramethyl bisphosphonate, which is then acid hydrolyzed to form ABP in good yield and purity.

In addition, the process is applicable to the preparation of other omega-amino-1-hydroxy-C_2–C_6 alkyl disphosphonates as well.

By this invention there is provided a process for producing omega-amino-1-hydroxy-C_2–C_6 alkylidene-bisphosphonic acid comprising the steps of:

(a) contacting omega-phthalimido C_2–C_6 alkanoyl chloride with a tri C_1–C_4 alkyl phosphite in a dry inert organic solvent at a temperature in the range of 0° to 60° C. to form di C_1–C_4 alkyl omega-phthalimido-C_2–C_6 alkanoyl phosphonate;

(b) contacting di C_1–C_4 alkyl omega-phthalimido-C_2–C_6 alkanoyl phosphonate from Step (a) with di C_1–C_4 alkyl phosphite in a dry inert organic solvent in the temperature range of 0° to 60° C. to form tetra C_1–C_4 alkyl omega-phthalimido-1-hydroxy-C_2–C_6 alkylidene-bisphosphonate;

(c) contacting tetra C_1–C_4 alkyl omega-phthalimido-1-hydroxy-C_2–C_6 alkylidene-bisphosphonate from Step (b) with aqueous strong acid at a temperature in the range of 90° C. to reflux to form omega-amino-1-hydroxy-C_2–C_6 alkylidene-bisphosphonic acid.

Specifically there is provided a process for producing 4-amino-1-hydroxybutylidene-bisphosphonic acid comprising the steps of:

(a) contacting 4-phthalimidobutanoyl chloride with trimethyl phosphite in a dry inert organic solvent at a temperature in the range of 0° to 60° C. to form dimethyl 4-phthalimidobutanoyl phosphonate;

(b) contacting dimethyl 4-phthalimidobutanoyl phosphonate from Step (a) with dimethyl phosphite in a dry inert organic solvent in the temperature range of 0° to 60° C. to form tetramethyl phthalimido-1-hydroxy butylidene-bisphosphonate;

(c) contacting tetramethyl phthalimido-1-hydroxybutylidene-bisphosphonate from Step (b) with aqueous hydrochloric acid at a temperature range of 80° C. to reflux to form 4-amino-1-hydroxybutylidene-bisphosphonic acid.

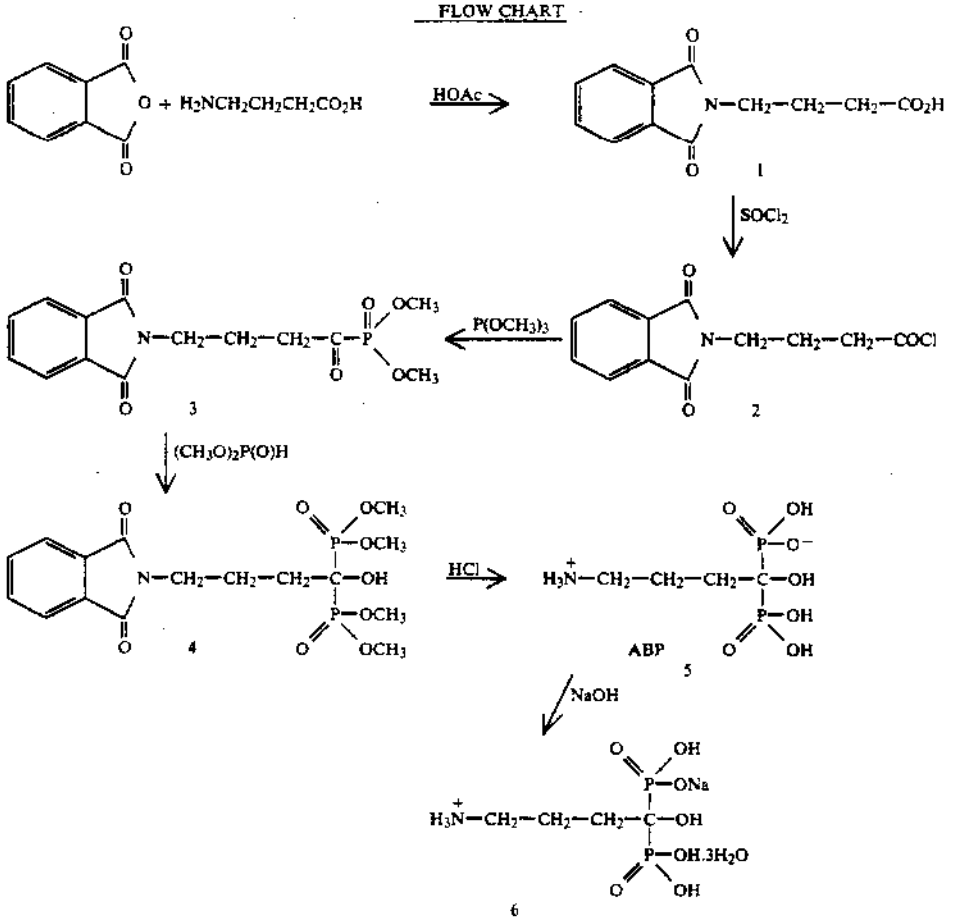
BRIEF DESCRIPTION OF PREFERRED EMBODIMENTS

The invention process can be more readily seen and appreciated by referring to the following Flow Chart 1. This new process for the preparation of ABP can proceed in good overall yield from gamma-4-aminobutyric acid (GABA). As depicted in the flow chart, phthalic anhydride is reacted with GABA, e.g. in acetic acid, to form the known 4-phthalimidobutyric acid 1 which can be isolated by e.g., crystallization from acetic acid-water. It is converted into the known acid chloride 2 by reaction with about 1.2 equivalents of thionyl chloride in, e.g. toluene, and without isolation can be converted to the acyl phosphonate 3 with about 1.05 equivalents of trimethyl phosphite. The acyl phosphonate 3 can then be in turn converted, without isolation, into the bisphosphonate 4 by reacting with dimethyl phosphite (in e.g. toluene) in the presence of an amine base, e.g., triethylamine. The bisphosphonate can crystallize as it is formed and can be isolated by filtration in good overall yield. Hydrolysis of the bisphosphonate with a strong aqueous acid, e.g., 6N HCl, provides ABP which can then be converted into the monosodium salt, which is the preferred pharmaceutical dosage form, with sodium hydroxide at about a pH of 4.3, in which the sodium aqueous salt can easily be isolated.

In addition to utilizing 4-aminobutanoic acid, also operable are glycine, 3-aminopropanoic acid, 5-aminopentanoic acid and 6-aminohexanoic acid, which yield the corresponding omega-amino-1-hydroxy C_2–C_6 alkylbisphosphonates in the invention process, e.g., 2-amino-1-hydroxyethylidene-1,1-bisphosphonic acid, 3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid, 5-amino-1-hydroxypentylidene-1,1-bisphosphonic acid, 6-amino-1-hydroxy-hexylidene-1,1-bisphosphonic acid.

More detail concerning the individual steps is as follows:

FLOW CHART



The 4-phthalimidobutanoic acid is known in the art. The compound can be easily made in our process by for example, reacting phthalic anhydride and aqueous aminobutyric acid in a 1:1 mole ratio in a liquid alkanoic acid, e.g. acetic acid, at about a 40% concentration, at a temperature in the range of 60° to reflux, preferably 110° C., for about 1–4 hours at 1 atmosphere pressure, under anhydrous conditions and then quenching the reaction mixture with water to isolate the resulting acid (1).

The acid chloride (2) also known in the art can easily be made by heating a mixture of the acid (1) with thionyl chloride in a 1:1.2 molar ratio in a dry inert solvent, including C_6–C_{10} aromatic hydrocarbons, chlorinated C_6–C_{10} aromatic hydrocarbons, chlorinated alkyl hydrocarbons, C_2–C_3 alkylnitriles, C_4–C_6 linear or cyclic ethers. Representative examples are: toluene, xylene, methylene chloride, chloroform, chlorobenzene, acetonitrile, ethylene dichloride, dichlorobenzene, THF, dioxane, dimethoxyethane, and the like, at a temperature of about 40° C.-reflux, preferably 45° C., at atmospheric pressure, under a dry atmosphere, e.g. under nitrogen, for 1–2 hours. The resulting acid chloride does not need to be isolated at this point but can be used directly in the next step by evaporating off the excess thionyl chloride and concentrating the solvent toluene to about one-half its original volume.

Step (a) in the process is conducted by reacting the acid chloride (2) with a tri C_1–C_4 alkylphosphite, wherein C_1–C_4 alkyl includes methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, sec-butyl t-butyl, e.g., trimethyl phosphite. In general, a 1:1.05 molar ratio of acid chloride/trimethylphosphite is used, in which a slight excess of phosphite is employed. The solvent used can be the same as that described above used in forming the acid chloride, e.g. toluene, et al., and preferably the same reaction vessel is employed. The concentration of the reactants is about 5–50% and the reaction is carried out at a temperature of 0°–60° C., preferably 20°–25° C., in the solvent in a dry atmosphere, e.g. under nitrogen, for 4–20 hours at atmospheric pressure. The resulting mono-phosphonate (3) does not need to be isolated but can be directly reacted without isolation with dimethylphosphite in Step (b).

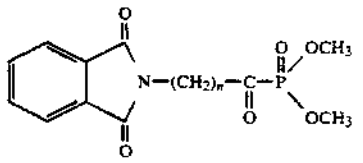
The acylphosphonate (3) is next reacted in Step (b) with or without prior isolation, preferably without isolation, with a di C_1–C_4 alkyl phosphite, wherein "C_1–C_4 alkyl" is defined above, and preferably dimethylphosphite, in a 1:1.1 molar ratio, the dimethylphosphite being in slight excess, also in the presence of a hydrogen acceptor, e.g. tertiary nitrogen amine. Large amounts of the phosphite can also be used but are not necessary. The amine, preferably a tertiary nitrogen amine, e.g. trimethylamine, triethylamine, phenyldimethylamine, and the like, is used in a 0.25–1:1 molar ratio of amine/acylphosphonate (3). The inert solvent used in

this step can be the same as used for Step (a), e.g. toluene, methylene chloride, chloroform, and the like, preferably toluene. The temperature for the step is carried out at 0°–60° C., preferably 20°–25° C., wherein higher temperatures may cause degradation. The pressure is atmospheric, and the reaction is conducted under a dry atmosphere, e.g. nitrogen, for 1–2 hours and then cooled and filtered to isolate the product. Alternatively, the product can be directly treated in Step (c) with aqueous strong acid in the hydrolysis, but preferably for purity consideration, at this point, the tetramethyl ester (4) is isolated by filtration.

Step (c), the strong acid hydrolysis, is conducted by treating the bisphosphonate (4) with aqueous strong acid at a temperature in the range of 85°–100° C. to reflux, and preferably at reflux. Strong acids operable in the process are: HCl, H_2SO_4, benzenesulfonic acid, p-toluenesulfonic acid, methanesulfonic acid, HBr, trichloroacetic acid, and the like. Preferably, 6N HCl is used. Generally the reaction is conducted from 4–24 hours at reflux at atmospheric pressure. The product can be isolated by the addition of e.g. ethanol, to precipitate the product and the solution. Or preferably, the monosodium salt can be formed in-situ by the addition of aqueous sodium hydroxide to the cooled hydrolysis reaction mixture, sufficient caustic being added to dissolve the acid and produce a pH of about 4.3, allowing the reaction mixture to age for 1 hour, then filtering the monosodium salt. The obtained salt can be used directly or purified by conventional purposes, e.g. recrystallization from water to form suitable material for pharmaceutical purposes.

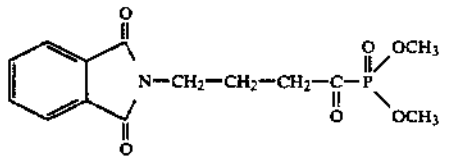
Apparatus for carrying out the above procedures is conventional in the art.

Also disclosed is the novel general process intermediate compound (III)



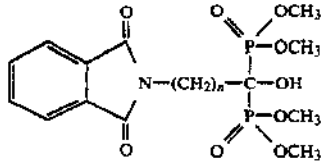
III

where n=1–5, and the specific intermediate (3),



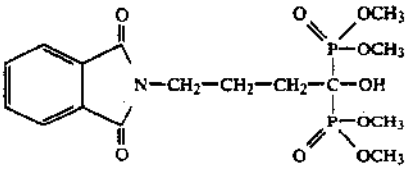
made by the above process and having the following physical properties described below in the Examples.

Also disclosed is the novel general process intermediate compound (IV)



IV

where n=1–5, and the specific intermediate (4):



made by the above process and having the above physical properties described below in the Examples.

The following Examples are illustrative of carrying out Applicant's novel process and should not be construed to limit the scope or spirit of Applicant's invention.

EXAMPLE

Step 1

Preparation of 4-Phthalimidobutanoic Acid (1)

A 2 liter nitrogen flushed flask fitted with a mechanical stirrer and a reflux condenser was charged with 103 g (1 mole) of 4-aminobutyric acid (GABA), 148 g (1 mole) of phthalic anhydride and 250 ml of glacial acetic acid.

The suspension was heated to reflux (120° C.) and the resulting clear solution was maintained at reflux for 2 hr. The solution was cooled to 25° C. over 1 hr during which time the product crystallized out. Water (1.5 liters) was added over 15 min. and the resulting suspension aged at 5°–10° C. for 2 hours. The product was collected by filtration and washed with an additional 0.5 l of water. The product was vacuum dried (house vac) at 60° C. to constant weight yielding 214 g (91.8%, 93% corrected for GABA purity), MP 114°–117° C.

Anal. Calcd. For $C_{12}H_{11}NO$: C, 61.80; H, 4.72; N, 6.00; Found: C, 61.78; H, 4.65; N, 5.98.

Step 2

Preparation of 4-Phthalimidobutanoyl Chloride (2)

A 250 ml flask flushed and blanketed with nitrogen and fitted with a mechanical stirrer was charged with 23.3 g of 4-phthalimidobutyric acid from Step 1, 100 ml of toluene, 9.0 ml of thionyl chloride and 0.1 ml of DMF. The slurry was agitated gently and warmed to 45°–50° C. resulting in a clear, colorless solution.

During the age, gentle gas evolution was observed and ceased approximately 1 hour into the age. The excess thionyl chloride was removed by distillation. The volume of the reaction was reduced to 50 ml by distillation under house vacuum (100 mm Hg) and a jacket temperature of 80° C. An additional 100 ml of toluene was added and distilled. The clear, colorless solution was used without purification.

The acid chloride was isolated for characterization as a crystalline solid by concentrating the solution to an oil, adding diethyl ether and filtering, MP 65°–68° C.

Anal. Calcd. For $C_{12}H_{10}NO_3Cl$: C, 57.26; H, 3.97; N, 5.56; Cl, 14.09; Found: C, 57.48; H, 4.07; N, 5.52; Cl, 14.05.

Step 3

Preparation of Dimethyl 4-Phthalimidobutanoyl Phosphonate (3)

The toluene solution from Step 2 containing a theoretical 25.1 g (0.1 mole) of acid chloride was stirred at

20°–25° C. under nitrogen. To this solution was charged 13.0 g (0.105 mole) of trimethyl phosphite in one portion. The reaction temperature increased slightly from 25° C. to 27° C. The clear colorless solution was aged at 20°–25° C. for 18 hours.

Once the formation of the acyl phosphonate was complete, the solution was used without purification for the next reaction in the sequence, formation of the tetraalkyl bisphophonate ester. The acyl phosphonate was isolated as a crystalline solid by concentrating in vacuo to almost dryness, adding hexanes and filtering, MP 60°–63° C.

Anal. Calcd. For $C_{14}H_{16}NO_6P$: C, 51.69; H, 4.92; N, 4.30; P, 9.53; Found: C, 51.27; H, 4.93; N, 4.25; P, 9.31.

Step 4

Preparation of Tetramethyl Phthalimido-1-Hydroxybutylidene)Bisphosphonate (4)

The toluene solution from Step 3 containing a theoretical 32.5 g (0.1 mole) of the acyl phosphonate was used without purification for formation of the tetraalkyl bisphophonate ester. To the solution stirred at 20°–25° C. under nitrogen was added dimethyl phosphite, 11.6 g (0.105 mole) in one portion. Triethylamine, 10.0 g (0.1 mole) was added dropwise over 15 minutes while maintaining a reaction temperature of 20°–25° C. with external cooling. During the addition of the triethylamine there was a rapid crystallization of the bisphosphonate resulting in a thick slurry. The slurry was stirred at 20°–25° C. for an additional 1 hour.

The reaction mixture was cooled to 0°–5° C., aged for 1 hour then filtered. The cake was washed with 50 ml of toluene and the product dried in vacuo (house vacuum) at 40° C. to constant weight yielding 40.0 g (92%) of white crystalline bisphosphonate, MP 140°–143° C.

Anal. Calcd. For $C_{16}H_{23}NO_9P_2$: C, 44.14; H, 5.28; N, 3.21; P, 14.24; Found: C, 44.10; H, 5.23; N, 3.09; P, 14.20.

Step 5

Preparation of (4-Amino-1-Hydroxybutylidene)Bisphosphonic Acid (ABP) (5)

Tetramethyl-1,1-bisphosphono-1-hydroxy-4-phthalimidobutane 40 g (0.091 mole) from Step 4 was dissolved in 200 ml of 6N HCl and the solution refluxed for 18 hours.

The resulting suspension was cooled to 0°–5° C. and the phthalic acid was removed by filtration. The phthalic acid cake was washed with 50 ml of 6N HCl and the combined filtrate concentrated to 25 ml then flushed with an additional 50 ml of water. The solution was cooled to 20°–25° C. during which time the ABP crystallizes. The crystallization was completed by adding 75 ml of 95% ethanol.

The suspension was cooled to 0°–5° C. and aged at that temperature for 2 hours. The titled product was collected by filtration and washed with 25 ml of 95% ethanol. The yield was 24.0 g (97.8%, but 89.8% based on starting GABA) after air drying to constant weight.

Step 6

Preparation of (4-Amino-1-Hydroxybutylidene)-Bisphosphonic Acid Monosodium Salt Trihydrate (6)

Ten grams (37.4 mmol) of (4-amino-1-hydroxybutylidene)biphosphonic acid, (ABP) was suspended in 300 mL of distilled deionized water with vigorous stirring at 25° C. The pH was 2.27 and was titrated to pH 4.3 to 4.4 by the gradual addition of 7.5 ml (37.4 mmol) 5N sodium hydroxide solution, resulting in a clear solution.

The clear solution was filtered through a medium sintered-glass funnel to remove any insoluble material. Twenty percent of the filtrate (~60 mL) was addedover 5 minutes to 400 mL of 95% ethanol at 20°–25° C. with vigorus stirring and aged for one hour.

The remaining 240 mL of aqueous solution was added over 15 minutes and the mixture aged for 2 hours at 20°–25° C. The white sodium salt was collected by filtration, washed with 100 ml of 2:1 EtOH:H_2O and air dried at 40° C. to yield 11.25 g (93%) of mono sodium salt trihydrate.

What is claimed is:

1. A process for producing omega-amino-1-hydroxy-C_2–C_6-alkylidene-bisphosphonic acid comprising the steps of:

(a) contacting omega-phthalimido-C_2–C_6 alkanoyl chloride with tri C_1–C_4 alkyl phosphite in a dry inert organic solvent at a temperature in the range of 0° to 60° C. to form di C_1–C_4 alkyl omega-phthalimido-C_2–C_6-alkanoyl phosphonate;

(b) contacting di C_1–C_4 alkyl omega-phthalimido-C_2–C_6-alkanoyl phosphonate from Step (a) with di C_1–C_4 alkyl phosphite in a dry inert organic solvent in the temperature range of 0° to 60° C. in the presence of a tertiary nitrogen amine, to form tetra C_1–C_4 alkyl omega-phthalimido-1-hydroxy-C_2–C_6-alkylidene-bisphosphonate;

(c) contacting tetra C_1–C_4 alkyl omega-phthalimido-1-hydroxy-C_2–C_6-alkylidene-bisphosphonate from Step (b) with aqueous strong acid at a temperature in the range of 90° C. to reflux to form omega-amino-1-hydroxy-C_2–C_6-alkylidene-bisphosphonic acid.

2. The process of claim 1 wherein said alkanoyl chloride is derived from glycine, 3-aminopropanoic acid, 4-aminobutanoic acid, 5-aminopentanoic acid or 6-aminohexanoic acid.

3. The process of claim 1 wherein the temperature range for Step (a) is in the range of 20° to 25° C.

4. The process of claim 1 wherein the temperature range for Step (b) is in the range of 20° to 25° C.

5. The process of claim 1 wherein the temperature for Step (c) is the reflux temperature of the solvent.

6. The process of claim 1 wherein the solvent for Step (a) is selected from C_6–C_{10} aromatic hydrocarbons, chlorinated C_6–C_{10} aromatic hydrocarbons, chlorinated C_1–C_4 alkyl hydrocarbons, C_2–C_3 alkylnitriles, C_4–C_6 linear or cyclic ethers.

7. The process of claim 1 wherein the solvent for Step (b) is the same as for Step (a).

8. The process of claim 1 wherein the strong acid in Step (c) is aqueous hydrochloric acid.

9. The process of claim 1 wherein the product phosphonate from Step (a) is not isolated prior to conducting Step (b).

10. A process for producing 4-amino-1-hydroxybutylidene-bisphosphonic acid comprising the steps of:

(a) contacting 4-phthalimidobutanoyl chloride with trimethyl phosphite in a dry inert organic solvent at a temperature in the range of 0° to 60° C. to form dimethyl 4-phthalimidobutanoyl phosphonate;

(b) contacting dimethyl 4-phthalimidebutanoyl phosphonate from Step (a) with dimethylphosphite in a dry inert organic solvent in the temperature range of 0° to 60° C. to form tetramethyl phthalimido-1-hydroxybutylidene-bisphosphonate;

(c) contacting tetramethyl phthalimido-1-hydroxybutylidene-bisphosphonate from Step (b) with aqueous hydrochloric acid at a temperature in the range of 80° C. to reflux to form 4-amino-1-hydroxybutylidene-bisphosphonic acid.

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