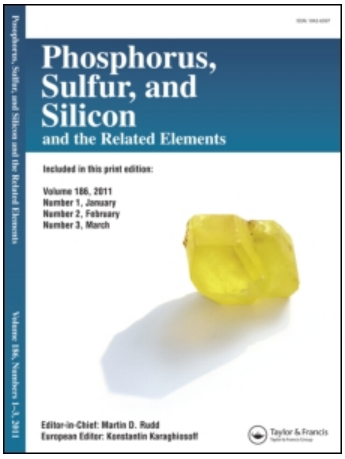


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

SYNTHESIS AND CHARACTERIZATION OF AMINOPYRIDIN-2-YL-METHYL-PHOSPHONIC ACIDS

Salvatore Failla[a]; Paolo Finocchiaro[a]; Mario Latronico[b]; Manuela Libertini[b]
[a] Istituto Chimico, Facoltà di Ingegneria, Università di Catania, Catania, Italy [b] Dipartimento di Ingegneria e Fisica dell'Ambiente, Università della Basilicata, Potenza, Italy

To cite this Article Failla, Salvatore , Finocchiaro, Paolo , Latronico, Mario and Libertini, Manuela(1994) 'SYNTHESIS AND CHARACTERIZATION OF AMINOPYRIDIN-2-YL-METHYL-PHOSPHONIC ACIDS', Phosphorus, Sulfur, and Silicon and the Related Elements, 88: 1, 185 — 188
To link to this Article: DOI: 10.1080/10426509408036920
URL: http://dx.doi.org/10.1080/10426509408036920

Phosphorus, Sulfur, and Silicon, 1994, Vol. 88, pp. 185–188
Reprints available directly from the publisher
Photocopying permitted by license only

SYNTHESIS AND CHARACTERIZATION OF AMINO-PYRIDIN-2-YL-METHYL-PHOSPHONIC ACIDS

SALVATORE FAILLA,† PAOLO FINOCCHIARO,*†
MARIO LATRONICO‡ and MANUELA LIBERTINI*‡

†Istituto Chimico, Facoltà di Ingegneria, Università di Catania, Viale A. Doria, 6-95125 Catania, Italy; ‡Dipartimento di Ingegneria e Fisica dell'Ambiente, Università della Basilicata, Via Nazario Sauro, 85100 Potenza, Italy

(Received January 11, 1994; in final form February 8, 1994)

Amino-phosphonic acids and their diethyl esters containing one or two pyridyl moieties were synthetized in good yields, starting from the corresponding Shiff base as precursors. The new compounds were characterized by ^{1}H- and ^{31}P-NMR spectroscopy and preliminary results indicate that they are able to complex with transition metals. Therefore, such compounds can be of utility in diagnostic medicine, NMR imaging and in agrochemistry.

Key words: Amino-pyridylmethyl mono- and di-phosphonate esters; amino-phosphonic acids; NMR spectroscopic properties; chelating agents.

INTRODUCTION

In our continuing program aimed at synthetizing new aryl-amino-methyl phosphonates and phosphonic acids[1–3] we decided to introduce in our series, compounds which possess one or two pyridine moieties, having in mind the main following objectives:

i) Enhance the complexation properties towards metals in general and towards lanthanides in particular.
ii) Increase water solubility, with the concomitant possibility of forming pyridinium salts.
iii) Broaden our synthetic methodologies aimed to the synthesis of hetero-aromatic amino-methyl phosphonates whose preparation and characterization were not reported as yet in the literature.

In fact, inspection of the chemical formulas of our new compounds listed below reveals that such compounds possess a structure which was already found suitable (as Schiff bases, for example[4,5]) for complexing transition metals and lanthanides. Therefore, in this context our compounds can be viewed as good chelating agents possessing in addition the $—P(O)(OH)_2$ functionalities which render them water-soluble and prone to complex more strongly with metals. This peculiarity can be of great utility in diagnostic medicine,[6] NMR imaging,[7] fluoroimmunoassays[8] and in biological screenings in general where such complexes could also exhibit tissue specificity in their biodistribution.

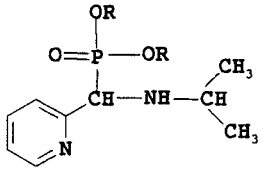
Furthermore, in agrochemistry such compounds may act as carriers for trace-metal cations i.e., Cu^{++}, Fe^{++}, Zn^{++}, Mn^{++} essential to plants.

RESULTS AND DISCUSSION

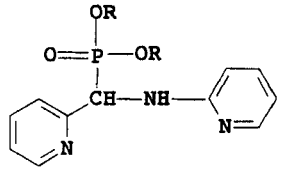
In our approach,[2,3] the best and simplest synthetic route to aryl-amino-methyl phosphonates was found to be the addition of diethyl phosphonate to Schiff bases, which are readily available through the condensation of primary amines with aldehydes. The diethyl phosphonates were then hydrolyzed to the corresponding phosphonic acids with conc. HCl or using $(Me)_3SiBr$ (see Experimental section).

All phosphonic acid diethyl esters synthetized are white solids very soluble in organic media. The ^1H- and ^{31}P-NMR spectra of phosphonate **1a**, **2a**, and **3a** (reported in the Experimental section) are consistent with the assigned structure and show a similar pattern, both in chemical shifts and multiplicities, to the previously described aryl-amino-methyl-phosphonates.[2,3] In particular, the methyl hydrogens of the ethoxy group resonate as two distinct triplets, very diagnostic for such derivatives[2,3]; the methyne hydrogen of the group —NH—CH—$P(O)(OEt)_2$, in deuterated solvents which exchange with the NH proton resonates as a doublet with J_{HP} in the range of 20 ÷ 23 Hz; in all other solvents, the CH proton appears as a doublet of doublets which is part of an ABX system, due to the additional coupling with the NH proton.[3]

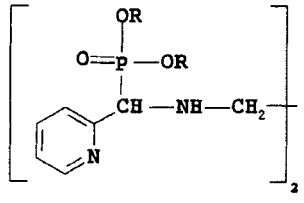
The ^{31}P-NMR spectra show a single resonance for compounds **1a** and **2a**, whereas the bi-functional derivatives **3a** exhibit two signals of different intensities, corresponding to the two possible diastereoisomers, i.e. *meso* and *racemic* which are generated by the addition of $H—P(O)(OEt)_2$ to the Schiff base precursor. However, also in the case of compound **3a**, by judging from the relative population of the two diastereomers (90/10) we can conclude that such an addition is occurring with high stereo-specificity, as already pointed out in previous papers.[2,3]



1a, R = Et
1b, R = H



2a, R = Et
2b, R = H



3a, R = Et
3b, R = H

The phosphonic acids **1b**, **2b**, and **3b** are white high melting materials very soluble in water and able to complex transition metals. In this respect, experiments are in progress in order to determine their solid state structure and their solution equilibria by potentiometric techniques and ^{31}P-NMR titrations.

EXPERIMENTAL

Amines, aldehydes, diethylphosphonate, $(Me)_3SiBr$, 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 D_2O or $CDCl_3$ 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 at Düsseldorf University with a Bruker AM 200 MHz spectrometer with a resolution ≥0.003 ppm using 85% H_3PO_4 as external reference. Melting points were determined on a Büchi 530 melting point apparatus and are uncorrected.

Schiff bases were obtained by direct reaction between a primary amine and the aldehydes with the simultaneous removal of water by azeotropic distillation. Their characteristics are given below.

Pyridine-2-carbaldehyde N-isopropyl imine. Condensation of 2-pyridinecarboxyaldehyde with isopropylamine yielded[9] a pale yellow oil which was purified by vacuum distillation, b.p. 65°C/1 mmHg; (Nujol mulls) (C=N) 1560 cm^{-1}; ^{1}H-NMR δ ($CDCl_3$, TMS): 1.27 (6H, d, CH_3, $^3J_{H,H}$ = 6.23 Hz), 3.64 (1H, m, CH, $^3J_{H,H}$ = 6.23 Hz), 7.28 (1H, m, ArH), 7.70 (1H, m, ArH), 8.01 (1H, m, ArH), 8.41 (1H, s, CH) and 8.62 (1H, m, ArH).

2-(2-Pyridylmethylenamino) pyridine. The Schiff base was obtained by condensing 2-amino-pyridine with 2-pyridinecarboxyaldehyde; the pale-yellow solid obtained was crystallized from toluene, m.p. 116–117°C (lit[5] m.p. 119); (Nujol mulls) (C=N) 1610 cm^{-1}; ^{1}H-NMR δ ($CDCl_3$, TMS): 5.94–8.58 (9H, ArH + CH).

1,2-Ethanediamine,N,N'-bis(pyridin-2-yl methylene). The yellow Schiff base obtained from the condensation of 2-pyridinecarboxyaldehyde with ethylenediamine was crystallized from ethyl ether, m.p. 66–67[4,10] °C, ν (Nujol mulls) (C=N) 1645 cm^{-1}; ^{1}H-NMR, δ ($CDCl_3$, TMS): 4.06 (2H, s, CH_2), 7.30 (1H, m, ArH), 7.71 (1H, m, ArH), 7.99 (1H, m, ArH), 8.43 (1H, s, CH), 8.55 (1H, m, ArH).

O,O diethyl-(isopropylamino-pyridin-2-yl-methyl) phosphonate **1a**. 10 g of pyridine-2-carbaldehyde N-isopropyl imine and 20 ml of diethyl phosphite are heated over a period of 18 hours at 70–80°C (the progress of the reaction was controlled by thin layer chromatography). The reaction mixture was concentrated in vacuo and 20 ml of ethyl acetate is added and the solution left at −20°C for 24 hrs. The solid obtained was filtered and purified by crystallization from ethyl acetate and rapidly washed with cold ethyl ether to yield 9.8 g (51%) of a white solid, m.p. 40–41°C; (Nujol mulls) (P—O—C) 1020, (P=O) 1230, (N—H) 3300 cm^{-1}; ^{1}H-NMR δ ($CDCl_3$, TMS): 1.00 and 1.03 (6H, 2d, J_{HH} = 6.2 Hz, CH—$\underline{CH}_3$), 1.18 and 1.29 (6H, 2 t, J_{HH} = 7.0 Hz, $CH_2\underline{CH}_3$), 2.47 (1H, s, NH), 2.68 (1H, m, CH), 4.07 (4H, m, CH_2), 4.31 (1H, d, CH, J_{HP} 22.7 Hz), 7.11–7.78 (3H, m, ArH), 8.58 (1H, m, ArH); ^{31}P-NMR δ ($CDCl_3$): 23.42.

O,O diethyl-(2-pyridylamino-pyridin-2-yl-methyl) phosphonate **2a**. 10 g (54 mmol) of 2-(2-pyridylmethylenamino)pyridine and 15 ml (116 mmol) of diethylphosphite are heated over a period of 18 hrs at 80°C. The reaction mixture was concentrated in vacuo and separation of phosphonate from the red oil was accomplished in cold ethyl acetate (−20°C). The pale-red solid (7 g, 40% yield) was purified by column chromatography on SiO_2 using tetrahydrofuran as eluent; a white crystalline product was obtained from ethylacetate; m.p. 78–80°C, ν (Nujol mulls) (P—O—C) 1040, (P=O) 1250, (N—H) 3310 cm^{-1}; ^{1}H-NMR δ ($CDCl_3$, TMS): 1.19 and 1.25 (6H, 2 t, J_{HH} = 7.0 Hz, CH_2—$\underline{CH}_3$), 4.06 (4H, m, CH_2), 5.90 (1H, ABX, J_{HP} = 20 Hz, J_{HH} = 7.5 Hz, CH—P), 6.04 (1H, ABX, $J_{HH} \approx J_{HP}$ = 7.5 Hz, NH), 6.60–8.57 (8H, m, ArH); ^{31}P-NMR ($CDCl_3$): 22.17.

O,O diethyl-1,2-ethylene diamino-N,N'-bis(pyridin-2-yl methyl phosphonate) **3a**. As in the case of **1a**, the addition of diethylphosphite to 1,2-ethanediamine,N,N'-bis(pyridin-2-yl methylene) was carried out by heating at 80°C for 18 hrs the two reagents without solvents. After concentration of the resulting mixture in vacuo to eliminate the excess of diethylphosphite, crystallization of the phosphonate from the crude product was accomplished in cold ethylacetate (−20°C). The white solid (72% yield) was

filtered and rapidly washed with cold ethyl ether, m.p. 92–94°C; (Nujol mulls) (P—O—C) 1030, (P=O) 1250, (NH) 3310 cm^{-1}; ^{1}H-NMR δ ($CDCl_3$, TMS): 1.18 and 1.29 (12H, 2 t, J_{HH} = 7.0 Hz, CH_2—$\underline{CH_3}$), 2.59 (2H, br s, NH), 2.63 (4H, s, CH_2), 4.05 (8H, m, $\underline{CH_2}$—CH_3), 4.20 (2H, d, J_{HP} = 20 Hz, CH), 7.19 (2H, m, ArH), 7.44 (2H, m, ArH), 7.64 (2H, m, ArH), 8.55 (2H, m, ArH); ^{31}P-NMR δ ($CDCl_3$): 22.88 (90%) and 22.96 (10%).

(Isopropyl amino-pyridin-2-yl methyl) phosphonic acid **1b**. To 5 g (17.4 mmol) of **1a** dissolved in 40 ml of fresh distilled acetonitrile, in the presence of 5.23 g (34.9 mmol) sodium iodide, was added 5.34 g (34.9 mmol) of $(CH_3)_3SiBr$ and the mixture stirred for 18 hrs at ambient temperatures. After filtration, the solution with the silyl phosphonate was evaporated to give a slightly yellow resin. This was treated with 50 ml of ethanol and stirred for 3 hrs at r.t. The white solid formed was filtered (2 g, 50% yield) and crystallized from methanol, m.p. 203–205°C (dec.), ^{1}H-NMR δ (D_2O, DDS): 1.30 and 1.36 (12H two doublets,[3] J_{HH} = 6.5 Hz, CH$\underline{CH_3}$), 3.57 (2H, m, CH + NH), 4.7 (1H, d, J_{HP} = 16.8 Hz, CH), 7.70 (2H, m, ArH), 7.90 (1H, m, ArH) and 8.61 (1H, m, ArH); ^{31}P-NMR δ (D_2O): 8.52. Microanalysis for $C_9H_{15}N_2O_3P$ (230.12) calcd. C 46.95, H 6.52, N 12.17; found: C 47.02, H 6.59, N 12.09.

(2-Pyridyl amino-pyridin-2-yl methyl) phosphonic acid **2b**. To 2 g (6.2 mmol) of **2a** dissolved in 20 ml of anhydrous CH_3CN, in the presence of 1.86 g (12 mmol) of NaI, was added 1.9 g (12 mmol) of $(CH_3)_3SiBr$ and the mixture was stirred for 18 hrs at ambient temperatures; and for additional 30 min at 40°C. After filtration, the solution was concentrated to give a yellow resin. This was treated with 20 ml of ethanol and stirred for 3 hrs at ambient temperatures. From this solution, after crystallization from EtOH/H_2O was then obtained the acid 0.32 g, 20% yield; m.p. 212°C (dec). Alternatively, 3 g of **2a** (9.3 mmol) were refluxed for 6 hrs in 50 ml of HCl (20%) and then the solution was evaporated at reduced pressure. The crude solid obtained was crystallized from EtOH (95%) yielding 1.48 g (60%) of the acid **2b** as a white solid with m.p. 205–207°C. ^{1}H-NMR δ (D_2O, DDS): 6.30–6.50 (m, 2H, CH + NH) and 6.80–7.10 (m, 8H, ArH); ^{31}P-NMR δ (KOD): 13.83; δ (D_2O): 10.43. Elemental analysis indicates that it recrystallizes with one molecule of HCl and two molecules of water. Calcd. for $C_{11}H_{12}N_3O_3P \cdot HCl \cdot 2H_2O$ (337.65), C 39.05, H 4.58, N 12.42; found: C 39.12, H 4.95, N 12.65. Mass spectra (LSIMS): parent ion at m/z = 266 $[M + 1]^+$, base peak at m/z = 184 $[\mathbf{2b} - H_3PO_3 + 1]^+$.

1,2-Ethylene diamino-N,N'-bis(pyridin-2-yl methyl phosphonic acid) **3b**. 2 g of **3a** (3.8 mmol) was refluxed for 6 hrs in 150 ml of HCl (20%) and the solution evaporated on a rotavapor. The brown-white solid was recrystallized from ethyl alcohol (95%) (0.75 g, 44% yield), m.p. 222–223°C (dec.); ^{1}H-NMR δ (D_2O, DDS): 3.56 (2H, s, CH_2), 7.91 (2H, m, ArH), 8.43 (1H, m, ArH), 8.73 (1H, m, ArH); ^{31}P-NMR δ (D_2O): 0.41. Elemental analysis indicates that it crystallizes with two molecules of water. Calcd for $C_{14}H_{20}N_4P_2O_6 \times 2H_2O$ (438.28), C 38.35, H 5.47, N 12.78; found C 38.74, H 6.02, N 12.86. Mass spectra: Base peak at M/Z = 243 $[\mathbf{3b} - 2HPO_3 + 1]^+$.

ACKNOWLEDGEMENTS

We thank C.N.R. and the Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST) for financial support.

REFERENCES

1. S. Failla, P. Finocchiaro, V. K. Belsky, V. E. Zavodnik and A. N. Sobolev, *Phosphorus, Sulfur and Silicon*, **80**, 75 (1993).
2. S. Caccamese, S. Failla, P. Finocchiaro, G. Hägele and G. Principato, *J. Chem. Research* (S), 242 (1992).
3. S. Failla, P. Finocchiaro, G. Hägele and R. Rapisardi, *Phosphorus, Sulfur and Silicon*, **82**, 79 (1993).
4. D. A. Durham and F. A. Hart, *J. Inorg. Nucl. Chem.*, **31**, 145 (1969).
5. Z. Holzbecher and H. Trung, *Coll. Czech. Chem. Commun.*, **41**, 1506 (1976).
6. J. R. Morphy, D. Parker, R. Kataky, M. A. W. Easton, A. T. Millican, R. Alexander, A. Harrison and C. Walker, *J. Chem. Soc. Perkin Trans.*, 573 (1990).
7. R. B. Lanffer, *Chem. Rev.*, **87**, 901 (1987).
8. R. A. Evangelista, A. Pollak, B. Allore, E. F. Templeton, R. C. Morton and E. P. Diamandis, *Chim. Biochem.*, **21**, 173 (1988).
9. H. Peter and D. Reinehr, *Helv. Chim. Acta*, **61**, 1115 (1978).
10. D. H. Busch and J. C. Bailar, *J. Amer. Chem. Soc.*, **78**, 1137 (1956).