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(54) Titre : PROCEDE AMELIORE DE FABRICATION DE DERIVES BIPHOSPHONIQUES
(54) Title: AN IMPROVED PROCESS FOR THE PREPARATION OF BIPHOSPHONIC DERIVATIVES

(57) Abrégé/Abstract:
The present invention provides a novel process for preparation of bisphosphonic acid derivatives or pharmaceutical acceptable salt thereof, by reacting carboxylic acid having structural formula (II) with phosphorous acid and a halophosphorous compound, wherein halophosphorous compound is selected from the group comprising of PCl_3, PCl_5, $POCl_3$, PBr_3, $POBr_3$, and PBr_5 in presence of diphenyl ether.

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(54) Title: AN IMPROVED PROCESS FOR THE PREPARATION OF BIPHOSPHONIC DERIVATIVES

(57) Abstract: The present invention provides a novel process for preparation of bisphosphonic acid derivatives or pharmaceutical acceptable salt thereof, by reacting carboxylic acid having structural formula (II) with phosphorous acid and a halophosphorous compound, wherein halophosphorous compound is selected from the group comprising of PCl_3, PCl_5, $POCl_3$, PBr_3, $POBr_3$, and PBr_5 in presence of diphenyl ether.

AN IMPROVED PROCESS FOR THE PREPARATION OF BIPHOSPHONIC DERIVATIVES

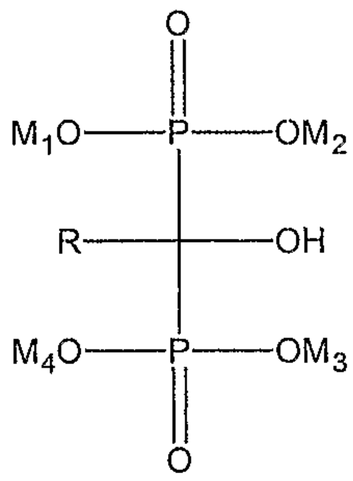
FIELD OF INVENTION:

The present invention relates to an improved process for the preparation of biphosphonic acids derivatives or pharmaceutical acceptable salts thereof.

BACKGROUND OF THE INVENTION:

The biphosphonic acids derivatives are an important class of medicaments useful in the treatment of bone disorders such as Paget's disease and osteoporosis.

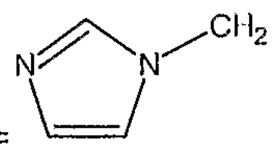
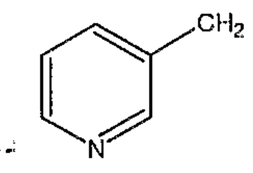
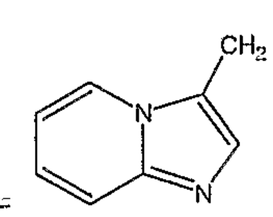
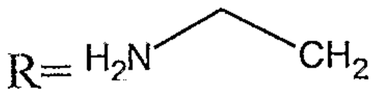
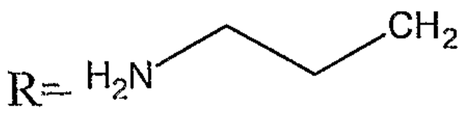
The bisphosphonic acids derivatives bisphosphonic acid derivatives or pharmaceutical acceptable salts thereof, having structural formula (I),

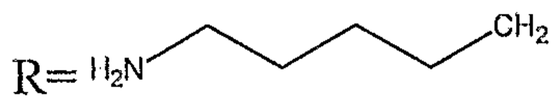


Formula (I)

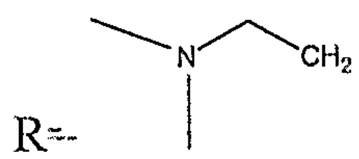
wherein M_1, M_2, M_3, M_4 represents H or a monovalent cation.

wherein R represents group as mentioned hereinbelow

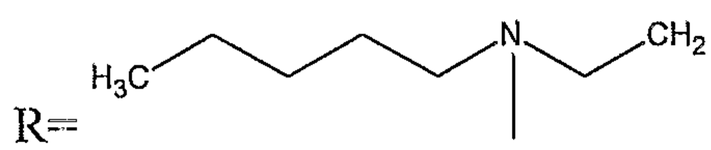
R= CH_3	Etidronic acid
R= 	Zoledronic acid
R= 	Risedronic acid
R= 	Minodronic acid
R= 	Pamidronic acid
R= 	Alendronic acid



Neridronic acid



Olapdronic acid



Ibandronic acid

The synthesis of 1-hydroxy-1,1-biphosphonic acids are based on reacting a carboxylic acid with a mixture of phosphorous acid and phosphorous halides such as PCl_3, PCl_5, $POCl_3$, then quenching the reaction mixture with water or a nonoxidizing aqueous acid, followed by heating to hydrolyze the phosphorous intermediates to final product.

U.S. Pat. No. 4,621,077, which relates to the preparation of alendronic acid and neridronic acid, describes the preparation by treating carboxylic acid with a phosphonation reactant in the presence of chlorobenzene, followed by hydrolysis of the reaction mixture by the addition of concentrated hydrochloric acid and subsequent heating of said mixture. The said patent describes the use of three phosphonation mixtures: H_3PO_3/PCl_3, H_3PO_3/PCl_5 and $H_3PO_3/POCl_3$. The application of this technique leads to obtaining solid and unstirrable masses in the course of the reaction. It is little difficult to adapt these processes to an industrial scale up, since the reaction mixture of the phosphonation step is not homogenous and tends to solidify, preventing stirring, and also the yields obtained are not consistent. Under these conditions, the subsequent hydrolysis step entails substantial risk, due to the presence of small drops of PCl_3 occluded in the reaction mixture and which may cause local overheating on contact with the hydrolyzing agent and also explosion of the gases generated.

A series of other patents i.e. U.S. Pat. No. 4,407,761, U.S. Pat. No. 4,327,039, U.S. Pat. No. 4,304,734, U.S. Pat. No. 4,267,108, U.S. Pat. No. 4,054,598 envisages the use of chlorobenzene as reaction solvent, but also in these cases the drawback described above is again met with.

U.S. Pat. No. 4,922,007, U.S. Pat. No. 5,019,651 and U.S. Pat. No. 5,510,517, as well as J. Org. Chem. 60, 8310, (1995), envisage the use of methanesulphonic acid as reaction solvent. This makes it possible to obtain stirrable masses in the course of the reaction. However, this technique, as reported in J. Org. Chem. 60, 8310, (1995), involves risks of safety in that this solvent gives rise to uncontrollable reactions in the reaction conditions, when the temperature of the reacting mixtures exceeds 85°C.

WO9834940 employs polyalkylene glycols as reaction solvents for synthesizing alendronic acid; however, these solvents have a high cost and are difficult to eliminate from the finished product, given their high boiling point.

In WO0049026, starting from a nitrogen-protected derivative of β-aminopropionic acid to prevent the known problems of stirrability of the reaction mixture, use is made of orthophosphoric acid as the reaction means. The derivatization of the starting product in any case renders the method of synthesis unwieldy and involves the need for introducing additional steps for protection and deprotection.

U.S. Pat. No. 5,792,885 synthesizes pamidronic acid starting from a nitrogen-protected derivative of γ-aminobutyric acid, in aromatic hydrocarbons as the reaction solvents. This method presents the same drawbacks illustrated for the method described in WO0049026.

WO0110874 regards the use of methanesulphonic anhydride as the solvent for producing alendronic acid, but the high cost of the solvent makes the process commercially less attractive.

The complexity and high cost of the prior art procedures has created a need for an improved process for the preparation of bisphosphonic acid or salts. The present invention provides a solution to the problem presented by the prior art.

Surprisingly, present inventors have found that when the reaction is carried out in the presence of diphenyl ether, operationally simple and easily adaptable at an industrial scale.

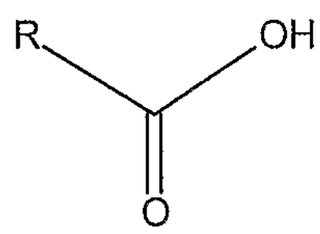
SUMMARY OF THE INVENTION:

A primary object of the present invention is to provide an improved process for the preparation of bisphosphonic acid derivatives or pharmaceutical acceptable salts thereof.

A further object of the present invention is to provide an improved process for preparing bisphosphonic acid derivatives, which is operationally simple, easy to handle and feasible at commercial scale.

Another object of the present invention is to provide cost effective process for the preparation of bisphosphonic acid derivatives or pharmaceutical acceptable salts thereof.

Yet another object of the present invention is to provide an improved process for the preparation of bisphosphonic acid derivatives or pharmaceutical acceptable salt thereof, comprising a step of, reacting carboxylic acid of formula (II),

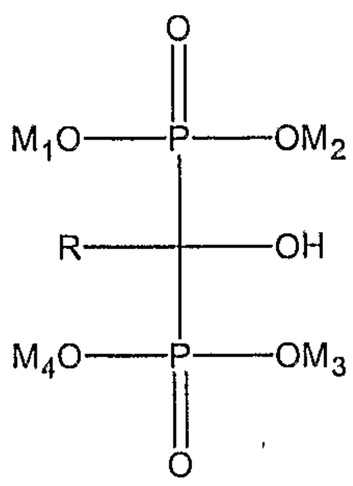


Formula II

wherein R is same as define hereinabove, with phosphorous acid and halophosphorous compound, wherein halophosphorous compound is selected from the group comprising of PCl_3, PCl_5, $POCl_3$, PBr_3, $POBr_3$, and PBr_5 in the presence of diphenyl ether.

DETAILED DESCRIPTION OF THE INVENTION:

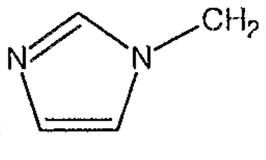
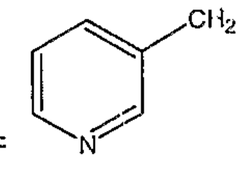
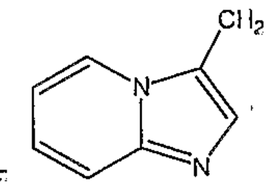
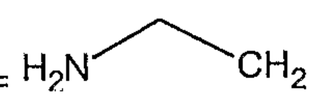
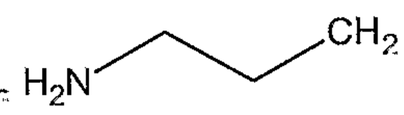
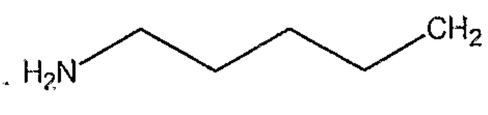
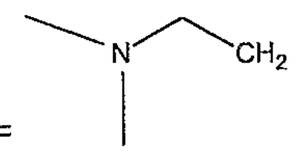
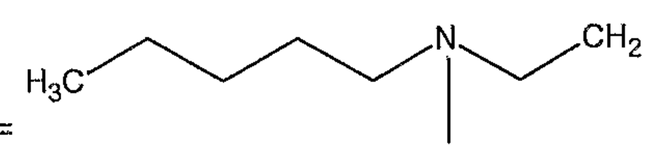
Accordingly, the present invention relates to provide a process for preparing bisphosphonic acid derivatives or pharmaceutical acceptable salt thereof, having structural formula (I),



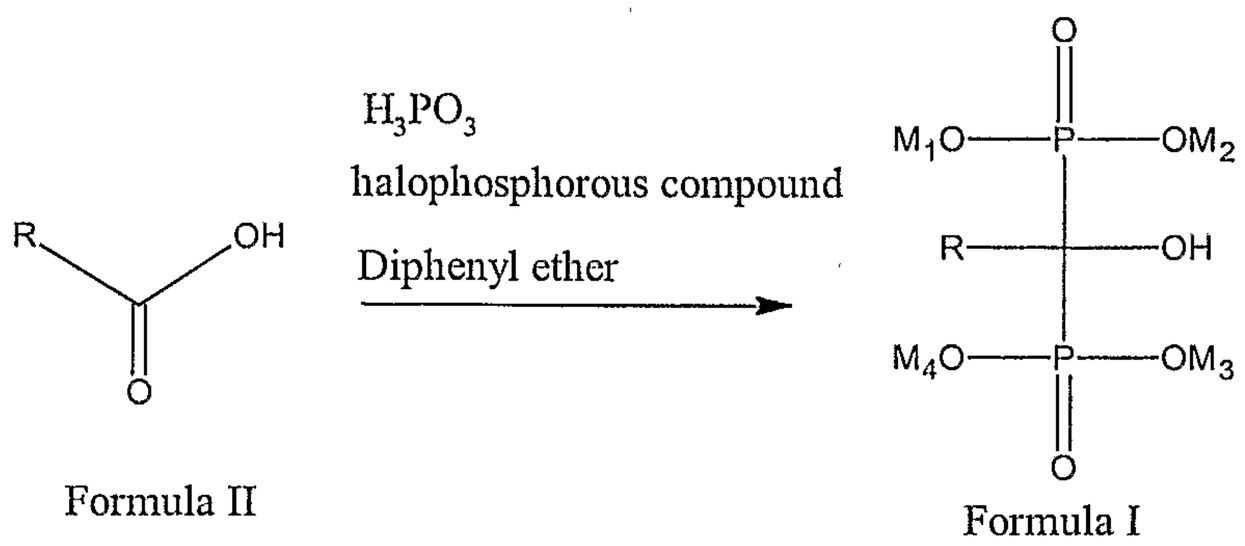
Formula (I)

wherein M_1, M_2, M_3, M_4 represents H or a monovalent cation.

wherein R represents group as mentioned hereinbelow

R= CH_3	Etidronic acid
R= 	Zoledronic acid
R= 	Risedronic acid
R= 	Minodronic acid
R= 	Pamidronic acid
R= 	Alendronic acid
R= 	Neridronic acid
R= 	Olapdronic acid
R= 	Ibandronic acid

The process of preparation of bisphosphonic acid derivatives or pharmaceutical acceptable salts thereof, comprising the step of reacting a carboxylic acid having structural formula (II) with phosphorous acid and a halophosphorous compound, wherein halophosphorous compound is selected from the group comprising of PCl_3, PCl_5, $POCl_3$, PBr_3, $POBr_3$, and PBr_5 in the presence of diphenyl ether.



Formula II Formula I

The carboxylic acid of formula (II) wherein R is defined herein above. The suitable example of carboxylic acid included but not limited to 4-aminobutanoic acid, (3-pyridyl)ethanoic acid, (1-imidazoyl)ethanoic acid, N-(n-pentyl)-N-methyl-3-aminopropanoic acid, 2(imidazo[1,2-a]pyridin-3-yl)ethanoic acid, β-aminopropanic acid and 6-aminohexanoic acid. The selection of appropriate carboxylic acid depends on the end of bisphosphonic acid derivatives to be prepared.

The reaction is carried out at temperature ranging 50°C to 100°C. Preferable temperature range is 65°C to 75°C. The reaction is carried out generally for about 3 to 8 hours. After completion of the reaction water and toluene is added, heated and optionally the reaction mixture is charcoalized.

After filtering the aqueous layer and toluene layer is separated. Aqueous layer is concentrated and refluxed for 12 to 14 hours. The reaction mass is cooled at about RT and methanol is added and then cooled at about 0°C. The resultant isolated compound is dried at about 60°C.

The bisphosphonic acid derivatives of present invention can be converted into its salt using conventional method.

In a preferred embodiment, a process for the preparation of Alendronate sodium comprising a step of,

a) reacting 4-amino butyric acid with phosphorous acid and a halophosphorous compound, wherein halophosphorous compound is selected from the group comprising of

PCl_3, PCl_5, $POCl_3$, PBr_3, $POBr_3$, and PBr_5 in the presence of diphenyl ether to obtain Alendronic acid

b) treating Alendronic acid with sodium hydroxide to obtain Alendronate Sodium

The present invention process has advantages over prior art such as:

(i) It provides a process which is operationally simple and industrially applicable.

(ii) It involves less reaction time then prior art process.

(iii) It provides high yield.

The process of the present invention is described by the following examples, which are illustrative only and should not be construed so as to limit the scope of the invention in any manner.

Examples-1

Preparation of (4-Amino-1-hydroxybutylidene) bisphosphonic acid (Alendronic acid)

The suspension of 4-amino butyric acid (10.0g) and phosphorous acid (23.9g) in diphenyl ether (50ml) was heated up to 70°C for 1 hour. Phosphorous trichloride (25.4ml) was slowly added to reaction mass at 70°C temperature and maintained reaction temperature for another 6 hours. Reaction mass was cooled to 25°C followed by addition of water (150ml) and toluene (30ml). Reaction mixture was again heated to 70°C and charged charcoal in hazy biphasic solution, stirred, filtered through Hyflo bed, washed the bed with hot water (30ml). Layers was separated from filtrate, aqueous layer was washed with toluene (20ml) and combined organic layer was then back extracted with water (20ml) and mixed with main aqueous layer. The water (140ml) was distilled out from combined aqueous layer at atmospheric pressure in 2 hours and then refluxed the concentrated mass for 13 hours. Reaction mass was cooled to 25°C followed by addition of methanol (150ml) in 1 hours. The reaction mixture was stirred and again cooled to 0°C followed filtration. The filtrate was washed with chilled 1:2 mixture (30ml) of water and methanol and dried at 60°C to get Alendronic acid.

Yield: 19.0gm (78.5%)

Examples-2

Preparation of Zoledronic Acid

The suspension of (1-imidazoyl)ethanoic acid (10.0g) and phosphorous acid (19.5g) in diphenyl ether (50ml) was heated up to 70°C for 1 hour. Phosphorous trichloride (20 ml) was slowly added to reaction mass at 70°C temperature and maintained reaction temperature for another 6 hours. Reaction mass was cooled to 25°C followed by addition of water (150ml) and toluene (30ml). Reaction mixture was again heated to 70°C and charged charcoal in hazy biphasic solution, stirred, filtered through Hyflo bed, washed the bed with hot water (30ml). Layers was separated from filtrate, aqueous layer was washed with toluene (20ml) and combined organic layer was then back extracted with water (20ml) and mixed with main aqueous layer. The water (140ml) was distilled out from combined aqueous layer at atmospheric pressure in 2 hours and then refluxed the concentrated mass for 13 hours. Reaction mass was cooled to 25°C followed by addition of methanol (150ml) in 1 hours. The reaction mixture was stirred and again cooled to 0°C followed filtration. The filtrate was washed with chilled 1:2 mixture (30ml) of water and methanol and dried at 60°C to get Zoledronic Acid.

Yield: 19.0gm (75%)

Examples-3

Preparation of Risedronic acid

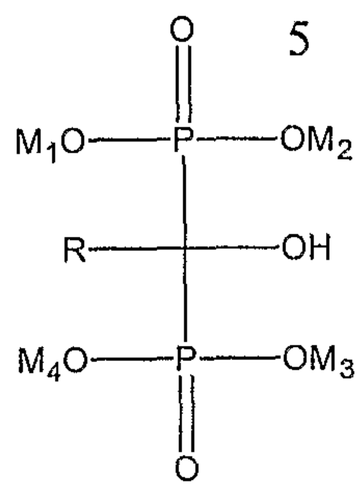
The suspension of (3-pyridyl)ethanoic acid (10.0g) and phosphorous acid (17.9g) in diphenyl ether (50ml) was heated up to 70°C for 1 hour. Phosphorous trichloride (19.1 ml) was slowly added to reaction mass at 70°C temperature and maintained reaction temperature for another 6 hours. Reaction mass was cooled to 25°C followed by addition of water (150ml) and toluene (30ml). The reaction mixture was again heated to 70°C and charged charcoal in hazy biphasic solution, stirred, filtered through Hyflo bed, washed the bed with hot water (30ml). Layers was separated from filtrate, aqueous layer was washed with toluene (20ml) and combined organic layer was then back extracted with water (20ml) and mixed with main aqueous layer. The water (140ml) was distilled out from combined aqueous layer at atmospheric pressure in 2 hours and then refluxed the concentrated mass for 13 hours. Reaction mass was cooled to 25°C followed by addition of methanol (150ml) in 1 hours, stirred and again cooled to 0°C, filtered, washed with

chilled 1:2 mixture (30ml) of water and methanol and dried at 60°C to get Risedronic acid.

Yield: 19.0gm (77%)

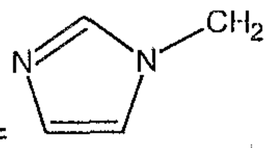
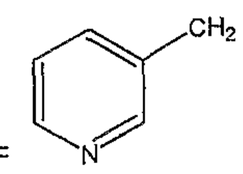
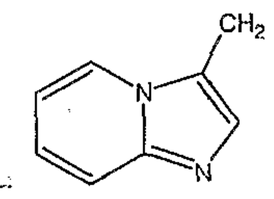
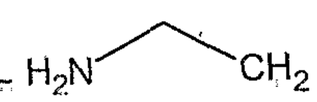
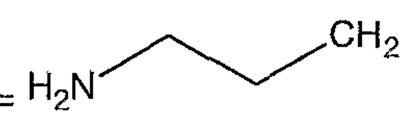
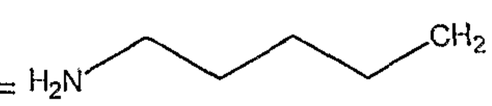
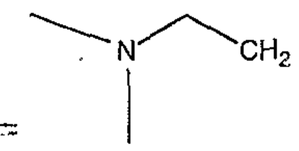
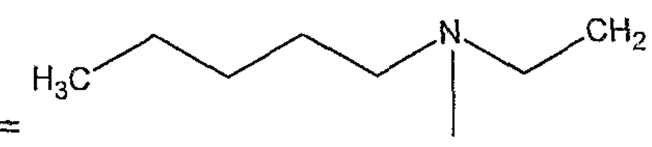
CLAIMS

1. A process for the preparation of bisphosphonic acid derivatives or pharmaceutical acceptable salt thereof, having structural formula (I),

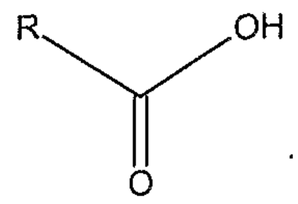


Formula (I)

wherein M_1, M_2, M_3, M_4 represents H or a monovalent cation, and R represents group as mentioned hereinbelow:

R= CH_3	Etidronic acid
R= 	Zoledronic acid
R= 	Risedronic acid
R= 	Minodronic acid
R= 	Pamidronic acid
R= 	Alendronic acid
R= 	Neridronic acid
R= 	Olapdronic acid
R= 	Ibandronic acid

comprising a step of, reacting a carboxylic acid having structural formula (II)



Formula II

wherein R has the aforesaid meaning, with phosphorous acid and a halophosphorous compound, wherein halophosphorous compound is selected from the group comprising of PCl_3, PCl_5, $POCl_3$, PBr_3, $POBr_3$, and PBr_5 in the presence of diphenyl ether.

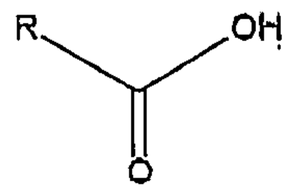
2. A process for the preparation of Alendronic acid comprising a step of, reacting 4-amino butyric acid with phosphorous acid and a halophosphorous compound, wherein halophosphorous compound is selected from the group comprising of PCl_3, PCl_5, $POCl_3$, PBr_3, $POBr_3$, and PBr_5 in the presence of diphenyl ether.

3. A process for the preparation of Alendronate sodium comprising steps of,

a) reacting 4-amino butyric acid with phosphorous acid and a halophosphorous compound, wherein halophosphorous compound is selected from the group comprising of PCl_3, PCl_5, $POCl_3$, PBr_3, $POBr_3$, and PBr_5 in the presence of diphenyl ether to obtain Alendronic acid

b) treating Alendronic acid obtained in step (a) with sodium hydroxide.

AMENDED CLAIMS
Received by the International Bureau on 04 June 2007 (04.06.07)
claims 1-3 amended.



Formula II

wherein R has the aforesaid meaning, with phosphorous acid and a halophosphorous compound, wherein halophosphorous compound is selected from the group comprising of PCl_3, PCl_5, $POCl_3$, PBr_3, $POBr_3$, and PBr_5 wherein the reaction is carried out in the presence of diphenyl ether.

2. A process for the preparation of Alendronic acid comprising a step of, reacting 4-amino butyric acid with phosphorous acid and a halophosphorous compound, wherein halophosphorous compound is selected from the group comprising of PCl_3, PCl_5, $POCl_3$, PBr_3, $POBr_3$, and PBr_5 wherein the reaction is carried out in the presence of diphenyl ether.

3. A process for the preparation of Alendronate sodium comprising steps of,
a) reacting 4-amino butyric acid with phosphorous acid and a halophosphorous compound, wherein halophosphorous compound is selected from the group comprising of PCl_3, PCl_5, $POCl_3$, PBr_3, $POBr_3$, and PBr_5 wherein the reaction is carried out in the presence of diphenyl ether to obtain Alendronic acid
b) treating Alendronic acid obtained in step (a) with sodium hydroxide.

STATEMENT UNDER ARTICLE 19 (1)

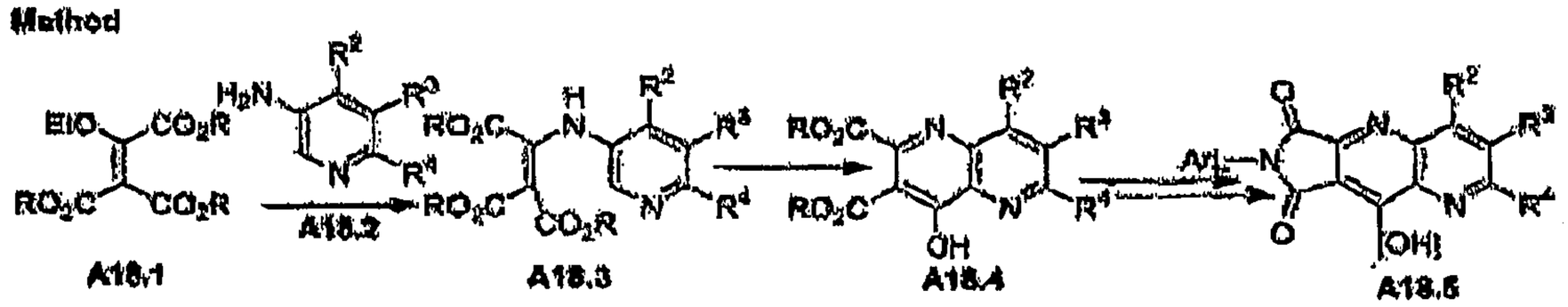
The present invention resides in process of preparation of bisphosphonic acid derivatives by reacting carboxylic acid of formula II with phosphorus acid and selected halo phosphorus compounds in presence of diphenyl ether. The invention resides in the surprise finding that when the reaction is carried out in presence of diphenyl ether it is operationally simple and is able to avoid hazardous and costly solvents and yet achieve higher yield and solve the problem of solidification associated with the prior art.

D1 (WO01/090367) teaches process for preparation of bisphosphonic acid/ its salt by reaction of 4- aminobutyric acid with a mixture of phosphorous compounds and then quenching the reaction with water followed by heating to hydrolyze the phosphorous intermediates. D1 solves the problems relating to the safety and the high cost of production by use of plant and animal oils as emulgators without the use additional solvent. Thus D1 is directed to providing a different solution to the problem and there is no teaching of motivation for use of diphenyl ether. Further D1 utilizes the solvent aralkyl or alkyl ethoxylates or triglycerides such as plant or animal oils for solubilization of the reaction mixture. But this process provides low yield (35-65%) whereas the present invention solved problem related to the solidification and the safety and provides high yield (78.5%).

D2 (WO 2005/117904) teaches HIV integrase inhibitor compound comprising a phosphonate group. D2 does not teach the use of solvent diphenyl ether for conversion from GABA to Alendronic acid. However, D2 utilized diphenyl ether for the cyclization of the compound (A18.3) to afford the compound 1, 5-naphthyridine derivative (A18.4) and reaction is carried out at 250°C. The brief description of the scheme as mention in D2 is reproduced below to highlight the difference between the reaction described in D2 and the reaction of present invention.

Scheme A18. Phosphonates IIaa.

Method



D3 (EP 741005) relates to film composites comprising a thin, flexible backing having one or more adhesive layers thereon, and to the use of the film composites on substrates exposed to organic solvents and, in particular, to fuels for internal combustion engines. D3 describes alkali metal salts of dodecyl diphenyl ether disulfonic acid as an anionic emulsfying agent whereas the present invention uses diphenyl ether as solvent for the bisphosphonic acids as claimed in the present invention.

Thus D1 does not mention use of diphenyl ether, D2 uses the same but for different purpose in preparation of a different compound while D3 though uses the same as emulsifying agent but for film composite. Combining the teachings would not motivate a person ordinarily skilled in the art to use diphenyl ether as solvent that too for preparation of bisphonic acid and yet achieve better yield, overcome the non homogeneity, solidification problems and be safe and economical. In order to further emphasize the inventive feature the applicant wishes to amend claims 1 to 3 which may kindly be taken on record as amendments with Statement under Article 19.