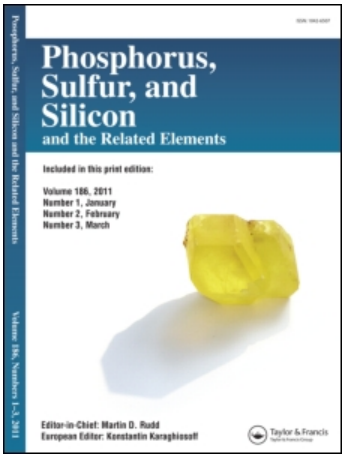


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Optimization, Continuation and Lack of the One-Step Diphosphorylation Reaction. Assay of Modification of the Tetraethyl(pyrrolidine-2,2-diyl)bisphosphonate

Gilles Olive[a]; Alain Jacques[b]
[a] Laboratoire OPEP, Belgium [b] Laboratoire CSTR, Belgium

Online publication date: 27 October 2010

To cite this Article Olive, Gilles and Jacques, Alain(2003) 'Optimization, Continuation and Lack of the One-Step Diphosphorylation Reaction. Assay of Modification of the Tetraethyl(pyrrolidine-2,2-diyl)bisphosphonate', Phosphorus, Sulfur, and Silicon and the Related Elements, 178: 1, 33 — 46
To link to this Article: DOI: 10.1080/10426500307821
URL: http://dx.doi.org/10.1080/10426500307821

Phosphorus, Sulfur and Silicon, 2003, Vol. 178:33–46

1042-6507/03 $12.00 + .00
DOI: 10.1080/10426500390170138

Taylor & Francis
Taylor & Francis Group

OPTIMIZATION, CONTINUATION AND LACK OF THE ONE-STEP DIPHOSPHORYLATION REACTION. ASSAY OF MODIFICATION OF THE TETRAETHYL-(PYRROLIDINE-2,2-DIYL)BISPHOSPHONATE

Gilles Olive[a] *and Alain Jacques*[b]
Laboratoire OPEP, Belgium[a] *and Laboratoire CSTR, Belgium*[b]

(Received July 9, 2002; accepted July 9, 2002)

The optimization of the one-step diphosphorylation reaction is reported. The synthesis of new α-aminobisphosphonates with four- and six-membered rings and acyclic species with several substituents on the nitrogen atom and on the carbon atom bearing the two phosphorus atoms is described.

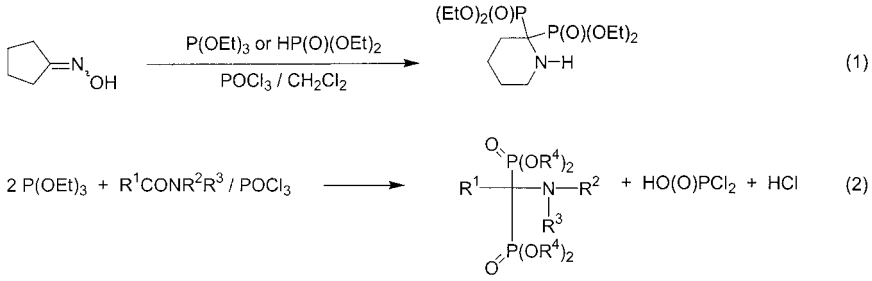
Keywords: Amide; bisphosphonates; diphosphorylation; lactam; trialkylphosphite

INTRODUCTION

The gem-bisphosphonates show a structural analogy with pyrophosphoric acid.[1] They are known for their various uses: dental (toothpastes and mouthwashes)[2–4] and medical applications (against rheumatoid arthritis,[5,6] for the inhibition of bone resorptive processes such osteoporosis and Paget's disease,[2,7–9] skeletal scintigraphy when combined with ^{99}Tc,[10–12] breast cancer therapy,[13] antiviral,[14,15] antiinflammatory[16,17] and antirheumatismal agents,[18] pain-easing activities,[16] antimoebic[15]), antibacterial agents,[19] plant growth regulators,[20] herbicides,[21–23] pesticides,[19] in the nuclear industry,[24–26] flame retardants,[21] and chelators in water treatment,[21] as well as many others. Gem-bisphosphonates and gem-bisphosphonic acids can readily form complexes with calcium and magnesium and this behavior is one of the principles sustaining their use as drugs.[3,15]

Recently, amino-gem-bisphosphonates have been involved in the conformational study of pyrrolinoxyl radicals[27] and they also work as spin trapping agents relevant to biology.[28]

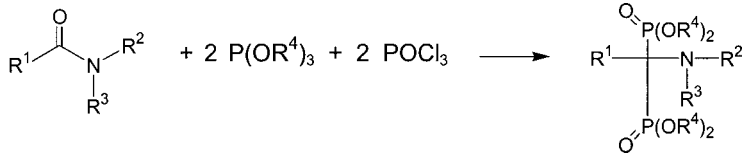
Address correspondence to Gilles Olive, Laboratoire OPEP, Rue Maison d'Orbais, 23/14, B-5032 Corroy-le Chateau, Belgium. E-mail: gilles.olive@excite.com



SCHEME 1 Yokomatsu and Qian procedures for bisphosphonates synthesis.

Several procedures for the synthesis of α-amino-bisphosphonates already have been reported in the literature.[29,30] Unfortunately most of them are quite awkward to perform and require several steps.[1,11,31–33] In 1994, Yokomatsu et al. were the first to describe an easy single step synthesis by a Beckmann rearrangement of oximes reagents (Scheme 1, Equation (1)).[15] However, we failed to extend this method to a five-membered ring bisphosphonate and found at least seven products by ^{31}P NMR in the crude reaction with only 10% of the target bisphosphonate.[28] In 1997 and 1999, Qian et al. detailed a one-pot but intricate two-step procedure involving Vilsmeier reagents and organophosphorus compounds with P–H bounds (Scheme 1, Equation (2)).[23,34] At the same time, we have designed an easy one-step method also employing Vilsmeier reagents (amide or lactam/$POCl_3$) with trialkylphosphite.[28,35]

Schematically the experimental procedure is as follows: At low temperature, under nitrogen, $POCl_3$ (0.22 mol) was slowly added to a mixture of lactam or amide (0.11 mol) and trialkylphosphite (0.21 mol). The reaction mixture was then stirred at room temperature and then poured over a cold aqueous solution saturated with NH_4OH (Scheme 2).



SCHEME 2 Our easy one pot procedure of bisphosphonates synthesis.

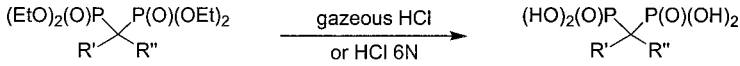
In this article, we describe our optimization studies for the latter reaction parameters, new kinds of synthesis, and also our failures. Because any change of the bisphosphonate properties is of interest for

their use as a drug, we also report our attempts toward modifying the tetraethyl(pyrrolidine-2,2-diyl)bisphosphonate.

RESULTS AND DISCUSSION

Optimization: All the optimizations were performed on the 2-pyrrolidinone.

Temperature: As elsewhere mentioned,[36] when the temperature raises above 40°C, the yield drops to about 5% due to the presence of gaseous HCl; it is well known that hydrochloric acid can hydrolyze phosphonate (Scheme 3).[8,16,37] Similarly, when the initial temperature is too low for the reaction to occur or when the amide is frozen, the consequent removal of the cold source induces an exothermic reaction and possibly brings it to boil. In these circumstances, the yield is somewhat low and the presence of polymers can be encountered as it was the case with *N*-benzylacetamide. For the 2-pyrrolidinone, an optimum yield of 58% is obtained at −7.5°C and the adverse effect starts at −10°C. It should be noted that a water bath at room temperature has to be used after the removal of the cold source in order to calm down the reaction.



SCHEME 3 Hydrolysis of bisphosphonate by HCl.

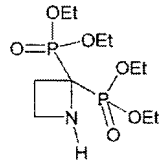
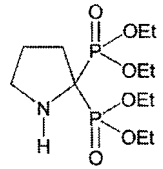
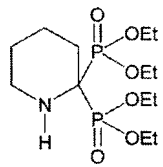
Equivalent of $POCl_3$: According to Qian,[23] only one equivalent of $POCl_3$ has to be used but more satisfactory results can be obtained by incorporating two equivalents.[28] Attempts with 1, 1.5, and 1.75 equivalents of $POCl_3$ on 2-pyrrolidinone provide a yield of 56–57%, close to what is obtained with two equivalents but the purity is lower as emphasized by the ^{1}H, ^{13}C, and ^{31}P spectra. Furthermore in these cases, we observed a change of color and, after a few weeks, the presence of a small quantity of crystals.

Timing at room temperature: During our preliminary attempts, the crude mixture was hydrolyzed on ice and NH_4OH just after the addition of $POCl_3$. The corresponding product was pure and obtained with a good yield (58%). It is actually advisable to wait for 1 h at room temperature in order to allow the less reactive amide to react.

Continuation: All the products were purified by normal work-up for an amine (an acido-basic extraction) unless stated in the text.

Ring size: Most of our efforts were focused on the five-membered rings. However we also investigated the synthesis from both

TABLE I Influence of the Ring Size on the Reaction

	Bisphosphonate	Yield[a]/%	^{31}P NMR[b] δ/ppm
1		28	22.2
2		58	24.7
3		19[c]	24.0

[a]With optimized condition.
[b]In $CDCl_3$.
[c]43% from Yokomatsu.[15]

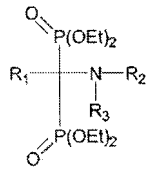
2-azitidinone and 2-piperidone (or δ-valerolactam). Table I summarizes the results.

It has to be noticed that the synthesis of **3** by our procedure is less efficient than the one propounded by Yokomatsu (19% yield versus 43%).[15]

Linear compounds: The results for the acyclic series are displayed on Table II; the yields have to be compared with those asserted in the literature.

The yield of **4**, the simplest bisphosphonate in the series, is higher than the one reported by Qian.[23] If a second methyl group is added on the nitrogen (tertiary amine), the corresponding return is almost divided by a factor of two, being reduced from 68% to 30%. This behavior has been previously described for the cyclic series by comparing the tetraethyl(pyrrolidine-2,2-diyl)bisphosphonate **2** and the tetraethyl(*N*-methyl-pyrrolidine-2,2-diyl)bisphosphonate for which the yield drops from 47% to 17%.[35] Qian has obtained a better yield of 66% for compound **5**. As emphasized by entries **6** and **12**, a methyl group addition on the carbon atom bearing two phosphorus atoms significantly increases the yield, at least up to 80%. If a phenyl group takes the place of the

TABLE II Linear α-Aminobisphosphonate



	R^1	R^2	R^3	Yield/%	^{31}P NMR[a] δ/ppm	Yield from literature/%	Ref.
4	H	Me	H	68	20.7	50	23
5	H	Me	Me	30	20.3	66	23
6	Me	Me	H	85	23.8		
7	Ph	Me	H	15	20.5		
8	H	Ph	H	b	18.6	80[c]	38
9	Me	Ph	H	b	22.4	43, 60 or 68	15
10	Ph	Ph	H	0		47	31
11	H	Bn	H	78	20.9	71[c]	32
12	Me	Bn	H	88	23.3		
13	CF_3	Bn	H	0			
14	Et	Bn	H		23.7	57	35

[a]In $CDCl_3$.
[b]Not isolated.
[c]Several steps.

latter methyl, the corresponding yield is reduced to 15% (compound **7**). In order to consolidate these observations, the *N*-benzyl series were synthesized (compounds **11**, **12**, **13**, and **14**). The best results were obtained with a methyl group, followed by a hydrogen atom and finally by an ethyl group. The synthesis of the trifluoromethyl compound failed, as mentioned in the lack section.

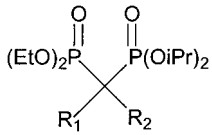
Considering the influence of the *N*-substitution, it appears that, in all the occurrences, the best yield is obtained with a benzyl group and to a lesser extent with a methyl group (compounds **4** and **11**, **6** and **12**). Unfortunately, the syntheses involving phenyl groups are hampered by inherent difficulties. The reactions occur but, in many cases, are incomplete: For compound **8** some of the triethylphosphite reactant remains and, for compound **9**, some of the amide. Furthermore, these compounds cannot be satisfactorily purified due to the large number of spots found on the TLC.

As a general rule, it appears that the yields obtained by our procedure are higher than those reported in the literature with some exceptions regarding inefficient reactions as for tertiary amide and for *N*-phenyl compounds.

A NMR study of these linear bisphosphonates shows a dependable behavior. The ^{31}P chemical shift are around δ 20.5 ppm and δ 23.5 ppm, respectively for the formamide and acetamide. Similar observations are made on compound **10** in reference 35 and on compound **7** from Olive and van Genderen.[39] The presence of a phenyl group on the nitrogen affects these ^{31}P chemical shifts with a respective increase of 2 and 1 ppm.

The ^{13}C NMR spectrum of compound **7** displays a distinctive upfield shift at 67 ppm for the quaternary carbon bearing two phosphorus atoms when compared to the 57 ppm shift measured on compounds **6** and **12**. A small coupling of around 5 Hz between the quaternary phenyl carbon and the two phosphorus atoms can be measured on compounds **8** and **9**. This is in agreement with the value reported by Yokomatsu.[15]

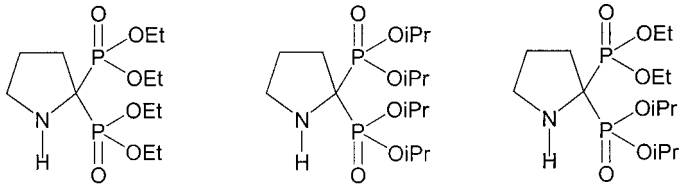
Synthesis of non symmetrical bisphosphonates: In the existing literature,[33,40] there have been very few reports devoted to non symmetrical bisphosphonates as depicted in Scheme 4.



SCHEME 4 Asymmetric bisphosphonate.

By applying our procedure to 2-pyrrolidinone in the presence of one equivalent of $P(OEt)_3$ and one equivalent of $P(OiPr)_3$, a mixture of three products **2**, **15**, and **16** is obtained (Scheme 5). Unexpectedly, 25%–25%–50% proportions have been measured by ^{31}P NMR and HPLC analysis instead of the expected 33%–33%–33% ratios. Considering that the distillation treatment failed, a pure sample of compound **16** was only achieved by a preparative HPLC.

In a previous publication,[28] the study of the ^{13}C NMR spectrum of the methyl on the phosphono group led to the conclusion that the $^{2}J_{pp}$

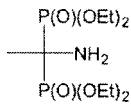
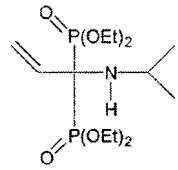
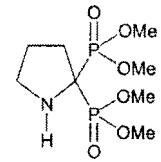
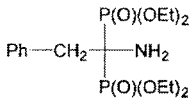
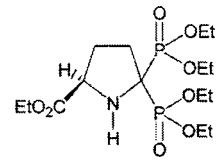
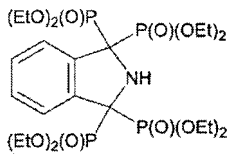
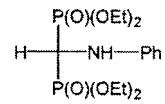
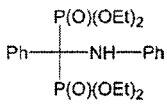
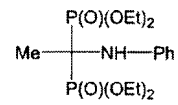
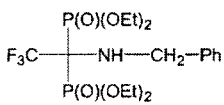


SCHEME 5 Synthesized non symmetric bisphosphonates.

coupling constant had to be larger than 15 Hz. In the view of the newly synthesized bisphosphonates, this coupling constant has been resolved to 58 Hz. It has to be noticed that all NMR spectra obtained from these compounds are the sum of the data corresponding to **2** and **15** with the exception of the ^{31}P spectra.

Lacks: All the cases of deficiencies that we encountered fall into three categories that are summarized on Table III: The reactants failed to react, the reaction went wrong, the products were unstable or could not be purified.

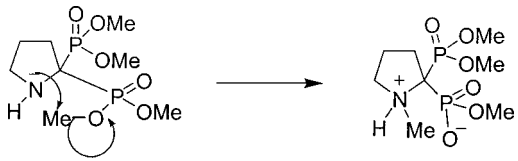
TABLE III Lack

No reaction	Wrong reaction	Unstable
 **17**	 **20**	 **21**
 **18**	 **22**	
 **19**	 **8**	
 **10**	 **9**	
 **13**		

Surprisingly, primary amides as in **17** and **18** are not keen to react and only the corresponding hydrolysis product of the triethylphosphite has been found. Compound **19** only duplicates a lack that has been already described for succinimide[35] and confirms that tetraphosphonates cannot be obtained in this way. The failure of compound **10** probably comes from steric hindrance. Nevertheless the latter can be attained by the Kreutzkamp synthesis.[31] It is likely that the high electronegativity of the fluorine prevents the *N*-benzyltrifluoroactamide from reacting (compound **13**).

Fortunately, compound **20** is the only case where the reaction goes wrong. However a ^{31}P NMR study on its products allows to rule out a potential polymerization.

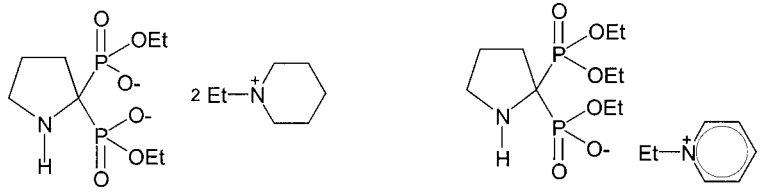
All the compounds reported in the third column of Table III have been identified by their respective NMR spectra.



SCHEME 6 Aminolysis of bisphosphonate.

α-Amino methoxyphosphonates are known to undergo aminolysis reactions (Scheme 6).[41,42] This probably happens while synthesizing compound **21** which appears to be awkward to purify due to its instability. However, its NMR spectrum has been quickly acquired after several preparative TLC. The presence of an ester group apparently hinders a proper build-up of compound **22**. Its formation can be assumed by the appearance of two peaks in the ^{31}P NMR spectrum and of a characteristic quaternary carbon triplet at 62.3 ppm with a coupling constant of 129 Hz in the ^{13}C NMR spectrum. Unfortunately, these spectra also reveal several by-products as validated by a TLC (11 spots). As earlier discussed, compounds **8** and **9** could not be purified; their TLC carry 16 and 12 spots respectively.

Assay of modification of the tetraethyl(pyrrolidine-2,2-diyl)bisphosphonate: Two different sites of the α-aminophosphonates can potentially be modified; the phosphorus atoms and the nitrogen atom. However, most of our attempts led to failures. In order to enhance the biodisponibility of the phosphonates, these alterations are usually required. It seems that the most problematic task is to enhance their lipophilicity by lowering the polarity while maintaining their complexing behavior.[26]

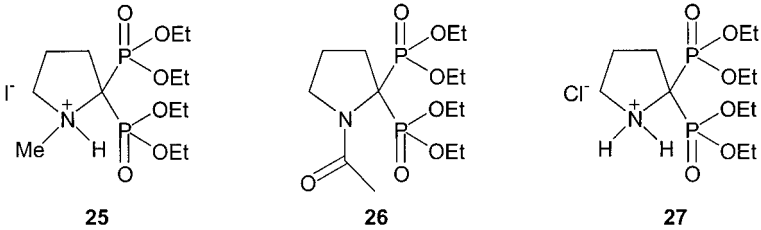


SCHEME 7 Modification on the phosphorus atoms.

Modifications on the phosphorus atoms: Our first efforts were devoted to synthesize compound **23** (Scheme 7) by applying the second procedure described by Vepsäläinen.[43] Therefore compound **2** from Table I has been heated at 110°C with 10 equivalents of piperidine for 20 min. The resulting mixture still contains some of the starting reactants but its ^{31}P NMR study reveals the presence of two coupled phosphorus atoms at 29 ppm and 18 ppm shifts with a 43 Hz coupling constant which is incompatible with the structure of equivalent phosphorus atoms.

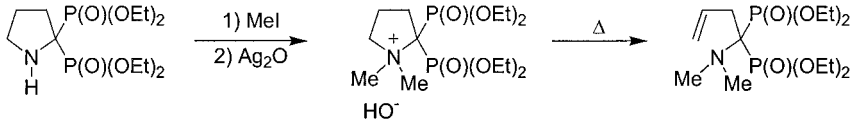
The aim of our second attempt was to synthesize compound **24**. Nothing arose from adding twenty equivalents of pyridine to molecule **2** and warming the mixture to 120°C for 15 min. If it is left to stand for one night, a complete degradation of compound **2** occurs.

Our conclusion is the same as Herlinger's[26] introduction: The preparation of a partial ester is difficult due to the poor selectivity of the involved reactions.



SCHEME 8 Modification on the nitrogen atom.

Modifications on the nitrogen atom: At first, the synthesis of the quaternary ammonium molecule **25** has been attempted (Scheme 8). The objective was to open the five-membered ring by an Hofmann elimination. The resulting molecule would have provided a convenient building block for different kinds of pathways (Scheme 9). Unfortunately, no reaction takes place when molecule **2** is mixed with iodomethane in diethyl ether. However a complex mixture is obtained after 72 h in pure CH_3I; the corresponding ^{31}P NMR spectrum shows 21 peaks and



SCHEME 9 Hoffmann elimination.

some of the starting reactant remains. This result is compatible with reference 44.

Our second attempt was to build compound **26** and, from it, a tetraphosphorus molecule, whose direct synthesis appears not feasible. The reaction yields an inseparable mixture of three components (the expected end product, the related ammonium form and the starting acylchloride). Unfortunately, it degrades after a few days.

The synthesis of compound **27** is our only successful alteration on the nitrogen. It is readily obtained by dissolving **2** in hydrochloric acid and by freely evaporating the remaining water. Its NMR study provides a valuable insight into the reaction mechanism. Furthermore, it shows a similar behavior as described by Pietri et al. in Krebs conditions: the conversion from the acidic to the basic form comes with an NMR shift from 24 to 17 ppm.[45]

CONCLUSION

By optimizing the temperature during the addition of $POCl_3$, the quantity of $POCl_3$ equivalents and the amount of time at room temperature, we have significantly increased the yields as for example from 48% to 58% in the case of **2**. The synthesis of new cyclic or acyclic compounds and the modifications brought to some of the aminobisphosphonates give a valuable insight into the reaction process. These are still under investigation in our laboratory. Apart from the tertiary amides and from the *N*-phenyl compounds, it appears that the yields obtained by our procedure for linear compounds are higher than those reported in the literature. Furthermore we hope that the description of our failures provides some interesting information.

EXPERIMENTAL SECTION

Synthesis and Characterizations. General

NMR spectra were performed on a Varian Inova 400 (^{1}H, 400.16 MHz, ^{13}C, 100.63 MHz, ^{31}P, 162.00 MHz) or on a Varian Gemini 300 (^{1}H, 300.046 MHz, ^{13}C, 75.454 MHz, ^{31}P, 121.460 MHz) spectrometer. δ are given in ppm and referred to internal TMS for ^{1}H and ^{13}C and

to external 85% H_3PO_4 for ^{31}P. ^{15}N-NMR spectra were recorded on a Varian Inova 500 at 50.649 MHz (Inverse gated method) and the chemical shifts (δ) in ppm referred to external CD_3NO_2. All J values are given in Hz. Elemental analyses were determined in the Eindhoven University of Technology. Solvents were purchased from Biosolve. All starting materials were Aldrich reagents and were used as purchased, unless otherwise indicated.

General Optimized Procedure

In a double walled flask, under nitrogen, phosphorus oxichloride (20 ml, 0.22 mol) was added in 1 h time to a mixture at -7.5°C of amide or lactam (0.11 mol) and trialkylphosphite (0.21 mol). The reaction mixture was stirred for 1 h at room temperature and then poured over a mixture of ice (200 g) and ammonia 30% (400 ml). The aqueous layer was extracted with methylene chloride (3×100 ml) and then the latter was removed to obtain an oil. The oil was dissolved in 100 ml of methylene chloride. An aqueous solution of hydrochloric acid (10 ml of 32% HCl solution, 190 ml of water) was added (check that pH 1) and the aqueous layer was washed with methylene chloride (3×100 ml). A solution of sodium hydroxide (200 $g \cdot l^{-1}$) was added up to pH 10 and the aqueous layer was extracted with methylene chloride (4×100 ml). The organic layer was dried over sodium sulfate, filtered and the removal of the solvent afforded the desired bisphosphonates.

Tetraethyl(azetidine-2,2-diyl)bisphosphonate ***1*** *(slightly yellow liquid, 10.14 g, 28%).* ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.17 (12H, t, $J = 7.2$, 4 CH_3CH$_2$O), 2.23 (**1H**, s, NH), 2.64 (2H, tt, $J_{PH} = 17.4$, $J_{HH} = 8.0$, CH_2CP$_2$), 3.54 (2H, t, $J = 7.8$, CH_2N), 4.06 (8H, m, 4 CH$_3$CH_2O). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 16.1 (2 t, $J = 3.1$, 4 CH$_3$CH$_2$O), 25.2 (t, $J = 6.1$, CH$_2$CP$_2$), 45.3 (t, $J = 7.2$, CH$_2$N), 60.3 (t, $J = 149.2$, CP$_2$), 62.6 (t, $J = 3.0$, 2 CH$_3$$CH_2$O), 63.1 (t, $J = 3.5$, 2 CH$_3$$CH_2$O). ^{31}P-NMR (162 MHz, $CDCl_3$) δ 22.2. Anal. Calcd for $C_{11}H_{25}NO_6P_2$: C, 40.13; H, 7.65; N, 4.25. Found: C, 40.21; H, 7.55; N, 4.12.

*Tetraethyl(*N*-methyl-1-aminoethan-1,1-diyl)bisphosphonate* ***6*** *(slightly yellow liquid, 29.20 g, 84%).* ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.36 (12H, t, $J = 6.9$, 4 CH_3CH$_2$O), 1.56 (3H, t, $J_{PH} = 17.0$, CH_3CP$_2$), 1.77 (1H, ls, NH), 2.55 (3H, s, CH_3N), 4.23 (8H, m, 4 CH$_3$CH_2O). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 14.8 (t, $J = 3.8$, CH$_3$CP$_2$), 15.8 (t, $J = 2.7$, 4 CH$_3$CH$_2$O), 29.5 (t, $J = 6.5$, CH$_3$N), 56.8 (t, $J = 143.8$, CP$_2$) 62.0 (t, $J = 3.8$, 2 CH$_3$$CH_2$O), 62.3 (t, $J = 3.2$, 2 CH$_3$$CH_2$O). ^{31}P-NMR (121 MHz, $CDCl_3$) δ 23.8. Anal. Calcd for $C_{11}H_{27}NO_6P_2$: C, 39.88; H, 8.21; N, 4.23. Found: C, 40.02; H, 8.30; N, 4.20. R_f (EtOH/CH_2Cl_2 0.5/9.5) = 0.52.

*Tetraethyl(*N-*methyl-1-amino-1-phenylmethane-1,1-diyl)bisphosphonate* **7** *(colorless liquid, 6.00 g, 15%).* ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.20 (6H, t, $J = 6.9$, 2 CH_3CH$_2$O), 1.29 (6H, t, $J = 7.1$, 2 CH_3CH$_2$O), 2.48 (3H, s, CH_3N), 4.11 (8H, m, 4 CH$_3$CH_2O), 7.35 (3H, m, Aromatics *ortho* and *para*), 7.82 (2H, m, Aromatics *meta*). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 15.8 (t, $J = 3.2$, 2 *C*H$_3$CH$_2$O), 15.9 (t, $J = 3.2$, 2 *C*H$_3$CH$_2$O), 30.6 (t, $J = 9.1$, *C*H$_3$N), 62.9 (t, $J = 3.8$, 2 CH$_3$*C*H$_2$O), 63.0 (t, $J = 3.2$, 2 CH$_3$*C*H$_2$O), 67.4 (t, $J = 136.8$ *C*P$_2$), 126.8 (t not resolved, Aromatics *para*), 127.0 (t not resolved, Aromatics *meta*), 128.4 (t, $J = 5.4$, Aromatics *ortho*), 131.8 (t, $J = 3.8$, quaternary aromatic). ^{31}P-NMR (121 MHz, $CDCl_3$) δ 20.5 Anal. Calcd for $C_{16}H_{29}NO_6P_2$: C, 48.86; H, 7.43; N, 3.56. Found: C, 49.32; H, 7.03; N, 3.76. R_f (EtOH/CH_2Cl_2 0.5/9.5) = 0.60.

*Tetraethyl(*N-*benzyl-1-aminoethan-1,1-diyl)bisphosphonate* **12** *(orange liquid, 33.48 g, 88%).* ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.38 (12H, m, 4 CH_3CH$_2$O), 1.67 (3H, t, $J_{PH} = 16.8$ CH_3CP$_2$), 4.06 (2H, s, CH_2N), 4.38 (8H, m, 4 CH$_3$CH_2O), 7.36 (5H, m, Aromatics).^{13}C-NMR (75 MHz, $CDCl_3$) δ 16.1 (t, $J = 3.2$, 4 *C*H$_3$CH$_2$O) and *C*H$_3$CP$_2$), 47.4 (t, $J = 5.9$, *C*H$_2$N), 57.4 (t, $J = 142.7$, *C*P$_2$), 62.4 (t, $J = 3.8$, 2 CH$_3$*C*H$_2$O), 62.9 (t, $J = 3.2$, 2 CH$_3$*C*H$_2$O), 126.3 (Aromatic *para*), 127.6 and 127.7 (Aromatics *ortho* and *meta*), 139.8 (quaternary aromatic). ^{31}P-NMR (121 MHz, $CDCl_3$) δ 23.3 Anal. Calcd for $C_{17}H_{31}NO_6P_2$: C, 50.12; H, 7.67; N, 3.44. Found: C, 49.88; H, 7.41; N, 3.04.

P,P-*Diethyl*-P′,P′-*diisopropyl(pyrrolidine-2,2-diyl)bisphosphonate* **16** *(colorless liquid, 9.85 g, 25%).* **16** was purified by preparative HPLC on a Kromasil column (10 μm, Φ int = 50 mm, L = 25 cm) with CH_3CN/H_2O 60/40 as eluent. Rate: 50 ml·mn^{-1}. 70 mg by injection. UV detector at 204 nm. T_R (Kromasil column 10 μm, CH_3CN/H_2O 60/40, rate: 0.5 ml·mn^{-1}, UV detector at 204 nm) = 7.57 mn.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.35 (6H, t, $J = 7.8$, 2 CH_3CH$_2$O), 1.37 (12H, d, $J = 6.6$, 2 (CH_3)$_2$CHO), 1.88 (2H, t, $J = 6.7$, CH$_2$CH_2CH$_2$), 2.30 (2H, m, CH_2CP$_2$), 3.07 (2H, t, $J = 6.5$, CH_2N), 4.21 (4H, m, 2 CH$_3$CH_2O), 4.82 (2H, m, 2 (CH$_3$)$_2$C*H*O). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 16.2 (t, $J = 4.9$, 2 *C*H$_3$CH$_2$O), 23.5 (t, $J = 5.4$, 2 (*C*H$_3$)$_2$CHO), 24.0 (d, $J = 3.2$, (*C*H$_3$)$_2$CHO), 24.1 (d, $J = 3.2$, (*C*H$_3$)$_2$CHO), 25.8 (t, $J = 3.2$, CH$_2$*C*H$_2$CH$_2$), 30.2 (t, $J = 2.7$, *C*H$_2$P$_2$), 47.1 (t, $J = 4.3$, *C*H$_2$N), 61.5 (t, $J = 152.9$, *C*P$_2$), 62.4 (d, $J = 7.5$, CH$_3$*C*H$_2$O), 62.9 (d, $J = 7.5$, CH$_3$*C*H$_2$O), 71.0 (d, $J = 7.5$, (CH$_3$)$_2$*C*HO), 71.6 (d, $J = 7.5$, (CH$_3$)$_2$*C*HO). ^{31}P-NMR (162 MHz, $CDCl_3$) δ 22.7 (d, $J_{PP} = 59$, *P*(O*i*Pr)$_2$, 24.9 (d, $J_{PP} = 58$, *P*(OEt)$_2$. ^{15}N-NMR (C_6D_6) δ -340.4 (t, $J_{N-P} = 9.3$). Anal. Calcd for $C_{14}H_{31}NO_6P_2$: C, 45.28; H, 8.41; N, 3.77. Found: C, 45; 21; H, 8.55; N, 4.02.

Tetraethyl(pyrrolidine-2,2-diyl)bisphosphonate hydrochloride ***27*** *(1.08 g, 98%).* In a 10 ml flask, tetraethyl(pyrrolidine-2,2-diyl)bisphosphonate **2** (1.00 g, 2.9 mmol) and an hydrochloric acid solution (10 ml HCl 32% and 90 ml H_2O) was kept at room temperature for 3 days and then the water was removed under reduced pressure to give 1.08 g (yield = 98%) of dark yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.30 (12H, t, $J = 7.2$, 4 CH_3CH_2O), 2.11 (2H, quint., $J = 7.0$, $CH_2CH_2CH_2$), 2.49 (2H, m, CH_2CP_2), 3.55 (2H, t, $J = 7.0$, CH_2N), 4.22 (8H, m, 4 CH_3CH_2O), 8.30 (2H, s, 2 NH_2). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 15.9 (4 CH_3CH_2O), 24.1 ($CH_2CH_2CH_2$), 31.0 (CH_2P_2), 49.0 (CH_2N), 62.9 (t, $J = 146.0$, CP_2), 65.3 (4 CH_3CH_2O). ^{31}P-NMR (162 MHz, $CDCl_3$) δ 16.9. Anal. Calcd for $C_{12}H_{28}ClNO_6P_2$: C, 37.95; H, 7.43; N, 3.69. Found: C, 38.12; H, 7.64; N, 3.37.

REFERENCES

[1] G. Sturtz and H. Couthon, *C. R. Acad. Sc. Paris*, **316** ***(Serie II),*** 181 (1993).

[2] A. Ebrahimpour, F. H. Ebetino, G. Sethuraman, and G. H. Nancollas, *Determination of Solubility and Calcium Ion Stability Constants of a Phosphonoalkylphosphinate (PAP) and Bisphosphonates (BPs) Such as EHDP, Risedronate, Alendronate, 3-pic AMBP, and 3-pic AMPMP*, edited by Z. Amjad (Plenum Press, New York, 1995), p. 295.

[3] W. Plöger, M. Schmidt-Dunker, and C. Gloxhuber, US PAT. 3,988,443 (1976).

[4] D. Nelson and H. Smitherman, US PAT. WO 92/00721 (1992).

[5] M. Nakamura, T. Ando, M. Abe, K. Kumagai, and Y. Endo, *Br. J. Pharmacol.*, **119,** 205 (1996).

[6] J. G. Slatter, K. L. Feenstra, M. J. Hauer, D. A. Kloosterman, A. H. Parton, P. E. Sanders, G. Scott, and W. Speed, *Drug Metab. Dispos.*, **24,** 65 (1996).

[7] J. P. Räsänen, E. Pohjala, H. Nikander, and T. A. Pakkanen, *J. Phys. Chem.*, **100,** 8230 (1996).

[8] C. Dufau and G. Sturtz, *Phosphorus, Sulfur, Silicon Relat. Elem.*, **69,** 93 (1992).

[9] J. H. Lin, *Bone*, **18,** 75 (1996).

[10] F. Hosain, R. P. Spencer, H. M. Couthon, and G. L. Sturtz, *J. Nucl. Med.*, **37,** 105 (1996).

[11] D. V. Griffiths, J. M. Hughes, J. W. Brown, J. C. Caesar, S. P. Swetnam, S. A. Cumming, and J. D. Kelly, *Tetrahedron*, **53,** 17815 (1997).

[12] R. K. Harris, P. Jackson, L. H. Merwin, B. J. Say, and G. Hägele, *J. Chem. Soc., Faraday Trans. 1,* **84,** 3649 (1988).

[13] R. T. Chlebowski and A. McTiernan, *J. Clin. Oncol.*, **17,** 130 (1999).

[14] M. Mimura, M. Hayashida, K. Nomiyama, S. Ikegami, Y. lida, M. Tamura, Y. Hiyama, and Y. Ohishi, *Chem. Pharm. Bull.*, **41,** 1971 (1993).

[15] T. Yokomatsu, Y. Yoshida, N. Nakabayashi, and S. Shibuya, *J. Org. Chem.*, **59,** 7562 (1994).

[16] F. Cheng, X. Yang, C. Fan, and H. Zhu, *Tetrahedron*, **57,** 7331 (2001).

[17] R. A. Nugent, M. Murphy, S. T. Schlachter, C. J. Dunn, R. J. Smith, N. D. Staite, L. A. Galinet, S. K. Shields, D. G. Aspar, K. A. Richard, and N. A. Rohloff, *J. Med. Chem.*, **36,** 134 (1993).

[18] J. C. Brelière, X. Edmonds-Alt, and G. Garcia, Eur. Pat. 100 718; *Chem. Abstr.*, **1984,** *100*, 192078j (1983).
[19] H.-J. Cristau, C. Brahic, and J.-L. Pirat, *Tetrahedron*, **57,** 9149 (2001).
[20] D. Kantoci, J. K. Denike, and W. J. Wechter, *Synth. Commun.*, **26,** 2037 (1996).
[21] K. Fisher, F. Woolard, M. Leadbetter, and J. Gerdes, US PAT. WO 96/31124 (1996).
[22] T. H. Cromartie, K. J. Fisher, and J. N. Grossman, *Pestic. Biochem. Physiol.*, **63,** 114 (1999).
[23] D. Q. Qian, X. D. Shi, R. Z. Cao, and L. Z. Liu, *Heteroat. Chem.*, **10,** 271 (1999).
[24] J. Ohanessian, D. Avenel, D. El Manouni, and M. Benramdane, *Phosphorus, Sulfur, Silicon Relat. Elem.*, **129,** 99 (1997).
[25] L. Lemée, M. Gulea, M. Saquet, S. Masson, and N. Collignon, *Heteroat. Chem.*, **10,** 281 (1999).
[26] D. C. Stepinski, D. W. Nelson, P. R. Zalupski, and A. W. Herlinger, *Tetrahedron*, **57,** 8637 (2001).
[27] A. Rockenbauer, A. Mercier, F. Le Moigne, G. Olive, and P. Tordo, *J. Phys. Chem. A*, **101,** 7965 (1997).
[28] G. Olive, F. Le Moigne, A. Mercier, A. Rockenbauer, and P. Tordo, *J. Org. Chem.*, **63,** 9095 (1998).
[29] F. Palacios, M. J. Gil, E. Martínez de Marigorta, and M. Rodríguez, *Tetrahedron*, **56,** 6319 (2000).
[30] G. Sturtz, H. Couthon, O. Fabulet, M. Mian, and S. Rosini, *Eur. J. Med. Chem.*, **28,** 899 (1993).
[31] N. Kreutzkamp and G. Cordes, *Ann.*, **623,** 103 (1959).
[32] L. Maier, *Phosphorus and Sulfur*, **11,** 311 (1981).
[33] A. Köckritz, G. Röhr, and M. Schnell, *Phosphorus, Sulfur, Silicon Relat. Elem.*, **63,** 95 (1991).
[34] D. Q. Qian, X. D. Shi, R. Z. Cao, and L. Z. Liu, *Tet. Lett.*, **38,** 6245 (1997).
[35] G. Olive, F. Le Moigne, A Mercier, and P. Tordo, *Synth. Commun.*, **30,** 629 (2000).
[36] G. R. F. M. Olive, Ph.D. Thesis, Université d'Aix, Marseille III (1998).
[37] E. W. Petillo and R. Spitzmiller, *Tetrahedron Lett.*, **51,** 4929 (1979).
[38] H. Gross, B. Costisella, and L. Brennecke, *Phosphorus*, **4,** 241 (1974).
[39] G. Olive and M. H. P. van Genderen, *Magn. Res. Chem.*, **38,** 379 (2000).
[40] G. M. Blackburn, D. Brown, S. J. Martin, and M. J. Parratt, *J. Chem. Soc., Perkin Trans. 1,* 181 (1987).
[41] E. E. Nifant'ev, L. M. Runova, T. G. Shestakova, E. V. Bogatyreva, and V. I. Ronkov, *Zh. Obshch. Khim.*, **50,** 304 (1980).
[42] U. Jahn, J. Andersch, and W. Schroth, *Synthesis*, 573 (1997).
[43] J. J. Vepsäläinen, J. Kivikoski, M. Ahlgén, H. E. Nupponen, and E. K. Pohjalad, *Tetrahedron*, **51,** 6805 (1995).
[44] H. Gross and B. Costisella, *J. Prakt. Chem.*, **328,** 231 (1986).
[45] S. Pietri, M. Miollan, S. Martel, F. Le Moigne, B. Blaive, and M. Culcasi, *J. Biol. Chem.*, **275,** 19505 (2000).