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Short Communication

Orthoformates as reagents for derivatization of aminoalkanephosphonic acids for characterization by gas chromatography–mass spectrometry☆

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ABSTRACT

Studies of the derivatization of aminoalkanephosphonic acids by trialkyl orthoformates are reported. Gas chromatographic retention data and low-resolution electron impact mass spectra for the derivatives are presented.

INTRODUCTION

Functionalized alkanephosphonic acids constitute technologically important class of phosphoroorganic compounds [1,2]. Many phosphonic acids, *e.g.*, aminophosphonic acids, also exhibit biological activity and are therefore of pharmacological interest [3,4]. For these reasons their analysis, mostly based on chromatographic methods, is a continuing problem in the analytical chemistry of organophosphorus compounds [5–7].

However, nonvolatile phosphonic acids are only suitable for liquid chromatographic techniques [6,8–11] and their study by gas-phase methods necessitates prior derivatization to volatile compounds, usually diester-based derivatives [5]. Such derivatization, occurring smoothly for several acids derived from phosphorus with a variety of reagents (*e.g.*, silylating agents [9–23], benzyl- and benzacyl-based bromides [23,24], diazoalkanes [25–31]) became more difficult when applied to alkanephosphonic acids bearing an amino function. Thus silylation, widely used in the derivatization of organophosphorous

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acids, when applied to aminoalkanephosphonic acids does not give satisfactory results owing to the lability of the silylamino functions [11,20,32]. Also, the conversion of alkanephosphonic acids by means of diazoalkanes, which leads to diester derivatives [25,30,31], cannot be recommended for the direct esterification of aminophosphonic acids owing to a non-selective N-alkylation of the amino group [33,34].

Therefore, the derivatization procedures of aminoalkanephosphonic acids include the protection stage of the amino function (in the form of a Schiff base [20], isothiocyanate [20] or amide [20,29,35]) in addition to the esterification of the phosphonic moiety. O,O-Diethyl 1-aminoalkanephosphonates were also found to be suitable for gas chromatographic (GC) and gas chromatographic–mass spectrometric (GC–MS) characterization [36].

Esters of phosphonic and polyphosphonic acids [37], N-trifluoroacetyl derivatives of aminoalkanephosphonic acids [35] and free 1-aminoalkanephosphonic acids (synthetic application) [38] have also been obtained using trialkyl orthoformates. In the last application, the formation of the corresponding 1-(N-formylamino)alkanephosphonate diesters has been reported [38]. Recently we have reported on the scope of the derivatization of functionalized alkanephosphonic acids by means of orthoformates [39].

In this paper, we present our findings on the application of orthoformates to the derivatization of various aminoalkanephosphonic acids.

EXPERIMENTAL

Materials

Trimethyl and triethyl orthoformates, trifluoroacetic acid and tridecane were purchased form Aldrich (Milwaukee, WI, USA). Triisopropyl orthoformate was prepared according to ref. 40 and aminoalkanephosphonic acids according to refs. 41–43. All compounds applied were of the purity previously reported.

Preparation of derivatives

The reaction was carried out in Wheaton 1-ml microproduct V-vials equipped with a spin vane, placed in a thermostated oil-bath. The samples of aminoalkanephosphonic acids (0.1–5 mg) were suspended in a mixture of trifluoroacetic acid (0.075 ml) and orthoformate (0.30 ml) and the suspensions were stirred at 120°C (at 100°C for trimethyl orthoformate) for 2 h. Aliquots of these reactions mixtures were diluted with acetonitrile (0.2 ml) and analysed.

Gas chromatography

Gas chromatographic analyses were performed with a Chrom 5 gas chromatograph equipped with a flame ionization detector and a CI 100 integrator (Laboratórní Přístoje, Prague, Czech Republic). The columns were 2.8 m × 4 mm I.D. glass columns packed with 5% OV-17 on acid-washed and silanized Chromosorb W AW DMCS (80–100 mesh). Helium was used as the carrier gas and the flow-rate was adjusted to 30 ml min^{-1} at 200°C. The injector and the detector temperatures were maintained at 250°C.

Mass spectrometry

An LKB 2091 GCMS instrument was used to record the low-resolution mass spectra of the derivatives. Sample introduction was via the chromatographic column inlet, a 2.7 m × 2 mm I.D. glass coil packed with 3% OV-17 on 80–100-mesh Waraport. The initial column temperature was 50°C, programmed at 10°C min^{-1} to 250°C. Electron ionization mass spectra were recorded at an electron energy of 70 eV, ion source temperature 250°C and accelerating voltage 3.5 kV.

A Finnigan MAT 95 mass spectrometer was used for the GC–MS analysis of multi-component mixtures of derivatives. Sample introduction was via a Varian 3400 gas chromatograph equipped with a 25 m × 0.22 mm I.D. BP-5 capillary column (SGE). The column temperature was 100°C for 2 min, then programmed at 10°C min^{-1} to 250°C. The injector temperature was maintained at 200°C and the transfer line temperature was 250°C. The column was directly introduced to the ion source of the mass spectrometer. Mass spectra were recorded at an electron energy of 70 eV.

^{31}P NMR

^{31}P NMR spectra were recorded on a Bruker AC 200 spectrometer operating at 81.01 MHz.

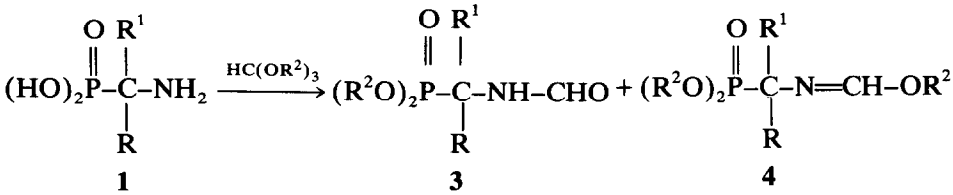
RESULTS AND DISCUSSION

Derivatization

The esterification of aminoalkanephosphonic acids (**1**) by means of trialkyl orthoformate afforded a mixture of diester derivatives (**3** and **4**), according to eqn. 1 [the formation of the diester derivative **2**, with a free amino function, was found to occur only in trace amounts, during esterification of 1-amino-1-methylethanephosphonic acid (**1h**)].

The structural assignment of derivatives **3** and **4** was accomplished on the basis of the chromatographic and mass spectral analysis of compounds **3**, **3A** and **4** obtained during esterification of 1-aminoethanephosphonic acid [Ala(P); **1a**] and 1-(N-methylamino)ethanephosphonic acid [Me-Ala(P); **1Aa**] by means of triethyl and trimethyl orthoformate, respectively [39].

The structure of aminoalkanephosphonic acids and the acidic catalysis exert a substantial influence on the course of derivatization and the



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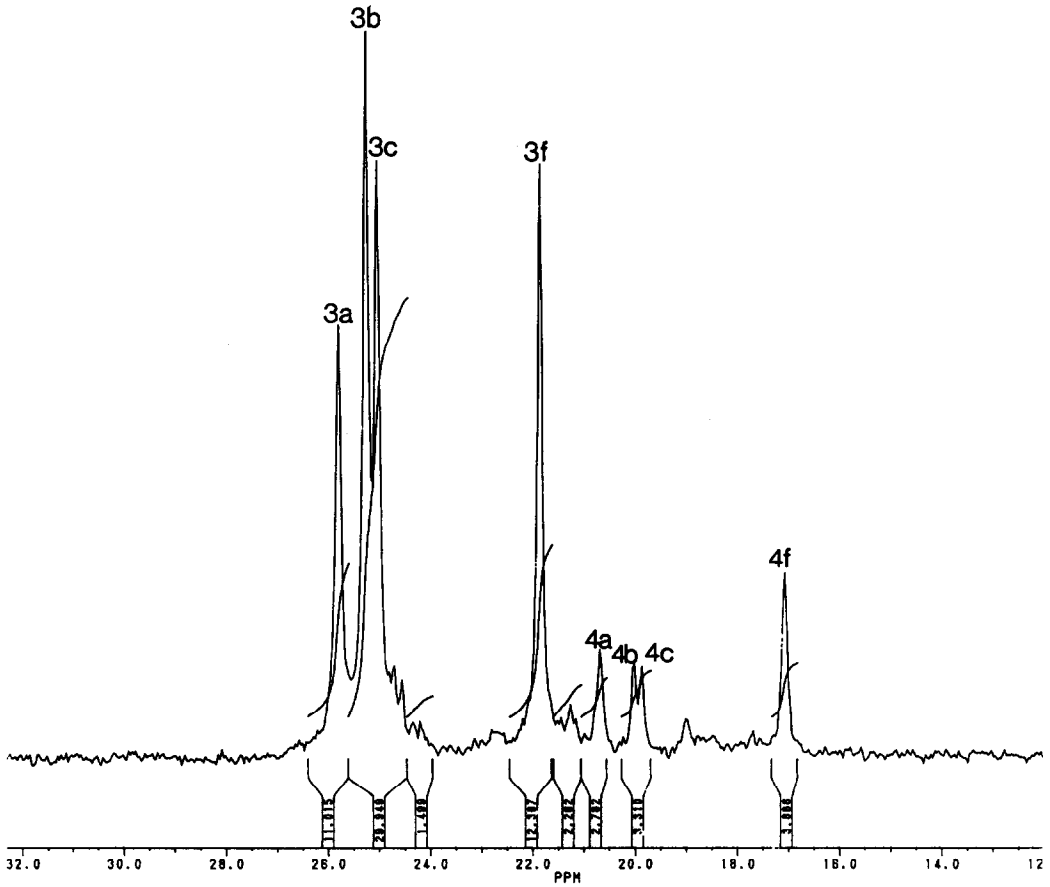

Fig. 1. ^{31}P NMR spectrum of the derivatization products of the mixture of aminophosphonic acids **1a**, **1b**, **1c** and **1f** obtained by means of triethyl orthoformate. Conditions as described under Experimental.

reaction rate [39]. Thus, the optimum reaction conditions were obtained in the reaction system consisting of triethyl orthoformate, trifluoroacetic acid and aminoalkanephosphonic acid in amounts of 0.30 ml, 0.075 ml and 1 mg, respectively. In this rection system the amino acids **1** were found to form homogeneous solutions in which at 120°C the derivatizations were usually completed in 1 h. The results on the reaction course of various types of aminophosphonic acids with trialkyl orthoformates will be presented elsewhere.

The optimization of the reaction course was carried out using ^{31}P NMR monitoring. These investigations revealed the complete conversion of aminoalkanephosphonic acids to mixtures of derivatives **3** and **4** with only small amounts of unidentified by-products. The ^{31}P NMR spectrum of the derivatization products of a mixture of amino acids **1a**, **1b**, **1c** and **1f** for the reaction run under standard conditions is presented in Fig. 1. A comparison of this and other representative procedures for the derivatization of aminoalkanephosphonic acids is given in Table I. It is worth noting that in earlier reports [11,29,35] the application of ^{31}P NMR spectroscopic investigations for optimization and confirmation of the quantitative course of the derivatization procedure was omitted.

Chromatographic properties of derivatives 3 and 4

Two sets of peaks of varying height were obtained on OV-17 for all the compounds studied. Analysis by mass spectrometry revealed that the first compounds eluted are formino-alkoxy derivatives **4** and the second are N-formyl derivatives **3**. These derivatives could be stored for several weeks at 0°C without extensive decomposition and were found to be suitable for characterization by means of GC. Both types of compounds give reproducible retention data. The results for their relative retention volumes (*vs.* tridecane) as a function of temperature (OV-17) are given in Fig. 2. The separation of derivatives **3** and **4** obtained from derivatization of the mixture of aminoalkanephosphonic acids **1a**, **1b**, **1c** and **1f** is presented on the Fig. 3.

TABLE I

COMPARISON WITH REPRESENTATIVE METHODS OF AMINOALKANEPHOSPHONIC ACIDS DERIVATIZATION

Conversion to derivative	Reagent[a]	Time (h)	Temperature (°C)	Range (mg)	Ref.
(I) O,O-Bis(trimethylsilyl)	(Ms. pr.)	≤8		1	11
1-(N-acetylamino)alkane-	(1) BSTFA–TMSC	≤4	80		
phosphonate	(2) Py–Ac_2O	0.5	80		
	(3) BSTFA–TMSC	0.2	80		
(II) O,O-Bis(trimethylsilyl)	(Ms. pr.)	≤8		1	11
1-(2-propenimine)-	(1) BSTFA–TMSC	≤4	80		
alkanephosphonate	(2) Acetone	0.5	80		
	(3) BSTFA–TMSC	0.2	80		
(III) O,O-Bis(trimethylsilyl)	(Ms. pr.)	16–18		1	11
1-isothiocyanato-alkanephosphonate	(1) BSTFA–TMSC	≤4	80		
	(2) CS_2	ca. 12	20		
(IV) O,O-Dibutyl	(Ms. pr.)	*ca.* 3		10	29
1-(N-trifluoroacetyl-amino)alkane-	(1) TFA–TFAA	1	40	0.25–0.5	
phosphonate	(2) Diazobutane	0.2	20		
(V) O,O-diethyl	(Ms. pr)	*ca.* 10		10	35
1-(N-trifluoroacetyl-amino)alkane	(1) TFA–TFAA	1	20		
phosphonate	(2) $HC(OEt)_3$	8	r.t.[b]		
(VI) This work	TFA–$HC(OEt)_3$	2	120		

[a] Ac = acetyl; Ac_2O = acetic anhydride; BSTFA = bis(trimethylsilyl)trifluoroacetamide; TFA = trifluoroacetic acid; TFAA = trifluoroacetic anhydride; TMSC = trimethylchlorosilane; Py = pyridine; Ms. pr. = multi-stage procedure.

[b] Reflux temperature.

TABLE II

REDUCED MASS SPECTRA OF DERIVATIVES OF 3

No.	Derivative of 3		Molecular formula (mass)	Mass spectrometry: m/z (relative intensity, %)											
	R($R^1 \neq H$)	O-R^2		M + 1	M	Others									
3a	Me	O-Et	$C_7H_{16}NPO_4$	210	209	192	181	166	155	138	111	82	72	44	
			209.9	(1.2)	(3.3)	(1.3)	(2.5)	(4.5)	(17)	(54)	(60)	(50)	(50)	(100)	
3ba	Et	O-Me	$C_6H_{14}NPO_4$	196	195	180	166	152	138	137	127	111	110	86	58
			195.2	(0.6)	(4.3)	(0.4)	(3.6)	(2.3)	(3.1)	(2.1)	(13)	(12)	(28)	(100)	(63)
3b	Et	O-Et	$C_8H_{18}NPO_4$	224	223	208	180	178	166	138	86				
			223.3	(1.6)	(8.9)	(0.7)	(3.2)	(4.1)	(3.9)	(2.3)	(100)				
3ca	Bu	O-Me	$C_8H_{18}NPO_4$	224	223	194	181	180	167	166	138	114	110	86	
			223.2	(0.5)	(1.0)	(1.2)	(2.4)	(1.7)	(2.7)	(2.6)	(2.6)	(100)	(16)	(16)	
3c	Bu	O-Et	$C_{10}H_{22}NPO_4$	252	251	222	209	195	166	155	138	114	86		
			251.4	(2.8)	(2.4)	(3.3)	(6.8)	(4.9)	(3.3)	(14)	(50)	(100)	(51)		
3d	$EtSCH_2$	O-Et	$C_9H_{20}NPO_4S$	270	269	240	226	224	212	209	208	191	139	138	131
			269.3	(3.5)	(8.0)	(1.0)	(2.3)	(31)	(1.2)	(5.3)	(6.4)	(15)	(8.9)	(51)	(100)
3e	$EtSCH_2CH_2$	O-Et	$C_{10}H_{22}NPO_4S$	284	283	254	223	208	195	180	167	139	124	75	
			283.3	(2.4)	(13)	(3.7)	(5.0)	(20)	(100)	(7.5)	(16)	(25)	(12)	(38)	
3f	Ph	O-Et	$C_{12}H_{18}NPO_4$	272	271	243	242	226	197	162	155	134	138	106	
			271.2	(1.3)	(7.0)	(0.9)	(1.3)	(0.8)	(0.4)	(5.6)	(5.9)	(100)	(1.8)	(33)	
3g	$PhCH_2$	O-Et	$C_{13}H_{20}NPO_4$	286	285	242	241	240	194	166	148	147	139	138	
			285.2	(2.5)	(4.9)	(1.5)	(3.1)	(8.1)	(10)	(16)	(16)	(100)	(2.1)	(26)	
3h	Me (Me)	O-Et	$C_8H_{18}NPO_4$	224	223	205	194	180	155	138	111	86	82	58	
			223.3	(3.1)	(0.6)	(1.6)	(0.9)	(4.1)	(6.8)	(13)	(11)	(100)	(11)	(10)	

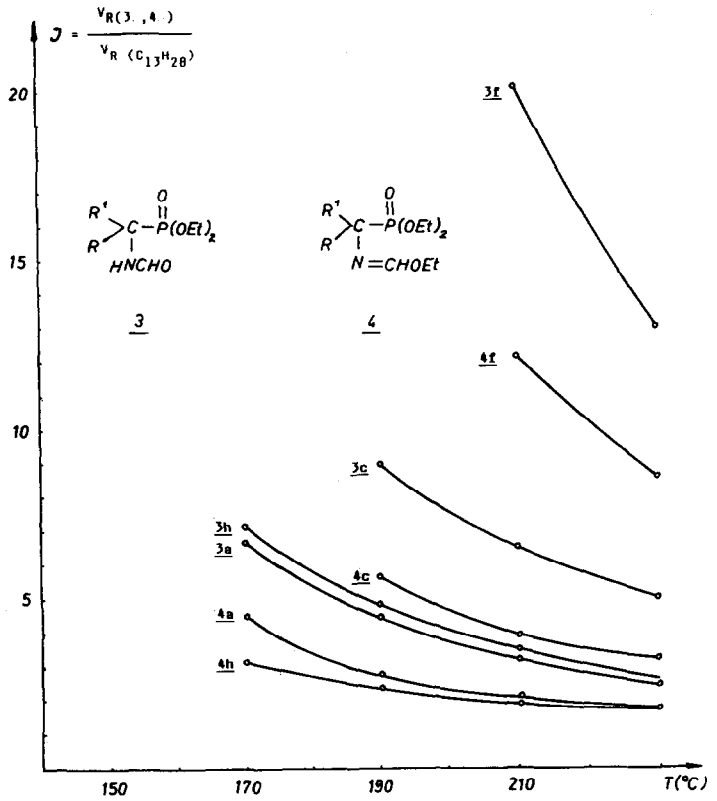

Fig. 2. Relationship between relative retention volume (J *vs.* tridecane) and temperature for the N-formyl (**3**) and N-forminoethoxy (**4**) derivatives.

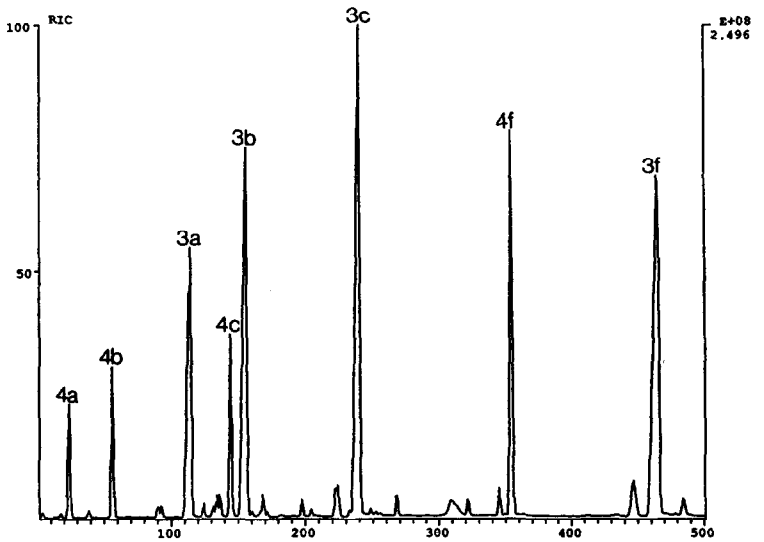

Fig. 3. GC–MS of the derivatization products of the mixture of aminophosphonic acids **1a**, **1b**, **1c** and **1f** obtained by means of triethyl orthoformate. Conditions as described under Experimental. The ^{31}P NMR spectrum of the derivatization products of this reaction mixture is presented in Fig. 1.

TABLE III

REDUCED MASS SPECTRA OF DERIVATIVES OF 4

No.	Derivative of 4		Molecular formula (mass)	Mass spectrometry: m/z (relative intensity, %)											
	$R(R^1 \neq H)$	$O\text{-}R^2$		M + 1	M	M − 1	Others								
4a	Me	O-Et	$C_9H_{20}NPO_4$	238	237	208	191	180	166	152	138	100	72	44	
			137.3	(0.5)	(0.8)	(5.9)	(0.5)	(2.7)	(4.2)	(6.9)	(1.8)	(100)	(37)	(33)	
4ba	Et	O-Me	$C_7H_{16}NPO_4$	210	209	194	180	166	152	151	149	137	109	100	
			209.3	(0.1)	(0.4)	(3.6)	(1.4)	(0.9)	(1.6)	(1.4)	(4.3)	(3.9)	(7.1)	(100)	
4b	Et	O-Et	$C_{10}H_{22}NPO_4$	252	251	250	222	194	180	166	138	123	114	86	
			251.4	(0.5)	(0.3)	(0.1)	(3.7)	(1.9)	(1.7)	(3.9)	(2.3)	(1.2)	(100)	(25)	
4ca	Bu	O-Me	$C_9H_{20}NPO_4$	238	237	236	222	180	179	128	109	99	93	72	
			237.2	(−)	(0.2)	(0.3)	(1.0)	(1.1)	(1.0)	(100)	(4.4)	(3.3)	(8.1)	(20)	
4c	Bu	O-Et	$C_{12}H_{26}NPO_4$	280	279	278	264	250	222	208	194	166	165	142	114
			279.4	(0.5)	(0.2)	(0.2)	(0.3)	(3.5)	(3.1)	(0.7)	(5.0)	(2.5)	(3.4)	(100)	(16)
4d	$EtSCH_2$	O-Et	$C_{11}H_{24}NPO_4S$	298	297	268	251	237	225	224	166	160	139	138	100
			297.4	(2.7)	(5.1)	(1.3)	(3.0)	(12)	(2.5)	(4.4)	(11)	(13)	(3.4)	(15)	(100)
4e	$EtSCH_2CH_2$	O-Et	$C_{12}H_{26}NPO_4S$	312	311	310	283	282	236	223	194	166	152	114	75
			311.4	(2.0)	(6.2)	(0.7)	(6.8)	(19)	(26)	(46)	(19)	(21)	(30)	(52)	(100)
4f	Ph	O-Et	$C_{14}H_{22}NPO_4$	300	299	298	227	199	187	162	134	117	106	91	79
			299.3	(0.2)	(0.4)	(0.3)	(0.2)	(0.4)	(0.4)	(100)	(13)	(1.1)	(14)	(4.3)	(8)
4g	$PhCH_2$	O-Et	$C_{15}H_{24}NPO_4$	314	313	312	284	268	256	240	222	176	175	146	138
			313.3	(3.0)	(6.0)	(8.2)	(5.2)	(1.5)	(1.9)	(2.5)	(38)	(100)	(35)	(40)	(31)
4h	Me (Me)	O-Et	$C_{10}H_{22}NPO_4$	252	251	236	222	194	180	151	138	114	86	58	
			251.4	(0.1)	(0.2)	(0.2)	(0.4)	(0.2)	(0.5)	(0.5)	(0.6)	(100)	(16)	(18)	

Mass spectral properties of derivatives 3 and 4

N-Formylaminoalkanephosphonates (3). The partial spectra of N-formyl derivatives **3** are summarized in Table II. The molecular ions $[M]^{+\cdot}$ (and $[M+1]^+$) of these derivatives were observed in low abundance. Charge localization on the nitrogen atom produced ions $[M-(R^2O)_2P(O)]^+$ ($[M-109]^+$ or $[M-137]^+$ for the O-methyl or O-ethyl derivatives, respectively) and $[M-R]^+$ ions (R is the alkyl chain at C-1) resulting from α-cleavage. The ions $[M-(R^1O)_2P(O)]^+$ or $[RCH=NH_2]^+$ represent the base peaks for majority of the N-formyl derivatives **3**. For derivatives **3** with R < Et the latter ions were dominant. This tendency turned in favour of $[M-(R^1O)_2P(O)]^+$ for higher homologues of **3** (R > Et), especially for the O-methyl esters (**3ba** and **3ca**). All compounds **3** exhibited in distinct abundance (1.7–5.1%, except for **3f**) the ions $[M-43]^+$, formed presumably by elimination of a molecule of isocyanic acid from the molecular ions of **3**.

The mass spectra of the sulphur-containing derivatives **3d** and **3e** differ from those of the other compounds **3**. They contained molecular ions $[M]^{+\cdot}$ and $[M+1]^+$ in relatively higher abundance. The base peaks were $[M-R+1]^+$ for **3e**, formed by elimination a molecule of olefin from the molecular ion, and $[M-(EtO)_2P(O)H]^+$ for **3d**. The ions $[M-(EtO)_2P(O)]^+$ and $[RCH=NH_2]^+$ (for **3e**) were of relatively low abundance (1.4% and 5.4%, respectively).

The ions at *m/z* 138, 137, 110 and 82 were characteristic of the presence of the diethylphosphonate system (or the ion at *m/z* 109 and related ions for O-methyl esters **3**) and had the mechanism of formation reported previously [44].

Forminoalkoxyalkanephosphonates (4). The partial spectra of derivatives **4** are summarized in Table III. Molecular ions of these derivatives were observed in low abundance and the latter decreased slightly with increasing molecular mass (0.8% in **4a** to 0.2% in **4c**). The presence of a sulphur atom in the molecule of compounds **4** caused a substantial increase in the molecular ions (5.7% in **4d** and 6.2% in **4e**).

Fragmentation was found to be predominantly directed by charge localization on the nitrogen atom. α-Cleavage, resulting in the loss of the O,O-diethyl phosphonate moiety, $[M-137]^+$, produced the base peaks most of the forminoethoxyphosphonates **4**, with the exception for sulphur-containing derivatives (13% for **4d** and 21% for **4e**). Further cleavage of the C-1–C-2 bond in compounds **4** produced the ions $[M-R]^+$, *m/z* = 180 for O-methyl and *m/z* = 222 for O-ethyl derivatives, respectively. The third α-cleavage (C-1–H) resulted in the formation of ions $[M-1]^+$, which were observed in low abundance in the spectra of **4b**, **4ca**, **4c**, **4e** and **4f** (0.1–0.3%), and in distinct abundance in the spectrum of **4g** (12%). The ion at *m/z* 223 in **4d** and **4e** was produced by the migration of an aliphatic hydrogen to the phosphonate moiety and the loss of the alkyl chain by cleavage at C-1–C-2, respectively. Its higher abundance in the spectrum of **4e** implied its formation via a McLafferty rearrangement from the molecular ion. The ions at $[M-58]^+$ and $[M-72]^+$ (for O-methyl and O-ethyl derivatives) resulted from the α-cleavage of the imine moiety from the molecular ions. These ions were accompanied by $[M-57]^+$ and $[M-71]^+$ ions derived from the migration of aliphatic hydrogen from the alkoxyimine function to the phosphonate moiety and subsequent cleavage of the C-1–N bond in compounds **4**.

CONCLUSIONS

A general derivatization procedure for aminoalkanephosphonic acids by means of triethyl orthoformate has been developed. ^{31}P NMR spectroscopic investigations confirmed the complete conversion of 1-aminoalkanephosphonic acids into volatile diester derivatives in 2 h, which is faster than in earlier procedures. The ester products of this reaction, N-formyl derivatives **3** and forminoalkoxy derivatives **4**, are satisfactory for characterization by both GC and combined GC–MS. The mass spectra of derivatives **3** and **4** were structurally informative. Ions characteristic of the phosphonate system were present in the mass spectra of all derivatives **3** and **4**, permitting rapid identification of these compounds.

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