



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>5</sup> :  C07F 9/38	A1	(11) International Publication Number: <b>WO 91/03480</b>  (43) International Publication Date: 21 March 1991 (21.03.91)
<p>(21) International Application Number: PCT/FI90/00197</p> <p>(22) International Filing Date: 15 August 1990 (15.08.90)</p> <p>(30) Priority data: 894245 8 September 1989 (08.09.89) FI</p> <p>(71) Applicant (for all designated States except US): HUHTAMÄKI OY [FI/FI]; P.O. Box 415, SF-20101 Turku (FI).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only) : LAMPLI, Klaus [FI/FI]; Rusthollinkatu 4, SF-20880 Turku (FI). NIEMINEN, Kauko [FI/FI]; Metsätie 7, SF-21250 Masku (FI). RUOHONEN, Jarkko [FI/FI]; Vanhahärkätie 6, SF-21410 Vanhalinna (FI).</p>		<p>(74) Agent: OY JALO ANT-WUORINEN AB; Laivuririnne 2 A, SF-00120 Helsinki (FI).</p> <p>(81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent)*, DK (European patent), ES (European patent), FR (European patent), GB (European patent), IT (European patent), JP, LU (European patent), NL (European patent), NO, SE (European patent), SU, US.</p> <p><b>Published</b> <i>With international search report.</i></p>
(54) Title: PROCESS FOR THE PREPARATION OF METHYLENEBISPHOSPHONIC ACIDS		
(57) Abstract		
<p>The object of the invention is a process for the preparation of optionally mono- or dihalogen substituted methylenebisphosphonic acids, whereby the corresponding lower alkyl tetraester is hydrolyzed in an aqueous solution of the tetraester and hydrochloric acid, which solution contains 1 to 5 % by weight of HCl, calculated on the mixture.</p>		

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cesses is the impurity of the products obtained and the numerous purification steps needed to remove byproducts and excess acid. In addition, the processes are connected with substantial corrosion problems. From the EP-patent application 0200980 is known a process according to which methylenebisphosphonic acids have been prepared by hydrolysing tetraesters with plain water, by boiling at reflux temperature of the reaction mixture. In this case the above mentioned problems of impurities and corrosion are largely overcome, but another problem is the very long reaction time, which may be as long as 16 hours, which is disadvantageous, i.a. from the viewpoint of production economics.

Now a process has been invented for the preparation of the above mentioned methylenebisphosphonic acids and their salts according to the formula I, with a good yield and in a very pure form, whereby the corrosion problems caused by the use of a strong acid are avoided. By means of the process according to the invention it has also been possible to shorten the reaction time even up to one quarter or more as compared to the process known from the EP-patent application 0200980.

The process according to the invention is thus characterized in that the hydrolysis is performed in an aqueous solution of the tetraester and hydrochloric acid, which solution contains from 1.0 to 5 % by weight of HCl, based on the whole mixture. Below the said limit the hydrolysis proceeds too slowly from a practical viewpoint and above the said limit no substantial rate increase is achieved in relation to the amount of chloride ions added to the mixture.

The hydrolysis is advantageously performed by boiling the aqueous solution of the tetraester and hydrochloric acid at reflux temperature. Thus the reaction mixture contains

an excess of water with regard to the stoichiometric amount of water necessary for the complete hydrolysis of the tetraester. This excess of water is not critical and thus a multiple excess with regard to the stoichiometric amount may be used. A practical volumetric amount of aqueous hydrochloric acid solution from the viewpoint of carrying out the hydrolysis is approximately 6 to 7 times the weight of the tetraester, whereby, on the one hand, a sufficient degree of dissolution of the tetraester in the aqueous medium is obtained, but at the same time the difficulties caused by the increase in volume in the subsequent hydrolysis stage are avoided.

According to one advantageous embodiment the amount of hydrochloric acid in the mixture is approximately 2.5 to 5 % by weight, whereby an optimal result from the viewpoint of byproduct formation and reaction time is achieved.

The free tetraacid obtained as a result of the hydrolysis may, if desired, be converted to its salt, also its partial salt, in a per se known manner by using a suitable organic or inorganic base, for example alkali or alkaline earth metal hydroxides, carbonates or hydrogen carbonates. The salt formation may take place either after the isolation of the acid or by adding the desired base directly to the reaction mixture after the hydrolysis, without isolating the free acid.

The following example illustrates the invention.

#### Example 1

#### Dichloromethylenebisphosphonic acid disodiumtetrahydrate

Into a three-necked flask equipped with a thermometer, a stirrer and a reflux condenser, 420 ml of a 3 % hydrochlo-

ric acid solution and 65 g of tetraisopropyl dichloromethylenebisphosphonate are added. The HCl-concentration of the reaction mixture is then approximately 2.6 % by weight of HCl. The mixture is boiled under reflux and the progress of the hydrolysis is followed by determining the concentration of the acid formed in the solution by  $^{31}\text{P}$ -NMR. The solution is cooled to 20 to 25°C and is treated with activated carbon. To the solution a calculated amount of a sodium hydroxide solution is added until the pH is 3.2. The solution is concentrated and cooled, whereby the disodiumtetrahydrate salt of dichloromethylenebisphosphonic acid crystallizes. The crystals are filtered and dried, whereby appr. 50 g of the product is obtained, purity >99%.

By performing the hydrolysis as described above but by using instead of the 3% hydrochloric acid solution, aqueous hydrochloric acid solutions of varying strength, the hydrolysis results shown in the appended drawing were obtained. Next to each curve on the one hand the acid strength of the hydrolysis mixture, and on the other hand, in paranthesis, the acid strength of the aqueous hydrochloric acid solution used, are indicated. In the drawing the yield of hydrolysis (mol-% free acid) are indicated as a function of reaction time, and as comparison, hydrolysis with plain water according to the EP-patent application 0200980 is used. As is seen from the drawing, complete yields are obtained with the process according to the invention, by using catalytic amounts of hydrochloric acid, in a substantially shorter reaction time as compared to the process according to the said EP-patent application.



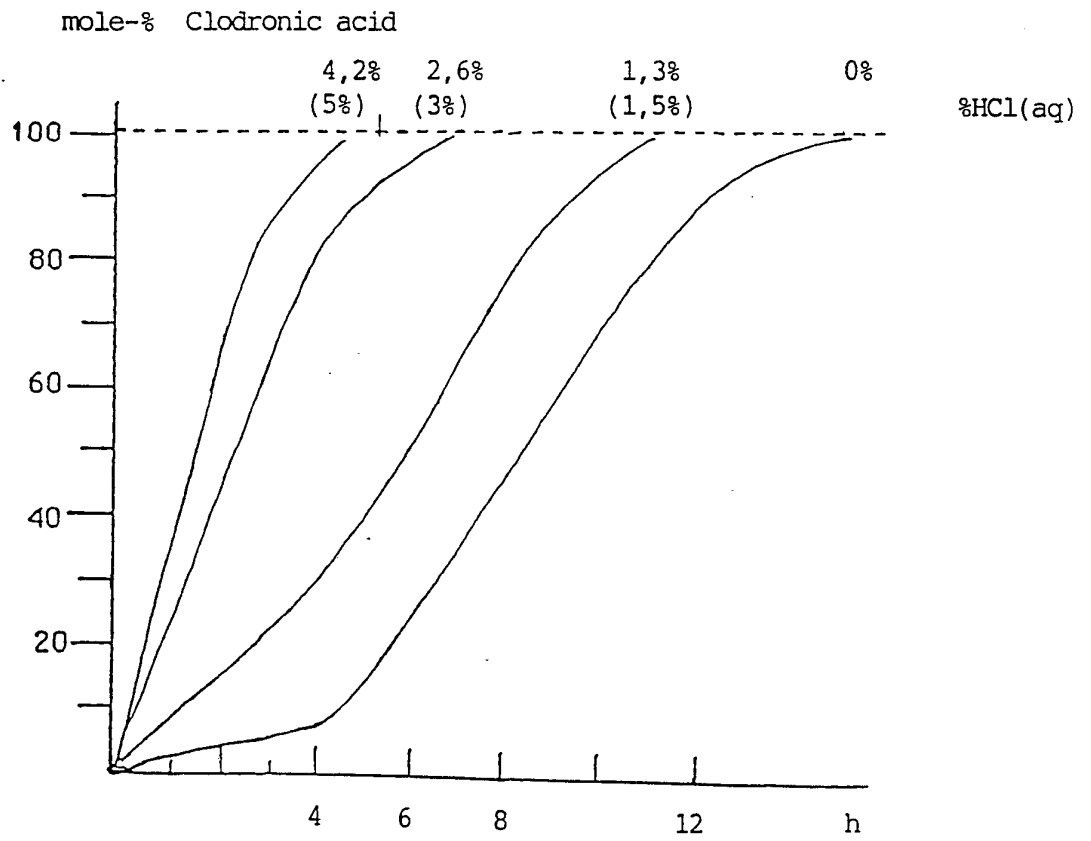
3. Process according to the claim 1, characterized in that the hydrolysis is performed by boiling at the reflux temperature of the mixture.

4. Process according to any one of the claims 1 to 3, characterized in that the hydrolysis mixture contains 2.5 to 5 % by weight of HCl.

5. Process according to the claim 1, characterized in that as the starting material the tetraisopropylester of dichloromethylenebisphosphonic acid is used.

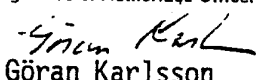


FIG. 1



# INTERNATIONAL SEARCH REPORT

International Application No PCT/FI 90/00197

<b>I. CLASSIFICATION OF SUBJECT MATTER</b> (if several classification symbols apply, indicate all) <sup>6</sup> According to International Patent Classification (IPC) or to both National Classification and IPC IPC5: C 07 F 9/38				
<b>II. FIELDS SEARCHED</b>				
Minimum Documentation Searched <sup>7</sup>				
Classification System	Classification Symbols			
IPC5	C 07 F			
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in Fields Searched <sup>8</sup>				
SE,DK,FI,NO classes as above				
<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT<sup>9</sup></b>				
Category *	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>		
A	GB, A, 1026366 (THE PROCTER & GAMBLE COMPANY) 20 April 1966, See example VI --	1-5		
A	US, A, 4621077 (SERGIO ROSINI ET AL.) 4 November 1986, See column 3, lines 1-20 --	1-5		
A	EP, A1, 0200980 (ISTITUTO GENTILI S.P.A.) 12 November 1986, see the whole document --	1-5		
A	EP, A2, 0230068 (NORWICH EATON PHARMACEUTICALS, INC.) 29 July 1987, See example I-III -- -----	1-5		
<table style="width: 100%; border: none;"> <tr> <td style="width: 50%; vertical-align: top; padding: 5px;"> <p>* Special categories of cited documents: <sup>10</sup></p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </td> <td style="width: 50%; vertical-align: top; padding: 5px;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&amp;" document member of the same patent family</p> </td> </tr> </table>			<p>* Special categories of cited documents: <sup>10</sup></p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p>	<p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&amp;" document member of the same patent family</p>
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<b>IV. CERTIFICATION</b>				
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report			
3rd December 1990	1990 -12- 10			
International Searching Authority	Signature of Authorized Officer			
SWEDISH PATENT OFFICE	 Göran Karlsson			

**ANNEX TO THE INTERNATIONAL SEARCH REPORT  
ON INTERNATIONAL PATENT APPLICATION NO.PCT/FI 90/00197**

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.  
The members are as contained in the Swedish Patent Office EDP file on **90-11-01**  
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB-A- 1026366	66-04-20	AU-A- 289589	00-00-00
		AU-D- 4194564	00-00-00
		BE-A- 672205	66-05-10
		CA-A- 777769	00-00-00
		CH-A- 465745	00-00-00
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		US-A- 3404178	00-00-00
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		US-A- 4621077	86-11-04
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		US-A- 4902679	90-02-20