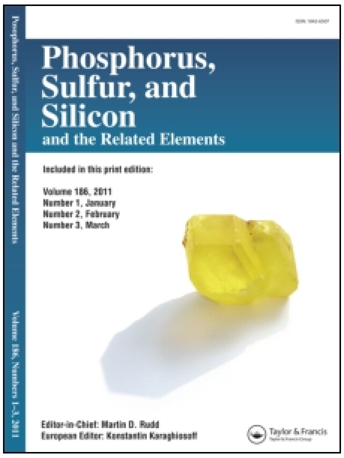

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# 1-AMINO-1-ARYLMETHYL PHOSPHONIC ACID DERIVATIVES. SYNTHESES, CHARACTERIZATION AND COMPLEXING PROPERTIES

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*Abstract.* In this paper we shall review the salient aspects concerning the syntheses, characterization and complexing properties of variously substituted mono- and bis-amino-phosphonates.

## INTRODUCTION

α-Aminophosphonic acids,bioisosters of natural aminoacids, serve for inhibiting enzyme activity,[1] bacterical growth[2] and in agrochemistry as antifungal agents,[3] herbicides[4] and plant regulators. In addition, α-aminophosphonic acids and their mono-alkyl esters are of interest also in hydrometallurgy in order to extract metals[5] and in diagnostic medicine as screening agents, once complexed with lanthanides and actinedes.[6,7] Therefore considering the interest and the wide applications of such compounds we decided to synthesize a great variety of mono- and bis-α-aminophosphonic acid dialkylesters, as well as some of their mono-esters, as described in the text.

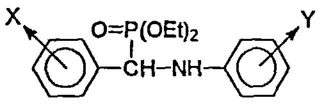
## RESULTS AND DISCUSSION

### *Mono-amino-phosphonic acid derivatives.*

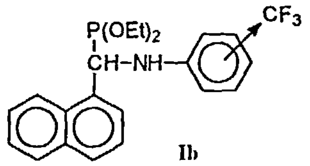
α-Aminophosphonic acid dialkyl esters were prepared by addition in neat or in solvents (polar or apolar) of dialkylphosphite to the Schiff base precursors.

According to this procedure we prepared in good yields α-aminophosphonic dialkyl esters **Ia-If**, where the X and Y substituents range from H, halogens, trifluoromethyl groups, methoxy and carbomethoxy moieties, phenylazo, to free carboxylic groups.

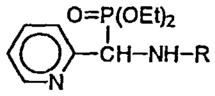
In the $^1$H-NMR spectra the most diagnostic signals are observed in the phosphorus alkoxy and in the methyne regions; in fact, the diethyl esters give rise to *two* distinct triplets at *ca.* 1.1÷1.3 ppm for the methyl groups and a complex multiplet for the methylene protons; the dimethyl esters show *two* distinct doublets ($J_{HP}$ ≅10.5 Hz) for the $OCH_3$ protons at ca. 3.1÷3.8 ppm. This pattern is due to the close proximity of the stereocenter N-C-P and the chemical shift difference between the two triplets or the two doublets is very sensitive to the moiety attached to the methyne carbon bearing the phosphonate group. The methyne hydrogen of the $-CH-P(O)(OR)_2$ group appears as a sharp doublet ($J_{HP}$ *ca.* 22÷24 Hz) or as a quartett of an ABX pattern, due to the additional coupling with the NH proton. Interesting enough, in phosphonates **Ia**, **Ie**, **If**, bearing a carboxy or carbomethoxy group in the ortho position, the NH proton resonates below 8.00 ppm experiencing a dramatically down-field shielding effect due to the formation of a hydrogen bond between the NH and the ortho carbonyl oxygen, via a six-membered cyclic structure.



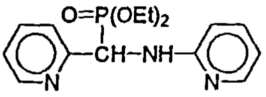
**Ia**



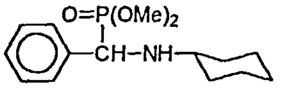
**Ib**



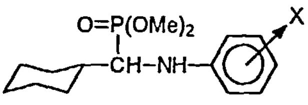
**Ic**



**Id**



**Ie**



**If**

The geometry adopted in the solid state by derivative **Ia** (X = Y = H) was investigated by X-ray diffraction techniques[8,9] and the experimental geometry was compared with that one obtained by using Molecular Modelling methods.[10] The results of our quantum mechanical structural analysis are in good agreement with the conformations obtained from X-ray diffraction studies and from $^1H$-NMR spectra.

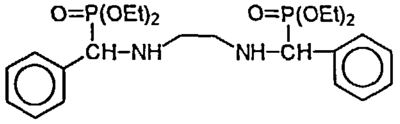
Since our amino-phosphonates **Ia** - **If** exist in two enantiomeric forms we developped a direct and efficient enantioselective resolution of some phosphonates **Ia** - **If** using commercially available HPLC chiral columns.[11,12] A great variety of racemic N-arylamino-1-arylmethyl phosphonic acid diethyl esters with various fluorinated substituents in one or both aryl rings (**Ia**, X = H; 3,4-$F_2$; 4-$OCF_3$; Y = H; 2-$CF_3$; 2$OCF_3$; 2-F; 3-F; 4-F; 3-$CF_3$; 4-$CF_3$; 3,4-$F_2$) have been resolved by using this technique.[12]

Amino-phosphonic acid diethyl esters containing the pyridine moiety (formulas **Ic** and **Id**) were also synthesized[13] with the aim of enhancing the complexation properties towards lanthanides in order to use such compounds in diagnostic medicine, NMR imaging techniques and in agrochemistry. Indeed, alkaline hydrolysis of derivatives **Ic** and **Id** gave the corresponding monoethyl esters phosphonates, which are very versatile complexing agents for transition metals.[14]

In order to enhance the hydrophilicity and the complexing properties towards II° group elements we introduced in our amino-phosphonates one or more carboxylic groups (**Ia**, **Ie**, **If**, X = Y = COOH). Furthermore, the presence of such functionalities should facilitate enantiomer resolution both by HPLC methods or by conventional chemical techniques and will allow the synthesis of disparate derivatives (amides, amines, nitriles) and of definite polycondensates bearing the amino-phosphono functionality.

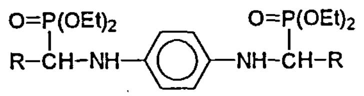
*Bis-α-amino-phosphonates.*

Addition of dialkylphosphite to bis-imines led us to obtain a variety of amino aryl-methyl-diphosphonate alkyl esters in good yields.[15] All compounds, whose structures are exemplified by formulas **IIa-c** and **III**, are crystalline solids and were characterized by $^1$H- and $^{31}$P-NMR and by MS-FAB techniques, which reveal the presence of peaks or fragmentation patterns very useful and diagnostic for constitutional assignments.[15]

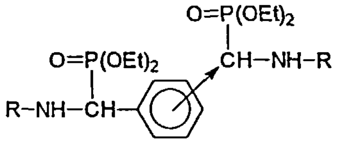


**IIa**

**IIb**



**IIc**



**III**

In the $^1$H-NMR the presence of only one set of signals observed in all compounds for the methyne and ethoxy groups indicates that only one of the two possible diastereomers (the *meso* or the *racemic*) is formed stereospecifically in our addition reactions.[15]

This observation was further confirmed analyzing the $^{31}$P-NMR spectra in which only one sharp phosphorus signal is observed in the majority of our samples.

Indeed, X-ray diffraction analyses clearly indicate that **IIa** has a *meso* configuration and the solid-state molecular conformation possesses a fully elongated trans-planar Ci structure along the P-C-N-C-C-N-P skeleton.[16]

The MS-FAB technique indicates that a protonated ion $[M + H]^+$ was observed in high intensity for all compounds, and the $[M + H - HPO(OEt)_2]^+$ ion or the $[M + H - (2 \times HPO(OEt)_2)]^+$ ion constitute the base peak.

Compounds of type **IIa** and **III** were hydrolysed to the corresponding mono-etsers, in alkaline solution.[17] Characterization of these mono-esters by MS-FAB technique can be performed only using the negative ion mode. All compounds examined show a pseudo-molecular ion $[M - Na]^-$ with very high intensity and peaks due to the cluster ions $[nM - Na]^-$, where n = 1, 2, 3. The presence of the ion $[2M - Na]^-$, is very diagnostic for determining the molecular masses of the salt molecules.[17]

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