Synthesis of Dimethylphosphinoyl Substituted α-Aminoarylmethanephosphonates

Tsvetanka Cholakova[a], Yulian Zagraniarsky[a], Gerhard Hägele[b], Tania Tosheva[c], Bojidarka Ivanova[a], Rosario Scopelliti[d], and Sabi Varbanov[c]

[a] University of Sofia, Faculty of Chemistry, 1, J. Bourchier av., 1126 Sofia, Bulgaria
[b] Institute of Inorganic and Structural Chemistry, Heinrich Heine University-Düsseldorf, D-40225-Düsseldorf, Germany
[c] Institute of Polymers, Bulgarian Academy of Sciences, 1113 Sofia, Bulgaria
[d] Laboratory of Lanthanide Supramolecular Chemistry, BCH 1402, Swiss Federal Institute of Technology, CH-1015 Lausanne, Switzerland

Reprint requests to Dr. T. Cholakova. E-mail: cholakova@chem.uni-sofia.bg

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New dimethylphosphinoyl-substituted α-aminoarylmethanephosphonates **1a – f** have been synthesized *via* addition of dimethyl or diethyl phosphites to Schiff bases and *via* Kabachnik-Fields reaction. The structure of the compounds was confirmed by elemental analysis, IR, ^{1}H and ^{31}P{^{1}H} NMR spectroscopy, mass spectrometry and in two cases by X-ray diffraction.

Key words: Dimethylphosphinoyl-Substituted Phosphonates, α-Aminoarylmethanephosphonates, Kabachnik-Fields Reaction, Arylmethylene-1-dimethylphosphinoylmethaneamines

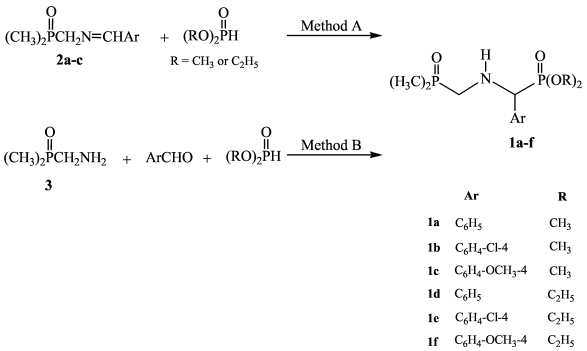
Introduction

Due to their unique biological properties, the aminophosphonic acids as analogues of the natural amino acids have played a central role in the investigation of biologically active molecules during the last twenty years [1]. It has been shown that some phosphorus analogues of phenylalanine such as 1-amino-2-arylphosphonic acids are strong inhibitors of phenylalanine ammonia lyase (PAL) or represent quite active botrycides [2]. In particular the synthesis of dialkylphosphinoyl derivatives has been of interest because these compounds exhibit higher activity in some cases in comparison with the corresponding phosphonic and phosphinic esters [3].

The present work is a continuation of our previous investigations of aminomethyl-dimethylphosphine oxide as a precursor for the preparation of new organophosphorus compounds. Some of these compounds exhibit biological activity, *e.g.* the nitrosourea derivatives [4] and the platinum complexes exert antitumor activity but are of low toxicity and triazolo- and pyrazolopyrimidine derivatives have plant growth regulating activity [5]. We report here the synthesis and characterization of dimethylphosphinoyl-substituted α-aminoarylmethanephosphonates. They have been used as precursors for the preparation of new α-aminophosphonic acids bearing a second phosphoryl group.

Results and Discussion

We report a simple and efficient method for the synthesis of *O,O'*-dimethyl- and *O,O'*-diethyl-*N*-(dimethylphosphinoylmethyl)amino-1-arylmethanephosphonates (**1**), based on the addition of dialkyl phosphites to azomethines. To our knowledge these compounds have never been synthesized before.



Scheme 1.

The starting arylmethylene-1-dimethylphosphinoylmethaneamines **2a** (Ar = C_6H_5), **2b** (Ar = 4-Cl-C_6H_4)

Table 1. Preparative and analytical data of the phosphonates **1a – f**.

No.	R	Ar	Yield[a] [%] Method A	Method B	M.p. [°C]	General formula (Mol. mass)	Elemental analysis [%] C calcd.	C found	H calcd.	H found	N calcd.	N found
1a	CH_3	C_6H_5	72 (53)		86 – 89	$C_{12}H_{21}NO_4P_2$ (305.25)	47.22	47.01	6.93	7.17	4.59	4.99
1b	CH_3	4-Cl-C_6H_4	98		oil	$C_{12}H_{20}ClNO_4P_2$ (339.69)	42.43	42.52	5.93	6.00	4.12	4.36
1c	CH_3	4-CH_3O-C_6H_4	93		oil	$C_{13}H_{23}NO_5P_2$ (335.27)	46.57	46.28	6.91	7.30	4.18	4.57
1d[b]	C_2H_5	C_6H_5	89 (75)	93 (69)	77 – 79	$C_{14}H_{25}NO_4P_2$ (333.31)	50.45	50.19	7.56	7.68	4.20	4.49
1e	C_2H_5	4-Cl-C_6H_4	96 (70)	84 (57)	103 – 107	$C_{14}H_{24}ClNO_4P_2$ (367.75)	45.73	45.83	6.58	6.46	3.81	4.13
1f	C_2H_5	4-CH_3O-C_6H_4	89 (69)	70 (53)	88 – 89	$C_{15}H_{27}NO_5P_2$ (363.33)	49.59	49.56	7.49	7.71	3.86	4.27

[a] Yields of the crude reaction product (TLC: one spot), yields after recrystallization – in brackets;[b] for **1d** see [17].

and **2c** (Ar = 4-CH_3O-C_6H_4) were prepared following the published [6] and slightly modified procedure. Phosphonates **1** were obtained by the addition of dimethyl or diethyl phosphite to the C=N double bond of the Schiff bases **2** in toluene (Method A), according to Scheme 1. The yields of the crude reaction products (TLC: one spot) were high (72 – 98%). After recrystallization we obtained the phosphonates **1a – f** as low melting crystals or oils. The preparative and analytical data of the compounds **1a – f** are given in Table 1.

In order to make the isolation of the Schiff bases **2** unnecessary and to simplify the procedure we performed one-pot syntheses of the phosphonates **1** *via* Kabachnik-Fields reaction (Method B), mixing all three components (amine **3**, dialkylphosphite and aldehyde) together in toluene and after standing overnight heating them for 8 h at 80 °C. The yields of the crude phosphonates **1c – f** (TLC: homogenous) were again high (70 – 93%). Structure and purity of the compounds **1** were confirmed by IR, ^{1}H and ^{31}P NMR and mass spectral data and elemental analysis (Tables 1, 2 and 3).

The IR spectra of carbon tetrachloride and chloroform solutions of **1e** in the region between 3500 – 3200 cm^{-1} exhibit a 3348 cm^{-1} peak assigned to ν_{NH} stretching vibration [7]. Its intensity and position is independent of variations of the concentration and phase state, suggesting a participation of the NH group in intramolecular hydrogen bond formation. The solid state IR spectrum of **1e** is characterized by an intensive peak at 1261 cm^{-1} assigned to the $\nu_{P=O}$ stretching vibration of the phosphonate fragment, while the second P=O group absorbs at 1167 cm^{-1} [8, 9]. In chloroform a high frequency shifting of the first band to 1291 cm^{-1} and an insignificant change of the second one is observed. This may indicate a participation of the dimethylphosphinoyl P=O group in the intramolecular hydrogen bonding and an eventual rotation around the Ar(C)-P=O bond causing the mentioned above high frequency shifting of the 1261 cm^{-1} band. For the other compounds **1a – f** the corresponding $\nu_{P=O}$ stretching modes of phosphonate and dimethylphosphinoyl groups appear between 1260 – 1270 and 1174 – 1156 cm^{-1} regions, respectively.

In the ^{1}H NMR spectra of **1a – f** (Table 2) the resonance signals for the $(CH_3)_2PO$ groups appear as two doublets at $\delta = 1.32 - 1.34$ and $1.37 - 1.39$ ppm with $^2J_{PH} = -10.0 - 12.9$ Hz. The signals of the methylene groups are multiplets but after D_2O exchange are transformed into doublets of doublets at $\delta = 2.59 - 2.72$ ppm, owing to the quenching of the coupling with the NH-protons. The corresponding coupling constants are $^2J_{HH} = -14.2 - 14.6$ Hz and $^2J_{PH} = -7.3 - 8.5$ Hz. Similar values for the chemical shifts of $(CH_3)_2P{=}O$ and $CH_2P{=}O$ groups, as well as of $^2J_{PH}$ data have been observed previously [5]. The signals of the methine protons in the phosphonate moiety (-C*H*(Ar)-P(O)OR) appear as doublets of doublets at $\delta = 4.13 - 4.37$ ppm with coupling constants $^2J_{PH} = -20.5 - 21.5$ Hz and $^3J_{HH} = 8.5 - 8.9$ Hz. After D_2O-exchange they are also transformed into doublets. The signals for the protons of the ester methoxy groups in compounds **1a – c** appear as two doublets at $\delta = 3.45 - 3.49$ and $3.67 - 3.70$ ppm with $^3J_{PH} = 10.5 - 10.6$ Hz. In the ^{1}H NMR spectra of the ethyl phosphonates **1d – f** the resonance signals for the ester methyl groups are two triplets at $\delta = 1.03 - 1.05$ and $1.20 - 1.22$ ppm with

Table 2. ^{1}H and ^{31}P{^{1}H} NMR data of phosphonates **1a – f** (δ in ppm, J in Hz).

No.	^{1}H																^{31}P{^{11}H}	
	$(CH_3)_2P{=}O$		P-CH_2-N			NH	N-CH-Ar			CH_3O-P=O		-CH_2O-P=O			CH_3CH$_2$		$(RO)_2P{=}O$	$(CH_3)_2P{=}O$
	δ	$^{2}J_{PH}$	δ	$^{2}J_{HH}$	$^{2}J_{PH}$	δ	δ	$^{2}J_{PH}$	$^{3}J_{HH}$	δ	$^{3}J_{PH}$	δ	$^{3}J_{PH}$	$^{3}J_{HH}$	δ	$^{3}J_{HH}$	δ	δ
1a	1.34d	−12.6	2.6 – 2.8m			[a]	4.33dd	−21.2	8.9	3.46d	10.5						24.98	42.62
	1.39d	−12.6								3.70d	10.5							
			2.61dd[b]	−14.4	−8.4	–[c]	4.28d[b]	−21.3	–									
			2.70dd[b]	−14.3	−7.4													
1b	1.34d	−12.8	2.6 – 2.7m			2.7 – 2.8m	4.37dd	−21.3	8.8	[d]							25.12	43.04
	1.39d	−12.8								3.69d	10.6							
			2.62dd[b]	−14.4	−8.5	–[c]	4.31d[b]	−21.5	–	3.49d[b]	10.6							
			2.72dd[b]	−14.6	−7.3					3.67d[b]	10.6							
1c	1.33d	−11.2	2.6 – 2.7m			[a]	4.24dd	−20.6	8.1	3.45d	10.5						25.31	43.79
	1.38d	−11.2								3.69d	10.5							
			2.6 – 2.7m[b]			–[c]	4.19d[b]	−20.7	–									
1d	1.34d	−11.2	2.6 – 2.7m			[a]	4.25dd	−21.0	8.8			4.05dq	7.8	7.1	1.03t	7.1	22.76	43.02
	1.39d	−11.2										3.7 – 3.9m	–	–	1.22t	7.1		
			2.62dd[b]	−14.3	−8.5	–[c]	4.20d[b]	−21.1	–									
			2.71dd[b]	−14.4	−7.6													
1e	1.32d	−12.9	2.6 – 2.7m			[a]	4.29dd	−21.1	8.5			4.04dq	7.8	7.1	1.05t	7.1	22.11	42.47
	1.37d	−12.9										3.7 – 3.9m	–	–	1.20t	7.1		
			2.61dd[b]	−14.5	−8.4	–[c]	4.24d[b]	−21.3	–									
			2.70dd[b]	−14.6	−7.8													
1f	1.33d	−10.0	2.6 – 2.7m			[a]	4.17dd	−20.5	8.6			4.04dq	7.8	7.1	1.05t	7.1	23.01	42.55
	1.38d	−10.0										3.7 – 3.9m	–	–	1.22t	7.1		
			2.59dd[b]	−14.2	−8.2	–[c]	4.13d[b]	−20.5	–									
			2.68dd[b]	−14.3	−7.4													

[a] Overlapping with the signals of PCH_2N-protons; [b] after D_2O exchange; [c] disappeared after D_2O exchange; [d] overlapping with the signal of H_2O.

Table 3. Significant mass spectrometric data [*m/z* (rel. int. %)] of the phosphonates **1a – f** (results of FAB-MS are indicated by [a], those of EI-MS by [b]).

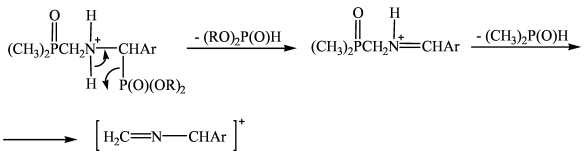
No.	Method	$[M+H]^+$	$[M]^{+\bullet}$	$[(CH_3)_2P(O)CH_2NH{=}CHAr]^+$	$[CH_2{=}NCHAr]^+$	$[(CH_3)_2P(OH)CH_2]^{+\bullet}$ *m/z* = 92
1a	a	306 (34)		196 (100)	118 (38)	(6)
	b		305 (2)	196 (34)	118 (70)	(43)
1b	a	340 (48)		230 (100)	152 (47)	(16)
	b		339 (6)	230 (69)	152 (100)	(50)
1d	a	334 (54)		196 (100)	118 (22)	(1)
	b		333 (1)	196 (70)	118 (100)	(54)
1e	a	368 (32)		230 (100)	152 (56)	(14)
	b		367 (1)	230 (16)	152 (18)	(33)
1f	a	364 (30)		226 (100)	148 (23)	(6)
	b		363 (2)	226 (66)	148 (65)	(100)

$^3J_{HH} = 7.1$ Hz. The signals for the two methylene groups of the ester moiety were registered as multiplets at $\delta = 3.7 - 3.9$ ppm and doublets of quartets at $\delta = 4.04 - 4.05$ ppm with $^3J_{PH} = 7.8$ Hz and $^3J_{HH} = 7.1$ Hz. The resonance of the CH_3O-C_6H_4 protons in **1c, f** is found as a singlet at $\delta = 3.75$ ppm.

The $^{31}P\{^1H\}$ NMR spectra of the phosphonates **1a – f** exhibit two resonance signals, at $\delta = 42.47 - 43.79$ ppm typical for tertiary phosphine oxides [5, 10] and at $\delta = 24.98 - 25.31$ and $22.11 - 23.01$ ppm for methyl and ethyl phosphonates, respectively [10].

Mass spectrometry provides additional confirmation of the identity of the compounds **1a – f**. The FAB-NBA mass spectra show prominent pseudomolecular ions, MH^+ (Table 3). The base peak in all spectra is formed by elimination of dimethyl or diethyl phosphite from the pseudomolecular ion *via* α-cleavage (Scheme 2), the so-formed iminium ion being stabilized by conjugation with the benzene ring [11]. The same peak appears in the EI-mass spectra, but lower in intensity. Another common peak in the spectra is that of the cations $[CH_2{=}N\text{-}CHAr]^+$ formed by elimination of $(CH_3)_2POH$ (-78 u) from the iminium ions. Prominent ions (especially for EI mass spectra) also arise for the ylidon $[(CH_3)_2P(OH)CH_2]^{+\cdot}$ ($m/z = 92$), formed from $M^{+\cdot}$ *via* McLafferty rearrangement [6].

Crystals, suitable for X-ray crystallographic analysis, were obtained for compound **1e** by crystallization from cyclohexane, and for compound **2b** from ethyl acetate. Details of crystal data and structure refinement of



Scheme 2.

Table 4. Crystal data and details of the structure determination for **2b** and **1e**.

	2b	**1e**
Chemical formula	$C_{10}H_{13}ClNOP$	$C_{14}H_{24}ClNO_4P_2$
Formula weight	229.63	367.73
Crystal system	monoclinic	monoclinic
Space group	$P2_1/c$	$P2_1/n$
a [Å]	11.6833(14)	12.0673(9)
b [Å]	11.7706(11)	11.1290(9)
c [Å]	8.4933(9)	14.4360(13)
β [°]	101.162(10)	103.181(7)
Volume [Å^3]	1145.9(2)	1887.6(3)
Z	4	4
D_{calc} [g cm^{-3}]	1.331	1.294
$F(000)$	480	776
μ [mm^{-1}]	0.441	0.386
Temp [K]	140(2)	140(2)
Wavelength [Å]	0.71073	0.71073
Measured reflections	6516	10332
Unique reflections	1989	3322
Unique reflections $[I > 2\sigma(I)]$	1441	2809
Data / parameters	1989 / 127	3322 / 222
R^a $[I > 2\sigma(I)]$	0.0327	0.0485
$wR2^a$ (all data)	0.0786	0.1384
GoF^b	0.983	1.085

[a] $R = \Sigma\|\|F_o| - |F_c\|\| / \Sigma|F_o|$, $wR2 = \{\Sigma[w(F_o^2 - F_c^2)^2] / \Sigma[w(F_o^2)^2]\}^{1/2}$; [b] GoF = $\{\Sigma[w(F_o^2 - F_c^2)^2]/(n-p)\}^{1/2}$ where n is the number of data and p is the number of parameters refined.

the Schiff base **2b** and the phosphonate **1e** are listed in Table 4. The molecular structures are shown in Fig. 1 and 2, respectively. Bond distances and angles are normal in both compounds [12]. In particular, in the case of compound **2b**, the distance N1-C7 is 1.270(3) Å, which confirms the nature of a C=N bond, whereas this distance N1-C7 in compound **1e** is 1.462(3) Å, which indicates a C-N bond. The sum of the bond angles around N1 (333.6°) in the product **1e** shows the change of the geometry from sp^2 to sp^3 for this nitrogen atom. Some interesting intermolecular hydrogen bonds occur in the solid-state structure for both com-

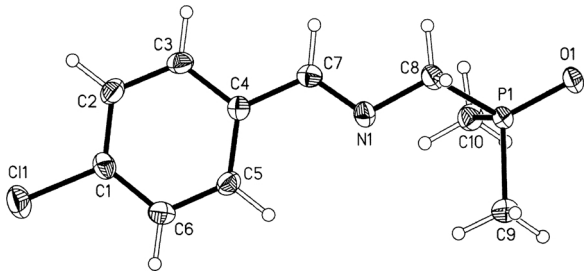


Fig. 1. X-ray structure of **2b** (ORTEP view).

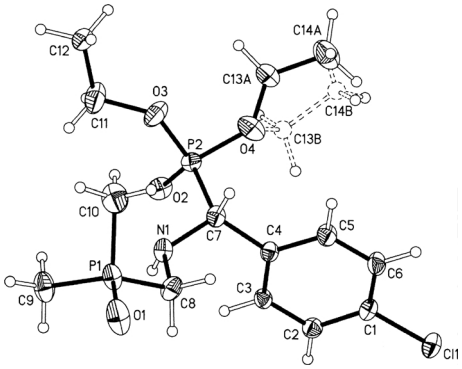


Fig. 2. X-ray structure of **1e** (ORTEP view).

pounds which are responsible for the crystal packing motifs. In the case of **2b** some weak C-H…O=P interactions occur between symmetry related molecules [C3-H3…O1, 2.42 Å, 170°; C10-H10A…O1, 2.54 Å, 145°]. The presence of an NH and two P=O moieties in **1e** explains why a larger number of hydrogen bond interactions occurs between neighbour molecules [N1-H1…O2, 2.29(3) Å, 146(2)°; C2-H2…O1, 2.27 Å, 175°; C6-H6…O3, 2.58 Å, 138°; C11-H11A…O1, 2.58 Å, 129°].

Experimental Section

Starting materials: The aminomethyl-dimethyl-phosphine oxide **3** [13] and the Schiff base **2** [6] were prepared according to the literature procedures. Dimethyl and diethyl phosphite (purum, Fluka) were purified by distillation prior to use.

Characterization of the compounds: Melting points (uncorrected): microhot stage Boetius PHMK 05. Infrared spectra: Bomem-Michelson 100 FTIR-spectrometer (4000 – 400 cm^{-1}). Solutions in CCl_4 and $CHCl_3$ were measured in the $10^{-1} - 5 \times 10^{-2}$ *M* concentration range using a 0.01 cm KBr cell. KBr disk and nujol mull-techniques were utilized for solid-state IR spectroscopy. ^{1}H NMR spectra: Bruker DRX 250 (250 MHz) spectrometer, [D_6]-DMSO as solvent. $^{31}P\{^1H\}$ NMR spectra: Bruker Avance 200 (81 MHz), $CDCl_3$ as solvent. Chemical shifts are measured relative to TMS as internal standard (^{1}H) or external 85% H_3PO_4 ($^{31}P\{^1H\}$). The electron impact (EI) mass spectra were measured on a Varian MAT 311A at 70 eV using the direct inlet system. Fast atom bombardment (FAB) mass spectra were obtained with a Finningan MAT 8200 mass spectrometer using 3-nitrobenzyl alcohol as matrix.

X-Ray crystallography: Data collection was performed with the aid of an Oxford Diffraction KM4 Sapphire CCD and a 4-circle kappa goniometer at 140 K. Cell refinement and data reduction were carried out with CrysAlis RED, release 1.7.0 [14]. The data set for compound **1e** was corrected for absorption using the DELABS algorithm [15]. Structure solutions, structure refinements, molecular graphics and geometrical calculations were performed with the SHELXTL software package [16]. The structures were refined using the full-matrix least-squares method on F^2 with all non-H atoms anisotropically defined. All H atoms were placed in calculated positions using the "riding model" except the hydrogen bonded to N1 in compound **1e** which was treated as free and isotropic. Some disorder problems, which have been solved using the split model, occur in the refinement of an ethyl chain in compound **1e**. Crystallographic data for both structures are in CIF format and have been deposited with the Cambridge Crystallographic Data Centre, CCDC reference numbers 244361 and 244362 for **1e** and **2b**, respectively. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: int.code+(1223)336-033; e-mail for inquiry:fileserv@ccdc.cam.ac.uk).

TLC: "Merck" Silicagel 60 F_{254} on aluminium sheets, layer thickness 0.2 mm.

Mobile phase: CH_2Cl_2 : CH_3OH = 20 : 1.

General procedure for the preparation of phosphonates **1a – f**

Method A: The Schiff base of type **2** (2 mmol) was dissolved in toluene (5 ml) and dimethyl or diethyl phosphite (0.28 g or 0.35 g, respectively, 2.5 mmol) was added. The mixture was heated for 8 h at 80 °C and after standing overnight at room temperature the solvent was removed in a vacuum. The residue was dissolved in 10 ml of H_2O and 2 ml of 2*M* HCl. The solution was washed with ether (3 × 20 ml) and the aqueous layer was made alkaline with solid Na_2CO_3 and then extracted with CH_2Cl_2 (3 × 20 ml). The organic layer was dried and evaporated. The crude product (TLC: one spot) was recrystallized from cyclohexane/ethyl acetate to give the phosphonates **1a – f** as low melting crystals or oils (**1b, c**).

Method B: A mixture of amine **3** (0.23 g, 2.15 mmol), dimethyl or diethylphosphite (0.28 g or 0.35 g, respectively, 2.5 mmol) and the corresponding aldehyde (2.15 mmol) was

allowed to stand overnight at room temperature. Then it was heated for 8 h at 80 °C and the mixture was worked up as in Method A.

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[1] J. Oleksyszyn, in V. Kukhar, K. Hudson (eds): Aminophosphonic and Aminophosphinic Acids, Chemistry and Biological Activity, Section 15, p. 537 – 542, John Wiley & Sons, Chichester-New York (2000).
[2] J. Uziel, J. Genet, Zh. Org. Khim. **33,** 1605 (1997).
[3] L. Maier, Phosphorus, Sulfur and Silicon **56**, 5 (1991).
[4] R. Gugova, S. Varbanov, Z. Raikov, G. Demirov, D. Todorov, M. Ilarionova, Pharmazie **46**, 603 (1991).
[5] E. Stanoeva, S. Varbanov, V. Alexieva, I. Sergiev, V. Vasileva, M. Rashkova, A. Georgieva, Phosphorus, Sulfur and Silicon **165**, 117 (2000).
[6] S. Varbanov, A. Georgieva, G. Hägele, H. Keck, V. Lachkova, Phosphorus, Sulfur and Silicon **159**, 109 (2000).
[7] N. Roeges, A Guide to the Complete Interpretation of Infrared Spectra of Organic Structures, p. 17 and 239, J. Wiley & Sons, New York (1993).
[8] M. Baranska, K. Chruszcz, K. Malek, J. Kulinowska, L. Proniewicz, Vibrational Spectroscopy **33**, 83 (2003).
[9] K. Chruszcz, M. Baranska, K. Lewinski, L. Proniewicz, Vibrational Spectroscopy **32**, 199 (2003).
[10] V. Mark, C. Dungan, M. Crutchfield, J. Van Wazer, in M. Grayson and E. J. Griffith (eds): Topics in Phosphorus Chemistry, Vol. 5, pp. 283 and 294, John Wiley & Sons, New York – Toronto (1967).
[11] D. Green, U. Gruss, G. Hägele, H. Hudson, L. Lindblom, M. Pianka, Phosphorus, Sulfur and Silicon **113**, 179 (1996).
[12] J. Andrieu, J.-M. Camus, R. Poli, P. Richard, New J. Chem. (Nouv. J. Chim.) **25**, 1015 (2001).
[13] S. Varbanov, G. Agopian, G. Borisov, Eur. Polym. J. **23**, 639 (1987).
[14] Oxford Diffraction Ltd, Abingdon, Oxfordshire, UK (2003).
[15] N. Walker, D. Stuart, Acta Crystallogr. ***A*39**, 158 (1983).
[16] G. Sheldrick, University of Göttingen, Germany, 1997; Bruker AXS Inc., Madison, Wisconsin, USA (1997).
[17] C. Franke, G. Hägele, unpublished results (1977).