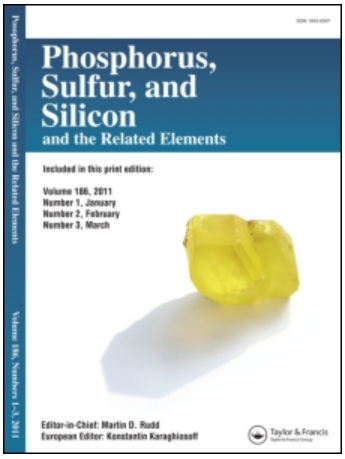

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SYNTHESIS OF α-HALOGENATED METHANEDIPHOSPHONATES[1a,b]

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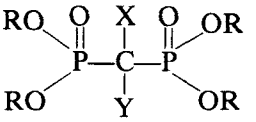
Methanediphosphonate (MDP) anions can exhibit anti-viral activity, inhibit bone resorption, and act as ligands in radiopharmaceuticals. α-Halo-substitution provides MDP derivatives (XYMDP, where X = H, F, Cl or Br; Y = F, Cl or Br) with modified acid-base, steric and other properties. These compounds are conveniently made from the corresponding α-halogenated XYMDP esters $(RO)_2P(O)CXYP(O)(OR)_2$. Detailed procedures are given for synthesis of R_4 XYMDP for R = Pr^i and X, Y = H, Cl; Cl, Cl; H, Br; Br, Br; F, Cl; F, Br and Cl, Br in 88–96% yield; for R = Et and X, Y = H, Cl; Cl, Cl; H, Br; Br, Br and Cl, F in 81–94% yield; and for R = Me and X, Y = Cl, Cl and Br, Br in 72–80% yield. NMR data (^1H, ^{31}P, ^{13}C, (^{19}F)) are presented for the products obtained. The XYMDP acids (X, Y = H, Cl; Cl, Cl; H, Br; Br, Br; F, Cl; F, Br and Cl, Br) were prepared by HCl hydrolysis of a corresponding ester and characterized as tris(dicyclohexylammonium) salts by elemental analyses and ^{31}P NMR.

INTRODUCTION

Methanediphosphonate[2] (MDP) **1**, and its α-substituted derivatives (XYMDP) are organophosphorus analogs of pyrophosphate in which the hydrolytically labile P—O—P bonds are replaced by more robust P—C—P bonds. Methanediphosphonates include compounds that show anti-viral activity,[3,4] inhibit osteoclastic bone resorption,[5,6] and find application as ligands for Tc^{99m} radiopharmaceuticals.[7]



1: X, Y = H; **1a**, R = Pr^i; **1b**, R = Et; **1c**, R = Me;
1d, R = H; **1e**, tris(dicyclohexylammonium) salt of **1d**;
2: X = H, Y = F; **3**: X = F, Y = F; **4**: X = H, Y = Cl; **5**: X = Cl, Y = Cl;
6: X = H, Y = Br; **7**: X = Br, Y = Br; **8**: X = H, Y = I; **9**: X = I, Y = I;
10: X = F, Y = Cl; **11**: X = F, Y = Br; **12**: X = Cl, Y = Br.

SCHEME 1

Substitution at the methylene carbon of MDP with one or two halogen atoms offers a means to modify the basicity, coordination aptitude, steric bulk and other properties of the molecule that may affect its behavior as a ligand or inhibitor.[8–14]

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In some cases, α-halogenation has resulted in compounds that are more active than the parent structure in particular biological systems: for example, α-chlorinated MDP derivatives inhibit the RNA transcriptase activity of influenza virus A more effectively than does MDP itself.[15] Dichloromethanediphosphonate (Cl_2MDP) has been found to be active in bone and calcium phosphate metabolism.[5,6,16] α-Halogenated MDP acids are also synthons for preparation of β,γ-halomethylene analogs of ATP and other nucleotides.[9,17–20]

Tetraalkyl esters provide the most convenient synthetic gateway to α-halo MDP acids, via classical hydrolysis in concentrated HCl or using silyldealkylation with bromotrimethylsilane (BTMS).[10,21,22] Tetraisopropyl and tetraethyl α-fluoro MDP esters (**2a–3b**) can be prepared from **1a–1b** in 42%–73% yield by treating the corresponding potassium carbanion with perchloryl fluoride at 5°C in the presence of $KOBu^t$. The ratio of tertiary alkoxide to starting ester can be adjusted to cause either monofluoro or difluoro product to predominate.[10] The sodium carbanion made from reaction of **1a** with NaH at 20°C similarly reacts with perchloryl fluoride to produce **2a** and **3a** in a 4:1 ratio (absolute yield not reported).[11] The difluoro ester **3b** was first prepared in 13% yield by reaction of triethyl phosphite with diethyl bromodifluoromethanephosphonate.[23] Mixed esters of **3** made by a related approach have also been reported.[11] Quimby *et al.*[24] reported ^{31}P NMR data for a number of different α-halo MDP tetraalkyl esters prepared by direct halogenation (Cl_2, Br_2, I_2) of metallated **1a**, **1b** or **1c**; this method gave mixtures of mono- and dihalo products and provided pure samples only in a few cases. These workers further noted that hypohalogenation (NaOCl, NaOBr) readily converts tetraalkyl esters of **1** to dihalo esters **5** or **7**,[24,25] and provided a detailed procedure for synthesis of **5a**, although the yield of pure product obtained was not given. Partial reduction of isopropyl and ethyl dihalo MDP esters to the corresponding monohalo derivatives **4a**, **4b**, **6a** and **6b** using various reducing agents has been examined,[26,27] and use of sodium hydrosulfide (NaSH) for this purpose has been advocated.[26] Nucleophilic monodehalogenation using *n*-butyllithium has also been used to synthesize **6a**.[28]

In more recent work, the NaSH reductive route[26] was stated to be unsatisfactory for the preparation of monochloro or monobromo MDP esters, and an alternative nucleophilic dehalogenation of dihalomethanediphosphonate tetraesters in an aprotic dipolar solvent was proposed.[29] Among a range of halide, hydride and other nucleophiles examined, KF-[18,6]-crown ether was found to give the best results. This method avoids the earlier use[28] of *n*-butyllithium in a similar conversion, but requires protracted reaction periods (7 days), results in mixtures requiring chromatographic separation, and is relatively costly on large scale (crown ether). The same authors subsequently applied the *n*-butyllithium procedure[28] to preparation of both tetraisopropyl chloro- and bromomethanediphosphonate, obtaining isolated yields of 71% and 64% respectively after chromatographic work-up.[30] Reaction of the thallium(I) derivatives of these compounds with alkyl iodides was found to provide a superior synthetic route to α-alkyl α-halo methanediphosphonates.[30]

α-Iodo MDP (**8, 9**) esters have been mentioned, but not fully characterized, in the literature.[26,27] They are less stable than other α-halo MDP esters[26,31] and are not further considered here. Mixed dihalomethanediphosphonates (*e.g.* **10**, **11**,

and **12**), in which the bridging α-carbon is substituted with two different halogen atoms, have not been previously described.[32]

We have discussed elsewhere synthesis of the stable triethyl α-halo phosphonoacetates[34–36] and corresponding salts.[14,34,36] The availability of the *integral set* of this family of compounds maximizes their potential use as probes of structure-activity relationships.[14,35] We report here canonical procedures for preparation in good (88–96%) isolated yield, without a chromatographic purification step, of every α-chloro and α-bromo MDP tetraisopropyl ester: the monochloro and monobromo esters **4a** (X, Y = H, Cl) and **6a** (X, Y = H, Br), the dichloro and dibromo esters **5a** (X, Y = Cl, Cl) and **7a** (X, Y = Br, Br) and the mixed halogenated esters **10a** (X,Y = F, Cl), **11a** (X, Y = F, Br) and **12a** (X, Y = Cl, Br), using the commercially available **1a** as a common starting material. Detailed procedures for preparation of the α-halo MDP tetraethyl esters **4b**, **5b**, **6b**, **7b** and **10b** from **1b**, and of the α-halo MDP tetramethyl esters **5c** and **7c** from **1c** are also given. The merits of employing **1a** vis à vis **1b** or **1c** as halogenation substrates are discussed. Preparation of the corresponding acids and their crystalline dicyclohexylamine (DCHA) salts (**4e**, **5e**, **6e**, **7e**, **10e**, **11e**, and **12e**) is also described. NMR spectral data for the tetraalkyl esters (^{1}H, ^{13}C, ^{31}P, (^{19}F)) and salts (^{31}P) are included. The resultant complete set of thoroughly characterized, analytically pure XYMDP derivatives, all (including the α-fluoro derivatives **2** and **3**[10]) made from a common starting material, will be of value in studies[14] of structure-activity relationships for biologically active methanediphosphonates.

EXPERIMENTAL

Solvents and reagents were analytical grade. Sodium hypochlorite (5.25%) was purchased as "Clorox bleach" from a local market; satisfactory results were also obtained using reagent quality sodium hypochlorite. Tetraisopropyl, tetraethyl and tetramethyl methanediphosphonate are currently available commercially (Lancaster Chemical Co.) but the isopropyl ester was prepared by the method of Roy[37] and the tetramethyl and tetraethyl esters were prepared by realkylation of methanediphosphonic acid (from hydrolysis of **1a**)[21] using the appropriate alkyl orthoformate.[38] TLC was performed using silica gel 60F-254 (EM Reagents) precoated plates. Preparative flash chromatography[39] was carried out by a modified technique described previously.[10] Proton (^{1}H, 270.13 MHz), carbon (^{13}C, 67.92 MHz), phosphorus (^{31}P, 109.35 MHz) and fluorine (^{19}F, 254.13 MHz) NMR spectra were measured on a Bruker WP-270SY spectrometer except in the case of tetraethyl and tetramethyl methanediphosphonate derivatives, for which ^{1}H (89.55 MHz) and ^{13}C (22.50 MHz) NMR spectra were obtained with a JEOL FX90Q spectrometer. Chemical shifts are reported relative to TMS (^{1}H: using internal $CHCl_3$, $\delta = 7.24$; ^{13}C: using internal $CDCl_3$, $\delta = 77.0$); external 85% H_3PO_4 (^{31}P); or external $CFCl_3$ (^{19}F). All chemical shifts downfield of the reference are given as positive values; note that in our earlier study of α-fluoro methanediphosphonates,[10] the reverse convention was used for ^{19}F chemical shifts. ^{31}P chemical shift values observed in monitoring product formation are given for convenience in individual procedures; full NMR data for the analytically pure products are presented in Tables I–III. Melting points were taken on a Thomas–Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were performed by Galbraith Laboratories.

Chlorinations Using Sodium Hypochlorite

Tetraisopropyl Dichloromethanediphosphonate **5a**. The procedure of Quimby[24] was modified. Tetraisopropyl methanediphosphonate **1a** (10 g, 29 mmol) was added dropwise with vigorous stirring to a solution of 5.25% sodium hypochlorite (332 g, 234 mmol) at ice-bath temperature. Following addition, stirring was continued for 20 min at room temperature. A white precipitate formed, and the

TABLE I

R_4XYMDP Esters: ^1H NMR Spectral Data[a]

Compound	R	X	Y	^1H, δ (J in Hz)
5a	Pr^i	Cl	Cl	1.38 (d, $^3J_{HH} = 6$, $8CH_3$) 4.95 (m, $4OCH$)
5b	Et	Cl	Cl	1.38 (t, $^3J_{HH} = 7$, $4CH_3$) 4.37 (m, $4OCH_2$)
5c	Me	Cl	Cl	3.97 (d, $^3J_{HP} = 11$, $4OCH_3$)
7a	Pr^i	Br	Br	1.39 (d, $^3J_{HH} = 6$, $8CH_3$) 4.95 (m, $4OCH$)
7b	Et	Br	Br	1.32 (t, $^3J_{HH} = 7$, $4CH_3$) 4.31 (m, $4OCH_2$)
7c	Me	Br	Br	4.00 (m, $4OCH_3$)
4a	Pr^i	H	Cl	1.35 (d, $^3J_{HH} = 6.5$, $8CH_3$) 3.85 (t, $^2J_{HP} = 17.5$, $CHCl$) 4.83 (m, $4OCH$)
4b	Et	H	Cl	1.29 (t, $^3J_{HH} = 7$, $4CH_3$) 3.93 (t, $^2J_{HP} = 17.5$, $CHCl$) 4.20 (m, $4OCH_2$)
6a	Pr^i	H	Br	1.35 (d, $^3J_{HH} = 6.5$, $8CH_3$) 3.72 (t, $^2J_{HP} = 17$, $CHBr$) 4.85 (m, $4OCH$)
6b	Et	H	Br	1.30 (t, $^3J_{HH} = 7$, $4CH_3$) 3.81 (t, $^2J_{HP} = 17$, $CHBr$) 4.21 (m, $4OCH_2$)
10a	Pr^i	F	Cl	1.38 (d, $^3J_{HH} = 6.5$, $8CH_3$) 4.82 (m, $4OCH$)
10b	Et	F	Cl	1.33 (t, $^3J_{HH} = 7$, $4CH_3$) 4.29 (m, $4OCH_2$)
11a	Pr^i	F	Br	1.39 (d, $^3J_{HH} = 6$, $8CH_3$) 4.94 (m, $4OCH$)
12a	Pr^i	Cl	Br	1.38 (d, $^3J_{HH} = 6$, $8CH_3$) 4.92 (m, $4OCH$)

[a] All samples prepared in $CDCl_3$.

turbid solution was extracted with 5 × 50 mL portions of hexane. The combined hexane extracts were dried ($MgSO_4$) and the solvent removed *in vacuo* at 50°C to give 10.5 g (88%) **5a**, white solid, bp 103–110°C (0.02 mm) (lit:[24] 119°C (0.5 mm)). ^{31}P NMR ($CDCl_3$): $\delta = 7.3$ ppm (lit:[24,30] 6.5 ppm, 6.86 ppm). Anal. calcd for $C_{13}H_{28}O_6Cl_2P_2$: C, 37.79; H, 6.83. Found: C, 37.54; H, 6.88.

Tetraisopropyl Chlorofluoromethanediphosphonate **10a**. In a similar reaction tetraisopropyl fluoromethanediphosphonate[10] (1.00 g, 2.75 mmol) was added with vigorous stirring to 5.25% sodium hypochlorite (32.4 g, 21.8 mmol). After further stirring (90 min) at room temperature, the solution was extracted with chloroform (3 × 25 mL), which was dried ($MgSO_4$) and the solvent removed *in vacuo*, to leave 1.0 g (93%) of the desired product **10a**: colorless oil, bp 96–98°C (0.01 mm). ^{31}P NMR ($CDCl_3$): $\delta = 4.9$ ppm. Anal. calcd. for $C_{13}H_{28}O_6ClFP_2$: C, 39.35; H, 7.11. Found: C, 39.44; H, 7.29.

Tetraethyl Dichloromethanediphosphonate **5b**. Tetraethyl methanediphosphonate (2.0 g, 6.9 mmol) was added dropwise at 0°C to a stirred solution of 5.25% sodium hypochlorite (64 mL, 45 mmol) and sodium chloride (20 g). After 20 min, the reaction mixture was extracted with ice-cold chloroform (4 × 50 mL). The chloroform phases were dried ($MgSO_4$) and concentrated *in vacuo* at 50°C. ^{31}P NMR analysis of the residue showed that **5b** made up 85% of the phosphorus-containing products. The remaining 15% was accounted for by a compound with $\delta = 11.2$ ppm, which was not identified. The desired product **5b** was isolated by vacuum distillation as a colorless oil (3.0 g, 82%), bp 92–93°C (0.05 mm) (lit:[24] 119–120°C (0.05 mm)). ^{31}P NMR ($CDCl_3$): $\delta = 9.0$ ppm (lit:[24] 8.5 ppm). Anal. calcd for $C_9H_{20}O_6Cl_2P_2$: C, 30.27; H, 5.64. Found: C, 29.94; H, 5.65.

TABLE II

R_4XYMDP Esters: ^{13}C NMR Spectral Data[a,b]

Compound	R	X	Y	^{13}C, δ (J in Hz)
5a	Pr^i	Cl	Cl	23.8 (q, $^1J_{CH}$ = 125, $^3J_{CP}$ = 5, CH_3) 73.9 (t, $^1J_{CP}$ = 147, CCl_2) 75.0 (d, $^1J_{CH}$ = 154, $^2J_{CP}$ = 5, OCH)
5b	Et	Cl	Cl	16.7 (q, $^1J_{CH}$ = 127, $^3J_{CP}$ = 3, CH_3) 66.5 (t, $^1J_{CH}$ = 150, $^2J_{CP}$ = 4, OCH_2) 72.9 (t, $^1J_{CP}$ = 151, CCl_2)
5c	Me	Cl	Cl	56.5 (q, $^1J_{CH}$ = 150, $^2J_{CP}$ = 6, OCH_3) 71.3 (t, $^1J_{CP}$ = 155, CCl_2)
7a	Pr^i	Br	Br	23.8 (q, $^1J_{CH}$ = 125, $^3J_{CP}$ = 5, CH_3) 49.8 (t, $^1J_{CP}$ = 141, CBr_2) 75.0 (d, $^1J_{CH}$ = 154, $^2J_{CP}$ = 5, OCH)
7b	Et	Br	Br	16.3 (q, $^1J_{CH}$ = 127, $^3J_{CP}$ = 4, CH_3) 44.2 (t, $^1J_{CP}$ = 144, CBr_2) 66.3 (t, $^1J_{CH}$ = 150, $^2J_{CP}$ = 4, OCH_2)
7c	Me	Br	Br	42.7 (t, $^1J_{CP}$ = 145, CBr_2) 56.7 (q, $^1J_{CH}$ = 150, $^2J_{CP}$ = 6, OCH_3)
4a	Pr^i	H	Cl	23.8 (q, $^1J_{CH}$ = 126, $^3J_{CP}$ = 5, CH_3) 45.1 (dt, $^1J_{CH}$ = 145, $^1J_{CP}$ = 146, CHCl) 73.0 (d, $^1J_{CH}$ = 150, $^2J_{CP}$ = 5, OCH)
4b	Et	H	Cl	16.2 (q, $^1J_{CH}$ = 127, $^3J_{CP}$ = 3, CH_3) 43.5 (dt, $^1J_{CH}$ = 143, $^1J_{CP}$ = 145, CHCl) 64.2 (t, $^1J_{CH}$ = 149, $^2J_{CP}$ = 4, OCH_2)
6a	Pr^i	H	Br	23.8 (q, $^1J_{CH}$ = 125, $^3J_{CP}$ = 5, CH_3) 31.5 (dt, $^1J_{CH}$ = 142, $^1J_{CP}$ = 144, CHBr) 73.0 (d, $^1J_{CH}$ = 150, $^2J_{CP}$ = 5, OCH)
6b	Et	H	Br	16.2 (q, $^1J_{CH}$ = 127, $^3J_{CP}$ = 3, CH_3) 29.6 (dt, $^1J_{CH}$ = 142, $^1J_{CP}$ = 142, CHBr) 64.3 (t, $^1J_{CH}$ = 149, $^2J_{CP}$ = 3, OCH_2)
10a	Pr^i	F	Cl	23.8 (q, $^1J_{CH}$ = 125, $^3J_{CP}$ = 5, CH_3) 74.6 (d, $^1J_{CH}$ = 150, $^2J_{CP}$ = 5, OCH) 103.9 (dt, $^1J_{CF}$ = 261, $^1J_{CP}$ = 157, CFCl)
10b	Et	F	Cl	16.3 (q, $^1J_{CH}$ = 127, $^3J_{CP}$ = 2, CH_3) 65.7 (t, $^1J_{CH}$ = 150, $^2J_{CP}$ = 4, OCH_2) 101.5 (dt, $^1J_{CF}$ = 269, $^1J_{CP}$ = 170, CFCl)
11a	Pr^i	F	Br	23.8 (q, $^1J_{CH}$ = 125, $^3J_{CP}$ = 5, CH_3) 74.6 (d, $^1J_{CH}$ = 150, $^2J_{CP}$ = 5, OCH) 95.2 (dt, $^1J_{CF}$ = 259, $^1J_{CP}$ = 150, CFBr)
12a	Pr^i	Cl	Br	23.8 (q, $^1J_{CH}$ = 125, $^3J_{CP}$ = 5, CH_3) 63.5 (t, $^1J_{CP}$ = 145, CClBr) 74.6 (d, $^1J_{CH}$ = 150, $^2J_{CP}$ = 5, OCH)

[a] All samples prepared in $CDCl_3$. [b] Mult. given for $J > 10$.

Tetraethyl Chlorofluoromethanediphosphonate **10b**. In a similar reaction, a solution of 5.25% sodium hypochlorite (33 mL, 23 mmol) containing sodium chloride (10.5 g) was cooled using a carbon tetrachloride-dry ice bath and then reacted with tetraethyl fluoromethanediphosphonate[10] (1.58 g, 5.25 mmol), cooled similarly. After 20 min the mixture was extracted with chloroform (3 × 100 mL). The extracts were dried ($MgSO_4$) and concentrated *in vacuo* at 50°C to leave a colorless oil (1.7 g). The predominant phosphorus-containing component (^{31}P NMR) was **10b** (87%). Purification by flash chromatography using an eluent of 30% benzene in ethyl acetate gave 1.42 g (81%) of **10b** (TLC: R_f 0.38): colorless oil, bp 107–108°C (0.02 mm). ^{31}P NMR ($CDCl_3$): δ = 6.5 ppm. Anal. calcd for $C_9H_{20}O_6ClFP_2$: C, 31.73; H, 5.92. Found: C, 31.41; H, 6.11.

Diethyl Chlorofluoromethanephosphonate **14**. The minor product fractions from the preceding reaction were combined, dried ($MgSO_4$) and evaporated *in vacuo* to leave 0.12 g of **14** as a colorless

TABLE III

R_4XYMDP Esters: ^{31}P and ^{19}F NMR Spectral Data[a]

Compound	R	X	Y	^{31}P, δ (J in Hz)	^{19}F, δ (J in Hz)
5a	Pr^i	Cl	Cl	7.3 (t, $^3J_{PH} = 6$)	
5b	Et	Cl	Cl	9.0 (p, $^3J_{PH} = 7$)	
5c	Me	Cl	Cl	11.0 (m)	
7a	Pr^i	Br	Br	7.5 (t, $^3J_{PH} = 6$)	
7b	Et	Br	Br	9.1 (p, $^3J_{PH} = 7$)	
7c	Me	Br	Br	11.1 (m)	
4a	Pr^i	H	Cl	12.2 (dt, $^2J_{PH} = 18$, $^3J_{PH} = 6$)	
4b	Et	H	Cl	13.9 (dp, $^2J_{PH} = 17$, $^3J_{PH} = 8$)	
6a	Pr^i	H	Br	12.3 (dt, $^2J_{PH} = 17$, $^3J_{PH} = 6$)	
6b	Et	H	Br	14.0 (dp, $^2J_{PH} = 17$, $^3J_{PH} = 8$)	
10a	Pr^i	F	Cl	4.9 (dt, $^2J_{PF} = 77$, $^3J_{PH} = 6$)	−150 (t, $^2J_{FP} = 77$)
10b	Et	F	Cl	6.5 (dp, $^2J_{PF} = 76$, $^3J_{PH} = 8$)	−149 (t, $^2J_{FP} = 76$)
11a	Pr^i	F	Br	5.2 (dt, $^2J_{PF} = 74$, $^3J_{PH} = 6$)	−155 (t, $^2J_{FP} = 74$)
12a	Pr^i	Cl	Br	7.4 (t, $^3J_{PH} = 6$)	

[a] All samples prepared in $CDCl_3$.

oil; TLC (30% benzene in EtOAc): R_f 0.64. ^1H NMR: $\delta = 1.36$, 1.37 ppm (2t, $^3J_{HH} = 7$ Hz, $2CH_3$); $\delta = 4.26$, $\delta = 4.30$ ppm (~2p, $^3J_{HP} \sim 7$ Hz, $^3J_{HH} \sim 7$ Hz, $2OCH_2$ (diastereotopic resonances not clearly distinguishable at 90 MHz); $\delta = 6.18$ ppm (dd, $^2J_{HF} = 47$ Hz, $^2J_{HP} = 10$ Hz, CHFCl. ^{13}C NMR: $\delta = 16.4$ ppm (qd, $^1J_{CH} = 129$ Hz, $^3J_{CP} = 3$ Hz, CH_3); $\delta = 64.9$ ppm (td, $^1J_{CH} = 149$ Hz, $^2J_{CP} = 4$ Hz, CH_2); $\delta = 93.5$ ppm (ddd, $^1J_{CF} = 226$ Hz, $^1J_{CP} = 195$ Hz, $^1J_{CH} = 178$ Hz, CHFCl). ^{19}F NMR: $\delta = -165$ ppm (dd, $^2J_{FP} = 78$ Hz, $^2J_{FH} = 47$ Hz). ^{31}P NMR: $\delta = 8.2$ ppm (dd of pentets, $^2J_{PF} = 78$ Hz, $^2J_{PH} = 8$ Hz, $^3J_{PH} = 8$ Hz). Anal. calcd for $C_5H_{11}O_3ClFP$: C, 29.36; H, 5.42. Found: C, 29.83; H, 5.74.

Tetramethyl Dichloromethanediphosphonate **5c**. A solution of sodium chloride (60 g) and 5.25% sodium hypochlorite (192 mL, 135 mmol) mixed with chloroform (40 mL), was cooled in a carbon tetrachloride-dry ice bath. When the reaction mixture became turbid (ca. 5 min), tetramethyl methanediphosphonate (4.8 g, 21 mmol) dissolved in chloroform (10 mL) was added at once. After 7 min, the reaction mixture was extracted with chloroform (3 × 200 mL). The chloroform extracts were dried ($MgSO_4$) and evaporated under reduced pressure to leave a colorless oil (5.74 g). ^{31}P NMR revealed the presence of **5c** (79%) and a cleavage side product, dimethyl dichloromethanephosphonate ($\delta = 13.5$ ppm) (21%). Fractional distillation gave the latter compound (bp: 105–107°C (6 mm)), followed by **5c** (4.5 g, 72%: bp 96–97°C (0.01 mm). ^{31}P NMR ($CDCl_3$): $\delta = 11.0$ ppm (lit:[24] 10.0 ppm; no other characterization data given). Anal. calcd for $C_5H_{12}O_6Cl_2P_2$: C, 19.95; H, 4.02. Found: C, 19.76; H, 4.06.

Dimethyl Dichloromethanephosphonate **13**. A two-phase mixture consisting of 30 g sodium chloride, 5.25% sodium hypochlorite (96 mL; 68 mmol), and 40 mL CCl_4 was cooled 10 min in a carbon tetrachloride-dry ice bath. Tetramethyl methanediphosphonate (2.4 g; 10 mmol) in CCl_4 (10 mL) was then added in one portion. After 2 h, the mixture was extracted with dichloromethane (3 × 200 mL). The dried ($MgSO_4$) organic phase was evaporated at reduced pressure, and the residue was distilled through a short-path column to give 1.5 g (64%) **5c**: colorless oil, bp 141–142°C (23 mm). ^1H NMR: $\delta = 3.94$ ppm (d, $^3J_{HP} = 11$ Hz, $2OCH_3$); 5.66 ppm (d, $^2J_{HP} = 2$ Hz, $CHCl_2$). ^{13}C NMR: $\delta = 55.5$ ppm (qd, $^1J_{CH} = 150$ Hz, $^2J_{CP} = 7$ Hz, CH_3); $\delta = 60.1$ ppm (dd, $^1J_{CP} = 179$ Hz, $^1J_{CH} = 173$ Hz, $CHCl_2$). ^{31}P NMR: $\delta = 13.5$ ppm (d of septets, $^2J_{PH} = 2$ Hz, $^3J_{PH} = 11$ Hz). Anal. calcd for $C_3H_7O_3Cl_2P$: C, 18.67; H, 3.66. Found: C, 18.82; H, 3.83.

Brominations Using Sodium Hypobromite

Tetraisopropyl Dibromomethanediphosphonate **7a**. A solution of 5.43 g (136 mmol) sodium hydroxide in H_2O (20 mL) was cooled to 0°C in an ice-salt bath, and bromine (10.8 g, 67.9 mmol) was added slowly with stirring. Tetraisopropyl methanediphosphonate (5.00 g 14.5 mmol) was then added and stirring was continued for 10 min at 0°C, followed by an additional 5 min at room temperature.

Chloroform extracts (4 × 50 mL) were dried ($MgSO_4$) and the solvent removed *in vacuo,* leaving tetraisopropyl dibromomethanediphosphonate (6.5 g, 89%): colorless oil, bp 120–122°C (0.01 mm) (lit:[24] 90°C (<0.04 mm)). ^{31}P NMR ($CDCl_3$): $\delta = 7.5$ ppm (lit:[24,30] 6.5 ppm, 6.74 ppm). Anal. calcd for $C_{13}H_{28}O_6Br_2P_2$: C, 31.10; H, 5.62. Found: C, 30.75; H, 5.62.

Tetraisopropyl Bromochloromethanediphosphonate **12a**. In a similar reaction, tetraisopropyl chloromethanediphosphonate (2.2 g, 5.8 mmol) (see below) was added at 0°C to a solution of NaOH (7.0 g, 0.18 mol) and bromine (13.9 g, 86.9 mmol) in H_2O (50 mL). After 10 min, cooling was discontinued and the mixture was stirred for an additional 40 min. Chloroform extraction (4 × 50 mL) yielded after drying ($MgSO_4$) and rotary evaporation **12a** as a colorless oil (2.5 g, 94%), bp 85–86°C (0.01 mm). ^{31}P NMR ($CDCl_3$): $\delta = 7.4$ ppm. Anal. calcd for $C_{13}H_{28}O_6BrClP_2$: C, 34.12; H, 6.17. Found: C, 33.96; H, 6.42.

Tetraisopropyl Bromofluoromethanediphosphonate **11a**. Similarly, tetraisopropyl fluoromethanediphosphonate (1.0 g, 2.8 mmol) was added to a solution of NaOH (6.3 g, 0.16 mol) and bromine (12.6 g, 78.8 mmol) in 19 mL H_2O at 0°C. After 10 min at 0°C (ice bath) and 45 min at room temperature, the reaction mixture was worked up with chloroform (5 × 50 mL) as described in the preceding example, giving 1.2 g (91%) **11a**: colorless oil, bp 110–112°C (0.01 mm). ^{31}P NMR ($CDCl_3$): $\delta = 5.2$ ppm. Anal. calcd for $C_{13}H_{28}O_6BrFP_2$: C, 35.39; H, 6.40. Found: C, 35.01; H, 6.19.

Tetraethyl Dibromomethanediphosphonate **7b**. Tetraethyl methanediphosphonate (2.0 g, 6.9 mmol) was added dropwise at 0°C for 30 min to a mixture of 5.6 M sodium hydroxide (12 mL, 67 mmol) and sodium chloride (4 g). After stirring for 30 min, 2.0 mL (39 mmol) bromine was added dropwise for 30 min. Stirring was continued for 60 min, whereupon the reaction mixture was extracted with ice-cold chloroform (4 × 50 mL). The organic phases were dried ($MgSO_4$) and evaporated to leave **7b** (87% by ^{31}P NMR) and two unidentified minor products ($\delta = 5$ ppm, $\delta = -0.2$ ppm). Vacuum distillation gave **7b** as a colorless oil, 2.6 g (85%), bp 129–131°C (0.02 mm) (lit:[24] 117–120°C (0.08 mm)). ^{31}P NMR ($CDCl_3$): $\delta = 9.1$ ppm (lit:[24] 8.5 ppm). Anal. calcd. for $C_9H_{20}O_6Br_2P_2$: C, 24.24; H, 4.52. Found: C, 24.02; H, 4.55.

Tetramethyl Dibromomethanediphosphonate **7c**. A two-phase mixture of 7 g sodium chloride, 5.6 M sodium hydroxide (18 mL; 0.10 mol), bromine (3.0 mL; 58 mmol), and chloroform (40 mL) was cooled briefly with a CCl_4-dry ice bath. Tetramethyl methanediphosphonate (2.4 g; 10 mmol) in chloroform (10 mL) was added with stirring. After 15 min, the mixture was poured into chloroform (200 mL). The aqueous phase was re-extracted with one volume of the same solvent, and the combined organic layers were dried ($MgSO_4$). Removal of $CHCl_3$ at reduced pressure (50°C) gave 3.21 g (80%) **7c** as a white solid: mp: 80–82°C. ^{31}P NMR ($CDCl_3$): $\delta = 11.1$ ppm. Anal. calcd for $C_5H_{12}O_6Br_2P_2$: C, 15.40; H, 3.10. Found: C, 15.43; H, 3.25.

Reductive Monodehalogenations

Tetraisopropyl Chloromethanediphosphonate **4a**. Sodium sulfite (5.5 g, 44 mol) in H_2O (160 mL) was added with stirring to tetraisopropyl dichloromethanediphosphonate (5.0 g, 12 mmol) in EtOH (40 mL) with ice bath cooling while the temperature was maintained below 15°C (15 min). After 60 min at room temperature, the reaction mixture was extracted with chloroform (5 × 50 mL). The chloroform extracts were combined, dried ($MgSO_4$) and the solvent removed *in vacuo* to give 4.4 g **4a** (96%): colorless oil, bp 95–97°C (0.01 mm) (lit:[26] 105–108°C (0.05 mm)). ^{31}P NMR ($CDCl_3$): $\delta = 12.2$ ppm (lit:[26,30] 11.5, 11.4 ppm). Anal. calcd for $C_{13}H_{29}O_6ClP_2$: C, 41.22; H, 7.72. Found: C, 41.19; H, 7.85.

Tetraethyl Chloromethanediphosphonate **4b**. A solution of 0.25 M sodium sulfite (87.4 mL, 21.9 mmol) was added dropwise over 25 min to tetraethyl dichloromethanediphosphonate (3.80 g, 10.6 mmol) in absolute ethanol (38 mL) cooled by an ice-bath. After 15 min at 0°C, the resulting mixture was allowed to warm to room temperature over 60 min. During this interval, the turbid reaction mixture clarified. It was then extracted with chloroform (5 × 100 mL) and the extracts were dried ($MgSO_4$) and evaporated *in vacuo* to leave 3.23 g (94%) **4b**: colorless oil, bp 110–111°C (0.4 mm). ^{31}P NMR ($CDCl_3$): $\delta = 13.9$ ppm. Anal. calcd for $C_9H_{21}O_6ClP_2$: C, 33.50; H, 6.56. Found: C, 33.40; H, 6.63.

Tetraisopropyl Bromomethanediphosphonate **6a**. A solution of $SnCl_2 \cdot 2H_2O$ (1.38 g, 6.12 mmol) in H_2O (15 mL) was added with cooling (ice-bath) to tetraisopropyl dibromomethanediphosphonate (3.2 g, 6.4 mmol) in EtOH (8 mL). After 5 min, the cooling bath was removed and stirring was

continued for an additional 5 min; the reaction mixture was then extracted with chloroform (4 × 25 mL). The extracts were dried ($MgSO_4$) and evaporated *in vacuo* to leave 2.5 g (93%) **6a**: colorless oil, bp 118–120°C (0.01 mm) (lit:[26] 140°C (0.03 mm)). ^{31}P NMR ($CDCl_3$): $\delta = 12.3$ ppm (lit:[26,30] 11.5, 11.4 ppm. Anal. calcd for $C_{13}H_{29}O_6BrP_2$: C, 36.89; H, 6.91; Found: C, 37.11; H, 7.09.

Tetraethyl Bromomethanediphosphonate **6b**. To tetraethyl dibromomethanediphosphonate (1.46 g, 3.27 mmol) in absolute ethanol (14.6 mL) at ice-bath temperature was added dropwise a solution of $SnCl_2 \cdot 2H_2O$ (0.83 g, 3.7 mmol) in H_2O (36 mL). After 15 min, the reaction mixture was extracted with chloroform (5 × 50 mL). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure to leave 1.08 g (90%) **6b**: colorless oil, bp 125–127°C (0.02 mm) (lit:[26] 127–128°C (0.08 mm)). ^{31}P NMR ($CDCl_3$): $\delta = 14.0$ ppm (lit:[26] 13.0 ppm). Anal. calcd for $C_9H_{21}O_6BrP_2$: C, 29.45; H, 5.77. Found: C, 29.52; H, 5.76.

Hydrolysis of α-Halogenated Methanediphosphonate Esters

A sample of a given tetraester was refluxed in excess of conc. HCl for 3-6 hours. The HCl was removed at reduced pressure, and the residue was dissolved in the minimum amount of absolute ethanol. Excess dicyclohexylamine was added to form the corresponding salt, which was recrystallized successively from ethanol/acetone and from absolute ethanol, producing a white crystalline solid (characterization data: Table IV.). The compounds were stable for at least several months when stored in a desiccator.

TABLE IV

Data for Characterization of α-Halomethanediphosphonate Dicyclohexylamine Salts

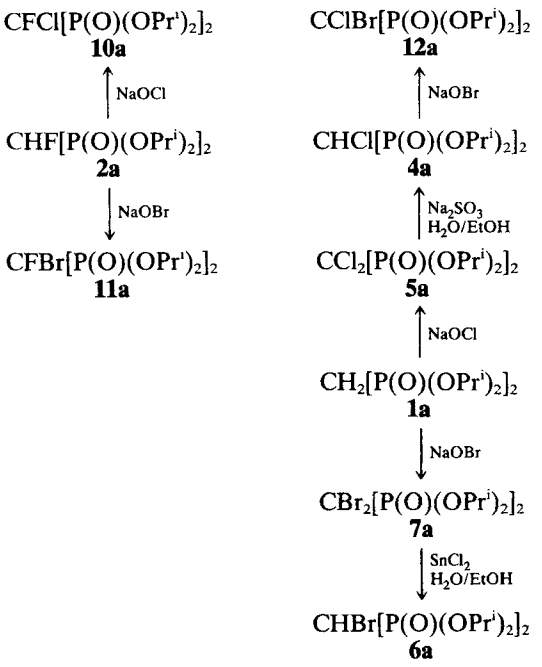
Compound	Formula	Calculated %C	Calculated %H	Calculated %N	Found %C	Found %H	Found %N	mp (°C)	^{31}P, δ[a] (J in Hz)
4e	$C_{37}H_{74}O_6ClN_3P_2$[b]	57.53	9.92	5.44	57.53	9.66	5.17	247–248	13.7 (d) $^2J_{PH} = 17$
6e	$C_{37}H_{74}O_6BrN_3P_2$[c]	55.01	9.36	5.20	54.92	9.21	4.99	244–245[d]	13.6 (d) $^2J_{PH} = 17$
5e	$C_{37}H_{73}O_6Cl_2N_3P_2$[c]	55.70	9.35	5.27	55.91	9.14	5.08	255–256[d]	9.8 (s)
7e	$C_{37}H_{73}O_6Br_2N_3P_2$[e]	49.21	8.47	4.64	49.24	8.49	4.49	249–250[d]	9.5 (s)
10e	$C_{37}H_{73}O_6ClFN_3P_2$[c]	56.87	9.55	5.38	56.83	9.56	5.38	220–221[d]	7.5 (d) $^2J_{PF} = 72$
11e	$C_{37}H_{73}O_6BrFN_3P_2$[c]	53.81	9.03	5.09	53.95	9.05	4.79	~150[d,f]	8.2 (d) $^2J_{PF} = 70$
12e	$C_{37}H_{73}O_6BrClN_3P_2$	53.33	8.83	5.04	53.00	8.87	4.84	246–247[d]	9.9 (s)

[a] All samples prepared in D_2O. [b] $1H_2O$. [c] $1/2H_2O$. [d] Dec. [e] $3/2H_2O$. [f] sint. ~165°C; sens. to imm. temp.

RESULTS AND DISCUSSION

Several workers have previously investigated routes to preparation of tetraalkyl α-halomethanediphosphonates. An early synthesis of tetraethyl dichloromethanediphosphonate by Michaelis–Arbuzov reaction of triethyl phosphite with bromotrichloromethane encountered problems in separation of the product **5b** from side products by vacuum distillation.[40] Reaction of molecular halogen with the sodium carbanion of a methanediphosphonate ester also is not a practical preparative

method due to formation of product mixtures which are difficult to separate.[24] Direct halogenation of methanediphosphonate using hypohalite reagents[24,25] provided analytically pure samples of the dichloro esters **5a** and **5b**, and of the dibromo esters **7a** and **7b** after H_2O-$CHCl_3$ partitioning and vacuum distillation of the organic evaporate, although isolated yields were not specified.[24] Modified hypohalogenation procedures employing flash chromatography for purification of **5a** and **7a** (isolated in 82% and 78% yields, respectively), were subsequently presented.[30] We confirm alkaline hypochlorite, used at 0°C for a shorter reaction time and in the absence of NaCl,[24] to be efficient in halogenation of **1a** to tetraisopropyl dichloro MDP **5a** (88% isolated yield), and find that extractive work-up using hexane obviates chromatographic purification. The resulting procedure can be applied with comparable success to chlorination of tetraisopropyl MDP monosubstituted with fluorine (**2a**) or bromine (**6a**) to form tetraisopropyl fluorochloro MDP **10a** (93%) and tetraisopropyl chlorobromo MDP **12a** (94%), respectively. Adjustment of the hypochlorite solution pH to 7, which was effective in chlorination of triethyl phosphonoacetate,[35] resulted in recovery of starting material. Hypobromination of **1a** to **7a**[24,25] proved straightforward, and with a slightly modified procedure dibromo product was isolated in 89% yield (pure by ^{31}P NMR) without the intervention of preparative chromatography.[30] This method also smoothly converted the α-monofluoro MDP ester **2a** into the corresponding bromofluoro derivative **11a** (91%), and the monochloro ester **4a** into the bromochloro ester **12a** (94%).



SCHEME 2

The applicability of these procedures to dihalogenation of tetraethyl and tetramethyl methanediphosphonate (**1b** and **1c**) was next examined, taking into account the greater susceptibility of **1b**, and especially of **1c**, to hydrolysis under the alkaline conditions used. Conversion of **1b** to the dichloro ethyl ester **5b** via hypochlorite chlorination has been referred to in the literature.[24] A specific procedure was not given, but use of a two-phase ($H_2O/CHCl_3$) reaction system was mentioned. This approach should allow immediate transfer of the more base-labile, but more hydrophobic, dihalogenated product into the organic phase. However, we did not find a saturated aqueous NaCl-NaOCl/chloroform chlorinating reagent to be convenient for preparation of **5b**. Seyferth and Marmor[25] have described a monophasic reaction procedure for hypochlorination of **1b** using saturated $NaHCO_3$ buffer to avoid base-induced cleavage of **5b**. In our hands, an 85% yield of pure **5b** was obtained using H_2O (0°C) alone as solvent, following extraction and vacuum distillation to remove a low-boiling byproduct. Similar chlorination of **2b** at lower temperature gave the chlorofluoro ester **10b**, which was separated in 81% yield from a side product, diethyl chlorofluoromethanephosphonate **14** by flash chromatography.

The greater sensitivity of dichloro methyl ester **5c** prompted reconsideration of a two-phase (H_2O-$CHCl_3$) solvent system, with careful adjustment of temperature and reaction time; the desired ester was then isolated in 72% yield, with the base cleavage product **13** constituting 21% of the total phosphorus-containing products. The yield of **5c** was further reduced when attempts were made to scale up this procedure. Use of a less polar organic phase (CCl_4) and a more prolonged reaction time gave a 64% isolated yield of **13**, previously prepared by treatment of dichloromethanephosphonyl dichloride[41] with methanol.[42]

$$\underset{\textbf{1c}}{CH_2[P(O)(OCH_3)_2]_2} \xrightarrow[OH^-]{OCl^-} \underset{\textbf{5c}}{CCl_2[P(O)(OCH_3)_2]_2} + \underset{\textbf{13}}{CHCl_2P(O)(OCH_3)_2}$$

SCHEME 3

Treatment of **1b** with aqueous hypobromite at 0°C provided the α-bromo MDP tetraethyl ester **7b** in 85% distilled yield. To prepare the dibromo methyl ester **7c**, we once again resorted to the two-phase[24] system used to make **5c**, attaining a yield of 80% isolated product. This procedure also was not readily scaled up.

The good yields and simplicity of the oxidative halogenations described above recommend subsequent monodehalogenation of a dihalo product as a route to the corresponding monohalo esters. The ability of a number of reducing agents to convert dihalomethanediphosphonate esters such as **5a**, **5b**, **7a**, or **7b** into corresponding monohalo esters (**4a**, **4b**, **6a** or **6b**) was surveyed by Nicholson.[26,27] Na_2S, NaCN/NaOH, $SnCl_2$, Et_3SiH and Na_2SO_3 were briefly explored and found to give variable yields of monohalomethanediphosphonates based on ^{31}P NMR analysis; the products were not isolated.[26] NaSH was described as the preferred reagent for these reductions, although sulfur precipitates as a byproduct; isolated compounds made by this method included **4a**, **4b** and **6a**.[26] However, other workers have recorded their dissatisfaction with this procedure,[30] advocating nucleophilic monodehalogenation as an alternative approach. Among a variety of

halide, hydride and other nucleophiles examined, KF-[18,6]-crown ether dissolved in an aprotic solvent was found to give the best results, although the reaction required 7 days at 60°C.[29] Nucleophilic monodehalogenation using n-butyllithium has also been used to synthesize **6a**.[29,30]

In our hands, reduction of dichloro MDP tetraisopropyl ester **5a** with sodium sulfite in sodium bicarbonate buffer[26] gave a low yield of monochloro MDP ester **4a**. However, we found that by adding more than 2 equivalents of sodium sulfite and using a homogeneous H_2O–EtOH solvent system, a nearly quantitative yield of **4a** was obtained. In reaction with dibromo MDP ester **7a**, sulfite reduction produced completely debrominated product (**1a**). We confirm $SnCl_2$[26] to be selective in the reduction of **7a** to bromo MDP ester **6a** in very good isolated yield. The above methods were readily extended to preparation of the ethyl esters **4b** and **6b** in yields of 94% and 90%, respectively.

Hydrolysis of the α-halo MDP tetraalkyl esters using reflux in concentrated HCl or by treatment with bromotrimethylsilane[10,21,30] produces the corresponding acids. These were converted to tris(dicyclohexylammonium) salts for ease of characterization and convenience of handling (Table IV). The non-hygroscopic salts are white, crystalline solids.

Based on the synthetic procedures elaborated in this study, the α-halo isopropyl MDP esters are the best source of α-halo acids **4d–7d** and **10d–12d**. Apart from the lower cost/easier synthetic accessibility of **1a** *vs.* **1b** and **1c**, the greater stability of the isopropyl compounds to alkaline hypohalogenation conditions is a factor of some importance. This is particularly true relative to the labile methyl esters.

A detailed discussion of NMR spectra of α-halo methanediphosphonate esters, and related compounds, will be given elsewhere,[31] but selected features for the compounds reported here will be briefly noted. The ^1H and ^{13}C NMR data are presented in Tables I and II. As expected, the ^1H chemical shifts of the alkyl ester groups show little variation with differing α-halogen substitution, and the α-H in **4a** (Y = Cl) is slightly more deshielded than the α-H in **6a** (Y = Br).

^{13}C NMR spectral data have not been previously reported for these compounds. The alkyl carbon chemical shifts show little sensitivity to α-halogen substitution, varying over a few ppm within the entire set of esters. The α-carbon resonance is highly sensitive to α-halo substitution varying over a range of some 70 ppm for the esters discussed in this paper between the extremes of **10** and **6**. This signal tends to be very weak in the dihalomethanediphosphonate esters.

In the ^{31}P NMR spectral data (Table III), a trend opposite to that for the α-carbon ^{13}C NMR chemical shift is observed: more electronegative α-halogen substitution produces an upfield shift.[31,43] The ^{19}F NMR data for **10** and **11** (Table III) are consistent with data for compounds of similar structure.[10,31,35]

LITERATURE

1. a) Taken in part from the Ph.D. dissertation of L. A. Khawli (University of Southern California, August, 1986) and from the M.S. dissertation of W.-Y. Ahmad (University of Southern California, December, 1986). b) A preliminary account of this work was given (by C. E. McKenna) at the Second International Symposium on Phosphorus Chemistry Directed Towards Biology, Lodz, Poland, Sept. 8-13, 1986. c) Malaysian Government Fellow on leave from the National University of Malaysia.

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32. At the time this work was presented in preliminary form,[1b] it was also reported that tetraisopropyl diazomethanediphosphonate reacted with N-bromosuccinimide/70% HF/ pyridine to give a 53% yield of **11a**; with N-chlorosuccinimide under similar conditions, a 35% yield of **12a** was obtained. No characterization data were presented for **11a** and **12a**.[33]
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