Bisphosphonic Compounds. Part 3.[1] Preparation and Identification of Tetraalkyl Methylene- and (α-Halomethylene)bisphosphonates by Mass Spectrometry, NMR Spectroscopy and X-Ray Crystallography

Jouko Vepsäläinen,*[a] Heikki Nupponen,[b] Esko Pohjala,[b] Markku Ahlgren[c] and Pirjo Vainiotalo[c]

[a] *Department of Chemistry, University of Kuopio, PO Box 1627 SF-70211, Kuopio, Finland*
[b] *Huhtamäki Oy Leiras, PO Box 33, SF-33721, Tampere, Finland*
[c] *Department of Chemistry, University of Joensuu, PO Box 111, SF-80101, Joensuu, Finland*

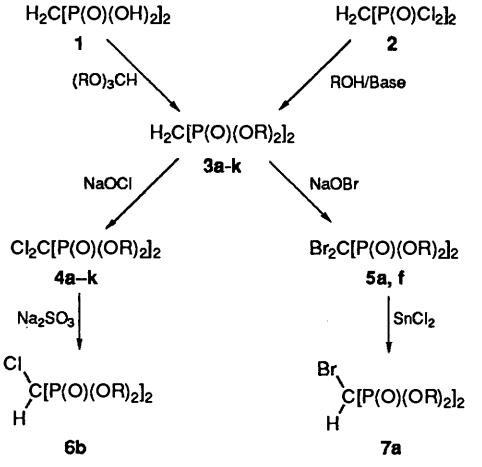
The preparation and identification of tetraalkyl methylenebisphosphonates {$XYC[P(O)(OR)_2]_2$; X = Y = H, Cl or Br and R = alkyl} have been studied. Detailed procedures are given for the synthesis of $XYC[P(O)(OR)_2]_2$ (X = Y = H; R = hexyl; X = Y = Cl or Br and R = Me). ^1H, ^{13}C and ^{31}P NMR data are reported including $^1J_{CH}$, $^2J_{CP}$, $^3J_{CP}$ and $^2J_{PP}$ coupling constants. The fragmentation of 19 $XYC[P(O)(OR)_2]_2$ has been studied in the gas phase. The solid state structures are given for two compounds (X = Y = Cl, R = Pr^i and X = Y = Br, R = Me).

Bisphosphonates, previously called diphosphonates, are widely used for the treatment of diseases in the skeletal system, bone formation and resorption disorders, as well as for the treatment of diseases in soft tissues.[2] Over the past few decades several methylenebisphosphonic acids (MDP), their salts and tetraesters have been prepared in order to modify their biological properties by varying the substituents at the central carbon.[3] Clodronate,[4] (dichloromethylene)bisphosphonic acid, disodium salt, tetrahydrate, (Cl_2MDP) is one of the best documented bisphosphonates used in the treatment of these diseases.[5] MDP and Cl_2MDP have been studied using NMR spectroscopy,[6] mass spectrometry[7] (MS) and X-ray crystallography.[8] Several tetraalkyl ester derivatives of methylene- and (dichloromethylene)bisphosphonates have been made and characterized using ^1H and ^{31}P NMR spectroscopy,[9] and in some cases using ^{13}C NMR spectroscopy.[10] Only some have been studied by MS[11] and very little is known about their X-ray structures.

In this work we examine the synthesis, solution structure, solid-state and in-detail gas-phase properties of tetraesters of the methylene- and (halomethylene)bisphosphonic acids, while keeping in mind the possibility of increasing production to the multikilo scale.

Results and Discussion

The compounds studied and their ^{13}C NMR chemical shifts are listed in Table 1. The synthesis of these compounds is described in Scheme 1. Tetraalkyl methylenebisphosphonates (**3a–k**), which were not commercially available, were obtained either by treating $H_2C[P(O)(OH)_2]_2$ (**1**) with trialkyl orthoformate[9b] or by alkylation of $H_2C[P(O)Cl_2]_2$[12] (**2**) with the appropriate alcohol using pyridine as an HCl binder. The first method was useful with short n-alkyls, but its preparative value was limited by the high excess of formiate needed and the inconvenience in purification of alkylformate from the product. The second method was more convenient and efficient, especially for branched alkyls, but some difficulty arose in the handling of **2**, which must be performed under dry conditions. The amounts and type of amine were also important factors, since an excess of amine led to dimerization of **2**, and insufficient amounts gave incomplete reactions. The best yields were achieved using aromatic amines, *e.g.* pyrene. If **2** was handled under dry nitrogen, and if all reagents and solvents were dry, very few impurities were found. In both cases, the only significant phosphorus-containing impurity was trialkyl methylenebisphosphonate.



Scheme 1 See Table 1 for nature of compounds **3–7**

The difficulty in the synthesis of tetra(n-alkyl) (dihalomethylene)bisphosphonates was cleavage of the P–C bond during halogenation with hypohalites.[10a] This problem was solved by carefully controlling the temperature, pH and reaction time during synthesis. Commercially available hypohalite solutions were normally too basic for halogenation of n-alkyl derivatives of **3a–g**, but by fixing the pH to 9 with $NaHCO_3$ the reaction occurred rapidly with shorter n-alkyls, and in a reasonable time with longer chains, without breaking any P–C bonds. On the other hand, branched tetraalkyl derivatives of **3** required a higher pH (≥ 10) for the halogenation reaction and they were not sensitive to temperature or reaction time. An alternative approach to controlling pH was achieved with hypobromide reagent by mixing solvent, **3** and bromine together followed by careful addition of a controlled amount of NaOH with efficient cooling.

Tetraethyl (chloromethylene)bisphosphonate (**6b**) and tetramethyl (bromomethylene)bisphosphonate (**7a**) were prepared according to the method of McKenna.[10a] We also tried producing **6a** from **4a** using Na_2SO_3 as the reducing agent, with poor success. This dehalogenation reaction was very rapid and unselective; even at 0 °C with one equivalent of reagent, the product was a mixture of **3a**, **6a** and **4a**. Moreover, all these methyl esters were to some extent water soluble. By contrast, the synthesis of **7a** from **5a** with $SnCl_2$ led to a reasonably pure product in 70% yield.

Table 1 List of studied compounds, $XYC[P(O)(OR)_2]_2$ and ^{13}C NMR chemical shifts (ppm)

Compound	X	Y	R	$XYCP_2$	C_α	C_β	C_χ	C_δ	C_ε	C_φ	C_γ
3a	H	H	Me	23.68	53.21	—	—	—	—	—	—
3b	H	H	Et	25.35	62.47	16.29	—	—	—	—	—
3c	H	H	Pr	24.86	67.71	23.54	9.72	—	—	—	—
3d	H	H	Bu	24.89	66.17	32.31	18.53	13.40	—	—	—
3e	H	H	Pen	25.00	66.46	30.04	27.49	22.10	13.79	—	—
3f	H	H	Hex	25.24	66.53	30.49	25.18	31.38	22.55	13.96	—
3g	H	H	Hep	25.00	66.49	30.39	25.33	28.74	31.61	22.44	13.89
3h	H	H	$CH(Me)_2$	27.79	71.17	24.01[a]	—	—	—	—	—
3i	H	H	*c*-Pen	27.20	79.67	34.05[b]	23.04	—	—	—	—
3j	H	H	CH(Me)Pr	27.6	74.4	39.8	18.4	13.9	21.8[c]	—	—
3k	H	H	$CH(Et)_2$	27.98	80.13	27.12[d]	9.03[e]	—	—	—	—
4a	Cl	Cl	Me	71.41	56.63	—	—	—	—	—	—
4b	Cl	Cl	Et	71.88	66.29	16.56	—	—	—	—	—
4d	Cl	Cl	Bu	72.02	69.88	32.60	18.64	13.59	—	—	—
4e	Cl	Cl	Pen	72.03	70.22	30.30	27.52	22.22	13.95	—	—
4f	Cl	Cl	Hex	72.03	70.22	30.58	25.06	31.34	22.55	13.98	—
4h	Cl	Cl	$CH(Me)_2$	72.43	75.12	23.95[f]	—	—	—	—	—
4i	Cl	Cl	*c*-Pen	72.32	83.43	34.22[g]	23.12[h]	—	—	—	—
4j	Cl	Cl	CH(Me)Pr	72.7	78.1	39.8	18.2	13.9	21.6[c]	—	—
4k	Cl	Cl	$CH(Et)_2$	73.01	83.52	26.86[i]	8.89[j]	—	—	—	—
5a	Br	Br	Me	42.62	56.49	—	—	—	—	—	—
5f	Br	Br	Hex	44.39	70.13	30.39	25.08	31.16	22.36	13.79	—
6b	Cl	H	Et	43.77	64.42[k]	16.38	—	—	—	—	—
7a	Br	H	Me	28.44	54.88[l]	—	—	—	—	—	—

[a] Peaks at 24.15 and 23.87. [b] Peaks at 34.10 and 33.95. [c] β-CH_3. [d] Peaks at 27.29 and 26.95. [e] Peaks at 9.08 and 8.98. [f] Peaks at 24.36 and 23.54. [g] Peaks at 34.66 and 33.78. [h] Peaks at 23.16 and 23.08. [i] Peaks at 27.22 and 26.50. [j] Peaks at 8.99 and 8.79. [k] Peaks at 64.59 and 64.26. [l] Peaks at 55.07 and 54.69.

NMR spectroscopy was the easiest way of following the progress of the reactions and of analysing the purity of the compounds. The ^1H and ^{31}P chemical shifts are listed in the Experimental part together with coupling constants. The ^{13}C chemical shifts are given in Table 1 and the coupling constants to hydrogen and phosphorus in Table 2. The most significant impurities were well separated in the spectra and easily assigned from the main signal(s). Because the ^1H NMR spectra of the compounds **3j**, **4i** and **4j** were rather complicated, the composition of these compounds was also confirmed by elemental analysis.

Others have previously investigated the ^1H, ^{13}C and ^{31}P NMR chemical shifts and coupling constants, but some variation occurs, especially in coupling constants.[9,10] Unfortunately some authors have used the solvent signal as a reference and determined the coupling constants without second-order analysis, and this practice may result in erroneous information.

The phosphorus spectra of the compounds studied were sensitive to the ester group and substituents at the central carbon. An increase in the chain length from methyl to heptyl led to an upfield shift of 3 ppm. A similar upfield shift of *ca.* 2 ppm was also observed using branched substituents instead of n-alkyls. More dramatic (*ca.* 12 ppm) upfield shifts were induced by halogen atoms on the middle carbon and this is explained by the increased electronegativity.[9j] Also, diastereochemical effects were clearly observed in the phosphorus spectra, *e.g.* the spectra of **3j** and **4j** contained more than 10 signals due to six asymmetric centres. This effect was also observed in the proton and carbon spectra.

The appearance of multiplets in the coupled phosphorus and proton spectra (the α and β signals) were characteristic but complex, due to the second-order nature of the spectra. Similar effects were also observed in the proton-decoupled carbon spectra for α and β carbon signals; however, the fine structure of these multiplets was even simpler. These two carbons gave second-order quintets, not two doublets as in the phosphorus spectra where the shifts were different. The symmetrical structures of these molecules resulted in an AA′X (**P′**–C–**P**–O–**C** or **P′**–C–**P**–O–C–**C**) spin system. The X spectrum from an AA′X system may give a maximum of six observable lines, being symmetrical around ν_C, but in practice two of these transitions collapse at ν_C. Therefore, only two of the three coupling contants $J_{AA'}$, J_{AX} and $J_{A'X}$ can be determined from the spectra; the third one must be known. In the computer-aided simulation (program MLDC8[13]) we assumed that $^5J_{CP'}$ was zero. If the iterative analysis were started on the presumption that both $^4J_{CP'}$ and $^5J_{CP'}$ are zero, a systematic variation (0.1–0.3 Hz) of $^2J_{PP}$ values between the α and β ^{13}C signals was observed. A fair approximation was to assume that $^5J_{CP'} = 0$. Then both $^2J_{PP}$ and $^3J_{CP}$ can be calculated from the **P′**–C–**P**–O–C–**C** system and the calculated $^2J_{PP}$ values can be used for the **P′**–C–**P**–O–**C**- system to obtain $^2J_{CP}$ and $^4J_{CP'}$. This approach gave rather poor confidence limits for the $^2J_{CP}$ and $^4J_{CP'}$ couplings. However, the sums of the J_{CP} couplings (the width of the virtual triplet) were well-defined and characteristic for the system. The other possibility of obtaining these coupling values from the AA′X system was to take the relative intensities of transitions into account, but this practice does not always give better results due to a weakness of the 'satellite' signals.[14]

The intensities of 'satellite' peaks (combination lines) are inversely proportional to $^2J_{PP'}$ coupling. For compounds with large $^2J_{PP}$ ($\geq$15 Hz) sufficiently long pulsing times and concentrated samples were required to observe these two lines unambiguously from the background. That is why only a few $^2J_{PP}$ constants have been determined from the dihalo compounds **4** and **5**. Furthermore, carbon spectra of halogenated methylenebisphosphonates (**4** and **5**) suffer from long relaxation times (for CP_2, 30–60 s), and a lack of nuclear Overhauser enhancement (NOE) from the central carbon. The refined (see Table 2 and Experimental) $^2J_{CP}$, $^3J_{CP}$ and $^2J_{PP}$ constants were in good agreement with those measured from mixed tetralkyl methylenebisphosphonates[15a] and dihalomethylenebisphosphonates.[15b]

Proton and carbon chemical shifts and $^1J_{CH}$ coupling constants were similar for the corresponding alcohols, as expected.[16] The proton-decoupled carbon spectra showed two signals due to different electronic environments of the

Table 2 The $^1J_{CH}$, $^1J_{CP}$, $^2J_{CP}(+^4J_{CP})$ and $^3J_{CP}$ coupling constants for the compounds studied[a]

Compound	$^1J_{CH}$								$^1J_{CP}$	$^2J_{CP}$	$^3J_{CP}$
	$XYCP_2$	C_α	C_β	C_χ	C_δ	C_ε	C_φ	C_γ	$XYCP_2$	C_α	C_β
3a	125.1	148.3	—	—	—	—	—	—	136.8	5.9	—
3b	124.8	148.0	127.1	—	—	—	—	—	137.1	5.9	6.4
3c	124.5	147.1	127.1	126.0	—	—	—	—	137.1	6.3	6.4
3d	124.5	147.1	126.6	124.7	124.9	—	—	—	137.2	6.2	6.4
3e	124.6	147.0	125.6	124.6	124.3	124.4	—	—	137.0	6.3	6.3
3f	124.6	147.1	126.3	125	126.9	124.8	124.5	—	137.1	6.2	6.3
3g	124.3	147.0	125.4	124.4	124.7	126.6	124.3	124.1	136.9	6.3	6.3
3h	124.0	147.3	126.5	—	—	—	—	—	138.3	6.2	*a*
3i	123.9	153.8	132	132	—	—	—	—	137.7	6.7	*b*
3j	*g*	*g*	*g*	126	124.9	126	—	—	*g*	*g*	*g*
3k	123.5	145.4	126	126	—	—	—	—	139.0	6.7	*c*
4a	—	149.9	—	—	—	—	—	—	155.3	6.9	—
4b	—	149.5	127.2	—	—	—	—	—	153.7	6.8	5.7
4d	—	148.8	126.6	125.7	125.1	—	—	—	154.1	7.4	5.8
4e	—	148.9	125.4	125.7	125.7	124.6	—	—	154.1	7.4	5.6
4f	—	148.9	126.0	126.7	125.7	125.9	124.5	—	154.1	7.4	5.7
4h	—	149.6	127	—	—	—	—	—	155.1	7.3	*d*
4i	—	154.5	130	131.7	—	—	—	—	155.0	7.8	*e*
4j	—	149	127	124	125	125	—	—	155	*g*	*g*
4k	—	147.5	127	126	—	—	—	—	157.0	8.0	*f*
5a	—	149.6	—	—	—	—	—	—	145.3	6.8	—
5f	—	148.9	125.1	124.7	125.9	124.5	124.3	—	144.0	7.4	5.8
6b	141.3	148.9	127.4	—	—	—	—	—	144.7	6.5	*g*
7a	141.7	149.1	—	—	—	—	—	—	143.2	6.2	—

[a] $^3J_{CP}$ = 3.9 Hz (24.15 ppm) and $^3J_{CP}$ = 5.3 Hz (23.87 ppm). [b] $^3J_{CP}$ = 3.8 Hz (34.19 ppm) and $^3J_{CP}$ = 5.3 Hz (33.95 ppm). [c] J_{CP} = 3.6 Hz (27.29 ppm) and $^3J_{CP}$ = 7.8 Hz (26.95 ppm). [d] $^3J_{CP}$ = 2.9 Hz (24.36 ppm) and $^3J_{CP}$ = 6.7 Hz (23.54 ppm). [e] $^3J_{CP}$ = 3.1 Hz (34.66 ppm) and $^3J_{CP}$ = 6.2 Hz (33.78 ppm). [f] $^3J_{CP}$ = 2.8 Hz (27.22 ppm) and $^3J_{CP'}$ = 5.7 Hz (26.50 ppm). [g] Not resolved due to complicated structure.

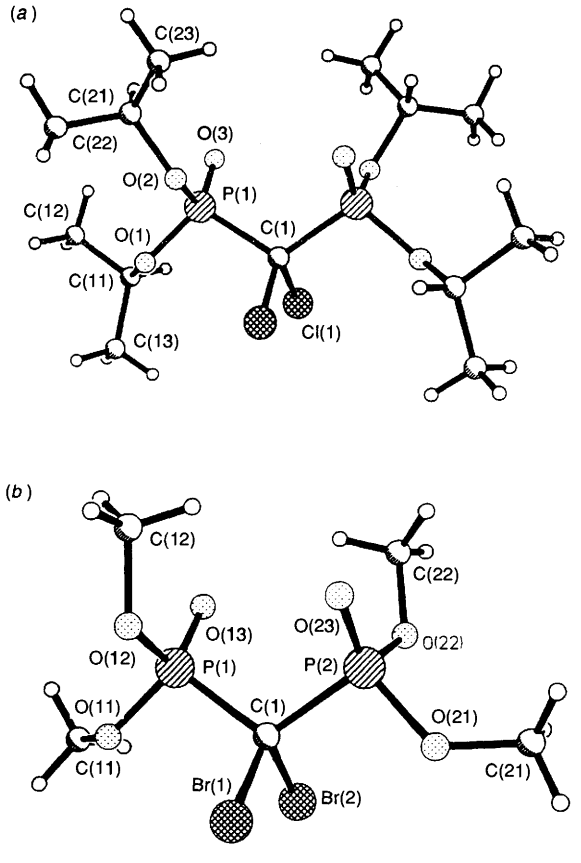


Fig. 1 The molecular structure of compounds **4h** (*a*) and **5a** (*b*)

symmetric β [see Fig. 1(*a*)] and χ carbons in the branched esters. The $^3J_{CP}$ couplings for β carbons offer an opportunity of comparing the X-ray and solution stereochemistry. The P–O–C–C dihedral angles for β carbons C(12) and C(13) in **4h** are 95° and 140°, respectively (see Fig. 1). The conformation can be considered as a twisted form from the one in which P and H are *gauche* to each other. Using the formula given by Thiem [17] for $^3J_{CP}$ couplings the calculated constants for crystal structure should be 0 and 10.2 Hz. Comparison of these values with the observed ones, 2.9 and 6.7 Hz, indicates that at least two conformations are involved in solution. Because the crystal structure informs us about a strong repulsion between the methyl groups and the O–P=O moiety, we may conclude that the Pr^i group is flipping between two conformations, in one the P–O–C–C dihedral angles of 95° and 140° (X-ray structure) and in the other with angles of 140° and 95°. Calculation of the rotamer populations for these two conformations resulted in 70% (the X-ray conformation) and 30%, corresponding to a free energy difference as low as 2 kJ mol^{-1}. For the corresponding methylene compound **3h**, $^3J_{CP}$ couplings of 3.9 and 5.3 Hz were observed, which means that both of the above-mentioned conformations are equally populated. Rather similar dihedral angles were also obtained for other branched derivatives (see Table 2).

The $^1J_{CP}$ couplings were sensitive to charge density variation,[18] this being *ca.* 137 Hz for methylene, 145 Hz for halomethylene and 154 Hz for the dihalomethylene compounds. By contrast, the $^2J_{CP}$ couplings were rather similar (6–7 Hz), regardless of the structure of the molecules studied.

Four of the compounds studied were crystalline solids at room temperature (m.p.): **4a** (32 °C), **4h** (52 °C), **4i** (44 °C) and **5a** (80 °C). Only **4h** and **5a** were stable enough for X-ray structure analysis. Their molecular structures are shown in Fig. 1 and the bond lengths and angles are listed in Tables 3 and 4, respectively. The compound **4h** has C_2 symmetry while **5a** is unsymmetrical although possessing nearly C_2 symmetry, as seen from Fig. 1 and Tables 3 and 4. The bond lengths and angles were quite similar for both compounds but the orientations of the isopropyl and methyl esters were slightly different due to the different space requirements and intermolecular interactions.

Table 3 Bond lengths/Å for $Br_2C[P(O)(OMe)_2]_2$ (**5a**) and corresponding distances in $Cl_2C[P(O)(OCHMe_2)_2]_2$ (**4h**)

	5a	**4h**
C(1)–Br(1)/Cl(1)	1.963(8)	1.790(3)
C(1)–Br(2)	1.943(10)	
P(1)–O(11)	1.554(9)	1.564(3)
P(2)–O(21)	1.562(8)	
P(1)–O(12)	1.561(7)	1.560(3)
P(2)–O(22)	1.550(7)	
P(1)–O(13)	1.472(6)	1.453(3)
P(2)–O(23)	1.438(9)	
P(1)–C(1)	1.822(8)	1.854(3)
P(2)–C(1)	1.846(10)	
C(11)–O(11)	1.398(17)	1.480(4)
C(21)–O(21)	1.356(12)	
C(12)–O(12)	1.435(15)	1.456(6)
C(22)–O(22)	1.418(15)	

Table 4 Bond angles/° for $Br_2C[P(O)(OMe)_2]_2$ (**5a**) and corresponding values in $Cl_2C[P(O)(OCHMe_2)_2]_2$ (**4h**)

	5a	**4h**
O(11)–P(1)–O(12)	102.2(4)	103.9(2)
O(11)–P(1)–O(13)	116.9(4)	115.9(1)
O(12)–P(1)–O(13)	115.9(4)	118.4(2)
O(11)–P(1)–C(1)	103.3(5)	104.7(2)
O(12)–P(1)–C(1)	105.6(4)	99.9(1)
O(13)–P(1)–C(1)	111.6(4)	112.0(1)
O(21)–P(2)–C(22)	102.6(4)	
O(21)–P(2)–C(23)	117.7(5)	
O(22)–P(2)–C(23)	117.1(5)	
O(21)–P(2)–C(1)	100.8(5)	
O(22)–P(2)–C(1)	106.7(4)	
O(23)–P(2)–C(1)	110.2(4)	
P(1)–O(11)–C(11)	125.8(7)	123.1(2)
P(1)–O(12)–C(12)	123.1(5)	122.5(3)
P(2)–O(21)–C(21)	126.7(8)	
P(2)–O(22)–C(22)	124.4(8)	
X(1)–C(1)–Y(1)[a]	109.7(5)	108.2(2)
X(1)–C(1)–P(1)[a]	110.1(4)	109.9(1)
Y(1)–C(1)–P(1)[a]	108.1(5)	106.9(1)
X(1)–C(1)–P(2)[a]	105.9(5)	
Y(1)–C(1)–P(2)[a]	110.0(4)	
P(1)–C(1)–P(2)	113.1(5)	115.0(3)

[a] X = Y = Br in **5a** and X = Y = Cl in **4h**.

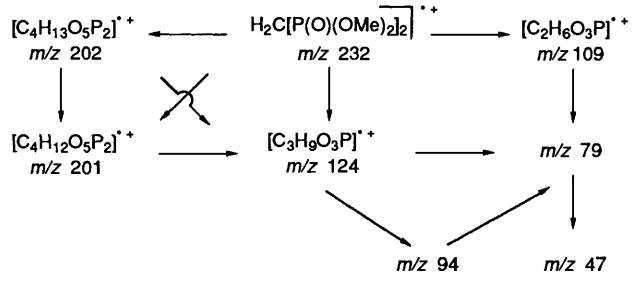
The mass spectra of the compounds **3a–f**, **h–k**, **4a**, **b**, **d–f**, **i**, **5a**, **6b** and **7a** were studied systematically with electron ionization (EI at 70 eV) and chemical ionization (CI), and fragmentation pathways were verified by metastable ion analysis using linked scans at constant *B*/*E*. Elemental composition of the ions was confirmed by accurate mass measurement. The relative abundances (≥5%) of the ions formed in the fragmentation processes are shown in Table 5. The molecular ion peaks were rather strong only in the methyl and ethyl esters but for the molecules with longer chains these ions were hardly detectable. Self-chemical ionization, the formation of the $[M + H]^+$, ions is also quite a favourable process, as shown from the spectra of some compounds, *e.g.* **3a**, **b**.

Fragmentation of the methylenebisphosphonates **3** depended mainly on the length and shape of the alkylester group. The formation of the $[CH_3P(O)(OR)_2]^{\cdot+}$ ion at *m*/*z* 124 and 152 gave rise to the base peak for **3a** and **3b**, respectively, but it was totally absent for other derivatives of **3**. For methyl esters the loss of one, or at most two, MeO$^\cdot$ groups and $H_2C{=}O$ from the molecular ion took place, but for longer alkyls the elimination of RO$^\cdot$ was observed only from the ethyl and n-propyl esters.

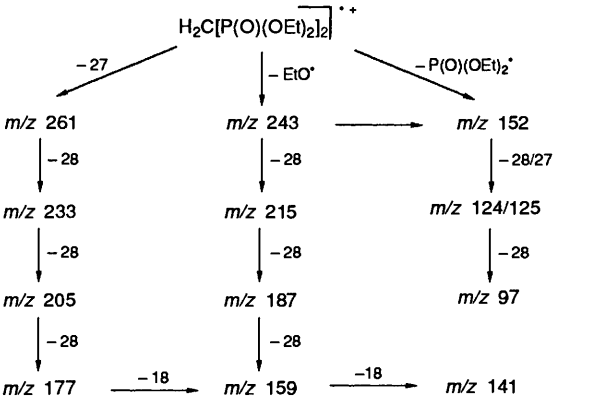
The main fragmentation routes for compound **3a** are presented in Scheme 2. The most important pathway started with P–C bond cleavage accompanied by simultaneous hydrogen migration leading to the base peak fragment $[Me–P(O)(OMe)_2]^{\cdot+}$ at *m*/*z* 124. The collision-induced dissociation (CID) spectrum of this ion closely resembled that measured by

Table 5 The 70 eV mass spectra of the compounds. Peaks with relative intensities (RI) greater than 5% (RI ≥ 10% marked with *) of the intensity of the base peak are included unless not due to a molecular ion. The spectra are uncorrected for isotopic contributions.

Compound	*m*/*z* (RI %)
3a	232 ($M^{\cdot+}$, 24), 202 (9), 201 (15), 187 (5), 125 (7), 124 (100), 109 (5), 107 (7), 94 (30), 93 (18), 79 (9), 63 (5).
3b*	289 (27), 288 ($M^{\cdot+}$, 8), 261 (54), 260 (10), 243 (16), 233 (39), 215 (15), 205 (36), 203 (10), 187 (22), 177 (37), 159 (84), 152 (100), 141 (14), 137 (12), 125 (50), 124 (25), 109 (28), 108 (15), 97 (28), 96 (15), 84 (8), 81 (26), 79 (17), 78 (11), 65 (26).
3c	304 (7), 303 (58), 285 (6), 261 (39), 243 (6), 231 (5), 219 (47), 201 (11), 189 (11), 177 (100), 175 (9), 159 (83), 142 (6), 141 (9), 139 (9), 123 (14), 99 (12), 97 (16), 96 (9), 79 (6), 65 (7).
3d	346 (5), 345 (38), 289 (21), 233 (20), 203 (6), 189 (7), 177 (100), 159 (80), 137 (9), 99 (12), 97 (11), 96 (6), 95 (5), 83 (12), 81 (19), 71 (6), 69 (19), 57 (24), 56 (25), 55 (23), 53 (6).
3e	388 (12), 387 (63), 345 (5), 317 (34), 247 (35), 205 (6), 189 (5), 177 (100), 169 (9), 159 (52), 99 (41), 97 (9), 71 (11), 70 (16), 69 (8), 57 (6), 56 (6), 55 (24).
3f	430 (17), 429 (80), 345 (20), 261 (18), 205 (5), 177 (100), 159 (44), 99 (6), 97 (6), 55 (8).
3h	303 (13), 287 (5), 261 (17), 245 (8), 243 (7), 219 (30), 218 (11), 203 (27), 201 (14), 185 (8), 177 (100), 176 (9), 160 (15), 159 (97), 158 (5), 142 (8), 141 (6), 99 (6), 97 (8), 96 (21), 79 (7), 65 (8).
3i	245 (12), 244 (6), 227 (5), 177 (52), 159 (28), 99 (6), 69 (7), 68 (42), 67 (100), 65 (6), 57 (14), 53 (16).
3j	387 (9), 317 (13), 299 (5), 273 (7), 247 (28), 246 (7), 231 (8), 229 (10), 203 (29), 185 (5), 177 (100), 160 (5), 159 (69), 99 (7), 96 (7), 71 (7), 70 (18), 55 (38).
3k	299 (5), 287 (5), 247 (17), 229 (16), 217 (48), 177 (100), 159 (68), 139 (5), 99 (7), 97 (9), 92 (25), 91 (35), 79 (7), 71 (5), 70 (10), 65 (5), 59 (34), 57 (5), 55 (22).
4a	302 (35), 300 ($M^{\cdot+}$, 52), 272 (8), 270 (12), 239 (8), 236 (9), 203 (5), 194 (15), 192 (25), 187 (100), 158 (8), 109 (61), 97 (11), 93 (75), 79 (24), 63 (11).
4b*	359 (22), 357 ($[M + H]^+$, 36), 330 (18), 328 (29), 302 (25), 300 (39), 274 (32), 272 (49), 248 (11), 246 (68), 244 (100), 227 (13), 222 (13), 220 (21), 192 (23), 166 (14), 164 (21), 109 (19), 99 (36), 81 (30), 65 (38).
4d	301 (6), 300 (5), 247 (6), 246 (11), 245 (10), 244 (17), 193 (12), 167 (22), 165 (34), 164 (6), 155 (11), 137 (90), 99 (38), 83 (6), 65 (5), 58 (5), 57 (100), 56 (18), 55 (20).
4e	244 (5), 221 (10), 169 (8), 167 (39), 165 (62), 153 (11), 151 (58), 131 (5), 99 (15), 83 (10), 72 (5), 71 (92), 70 (35), 69 (28), 65 (9), 57 (13), 56 (8), 55 (44).
4f	249 (14), 245 (6), 244 (6), 211 (28), 169 (10), 167 (61), 165 (100), 127 (93), 99 (49), 86 (5), 85 (72), 84 (9), 83 (21), 69 (17), 67 (6), 65 (5).
4i	167 (18), 165 (28), 151 (13), 149 (37), 99 (6), 85 (12), 83 (15), 69 (63), 68 (40), 67 (100), 65 (6), 57 (12), 53 (13).
5a	392 (9), 390 (16), 388 ($M^{\cdot+}$, 9), 284 (37), 282 (78), 280 (38), 267 (6), 265 (7), 251 (11), 249 (10), 237 (7), 235 (8), 204 (11), 202 (12), 201 (7), 189 (6), 187 (68), 173 (10), 171 (27), 143 (13), 141 (13), 124 (6), 109 (86), 95 (34), 93 (100), 82 (10), 80 (10), 79 (71), 65 (5), 63 (21), 62 (9).
6b*	324 (15), 323 (15), 322 ($M^{\cdot+}$, 47), 297 (20), 295 (60), 294 (29), 277 (14), 269 (20), 249 (12), 241 (15), 239 (49), 238 (27), 229 (19), 221 (15), 213 (16), 212 (30), 211 (50), 210 (100), 201 (19), 195 (23), 193 (72), 188 (21), 186 (66), 173 (13), 159 (47), 158 (21), 152 (15), 145 (13), 132 (11), 131 (11), 130 (34), 112 (15), 109 (25), 99 (46), 81 (35), 65 (62).
7a	312 (11), 310 ($M^{\cdot+}$, 12), 282 (6), 280 (8), 279 (5), 251 (7), 249 (7), 244 (6), 204 (11), 203 (6), 202 (65), 201 (18), 187 (81), 172 (8), 171 (42), 143 (5), 141 (7), 125 (13), 124 (55), 109 (45), 107 (8), 95 (7), 94 (27), 93 (100), 79 (30), 63 (20), 62 (14), 55 (7).



Scheme 2



Scheme 3

Holtzclaw *et al.* for dimethyl methylphosphonate.[19a] The alternative routes gave rise to a pair of ions at *m/z* 202 and 201, the elimination of MeO• and $H_2C{=}O$, respectively, a further fragmentation which also produced the base peak fragment. The fragmentation of the ion at *m/z* 124 produced ions at *m/z* 94 and 79 by elimination of $H_2C{=}O$ and Me• groups, respectively. This order was also energetically favoured according to *B/E* measurements. The other route to the peak at *m/z* 79 resulted from the ion $[P(O)(OMe)_2]^{\bullet+}$ at *m/z* 109 by cleavage of $H_2C{=}O$ group. Other fragments below *m/z* 100 were almost identical to those formed from monophosphonates and have been studied in detail by other authors.[11a,19]

Significant differences in the mass spectrum were observed when one of the methylene protons in **3a** was replaced by bromine. The spectrum of the monobromo derivative **7a** was dominated by four intense (≥55%) peaks at *m/z* 202, 187, 124 and 93. The only primary fragmentation pathway which gave rise to the metastable transition started with a double hydrogen rearrangement followed by loss of the BrHC=O unit leading to the $[C_4H_{12}O_5P_2]^{\bullet+}$ ion at *m/z* 202 (Found: *M*, 202.0150. Calc. M^+, 202.0160). Further fragmentation of this ion was complex, giving rise to peaks at *m/z* 201, 187, 171, 124 and 93. Comparing these ions with the fragmentation of **3a**, the main difference was the loss of bromine-containing fragments over cleavage of the P–C bond. On the other hand, the weak isotope peak at *m/z* 204 ($[C_3H_8{}^{81}BrO_3P]^{\bullet+}$; Found: 203.9377. Calc. 203.9373) indicated that this kind of fragmentation also appears.

The ion at *m/z* 202 may have two types of structures relative to the P–C bond, namely $[(MeO)_2P(O)CH_2P(O)H(OMe)]^{\bullet+}$ or $[(MeO)_2P(O)CH{=}P(OH)H(OMe)]^{\bullet+}$. The dominance of the former structure is more probable since it has two equal C–P bonds which are easily broken, thus making it a good precursor for the intense ions at *m/z* 124 and 93 as observed. Instead, the latter structure has only one C–P bond, which being bound to a double bond (P–C=P) does not break easily. An alternative fragmentation path to the ion at *m/z* 202 was started by the elimination of Me• and MeO• units corresponding to peaks at *m/z* 187 and 171, respectively, and followed by cleavage of the P–C bond leading to ions at *m/z* 94 and 93. Another route to the fragment at *m/z* 171 was initiated by the loss of a $BrH_2CO^{\bullet}$ radical from the ion at *m/z* 280 (310 − $H_2C{=}O$). Fragmentation of the ions at *m/z* 124, 109 and 93 was consistent for **3a**. The fragmentation of **4a** and **5a** closely resembles that of **7a**, because both prefer elimination of halogens over a P–C bond fragmentation, thus leading to intense peaks at *m/z* 187 and 171.

With increasing length of the ester chain in **3**, different types of processes became dominant in their mass spectrometric behaviour. Compound **3b** was the transition compound between the methyl type and the longer ester chain-type of fragmentation. The fragmentation of **3b** was started *via* three different routes (see Scheme 3); by elimination of $C_2H_3^{\bullet}$ (27), EtO• (45) and $P(O)(OEt)_2^{\bullet}$ (137) units. The loss of $C_2H_3^{\bullet}$ required the migration of two hydrogen atoms, one to the P=O oxygen and the other to the ester oxygen.[11a,19d] After this step the fragmentation was continued by consecutive losses of the remaining ethyl groups as ethylenes from the relevant precursor ion. In addition, the loss of water from ions containing three oxygen atoms is characteristic. Abundant ions at *m/z* 109 and 108 originated from ions at *m/z* 137 (loss of ethene) and 152 (loss of ethanal), respectively. Similar fragmentation pathways were also observed for **4b** and **6b**.

In general, fragmentation of the other methylenebisphosphonates (**3**) resembled those presented above for compounds **3a** and **3b**. The dominating features of fragmentation for molecules with higher and/or branched ester parts was consecutive losses of the $R{-}C_2H_2^{\bullet}$ unit followed by three $R{-}CH{=}CH_2$ units giving rise to the ion at *m/z* 177. The loss of an RO• radical was not very favourable although some ions above *m/z* 159 can be rationalized as resulting from the elimination of this unit. However, the most remarkable difference in the fragmentation between **3a** and **3b** was the absence of the $[Me{-}P(O)(OR)_2]^{\bullet+}$ and $[Me{-}P(O)(OH)(OR)]^{\bullet+}$ ions, with only **3c** showing a low intensity $[Me{-}P(O)(OH)(OC_3H_7)]^{\bullet+}$ ion peak.

The facile loss of $R{-}CH_2{=}CH_2$ units from the higher alkyl esters can be seen by comparing the relative intensity (%) at *m/z* 177 + $R{-}CH_2{=}CH_2$ (**A**) to *m/z* 177 (**B**) for different pentyl isomers. The ratio of intensities (**B**/**A**) in **3e**, **3j**, **3k** and **3i** is 0.35, 0.28, 0.17 and 0.12, respectively, which clearly indicates the stability of the double bond formed to the $R{-}CH_2{=}CH_2$ unit. On the other hand, the effect of chain lengthening was observed by comparing the ratios of the same ions from **3b**, **3c**, **3e** and **3f**, which were 0.97, 0.47, 0.35 and 0.18, respectively. Moreover, esters of **3** and **4** containing long chains tended to form $[M + H]^+$ ions, which were observed in accurate mass measurements.

Two main fragmentation pathways were observed from tetraalkyl (dichloromethylene)bisphosphonates (**4**). These were the consecutive losses of $R{-}C_2H_2^{\bullet}$ followed by three $R{-}CH{=}CH_2$ units or elimination of $P(=O)(OR_2]^{\bullet+}$ followed by losses of the two remaining alkyl groups, leading to ions at *m/z* 244 and 165, respectively. For **4i** only the latter fragmentation path was observed.

Conclusions

The products studied were easily achieved with good purity and yields using the approach developed. The structures of these compounds were identified using either NMR spectroscopy or mass spectrometry.

In NMR studies the characteristic AA'X spin system offered a possibility of resolving all coupling constants for the compounds. For branched alkyl ester derivatives the conformation of β-carbons was calculated by using the value of $^3J_{CP}$. Consistent results were obtained from X-ray data.

Table 6 Crystal data and details of the crystallographic analyses for compounds **4h** and **5a**

	4h	**5a**
Formula	$C_{13}H_{28}Cl_2O_6P_2$	$C_5H_{12}Br_2O_6P_2$
M_r	413.25	389.90
Space group	$C2/c$	$P2_1/n$
a/Å	12.895(3)	12.306(3)
b/Å	14.599(3)	7.226(1)
c/Å	11.513(2)	15.539(3)
β/°	95.04(2)	112.71(1)
V/Å^3	2159.0(8)	1274.7(5)
Z	4	4
D_c/g cm^{-3}	1.27	2.03
$F(000)$	872	760
Crystal dimensions/mm	0.40 × 0.40 × 0.40	0.30 × 0.35 × 0.40
Radiation	Mo-Kα	Mo-Kα
μ/cm^{-1}	4.67	65.5
Scan range/°	$4.0 \leq 2\theta \leq 55$	$5.0 \leq 2\theta \leq 55$
Scan type	ω	ω
Number of unique data	2474	2951
Number $F_{obs} \geq 6\sigma(F)$	1499	1506
Number of variables	105	136
Residue density:		
Maximum (e cm^{-3})	0.45	0.55
Minimum (e cm^{-3})	−0.39	−0.62
R	0.054	0.050
R_w	0.059	0.052
g	0.000 525	0.002
Goodness of fit	1.96	1.02

Table 7 Non-hydrogen atomic fractional coordinates (× 10^4) for $Cl_2C[P(O)(OCHMe_2)_2]_2$ (**4h**)

	x	y	z
Cl(1)	3876(1)	3611(1)	2513(1)
P(1)	4836(1)	2209(1)	1138(1)
O(1)	4782(2)	2935(2)	136(2)
O(2)	5953(2)	1798(2)	1134(3)
O(3)	3959(2)	1584(2)	1131(2)
C(1)	5000	2892(3)	2500
C(11)	3797(3)	3212(3)	−527(3)
C(12)	3625(4)	2620(3)	−1590(4)
C(13)	3897(4)	4201(3)	−807(5)
C(21)	6164(4)	961(3)	510(4)
C(22)	6511(9)	1105(6)	−555(7)
C(23)	6793(7)	372(5)	1231(6)

Table 8 Non-hydrogen atomic fractional coordinates (× 10^4) for $Br_2C[P(O)(OMe_2)_2]_2$ (**5a**)

	x	y	z
Br(1)	4879(1)	2287(1)	2778(1)
Br(2)	3055(1)	5580(2)	2540(1)
P(1)	5686(2)	6371(3)	3217(2)
P(2)	4367(2)	5076(3)	1205(2)
O(11)	5650(8)	5976(9)	4188(5)
O(12)	6867(5)	5437(8)	3303(4)
O(13)	5533(6)	8311(8)	2903(5)
O(21)	3427(8)	3542(11)	745(5)
O(22)	3671(7)	6881(10)	811(5)
O(23)	5496(7)	4884(11)	1141(4)
C(1)	4524(7)	4897(11)	2433(6)
C(11)	5479(15)	7277(17)	4785(10)
C(12)	7673(9)	6259(13)	2948(8)
C(21)	2661(10)	3468(17)	−158(7)
C(22)	4178(13)	8533(15)	642(8)

In the mass spectrometric studies of unhalogenated methyl and ethyl esters the characteristic feature was the loss of a P–C bond and, for longer esters, the consecutive losses of the R–$C_2H_2$$^{\cdot}$ unit followed by three R–CH=CH_2 units. Halogenated methyl esters tend to eliminate halogens over an P–C bond fragmentation, and for longer esters the consecutive losses of the ester groups and fragmentation of a P–C bond were typical.

Experimental

Melting points were determined with a Gallenkamp melting point apparatus and were uncorrected.

NMR Spectroscopy.—The ^{31}P NMR spectra were recorded on a Bruker AC 250 spectrometer operating at 101.256 MHz and the ^1H and ^{13}C NMR spectra on a Bruker AM 400 WB operating at 100.614 MHz for ^{13}C and 400.134 MHz for ^1H. For ^{31}P and ^{13}C measurements 190–210 μmol and for ^1H 45–55 μmol of sample were added to 0.4 cm^3 of $CDCl_3$. The sample solutions were prepared in 5 mm tubes using $(HO)_4P^+ClO_4^-$ (−0.07 ppm) as an external standard for ^{31}P measurements and TMS as reference for ^{13}C and ^1H measurements. The ^1H, ^{13}C and ^{31}P NMR spectra were acquired using 32 K data points with resolution enhancement and zero filling to point resolution better than 0.1 Hz. Decoupled ^{13}C and ^{31}P NMR spectra were measured using composite sequence (Waltz decoupling). Coupling constant values J are given in Hz throughout.

Mass Spectrometry.—The low resolution mass spectra were recorded on a JEOL JMS-D300 mass spectrometer equipped with a combined electron impact/chemical ionization source. The system was controlled by a JEOL JMA-2000H data system. The source conditions were: temperature 170 °C, electron energy 70 eV, acceleration voltage 3 kV and ionization current 300 μA. Samples were introduced through a direct inlet system. Accurate mass measurements were determined on a VG 70-250SE mass spectrometer at resolution 10,000 using a direct insertion probe. Fragmentation pathways were verified with metastable-ion transitions and/or CID spectra using linked scans at constant B/E with the JEOL JMS-D300.

Crystallography.—Details of crystal parameters, data collection parameters and refined data for compounds **4h** and **5a** are summarized in Table 6. Intensity measurements were made on a Nicolet R3m diffractometer using graphite-monochromatized Mo-Kα radiation (ω scan mode with a scan width of 1.0° for **4h** and 0.8° for **5a** from Kα1.2 and a scan speed 2.02–29.3° min^{-1}). Monitoring of two intensity check reflections showed no crystal decay during data collection. The data sets were corrected for Lorentz and polarization factors. Empirical absorption corrections were made from Ψ-scan data for both compounds.

Structure Analysis and Refinement.—The crystal structures were determined by direct methods and subsequent Fourier synthesis using the SHELXTL program package.[20] Non hydrogen atoms were refined anisotropically. Hydrogen atoms were placed at calculated positions with fixed isotropic thermal parameters (C–H 0.96 and U 0.09 Å^2 for **4a** and 0.07 Å^2 for **5a**). The final atomic coordinates are presented in Tables 7 and 8.

Additional material available from the Cambridge Crystallographic Data Centre (CCDC) comprises hydrogen atom coordinates and thermal parameters.*

Compounds.—$H_2C[P(O)Cl_2]_2$ was prepared according to the method of Althoff,[12] except for the use of toluene in

* For details of the CCDC scheme, see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 2*, 1992, in the January issue.

crystallization. Tetramethyl and tetraisopropyl methylenebisphosphonate were supplied by Lancaster Chemical Co. Tetraethyl and tetrabutyl methylenebisphosphonate were prepared in a similar manner to the method of Nicholson,[9b] and other esters were synthesized from **2**. Branched tetraalkyl (dichloromethylene)bisphosphonates were synthesized according to methods described earlier.[21] Tetra-n-alkyl (dichloro)- and (dibromo-methylene)bisphosphonates were achieved by a modification of the method of McKenna and the corresponding monochloro and monobromo compounds were produced as described by McKenna.[10a] Solid compounds were purified by crystallization and liquids by distillation or simply evaporation to dryness.* For mass spectrometric analysis, if necessary, a portion of undistilled material was purified by column chromatography using light petroleum (b.p. 35–60 °C)–acetone as eluent.[9g] The purity of the compounds (≥95 mol % for all compounds, unless stated otherwise) was routinely checked by ^1H and ^{31}P NMR spectroscopy.

Tetramethyl methylenebisphosphonate (**3a**). Purchased from Lancaster Chemical Co; δ_P 23.27 ($^2J_{PP}$ = 5.6); δ_H 3.83 (12 H, m) and 2.50 (2 H, t, $^2J_{PH}$ = 21.1).

Tetraethyl methylenebisphosphonate (**3b**). Prepared according to method of Nicholson[9b], yield 74%; δ_P 20.09 ($^2J_{PP}$ = 6.3); δ_H 4.18 (8 H, m), 2.45 (2 H, t, $^2J_{PH}$ = 21.1) and 1.36 (12 H, t + d, $^3J_{HH}$ = 7.1, $^4J_{HP}$ = 0.6).

Tetrapropyl methylenebisphosphonate (**3c**). Prepared as for **3b**, yield 76%; δ_P 20.09 ($^2J_{PP}$ = 6.9); δ_H 4.02 (8 H, m), 2.42 (2 H, t, $^2J_{PH}$ = 21.1), 1.66 (8 H, m) and 0.93 (12 H, t, $^3J_{HH}$ = 7.4).

Tetrabutyl methylenebisphosphonate **3d**. Prepared as for **3b**, yield 75%; δ_P 20.18 ($^2J_{PP}$ = 7.2); δ_H 4.10 (8 H, m), 2.43 (2 H, t, $^2J_{PH}$ = 21.1), 1.66 (8 H, m), 1.42 (8 H, m) and 0.95 (12 H, t, $^3J_{HH}$ = 7.4).

Tetrahexyl methylenebisphosphonate (**3f**). The reaction apparatus used was dried for 2 h at 120 °C and cooled under nitrogen. Methylene(bisphosphonodichloridate) (**2**) (40 g, 0.16 mol) was suspended in dry toluene (80 cm^3) under nitrogen. The solution was cooled to 0 °C and dry hexanol (69 g, 0.67 mol) in dry pyridine (48 g, 0.61 mol) was added over 80 min at this temperature with efficient stirring. After an additional 3 h of stirring at 20 °C, the solids were filtered off and washed twice with toluene (100 cm^3). The filtrate was dissolved in toluene (200 cm^3), washed twice with 2 mol dm^{-3} NaOH (400 cm^3) and water (120 cm^3). The residue was dried ($MgSO_4$) and evaporated to constant weight under reduced pressure to give 80 g (98%) of **3f**; δ_P 20.04 ($^2J_{PP}$ = 6.7); 4.08 (8 H, m), 2.43 (2 H, t, $^2J_{PH}$ = 21.0), 1.68 (8 H, m), 1.4–1.2 (24 H, m) and 0.89 (12 H, m); (Found: $[M + H]^+$, 513.3439. Calc. for $C_{25}H_{55}O_6P_2$: $[M + H]^+$, 513.3474).

Tetrapentyl methylenebisphosphonate (**3e**). Prepared as for **3f**, yield 94%; δ_P 20.06 ($^2J_{PP}$ = 7.1); δ_H 4.07 (8 H, m), 2.43 (2 H, t, $^2J_{PH}$ = 21.1), 1.67 (8 H, m), 1.4–1.2 (16 H, m) and 0.89 (12 H, m); (Found: $[M + H]^+$, 457.2883. Calc. for $C_{21}H_{47}O_6P_2$: $[M + H]^+$, 457.2848).

Tetraheptyl methylenebisphosphonate (**3g**). Prepared as for **3f**, yield 90%; δ_P 20.07 ($^2J_{PP}$ = 7.3); δ_H 4.08 (8 H, m), 2.43 (2 H, t, $^2J_{PH}$ = 21.1), 1.68 (8 H, m), 1.4–1.2 (32 H, m) and 0.88 (12 H, m); (Found: $[M + H]^+$, 569.4092. Calc. for $C_{29}H_{63}O_6P_2$: $[M + H]^+$ 569.4100).

Tetrakis(1-methylethyl) methylenebisphosphonate (**3h**). Purchased from Lancaster Chemical Co; δ_P 17.92 ($^2J_{PP}$ = 7.6); δ_H 4.78 (4 H, m), 2.37 (2 H, t, $^2J_{PH}$ = 21.1), 1.36 (12 H, d, $^3J_{HH}$ = 5.3) and 1.35 (12 H, d, $^3J_{HH}$ = 5.3).

Tetracyclopentyl methylenebisphosphonate (**3i**). Prepared as for **3f**, yield 85%; δ_P 18.74 ($^2J_{PP}$ = 10.1); δ_H 4.98 (4 H, m), 2.28 (2 H, t, $^2J_{PH}$ = 21.1) and 2.0–1.5 (32 H, m); (Found: $[M + H]^+$, 449.2237. Calc. for $C_{21}H_{39}O_6P_2$: $[M + H]^+$, 449.2222).

Tetrakis(1-methylbutyl) methylenebisphosphonate (**3j**). Prepared as for **3f**, yield 87%; δ_P 18.1 (>10 peaks due to diastereoisomers); δ_H 4.60 (4 H, m), 2.48–2.28 (2 H, m), 1.7–1.3 (28 H, m) and 0.93 (12 H, m); (Found: C, 55.0; H, 10.4; $[M + H]^+$ 457.2861. Calc. for $C_{21}H_{46}O_6P_2$: C, 55.3; H, 10.2%; $[M + H]^+$ 457.2848).

Tetrakis(1-ethylpropyl) methylenebisphosphonate (**3k**). Prepared as for **3f**, yield 88%; δ_P 18.37 ($^2J_{PP}$ = 9.4); δ_H 4.41 (4 H, m), 2.36 (2 H, t, $^2J_{PH}$ = 21.0), 1.68 (16 H, m) and 0.94 (24 H, m); (Found: $[M + H]^+$, 457.2809. Calc. for $C_{21}H_{47}O_6P_2$: $[M + H]^+$, 457.2848).

Tetramethyl (dichloromethylene)bisphosphonate (**4a**). $NaHCO_3$ (60 g) was suspended in aqueous 10% NaOCl (300 cm^3, 0.4 mol), the solution was cooled to 0 °C and kept at this temperature during the reaction by adding ice to the solution. Tetramethyl methylenebisphosphonate (**1a**) (20 g, 86 mmol) in methanol (60 cm^3) was added slowly with efficient stirring. After an additional 10 min of stirring at 0 °C, the mixture was extracted three times with cold (*ca.* 0 °C) CH_2Cl_2 (300 cm^3), washed with a cold saturated NaCl solution (30 cm^3), dried ($MgSO_4$) and evaporated to dryness to give 22 g (85%) of the solid **4a**, m.p. 32–34 °C; δ_P 10.88 ($^2J_{PP}$ = 23.6); δ_H 4.03 (m).

Tetraethyl (dichloromethylene)bisphosphonate (**4b**). Prepared as for **4a**, but methanol was replaced by CCl_4 (phase-transfer conditions), yield 81%; δ_P 8.82 ($^2J_{PP}$ = 23.0); δ_H 4.39 (8 H, m) and 1.41 (12 H, t, $^3J_{HH}$ = 7.4).

Tetrabutyl (dichloromethylene)bisphosphonate (**4d**). Prepared as for **4b**, yield 83%; δ_P 8.86; δ_H 4.31 (8 H, m), 1.72 (8 H, m), 1.44 (8 H, m) and 0.95 (12 H, m); (Found: $[M + H]^+$, 469.1429. Calc. for $C_{17}H_{37}Cl_2O_6P_2$: $[M + H]^+$, 469.1442).

Tetrapentyl (dichloromethylene)bisphosphonate (**4e**). Prepared as for **4b**, yield 90%; δ_P 8.85; δ_H 4.31 (8 H, m), 1.75 (8 H, m), 1.37 (16 H, m) and 0.92 (12 H, m); (Found: $[M + H]^+$, 525.1992. Calc. for $C_{21}H_{45}Cl_2O_6P_2$: $[M + H]^+$, 525.2068).

Tetrahexyl (dichloromethylene)bisphosphonate (**4f**). Prepared as for **4b**, yield 91%; δ_P 8.85 ($^3J_{PP}$ = 22.7); δ_H 4.31 (8 H, m), 1.73 (8 H, m), 1.40 (8 H, m), 1.31 (16 H, m) and 0.89 (12 H, m); (Found: $[M - C_6H_{11}]^+$, 497.1722. Calc. for $C_{19}H_{41}Cl_2O_6P_2$: $[M - C_6H_{11}]^+$ 497.1755).

Tetrakis(1-methylethyl) (dichloromethylene)bisphosphonate (**4h**). Prepared according to the method of Vepsäläinen *et al.*[21], yield 97%, m.p. 52–54 °C; δ_P 7.21 ($^3J_{PH}$ = 6.7); δ_H 4.97 (4 H, m) and 1.42 (24 H, d, $^3J_{HH}$ = 6.2).

Tetracyclopentyl (dichloromethylene)bisphosphonate (**4i**). Prepared as for **4h**, m.p. 44 °C, yield 97%; δ_P 7.89; δ_H 5.18 (4 H, m), 2.07–1.74 (24 H, m) and 1.68–1.54 (8 H, m); (Found: C, 48.9; H, 7.1. Calc. for $C_{21}H_{36}Cl_2O_6P_2$: C, 48.8; H, 7.0%).

Tetrakis(1-methylbutyl) (dichloromethylene)bisphosphonate (**4j**). Prepared as for **4h**, yield 95%; δ_P 7.69 (≥10 peaks due to diastereoisomers); δ_H 4.79 (4 H, m) and 1.85–1.25 (28 H, m); (Found: C, 48.4; H, 8.6. Calc. for $C_{21}H_{44}Cl_2O_6P_2$: C, 48.0; H, 8.4%).

Tetrakis(1-ethylpropyl) (dichloromethylene)bisphosphonate (**4k**). Prepared as for **4h**, yield 94%; δ_P 7.89; δ_H 4.59 (4 H, m), 1.77 (16 H, m) and 0.96 (24 H, t + d, $^3J_{HH}$ = 7.5, $^4J_{HH}$ = 4.6); (Found: $[M - C_{15}H_{32}]^+$ 313.9646. Calc. for $C_6H_{14}Cl_2O_6P_2$: $[M - C_{15}H_{32}]^+$, 313.9643).

Tetramethyl (dibromomethylene)bisphosphonate (**5a**). Tetramethyl methylbisphosphonate (**1a**) (4.0 g, 16 mmol) and bromine (5.9 g, 35 mmol) were dissolved in dichloromethane (80 cm^3). The solution was cooled to 0 °C and 1.00 mol dm^{-3} NaOH (40 cm^3) was added slowly at this temperature with efficient stirring. The dichloromethane layer was separated and washed with saturated NaCl solution (15 cm^3), dried ($MgSO_4$) and

* Compounds with long alkyl chains tend to produce by-products under distillation (probably dimers).

evaporated to dryness to give 5.7 g (92%) of solid **5a**, m.p. 80–82 °C; δ_P 10.96 ($^2J_{PP}$ = 20.8); δ_H 4.03 (m).

Tetrahexyl (dibromomethylene)bisphosphonate (**5f**). Prepared as for **5a**, but reaction time was 3 h at 5 °C, yield 91%; δ_P 8.98; δ_H 4.23 (8 H, m), 1.66 (8 H, m), 1.4–1.2 (24 H, m) and 0.82 (12 H, m).

Tetraethyl (chloromethylene)bisphosphonate (**6b**). Prepared according to the method of McKenna,[10a] yield 90%, b.p. 137–139 °C (*ca.* 2 mmHg); δ_P 13.51 ($^2J_{PP}$ = 8.9); δ_H 4.29 (8 H, m), 4.03 (1 H, t, $^2J_{PH}$ = 17.6) and 1.38 (12 H, t, $^3J_{HH}$ = 7.1).

Tetramethyl (bromomethylene)bisphosphonate (**7a**). Prepared according to the method of McKenna,[10a] yield 70%; δ_P 16.12 ($^2J_{PP}$ = 8.5); δ_H 3.96 (1 H, t, $^2J_{HP}$ = 17.1) and 3.92 (12 H, m); (Found: $M^{\bullet+}$, 309.9399. Calc. for $C_5H_{13}BrO_6P_2$: $M^{\bullet+}$, 309.9371.

Acknowledgements

We would like to thank Dr. Reino Laatikainen for helpful discussions on various aspects of this work, the expert technical assistance of Mrs. Ritva Romppanen (University of Joensuu) in obtaining elemental analyses, Mr. Jukka Knuutinen in obtaining accurate mass measurements (Research Centre Neulanen) and Mr. J. C. Gallaway (University of Kuopio) for English refinement.

References

1 Part 2, J. Vepsäläinen, H. Nupponen and E. Pohjala, *Synth. Commun.*, 1992, **22**, 271.
2 H. Fleisch, *Bone and Mineral Research*, ed. W. A. Peck, Annual 1, Excerpta Medica, Amsterdam, 1983.
3 See. *e.g.* (*a*) F. H. Ebetino, C. R. Degenhardt, L. A. Jamieson and D. C. Burdsall, *Heterocycles* 1990, **30**, 855; (*b*) W. K. Sietsema, F. H. Ebetino, A. M. Salvagno and J. A. Bevan, *Drugs Exp. Clin. Res.*, 1989, **XV**, 389; (*c*) L. M. Nguyen, E. Niesor and C. L. Bentzen, *J. Med. Chem.*, 1987, **30**, 1426.
4 Proctor & Gamble Co., Belgian Pat. 672,205/1966 (*Chem. Abstr.* 1967, **67**, 4040u).
5 For recent reviews see: (*a*) R. Hannuniemi, L. Laurén and H. Puolijoki, *Drugs of Today*, 1991, **27**, 375; (*b*) J. A. Kanis and E. V. McCloskey, *Prog. Basic Clin. Pharmacol.* 1990, **4**, 89.
6 (*a*) M. Menge, K. J. Münzenberg and E. Reimann, *Arch. Pharm.*, 1981, **314**, 218 (*b*) K. Z. Sommer, *Z. Anorg. Allg. Chem.*, 1970, **376**, 37; (*c*) O. T. Quimby, J. B. Prentice and D. A. Nicholson, *J. Org. Chem.*, 1967, **32**, 4111.
7 (*a*) S. Auriola, R. Kostiainen, M. Ylinen, J. Mönkkönen and P. Ylitalo, *J. Pharm. Biomed. Anal.*, 1989, **7**, 1623; (*b*) D. W. Hutchinson and G. J. Semple, *Org. Mass Spectrom.*, 1985, **20**, 143.
8 (*a*) P. N. Hmimid, J. P. Besse and R. Chevalier, *Acta Crystallogr., Sect. C*, 1987, **43**, 782; (*b*) W. S. Sheldrick, *J. Chem. Soc., Dalton Trans.*, 1975, 943; (*c*) M. Nardelli, G. Pelizzi, G. Staibano and E. Zucchi, *Inorg. Chim. Acta.*, 1983, **30**, 259.
9 (*a*) O. T. Quimby, J. D. Curry, D. A. Nicholson, J. B. Prentice and C. H. Roy, *J. Organomet. Chem.*, 1968, **13**, 199; (*b*) D. A. Nicholson, W. A. Cilley and O. T. Quimby, *J. Org. Chem.*, 1970, **35**, 3149; (*c*) T. H. Siddall and C. A. Prohaska, *Inorg. Chem.*, 1965, **4**, 783; (*d*) M-P. Teulade, P. Savignac, E. E. Aboujaoude, S. Liétge and N. Collignon, *J. Organomet. Chem.*, 1986, **304**, (*e*) T. Czekanski, H. Gross and B. Costisella, *J. Prakt. Chem.*, 1982, **324**, 537; (*f*) G. Paul and E. Herrmann, *Z. Chem.*, 1982, **22**, 307; (*g*) D. W. Hutchinson and G. Semple, *J. Organomet. Chem.*, 1985, **291**, 145; (*h*) D. Seyferth and R. S. Marmor, *J. Organomet. Chem.*, 1973, **59**, 237; (*i*) D. A. Nicholson and H. Vaughn, *J. Org. Chem.*, 1971, **36**, 1835; (*j*) G. M. Blackburn, D. A. England and F. Kolkmann, *J. Chem. Soc., Chem. Commun.*, 1981, 930.
10 (*a*) C. E. McKenna, L. A. Khawli, W-Y. Ahmad, P. Pham and J. P. Bongartz, *Phosphorus and Sulfur*, 1988, **37**, 1; (*b*) H. Gross, B. Costisella, L. Brennecke and G. Engelhardt, *J. Prakt. Chem.*, 1972, **314**, 969; (*c*) T. Bottin-Strzalko, J. Corset, F. Froment, M. J. Pouet, J. Seyden-Penne and M. P. Simonnin, *Phosphorus and Sulfur*, 1985, **22**, 217; (*d*) D. W. Hutchinson and G. Semple, *J. Organomet. Chem.*, 1986, **309**, C7.
11 (*a*) W. R. Griffiths and J. C. Tebby, *Phosphorus and Sulfur*, 1978, **5**, 101; (*b*) P. A. Cload and D. W. Hutchinson, *Org. Mass Spectrom.*, 1983, **18**, 57.
12 W. Althoff, M. Fild and R. Schmutzler, *Chem. Ber.*, 1981, **114**, 1082.
13 (*a*) R. Laatikainen, *J. Magn. Reson.*, 1991, **92**, 1; (*b*) R. Laatikainen, *QCPE Bull.*, 1992, **12**, 23.
14 S. Sorensen and H. J. Jakobsen, *Org. Magn. Reson.*, 1977, **9**, 101.
15 (*a*) G. Lang and E. Herrmann, *Z. Anorg. Allg. Chem.*, 1986, **536**, 187; (*b*) J. Vepsäläinen, unpublished data.
16 E. Breitmaier and W. Voelter, ^{13}C *NMR Spectroscopy*, Verlag Chemie, New York, 1978, p. 150.
17 J. Thiem and B. Meyer, *Org. Magn. Reson.*, 1978, **11**, 50.
18 G. A. Grey, *J. Am. Chem. Soc.*, 1971, **93**, 2132.
19 (*a*) J. R. Holtzclaw, J. R. Wyatt and J. E. Campana, *Org. Mass Spectrom.*, 1985, **20**, 90; (*b*) A. P. Snyder and C. S. Harden, *Org. Mass Spectrom.*, 1990, **25**, 301; (*c*) R. A. J. O'Hair, J. H. Bowie and R. N. Hayes, *J. Chem. Soc., Perkin Trans 2*, 1990, 473; (*d*) L. Zeller, J. Farrell, H. Kenttämaa and P. Vainiotalo *J. Am. Chem. Soc.*, in the press.
20 SHELXTL PLUS, Release 3.4, Nicolet Co., Madison, Wisconsin, 1988.
21 J. Vepsäläinen, H. Nupponen and E. Pohjala, *J. Labelled Compd. Radiopharm.*, 1991, **XXIX**, 1191.

Paper 2/00023G
Received 3rd *January* 1992
Accepted 30th *January* 1992