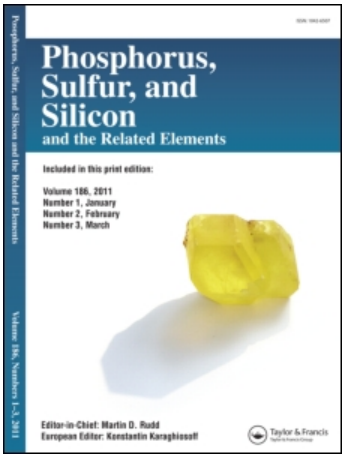

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METHYL-AMINO-PHOSPHONIC ACID DI-ALKYL ESTERS CONTAINING FREE CARBOXYLIC GROUPS. SYNTHESIS AND CHARACTERIZATION

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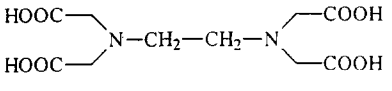
In order to enhance hydrophilicity and complexing properties of amino-phosphonates we synthesized a large variety of these compounds possessing one or two carboxylic groups in the aromatic ring(s). Such groups could facilitate enantiomer resolution and can be used for preparing a variety of interesting compounds as well as polycondensates. Characterization was performed by ^{1}H-NMR and MS-FAB techniques. All compounds synthesized are crystalline high melting materials soluble in water and/or in strong polar solvents, rendering them attractive both for complexation studies and biological applications.

Key words: Complexing agents, water-soluble phosphonates, NMR characterization, monomers for polycondensates.

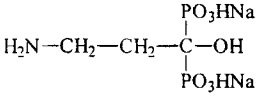
INTRODUCTION

Amino-phosphonic acid derivatives, besides possessing interesting biological and agrochemical properties, could be also used as suitable sequestring and complexing agents for many metals including calcium.[1]

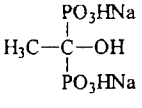
So far, the most widely used calcium complexing agents belong to the class of polycarboxylic molecules, such as EDTA or to organic bis-phosphonate compounds, analogs of the inorganic pyrophosphate, in which the oxygen atom linking the two phosphorus atoms has been replaced by a carbon atom, i.e, they possess the general structure P—C—P. Some examples of geminal bis-phosphonates already described in the literature and clinically used[2,3] are ABP, HEBP, CIMBP, MDPA, etc.



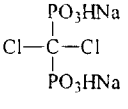
EDTA



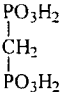
ABP



HEBP



CIMBP



MDPA

The clinical interest of such bis-phosphonates is connected with their potential use against several pathological conditions involving irregularities in calcium metabolism (i.e., osteoporosis, osteolysis in bone cancer)[4] or involving calcium deposition (i.e., arterosclerosis, arthritis, kidney and renal calculus).[5,6]

However, side-effects and the lack of selectivity militate against their diffuse use.[2] Therefore great interest is raising in the specialized literature in order to modify such drugs by separating along the molecular chain the two phosphoryl groups or by introducing some other complexing centers, besides the phosphonate ones.

Taking advantages of our synthetic approach to variously substituted 1-amino-1-aryl methyl-phosphonic and di-phosphonic acid dialkyl esters[7-12] we decided to introduce in our compounds both the carboxylic as well as the phosphoryl groups with the following ideas in mind: i) Enhance the hydrophilicity of amino-phosphonates even at the stage of dialkyl esters derivatives; ii) Enhance complexing properties toward II° groups elements by introducing two or more chemically different complexing groups; iii) Facilitate enantiomer resolution both by HPLC methods[7,11] or by conventional chemical techniques, considering the interest of disposing of enantiomerically enriched amino-phosphonates for biological screenings; iv) Use the carboxylic group in order to perform on it functionalization reactions for preparing a variety of interesting compounds as well as polycondensates.

Therefore in this paper we shall describe the synthesis, as well as the characterization, of variously substituted amino-phosphonates all bearing at least one carboxylic group whereas the other subunit of the molecule is bearing additional fragments able to interact with metals (see Tables I–III).

RESULTS AND DISCUSSION

In our approach to the synthesis of phosphonates 1–3 the best and simplest synthetic route was found in the direct addition (at room temperatures or in refluxing dioxane) of the dialkylphosphite to the corresponding Schiff bases, generally high melting solids, which are readily available through the condensation of primary amines with aldehydes. A small amount of NaH was used in order to catalyze the reaction, and then the desired phosphonate was purified by recrystallisation from dioxane or from ethylacetate.

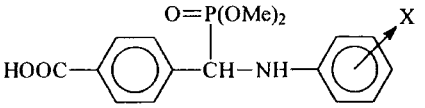
Our compounds are soluble both in polar organic solvents ($CHCl_3$, CH_3CN, DMSO, alcohols) as well as in water or in slightly alkaline solutions rendering them attractive for biological applications.

As far as the ^{1}H-NMR spectra are concerned, first of all, we remark that the aromatic or the alkyl proton chemical shifts are not listed in the Tables because these protons resonate in the expected region of the magnetic field and generally maintain the multiplicity already present in the precursor Schiff-bases.

The methyne hydrogen of the groups —CH—P(O)(OR)$_2$ generally resonates as a sharp doublet with a coupling constant H—P in the range of 22–24 Hz, except in **1b, 1c** and in all compounds of series **3** where the additional coupling with the NH proton generates an ABX pattern. In all these latter samples the CH resonances give rise at least to a four line pattern with J_{H-P} in the range of 18–24 Hz and J_{N-H} 8–9 Hz, whereas the NH protons appears as a triplet with J_{NH-P} nearly equal to

TABLE I

Physical properties of 1



N.	X	Yield %	m.p. °C	^{1}H-NMR δ ($CDCl_3$,TMS)		
				CH	NH	O=P(OMe)$_2$[a]
1a	3-CF_3	65	94-96	4.94 (d, J_{HP} = 25Hz)	6.93 (br s)	3.54, 3.84
1b	2-COOH	42	123 dec.	5.00 (ABX)[b]	8.94 (t)	3.55, 3.68
1c†	2-$COOCH_3$	53	199-200	5.02 (ABX)	8.89 (ABX)	3.74, 3.77
1d	4-N=N-Ph	63	205-207	5.00 (d, J_{HP} = 25Hz)	5.83 (br s)	3.55, 3.84

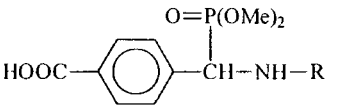
[a] doublet (J_{HP} = 10.5÷11 Hz)

[b] In DMSO as solvent

† Calc. for $C_{18}H_{20}NO_7P$: C 54.96, H 5.09, N 3.56; found 54.88, H 5.06, N 3.6.

TABLE II

Physical properties of 2



N.	R	Yield %	m.p. °C	^{1}H-NMR δ ($CDCl_3$,TMS)		
				CH	NH	O=P(OMe)$_2$[a]
2a	*i*-propyl	78	130-135	4.26 (d, J_{HP} = 22.4Hz)	2.66	3.52, 3.77
2b†	*t*-butyl	81	198-199	4.30(d, J_{HP} = 26.2Hz)	-	3.55, 3.82
2c	1-cyclohexyl	80	157-158	4.38(d, J_{HP} = 22.8Hz)	2.30	3.60, 3.82
2d	$-(CH_2)_3-O-CH(CH_3)_2$	63	94-97	4.20 (d, J_{HP} = 21Hz)	~ 3.50	3.62, 3.76

[a] doublet (J_{HP} = 10.6÷11 Hz)

† Calc. for $C_{14}H_{18}NO_5P$: C 54.02, H 5.78, N 4.5; found C 54.1, H 5.83, N 4.7.

TABLE III

Physical properties of 3

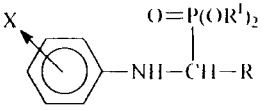
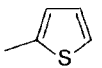
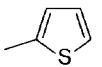
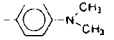


TABLE III. Physical properties of **3**

N.[a]	X	R	Yield %	m.p.	^{1}H-NMR δ ($CDCl_3$,TMS)			
					CH	NH	O=P(OR¹)₂	R¹
3a	2-COOH		65	153-154	5.24 (q, ABX)	8.75 (t)	4.05-4.19 (m); 1.24, 1.31[b]	Et
3b	4-COOH		31	196-198	5.50 (q, ABX)[c]	7.0 (q, ABX)	3.80-4.14 (m); 1.12, 1.20[b]	Et
3c†	4-COOH		73	154-156	4.78 (q, ABX)	5.88 (t)	3.45, 3.77[d]	Me

[a] In a previous work[12] we already described the following analogs (X = 2-COOH, R = Ph, cyclohexyl; X = 4-COOH, R = Ph, 4-methoxyphenyl, 1-cyclohexyl)

[b] Triplets

[c] Solvent DMSO

[d] doublets (J_{HP} = 10.4)

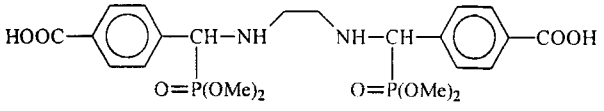
† Calc. for $C_{18}H_{23}N_2O_5P$: C 57.14, H 6.13, N 7.4; found C 57.09, H 6.18, N 7.48.

J_{-NH-CH}. The observation of an ABX pattern was already observed in some other related compounds[8-10,12] and the calculated spectrum was used in order to extract the coupling constant values.[8]

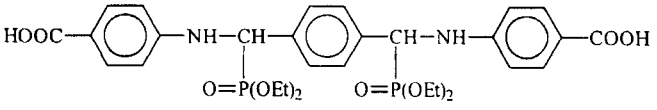
Due to the close proximity of the stereocenter N—C—P, the methyl hydrogen of the methoxy groups always appears as two distinct doublets of equal intensity; analogously, the ethoxy groups show two distinct triplets of equal intensity.

The large chemical shift difference between the two methoxy doublets, is due to the anisotropic ring current experienced by one of the methoxy groups attached to phosphorus which is lying in the close proximity of the aryl ring, whereas the other one is far away from it, as can be inferred from the molecular geometry adopted in the solid state by similar derivatives[13] and supported by quantum mechanical and force field studies.[14]

As a confirmation of what we already noticed in a previous work a dramatic downfield shift effect is evident looking at the NH resonance of compounds bearing carboxy or carbomethoxy group in the ortho position, when compared with the NH chemical shift of the isomeric compounds or of related derivatives possessing such groups in the para position. No doubt that this exceptional downfield effect is due to the formation of a hydrogen bond between the NH and the ortho carbonyl oxygen giving rise to a cyclic structure.[12]



4



5

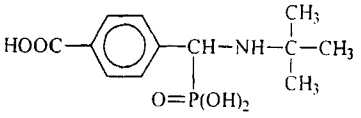
As examples of bis-phosphonate compounds bearing two carboxyl groups, we synthesized compounds **4** and **5**, which own their interest both as potential metal complexing agents, as well as starting monomers for obtaining linear polycondensates, e.g., polyamides, bearing phosphonyl pendant groups.

Due to the presence of two identical chiral centers **4** and **5** can exist both as *dl* pairs as well as meso derivatives.[7,13] For compound **4**, the product isolated from the phosphorylation reaction, as judged by its NMR spectrum is a 50/50 mixture of the two diastereomers. By recrystallization from dioxane one of the two isomers increases over the other, but no further attempts were made to isolate the pure forms or to assign their configuration.

Thus in **4**, contrary to what was observed in other related bis-phosphonates by us previous synthesized[7,8,13] no stereospecificity of the addition reaction was observed.

On the contrary, the ^{1}H-NMR spectrum of **5**, after washing the compound with dioxane/AcOEt, shows that the diastereomer ratio is $\geq$90/10, indicating that in the synthesis of **5** stereospecific addition of diethylphosphite is still occurring. Compounds **4** and **5**, are soluble in polar organic solvents (DMSO, EtOH) and in water.

Acid hydrolysis of dialkyl esters **1–3**, can be used in order to prepare the corresponding phosphonic acids. As an example, this reaction was performed on **2b** (Table II) which gave almost a quantitative yield of **6**, as a crystalline white solid, m.p. 198–199°C, insoluble in all organic solvents but soluble in slightly alkaline water solutions.



6

Compounds **6**, besides being a possible precursor of an amino-phosphonic acid bearing in addition a free carboxylic group (acidic cleavage of the N-*t*-butyl bond) is a good candidate for performing complexation studies with metals and calcium, in particular. Experiments along these lines are under progress.

EXPERIMENTAL

Amines, aldehydes, dimethyl- and diethyl-phosphite, as well as solvents and all other chemicals used were high purity commercial products from Aldrich. All syntheses were performed under a dry N_2 atmosphere.

^{1}H-NMR spectra were recorded in $CDCl_3$ with Me_4Si as an internal standard using a Bruker AC-250 instrument operating at 250 MHz.

Melting points were determined on a Büchi 530 melting point apparatus and are uncorrected. The Schiff base precursors were all prepared in high yield according to the procedure previously described.[8]

The compounds listed in Tables I–III were synthesized by direct reaction between the Schiff bases and the phosphite according to the following general procedure:

To a stirred solution of the Schiff base precursor (0.1 mol) in a mixture EtOH/dioxane (50 ml) were added dropwise 14 ml (0.15 mol) of $HP(O)(OMe)_2$ or $HP(O)(OEt)_2$ and a catalytic amount of NaH. After the addition was completed, the mixture was stirred for a few hours. The solvent was then evaporated and the solid formed was filtered off. All the phosphonates synthesized are white solids, except for compound **1d** (Table I) which is red. They were recrystallized from a mixture of dioxane and ethylacetate. Microanalytical data are consistent with the molecular formulas and for one compound each of the type **1–3** data are reported as footnote to Tables I–III.

Compound **4**. Condensation of 4-carboxy-benzaldehyde 7.5 g (0.05 mol) with 1,2-ethylenediamine 1.5 g (0.025 mol) in EtOH/dioxane solution, yielded the correspondent bisimine in quantitative yield, which is a white solid with m.p. 227–230°C. To a dioxane solution of 8 g (0.024 mol) of bis-imine precursor were added 7.7 g (0.07 mol) of dimethylphosphite and the mixture was heated over a period of 12 hours at refluxing temperature. The reaction mixture was concentrated in vacuo and a white powder was obtained, which was crystallized from dioxane to give 7.9 g (60%) of compound **4**; m.p. 180–185°C, ^{1}H-NMR: δ (DMSO d_6, TMS): 2.43 (4H, m, CH_2), 3.49 (6H, d, J_{HP} = 10.5 Hz, OCH_3), 3.68 (6H, d, J_{HP} = 10.5 Hz, OCH_3), 4.28 (2H, d, J_{HP} = 21.4 Hz, CHP), 7.51 (4H, d, ArH) and 7.90 (4H, d, ArH). The signals of the other diastereomer are shifted and are thus evident only in the methyl and methyne region of the spectrum: δ 3.48 (d, OCH_3), and 4.21 (d, J_{HP} = 21.6 Hz, CHP). FAB-MS: parent ion $[M + H]^+$ at m/z = 545, fragment $[(M + H)\text{-H-PO(OMe)}_2]^+$ at m/z = 435.

Compound **5**. 16.6 g (0.045 mol) of the yellow bis imine precursor was heated at 100°C with an excess of diethyl phosphite (30 ml) until the mixture became white. After cooling to room temperature 50 ml of diethyl acetate was added and the white solid formed was filtered off and washed several times with diethyl acetate and dioxane to yield 23.4 g (81%) of **5**; m.p. 245°C (dec.); ^{1}H-NMR: δ (DMSO d_6, TMS), 0.93 (6H, t, CH_3), 1.16 (6H, t, CH_3), 3.53–4.03 (8H, m, CH_2), 5.16 (2H, ABX, J_{HP} = 23.2 Hz, J_{HNH} = 9 Hz, CH), 6.81 (4H, d, ArH), 7.14 (2H, ABX, $J_{HP} \cong J_{HNH}$ = 9 Hz, NH), 7.50 (4H, s, ArH) and 7.58 (4H, d, ArH). The signals of the other diastereomer are shifted and are thus evident only in the ethyl and methyne region of the spectrum: δ 0.97 (t, CH_3), 1.25 (t, CH_3) and 5.12 (ABX, CH). FAB-MS: parent ion $[M + Na]^+$ at m/z = 671, base peak $[(M + H)\text{-H-PO(OEt)}_2]^+$ at m/z = 511 fragment $[(M + Na)\text{-H-PO(OEt)}_2]^+$ at m/z = 533.

Acid hydrolysis of compound **2b**. 2 gr (6.35 mmol) of compound **2b** was refluxed for 2 hrs in 40 ml of HBr (24%) and after cooling to room temperature a white solid was formed. After filtration, the solid was washed with dioxane, dried in vacuum to yield 1.6 gr (88%) of compound **6**; m.p. 200°C (dec.); ^{1}H-NMR δ (D_2O/Na_2CO_3), 0.91 (9H, s, CH_3), 3.99 (1H, d, J_{HP} = 18 Hz, CHP), 7.33 (2H, d, ArH) and 7.57 (2H, d, ArH).

ACKNOWLEDGEMENTS

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