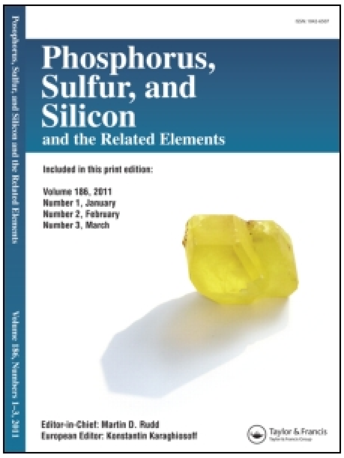

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

SYNTHESIS, NMR CHARACTERIZATION AND FAB-MS SPECTRA OF SOME ARYLMETHYL-AMINO-PHOSPHONIC ACID MONOETHYL ESTERS

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To cite this Article Failla, Salvatore and Finocchiaro, Paolo(1993) 'SYNTHESIS, NMR CHARACTERIZATION AND FAB-MS SPECTRA OF SOME ARYLMETHYL-AMINO-PHOSPHONIC ACID MONOETHYL ESTERS', Phosphorus, Sulfur, and Silicon and the Related Elements, 85: 1, 65 — 72

To link to this Article: DOI: 10.1080/10426509308038183

URL: http://dx.doi.org/10.1080/10426509308038183

Phosphorus, Sulfur, and Silicon, 1993, Vol. 85, pp. 65–72
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SYNTHESIS, NMR CHARACTERIZATION AND FAB-MS SPECTRA OF SOME ARYLMETHYL-AMINO-PHOSPHONIC ACID MONOETHYL ESTERS

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(Received September 28, 1993; in final form November 9, 1993)

Substituted arylmethyl-amino-phosphonic acid monoethyl esters have been synthetized by alkaline hydrolysis of the parent diester derivatives. Diastereoisomerizations due to racemization at the chiral —CH— centers were observed in the hydrolytic process. Our compounds are very soluble in water and strong polar organic solvents; therefore, these derivatives can be used for biological and agrochemical tests in hydrophilic media. Some of the prepared compounds are deeply coloured and their absorption maxima are pH-dependent. The ^{1}H and ^{31}P-NMR spectra show interesting features, whereas the MS-FAB obtained with negative ion source are diagnostic for structural assignments. In all MS spectra, peaks due to cluster ions $[nM - Na]^-$ where observed.

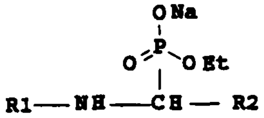
Key words: Water soluble phosphonic acid monoethyl esters; synthetic procedure; racemization; U.V., NMR, and MS spectroscopic properties; dyes.

INTRODUCTION

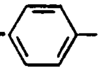
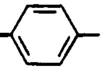
Recently we reported on the synthesis and NMR characterization of some 1-amino-2-aryl-methyl-bisphosphonate esters[1] as useful and stable intermediates for the preparation of amino-diphosphonic acids.

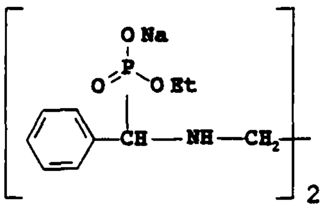
Recalling that amino-arylmethyl phosphonates are very promising compounds for use as antifungal and antibacterial agents,[1] as well as possible anti-cancer[2] and metal complexing molecules,[3] and considering that such peculiar properties, in most cases, should be exploited in hydrophilic solvents, we decided to synthesize molecules bearing one or two aminophosphonic acid monoethyl ester moieties, in order to have water soluble derivatives. Furthermore, some of the synthesized mono-esters bear one or two benzeneazo groups; thus, such compounds are deeply coloured and can be used as very resistant reactive dyes for cellulose and synthetic fibres,[4] as well as pH indicators in biological screenings.

Therefore, in this paper we wish to report on the synthesis and properties of some sodium salts of aryl-methyl-amino-phosphonic acid monoethyl esters of formulas as follows:



1

	R1	R2
1a	Ph	Ph
1b	Ph-N=N- 	Ph
1c	Ph-N=N- 	2-Pyridyl



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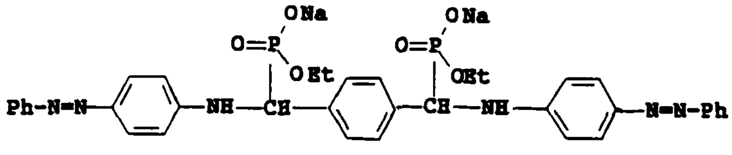

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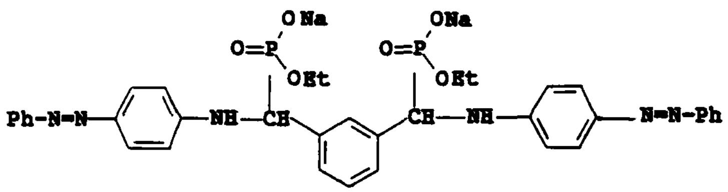

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RESULTS AND DISCUSSION

In Table I are listed the salient physical properties of the synthesized compounds, all obtained by alkaline hydrolysis of the parent esters, according to the procedure described in the literature.[3,5,6] The precursor phosphonic acid diesters were prepared in good yield by the synthetic methods described in a previous paper.[1]

All samples listed in Table I are crystalline, high melting materials, stable in air, and very soluble in water or in strong polar organic solvents (DMSO, DMF, etc.). Samples **1a** and **2** are white or pale yellow materials, whereas compounds **1b**, **1c**,

TABLE I

Physical properties of compounds 1–4

	Yield	m.p.	^{1}H-NMR in D_2O or DMSO-d_6[a]					^{31}P-NMR[b]	$[M-Na]^-$
No	(in %)	(°C)	CH̲P	OCH̲$_2$	NH	CH_2CH_3	Others		
1a	60	230-234 (232)[c]	4.24 (ABX, J_P 22)	3.56 (q)	5.49 (ABX, J 5.8)	0.95 (t)		19.43	290
1b	63	226-228 (232)[d]	4.39 (ABX, J_P 21, $J_{H-NH} \approx 8$)	3.60 (q)	6.53	0.97 (t)		18.34	394
1c	70	>290	4.12 (d, J_P 22)	3.64 (q)	-	0.93 (t)		16.44	395
2[e]	75	297	f	3.65 (q)	-	1.02 (t)	2.41 (s) (N-CH_2)	20.24 (70.2%) 20.29 (29.8%)	477
			3.74 (d, J_P 20)	3.49 (q)	g	0.94 (t)	2.37 (s)		
3	48	250 dec	3.38 (d, J_P 20)	3.50 (q)	-	1.07 (t)		18.57 (34.9%) 19.92 (65.1%)	-
4	50	240 dec	4.21 (d, J_P 20)	3.71 (q)	-	1.02 (t)		18.46 (51.8%) 18.58 (48.2%)	733

[a] ^{1}H-NMR of samples **1a** and **1b** measured in DMSO-d_6; **1c-4** measured in D_2O

[b] Chemical shifts measured in D_2O (ca 10%) with 85% H_3PO_4 as external reference.

[c] See reference 5

[d] See reference 6

[e] ^{1}H-NMR chemical shifts in the first row are measured in D_2O; in the second row in DMSO-d_6.

[f] Masked by OCH_2 resonances

[g] Masked by DMSO-d_6 resonances.

3, and **4** are deeply red-coloured due to the presence of the benzeneazo chromophor.

As far as the ^{1}H-NMR spectra are concerned, the aromatic or hetero-aromatic proton chemical shifts are not listed in Table I because these protons resonate in the expected region of the magnetic field and they generally maintain the multiplicity already present in the precursor Schiff-bases or diesters.

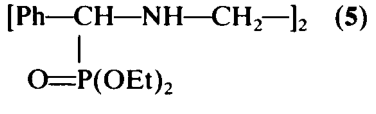
The methyne hydrogens of the group —CH—P(O)(ONa)(OEt), due to the couplings with the ^{31}P nucleus and with the NH protons generate an ABX spectrum, where the CH resonances give rise to a four line pattern with $J_{H—P}$ in the range of 20–24 Hz and $J_{H—NH}$ 6–7 Hz, whereas the NH protons appears as a triplet with $J_{NH—P}$ nearly equal to $J_{NH—CH}$. The ABX pattern is observed only in deuterated solvents which do not exchange with the N—H protons; in D_2O as solvent, due to a fast exchange process, the additional coupling with the N—H nucleus is missing and thus the CH signal appears as a sharp doublet, with $J_{H—P}$ in the range of 20–22 Hz.

In our monoesters, the methyl hydrogens of the ethoxy group always appear as a sharp triplet and the methylene protons as a quartet indicating that the two stereocenters (—C*H—) and —P*(O)(ONa)(OEt) are not affecting the multiplicity of the ethyl group. Thus, we can conclude that the presence of two distinct triplets for the ethoxy methyl groups in our previously investigated diesters,[1] arises from restricted rotation, on the NMR time scale, around the CH—P(O)(OEt)$_2$ bond.

The ^{31}P-NMR spectra of our samples, listed in Table I, show only one sharp signal for the mono-functional compounds **1a–1c**, whereas two signals, very close in chemical shifts, are always present in the case of the bi-functional derivatives **2–4**.

The presence of two distinct peaks for compounds **2–4** indicates that diastereoisomerization occurred during the alkaline hydrolysis of the corresponding diester precursors, thus generating the *meso* and *racemic* forms due to the presence of two identical chiral centers present in the molecules **2–4**.

In order to have a better insight on such isomerization we performed an alkaline hydrolysis in deuterated media (NaOD, D_2O) on the *pure meso* form of



$$[\mathrm{Ph{-}\underset{\substack{|\\ O{=}P(OEt)_2}}{CH}{-}NH{-}CH_2{-}}]_2 \quad (\mathbf{5})$$

whose ^{31}P-NMR spectrum showed the presence of only one sharp peak at δ 24.38 ppm.[1] From the deuterated media we obtained a white powder, which is soluble in water and was recrystallized from ethanol containing water. The FAB-MS spectrum of this compound showed the presence of more than one species.

As will be discussed later, for all compounds examined, a pseudo-molecular ion $[M - Na]^-$ was detected in the FAB-MS spectra. Thus, inspection of Figure 1 reveals that at least three different species were produced in the hydrolysis: a bis-deuterated monoester salt (52%) $[MD_2]$ which shows the base peak at m/z 479 $[MD_2 - Na]^-$; a mono-deuterated species (36%) with m/z 478 $[MHD - Na]^-$ whose peak is the second one in relative intensity; and finally, a peak at m/z 477 corresponding to $[MH_2 - Na]^-$, i.e., to the non-deuterated species (11%) which

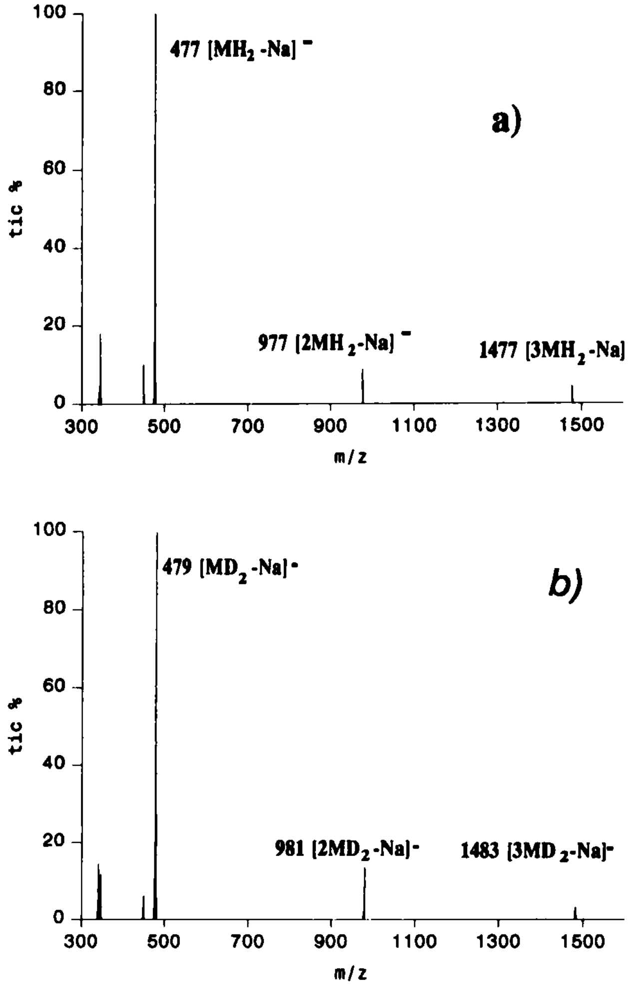


FIGURE 1 FAB-MS spectra of compound **2** (a) and of its deuterated derivative (b).

corresponds in chemical constitution to compound **2**. Such percentages are also maintained in the corresponding $[2M - Na]^-$ cluster peaks.

This result strongly indicates that some deuterium exchange occurred in the alkaline media. Such deuterium exchange can conceptually occur on two different centers: on the NH protons or on the methyne hydrogen of the groups —CH—P(O)(ONa)(OEt). The fragmentation patterns observed in the FAB-MS spectra of **2** and its deuterated analog were very helpful in deciding between these two alternatives. In fact, as previously repoted,[1] such kinds of phosphonates easily lose the fragment $H—P(O)(OR)_2$ in order to generate the more stable Schiff base precursor possessing the —C$\underline{H}$=N— functionality. Thus, the proton is coming out from the —NH— group and *not* from the —CH— one. Now in the mass spectra of compound **2** and its deuterated derivative, we observed strong fragment ions at 345 and 347, respectively, due to the loss of H—P(O)(ONa)(OEt), indicating that the nitrogen center still maintained the proton in both species; whereas, the deuterium was present in the methyne group, which thus suffered inversion of configuration during the hydrolytic process. Furthermore, the ^{1}H-NMR spectrum in DMSO-d_6 of the product obtained in the deuterated media is very similar to the spectrum of **2** (except for different multiplicities in the OEt peaks) and, more important, does not show any —CH—P— resonance, indicating once again that deuterium is linked with the methyne group. In this way we can explain the diastereoisomerization processes observed in our bi-functional derivatives **2–4**.

In addition, the presence in the ^{31}P-NMR of three distinct signals at 20.25 ppm (23.6%), 20.29 ppm (43.1%), and 20.34 (33.2%), indicates that in the white powder more than one diastereomeric species are present.

Inspection of the ^{31}P chemical shifts of our mono-esters reported in Table I reveals that electron withdrawing groups cause an up-field shift of such resonances, as already noticed in the case of the corresponding di-ester precursors.[1] Furthermore, the functionality [—P(O)(ONa)(OEt)] shows ^{31}P chemical shifts at much higher field with respect to the —P(O)(OEt)$_2$ moiety.

The characterization of the samples reported in Table I was also performed by the FAB-MS technique. First of all, we noticed that for all compounds investigated, good MS spectra were obtained only by using the negative ion mode.

Inspection of Table II indicates that always representing the base peak, a pseudomolecular ion $[M - Na]^-$ with very high intensity was observed for all compounds.

In comparison with the di-esters, the mono-esters do not show any fragmentation pattern; due to the easy loss of HPO_3NaEt (m/z 132), a fragment ion $[M - Na - 132]^-$ at m/z 345 and 347, respectively, was observed only for compound **2** and for the white sample obtained in the deuterated media.

In all spectra, peaks due to cluster ions $[nM - Na]^-$, where $n = 1, 2, 3$, were observed. The region at relatively high masses is characterized by the presence of the ion $[2M - Na]^-$, which is the second peak in relative intensity. This interesting

TABLE II

FAB-MS spectral data of samples listed in Table I

No	$[M - Na]^-$	$[2M - Na]^-$	$[3M - Na]^-$
1a	290 (100)	603 (15)	916 (5)
1b	394 (100)	811 (40)	1228 (10)
1c	395 (100)	813 (30)	1231 (9)
2	477 (100)	977 (10)	1477 (5)
3	-	-	-
4	733 (100)	1498 (12)	2245 (7)

Peak's intensities are reported in parentheses.

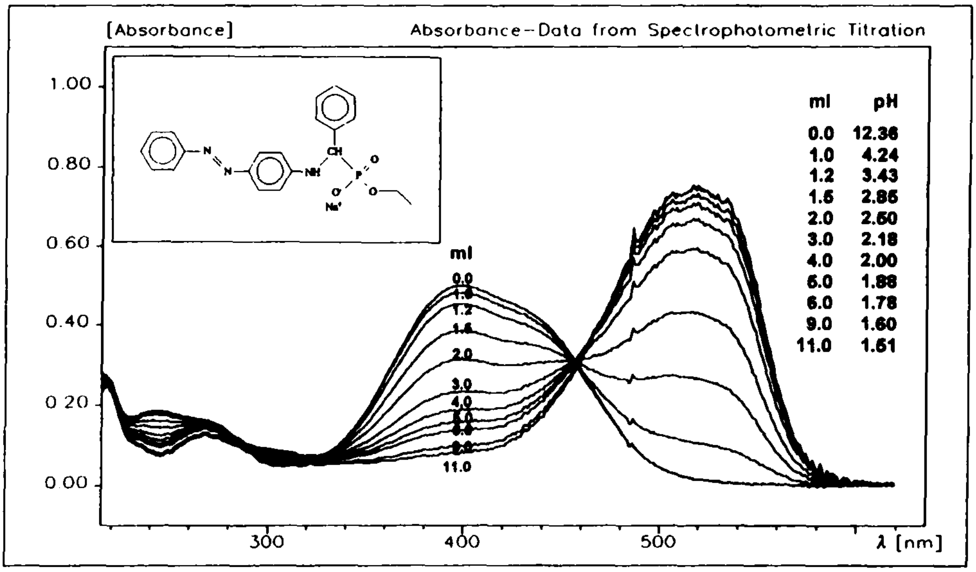


FIGURE 2 Overlay of 11 UV-visible spectra in H_2O of compound **1b**, as a function of pH.

peak is very diagnostic for determining the molecular masses of the salt molecules. In fact, the detection of both ions as the anion $[M - X]^-$ and the cluster ion $[2M - X]^-$ (where X is the cation), allows the determination of the relative molecular masses of the salt molecule and its ionic components, i.e., anion and cation.[7] A cluster with peak, at m/z $[3M - Na]^-$ mass unit above the molecular ion with relative intensities in the range 5–10%, is also present in all spectra.

As mentioned in the introduction part, samples **1b**, **1c**, **3**, and **4** are deeply coloured materials, and their electronic spectrum in the visible region is strongly pH-dependent. In fact, as shown in Figure 2, in acidic solution, compound **1b** shows an intense maximum at *ca.* 520 nm; increasing the pH, this maximum decreases, whereas the shoulder at 400 nm becomes the new absorption maximum, and several isosbestic points are observed between 220 and 600 nm. Therefore, such compounds can be utilized for spectrophotometric titrations in aqueous media and for complexation studies at different pH values. Experiments in this direction are in progress.

EXPERIMENTAL

The arylmethyl-diphosphonate ester precursors were synthetized by literature method.[1] Solvents and all other chemicals used were commercial products from Aldrich, which were purified before use. All hydrolyses were performed under dry N_2 atmosphere.

^{1}H-NMR spectra were recorded in D_2O or DMSO with DDS or Me_4Si as an internal standard, respectively, using a Bruker WP-80 instrument operating at 80 MHz. Phosphorus NMR-spectra were recorded in D_2O at Düsseldorf University with a Bruker AM 200 MHz spectrometer with a resolution ≥ 0.003 ppm using 85% H_3PO_4 as external reference.

Mass spectra were obtained using a double focusing Kratos MS 50S instrument equipped with a standard FAB source in negative mode and DS 90 data system. 3-Nitro-benzylalcohol was used as matrix. Melting points were determined on a Büchi 530 melting point apparatus and are uncorrected.

For the synthesis of our mono-esters we followed the procedure previously described by Jagodic.[3,5,6] As an example of the procedure used, we describe the preparation of compound **2**. To a stirred solution of the diester precursor (5.12 g, 10 mmol) in dry ethanol (100 ml) was added 1 g of NaOH (25 mmol). After the addition was completed, the mixture was warmed to reflux for 10 hr. To precipitate the excess of the base, carbon dioxide was added to the solution and the Na_2CO_3 formed was filtered off and the resulting solution was evaporated. A white powder was obtained which was recrystallized from ethanol to give 3.83 g (75%) of **2**.

The alkaline hydrolysis in deuterated media was made in CD_3OD as solvent and NaOD 40% in D_2O.

ACKNOWLEDGEMENTS

WE thank C.N.R. and the Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST) for financial support. We are indebted to Ruth Boetzel (Düsseldorf University) for running the ^{31}P-NMR spectra.

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