mL of a 1.0 M solution) at -30 to -35 °C. After addition was complete the solution was stirred for an additional hour at -35 °C. Crude distillation (0 to -10 °C bath temperature) at 0.1 torr into a cooled receiver led to essentially pure CH_2Cl_2 solutions of **4a** (polymers and phosphorus compounds remain behind). According to ^1H NMR spectral analysis the yield amounted to ca. 30%. In order to isolate a sample of **4a**, in analytically pure form, the CH_2Cl_2 was removed in vacuo until about 3-4 mL of a colorless solution remained. A portion was isolated by using GC (SE 30 column at 60 °C; receiver cooled to -78 °C): IR ($CDCl_3$) 3000, 2960, 2860, 2830, 2780, 1715, 1470, 1250, 1220, 1150, 1100; UV (*n*-hexane, qualitative) λ_{max} 225, 252 nm; ^1H NMR ($CDCl_3$, 90 MHz) δ 1.20-1.73 (m, AA'BB' system with δ_A at 1.32 and δ_B at 1.62, J_{gem} = -9.2 Hz, J_{trans} = 5.9 Hz, J_{cis} = 10.3 Hz, 4 H), 2.85 (s, 6 H); ^{13}C NMR ($CDCl_3$ at -10 °C, 25 MHz) δ 1.1, 7.5, 44.9 (br), 138.7; mass calcd for $C_5H_{10}N_2$ 98.0844, found (MS) 98.0845.

Alternatively, **4a** can be synthesized by dehydration of **6**. Triphenylphosphine (11.0 g; 40 mmol) in 100 mL of CH_2Cl_2 was treated with 6.4 g (40 mmol) bromine at 0 °C. To the resulting stirred white suspension was added 81 g (80 mmol) triethylamine. The mixture was cooled to -40 °C, and **6** (3.9 g; 34 mmol) in 3 mL of pentane was added dropwise. The brown mixture was stirred for 2 h at -30 °C and filtered, and the major part of the solvent was removed in vacuo at a temperature below -10 °C. The crude product contained 30-40% of **4a** (volatile **4a** was partially lost during solvent removal). The concentrated solution can be used as it is in further reactions, or solvents and product can be rapidly distilled.

1-(Cyclopropylideneamino)-2,2,6,6-tetramethylpiperidine (4b). The rapidly stirred solution of 16.2 g (60 mmol) of triphenylphosphine in 250 mL of CH_2Cl_2 was treated dropwise with 9.6 g (60 mmol) of bromine at 0 °C. After the suspension was stirred for 30 min, 12.2 g (120 mmol) of triethylamine was added, and the mixture was cooled to -35 °C. Then the cooled (-30 °C) solution of **10** (51 mmol in 50 mL of CH_2Cl_2) was added. The brown mixture was stirred 2 h at -35° C and stored at that temperature overnight. The solvent was removed in vacuo at about 10 °C until a paste-like material was obtained. It was triturated with 300 mL of pentane and filtered. The light brown residue was washed twice with 40 mL of pentane, the combined organic phases were concentrated in vacuo, and the residue was distilled [53 °C (0.1 torr)]. The colorless liquid (6.3 g; 64%) solidified in the refrigerator (mp 21 °C). In a somewhat less efficient procedure, **10** was heated in vacuo at ca. 70 °C (bath temperature), which also led to **4b**: IR (film) 2970, 2920, 2870, 1765, 1460, 1435, 1375, 1360, 1250, 1180, 1130, 1000, 975 cm^{-1}; UV (*n*-hexane) λ_{max} 216 (ϵ 1700), 332 (90) nm; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.03 (s, 12 H), 1.41-1.61 (m, 10 H); ^{13}C NMR ($CDCl_3$, 25 MHz) δ 4.0 (t), 6.8 (t), 17.6 (t), 26.8 (q), 40.0 (t), 57.0 (s), 165.0 (s); MS (70 eV), *m/e* (relative intensity) 194 (27, M^+), 179 (21), 151 (18), 140 (12), 125 (27), 97 (14), 83 (31), 70 (24), 69 (100), 58 (55), 56 (27), 55 (71), 44 (18), 43 (20), 42 (69). Anal. Calcd for $C_{12}H_{22}N_2$: C, 74.17; H, 11.41; N, 14.42. Found: C, 74.06; H, 11.67; N, 14.37.

1-[(2-(Trimethylsilyl)cyclopropylidene)amino]-2,2,6,6-tetramethylpiperidine (12a). To a stirred solution of lithium diisopropylamide (prepared at 0 °C from 330 mg (3.3 mmol) diisopropylamine in 25 mL dry THF and 1.9 mL of a 1.6 M solution of *n*-butyllithium) was added 585 mg (3.0 mmol) of **4b** at -78 °C under an atmosphere of N_2. After the mixture was stirred for 30 min at -78 °C, 350 mg (3.2 mmol) of chlorotrimethylsilane were slowly added. The stirred colorless solution was allowed to come to room temperature overnight, the solvent was removed in vacuo, 40 mL of pentane was added, and the solution was filtered. The solvent was stripped off in vacuo (0.5 torr), leaving a colorless oil **12a** (710 mg; 89%) which was essentially pure. A small portion was obtained in analytically pure form by GC (SE 30 column; 140 °C). The NMR spectra show that **12a** consists of a 2:1 mixture of *E/Z* isomers (the major isomer probably *E*): IR (film) 2970, 2930, 1750, 1435, 1370, 1360, 1250, 1180, 1130, 1105, 1025, 870, 840, 520 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 0.10, 1.02, 1.06, 1.15-1.60; ^{13}C NMR ($CDCl_3$, 25 MHz) δ -1.8, 5.9, 9.0, 11.7, 17.6, 17.7, 26.8, 27.1, 27.2, 27.5, 40.0, 40.4, 56.8, 57.5, 165.6, 166.7; FI-MS, *m/e* (relative intensity) 266 (100, M^+), 117 (4), 73 (5). Anal. Calcd for $C_{15}H_{30}N_2Si$: C, 67.60; H, 11.35; N, 10.51. Found: C, 67.52; H, 10.65; N, 10.54.

1-[(2-Methylcyclopropylidene)amino]-2,2,6,6-tetramethylpiperidine (12b). *tert*-Butyllithium (6.3 mL of a 1.6 M solution in hexane) was mixed with 40 mL of dry ether at -78 °C under an atmosphere of N_2. To the stirred solution was added 1.94 g 10.0 mmol) of **4b**, resulting in a white precipitate. After the mixture was stirred for 2 h at -78 °C, 20 mL of dry THF was added, which resulted in an almost clear solution. Methyl iodide (1.65 g, 11.7 mmol) was added dropwise, and the solution was stirred for 1.5 h at -78 °C and then overnight during which room temperature was reached. The clear colorless mixture was concentrated in vacuo, 60 mL of pentane was added, and the solids were removed by filtration. After removal of the solvent, distillation (15-cm Vigreux column) at 50-52 °C (0.1 torr) afforded 1.16 g (56%) of **12a** as a 2.5:1 mixture of isomers: IR (film) 2980, 2930, 2860, 1765, 1460, 1375, 1360, 1250, 1180, 1130, 975 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 1.03 (s), 1.19 (d, J = 8.5 Hz), 1.30 (d, J = 5.9 Hz), 1.47-2.05 (m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 11.4 (t), 11.7 (d), 13.9 (t), 14.4 (d), 15.8 (q), 16.3 (q), 17.6 (t), 17.7 (t), 26.9 (q), 40.1 (t), 40.3 (t), 56.6 (s), 56.7 (s), 170.0 (s), 170.5 (s); MS (70 eV), *m/e* (relative intensity) 208 (10, M^+), 193 (6), 151 (25), 125 (11), 84 (18), 83 (28), 70 (15), 69 (100), 58 (34), 57 (17), 56 (25), 55 (56), 43 (10), 42 (16), 41 (45). Anal. Calcd for $C_{13}H_{24}N_2$: C, 74.94; H, 11.61; N, 13.45. Found: C, 74.82; H, 11.77; N, 13.46.

1-[(2,2-Bis(trimethylsilyl)cyclopropylidene)amino]-2,2,6,6-tetramethylpiperidine (13). Diisopropylamine (750 mg, 7.4 mmol) in 50 mL of dry THF was treated with 4.0 mL of a 1.6 M solution of *n*-butyllithium in hexane (6.4 mmol) at 0 °C. After 15 min the solution was cooled to -78 °C, and 585 mg (3.0 mmol) of **4b** was added. The mixture remained clear and colorless. Then 690 mg (6.4 mmol) of chlorotrimethylsilane was added, and the stirred solution was allowed to reach room temperature overnight. After removal of the solvent in vacuo, 50 mL of pentane was added, and the mixture was stirred and finally filtered and concentrated. Kugelrohr distillation [150 °C (0.1 torr)] afforded 780 mg (77%) of **13** as a colorless oil, which was essentially pure. **13** exists as a single isomer, probably as shown. Additional purification can be accomplished by GC (SE 30 column, 150 °C): IR (film) 2960, 2940, 2880, 1740, 1380, 1270, 1260, 1180, 1140, 1120, 1040, 870, 850 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 0.1 (s, 18 H), 1.05 (s, 12 H), 1.40 (s, 2 H), 1.54 (mc, 6 H); ^{13}C NMR ($CDCl_3$, 25 MHz) δ -0.5 (q), 6.0 (s), 12.9 (t), 17.6 (t), 27.4 (q), 40.3 (t), 57.2 (s), 164.0 (s); FI-MS, *m/e* (relative intensity) 338 (100, M^+), 267 (19), 266 (60), 213 (11), 197 (12), 125 (16), 73 (22). Anal. Calcd for $C_{18}H_{38}N_2Si_2$: C, 63.83; H, 11.31; N, 8.27. Found: C, 62.45; H, 11.12; N, 8.58.

Reaction of 4a with H_2O and CH_3OH. A solution of **4a** in chloroform was shaken with H_2O for several minutes and the mixture allowed to stand for 1 day at room temperature. Inspection of the organic phase by NMR spectroscopy showed the presence of about 60% of unreacted **4a**. A similar result was obtained by treatment with CH_3OH.

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Synthesis of Halogenated Phosphonoacetate Esters[1]

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Phosphonoacetate (PAA) derivatives are of interest for a variety of reasons, including their connection with antiviral activity.[2,3] Consequently, we have investigated

(1) Presented at the 191st National Meeting of the American Chemical Society, New York City, NY, April 13-18, 1986; Abstr. ORGN 330.
(2) Shipkowitz, N. L.; Bower, R. R.; Appel, R. N.; Nordeen, C. W.; Overby, L. R. *Appl. Microbiol.* **1973**, *26*, 264.

0022-3263/86/1951-5467$01.50/0

Table I. Et_3PAA Derivatives: ^1H and ^{13}C NMR Spectral Data

compound	^1H, δ (J in Hz)[a]	^{13}C, δ (J in Hz)
Et_3Cl_2PAA	1.37 (m, 3 CH_3)	13.6 (q, $^1J_{CH}$ = 125, CH_3[CO])
6	4.35 (m, 3 CH_2)	16.2 (q, $^1J_{CH}$ = 125, $^3J_{CP}$ = 6, 2 CH_3[PO])
		64.3 (t, $^1J_{CH}$ = 145, CH_2[CO])
		66.1 (t, $^1J_{CH}$ = 158, $^2J_{CP}$ = 7, 2 CH_2[PO])
		74.6 (d, $^1J_{CP}$ = 166, CCl_2)
		163.3 (d, $^2J_{CP}$ = 4, C=O)
Et_3Br_2PAA	1.35 (m, 3 CH_3)	13.6 (q, $^1J_{CH}$ = 120, CH_3[CO])
7	4.37 (m, 3 CH_2)	16.3 (q, $^1J_{CH}$ = 120, $^3J_{CP}$ = 5, 2 CH_3[PO])
		47.0 (d, $^1J_{CP}$ = 159, CBr_2)
		64.4 (t, $^1J_{CH}$ = 149, CH_2[CO])
		66.2 (t, $^1J_{CH}$= 159, $^2J_{CP}$ = 7, 2 CH_2[PO])
		163.7 (d, $^2J_{CP}$ = 4, C=O)
Et_3ClPAA	1.32 (m, 3 CH_3)	13.8 (q, $^1J_{CH}$ = 125, CH_3[CO])
3	4.28 (m, 3 CH_2)	16.1 (q, $^1J_{CH}$ = 125, $^3J_{CP}$ = 6, 2 CH_3[PO])
	4.47 (d, $^2J_{HP}$ = 16.3, CHCl)	50.1 (dd, $^1J_{CH}$ = 150, $^1J_{CP}$ = 146, CHCl)
		62.8 (t, $^1J_{CH}$ = 146, CH_2[CO])
		64.4 (t, $^1J_{CH}$ = 150, $^3J_{CP}$ = 6, 2 CH_2[PO])
		164.7 (s, C=O)
Et_3BrPAA	1.32 (m, 3 CH_3)	13.7 (q, $^1J_{CH}$ = 124, CH_3[CO])
4	4.25 (m, 3 CH_2)	16.2 (q, $^1J_{CH}$ = 124, $^3J_{CP}$ = 6, 2 CH_3[PO])
	4.33 (d, $^2J_{HP}$ = 14.1 CHBr)	35.7 (dd, $^1J_{CH}$ = 150, $^1J_{CP}$ = 146, CHBr)
		62.9 (t, $^1J_{CH}$ = 146, CH_2[CO])
		64.5 (t, $^1J_{CH}$ = 148, $^3J_{CP}$ = 6, 2 CH_2[PO])
		164.9 (s, C=O)
$Et_3ClBrPAA$	1.34 (m, 3 CH_3)	13.7 (q, $^1J_{CH}$ = 127, CH_3[CO])
10	4.34 (m, 3 CH_2)	16.3 (q, $^1J_{CH}$ = 127, $^3J_{CP}$ = 6, 2 CH_3[PO])
		61.3 (d, $^1J_{CP}$ = 163, CClBr)
		64.5 (t, $^1J_{CH}$ = 153, CH_2[CO])
		66.3 (t, $^1J_{CH}$ = 154, $^2J_{CP}$ = 7, 2 CH_2[PO])
		163.8 (s, C=O)
$Et_3FClPAA$	1.35 (m, 3 CH_3)	13.8 (q, $^1J_{CH}$ = 128, CH_3[CO])
8	4.25 (m, 3 CH_2)	16.2 (q, $^1J_{CH}$ = 128, $^3J_{CP}$ = 6, 2 CH_3[PO])
		63.8 (t, $^1J_{CH}$ = 150, CH_2[CO])
		65.8 (t, $^1J_{CH}$ = 150, $^2J_{CP}$ = 7, 2 CH_2[PO])
		98.3 (dd, $^1J_{CF}$ = 268, $^1J_{CP}$ = 184, CFCl)
		163.2 (dd, $^2J_{CF}$ = 26, $^2J_{CP}$ = 10, C=O)
$Et_3FBrPAA$	1.35 (m, 3 CH_3)	13.4 (q, $^1J_{CH}$ = 127, CH_3[CO])
9	4.30 (m, 3 CH_2)	16.1 (q, $^1J_{CH}$ = 128, $^3J_{CP}$ = 5, 2 CH_3[PO])
		63.5 (t, $^1J_{CH}$ = 151, CH_2[CO])
		65.5 (t, $^1J_{CH}$ = 151, $^2J_{CP}$ = 7, 2 CH_2[PO])
		89.7 (dd, $^1J_{CF}$ = 267, $^1J_{CP}$ = 178, CFBr)
		163.6 (dd, $^2J_{CF}$ = 25, $^2J_{CP}$ = 10, C=O)
Et_3ClPPA	1.32 (m, 3 CH_3)	13.7 (q, $^1J_{CH}$ = 127, CH_3[CO])
13	1.92 (d, $^3J_{HP}$ = 14.6, CH_3)	16.2 (q, $^1J_{CH}$ = 124, $^3J_{CP}$ = 6, 2 CH_3[PO])
	4.27 (m, 3 CH_2)	24.9 (q, $^1J_{CH}$ = 135, CH_3CCl)
		62.0 (d, $^1J_{CP}$ = 152, CH_3CCl)
		62.8 (t, $^1J_{CH}$ = 144, CH_2[CO])
		64.4 (t, $^1J_{CH}$ = 149, $^2J_{CP}$ = 7, 2 CH_2[PO])
		167.4 (s, C=O)
Et_3BrPPA	1.32 (m, 3 CH_3)	13.6 (q, $^1J_{CH}$ = 127, CH_3[CO])
14	2.06 (d, $^3J_{HP}$ = 14.6, CH_3)	16.2 (q, $^1J_{CH}$ = 125, $^3J_{CP}$ = 6, 2 CH_3[PO]
	4.25 (m, 3 CH_2)	24.9 (q, $^1J_{CH}$ = 134, CH_3CBr)
		50.7 (d, $^1J_{CP}$ = 150, CH_3CBr)
		62.7 (t, $^1J_{CH}$ = 148, CH_2[CO])
		64.4 (t, $^1J_{CH}$ = 149, $^2J_{CP}$ = 7, 2 CH_2[PO]
		167.5 (s, C=O)

[a] δ values for CH_3/CH_2 resonances are given for multiplet midpoints.

preparation of the entire family of stable α-halogenated PAA triesters $EtO_2CCXYP(O)(OEt)_2$, where X = H, F, Cl, or Br and Y = F, Cl, or Br. These compounds would serve as convenient starting points for synthesis of the corresponding acids, salts, and similar derivatives.

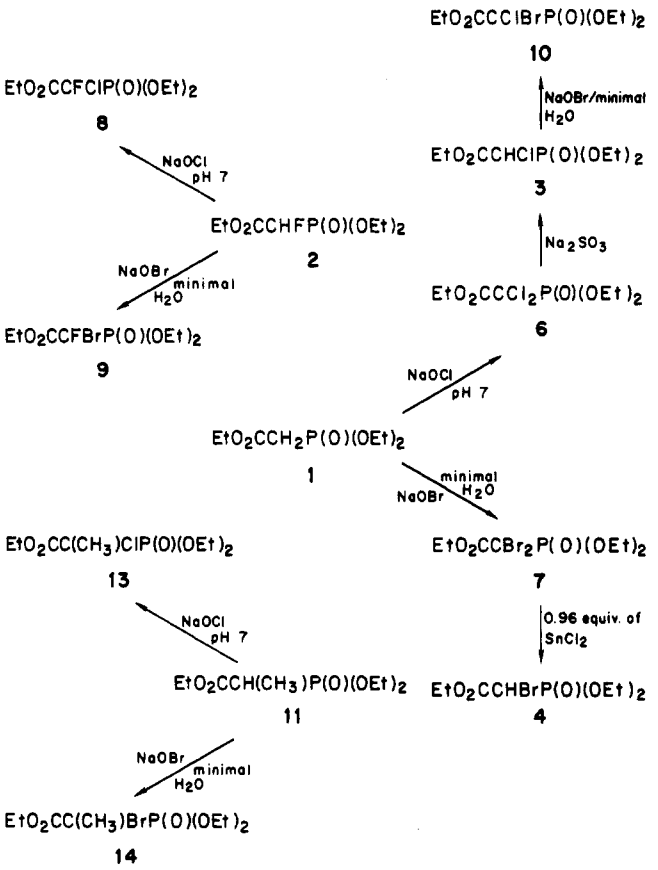
Conversion of triethyl PAA **1** into the monofluoro and difluoro PAA esters **2** (X, Y = H, F) and **5** (X, Y = F, F) is conveniently effected in good yield by treatment of the potassium carbanion of **1** with perchloryl fluoride[4a,b] using a modification of conditions previously described for the analogous fluorination of tetraalkyl methanediphosphonates.[5] However, examination of the literature reveals that several of the remaining possible halogenated PAA esters have never been described, while for others the available synthetic procedures are not fully satisfactory. We report here detailed methods for preparation in high yield of every chlorine- and bromine-containing member of this important group of compounds: the monochloro and monobromo triethyl esters **3** (X, Y = H, Cl) and **4** (X, Y = H, Br), the dichloro and dibromo triethyl esters **6** (X, Y = Cl, Cl) and **7** (X, Y = Br, Br), and the mixed halogenated triethyl esters **8** (X, Y = F, Cl), **9** (X, Y = F, Br), and **10** (X, Y = Cl, Br) (Scheme I). We also report ap-

(3) Boezi, J. A. *Pharmacol. Ther.* **1979**, *4*, 231.

(4) (a) McKenna, C. E.; Khawli, L. A.; submitted for publication. (b) Preliminary account: International Conference on Phosphorus Chemistry, Nice, France, Sept. 1–5, 1983; Abstr. 121. See: McKenna, C. E.; Khawli, L. A. *Phosphorus Sulfur* **1983**, *18*, 483.

(5) McKenna, C. E.; Shen, P. D. *J. Org. Chem.* **1981**, *46*, 4573.

Scheme I



plication of these procedures to preparation from triethyl phosphonopropionate (PPA, **11**) of the α-halogenated PPA triethyl esters $EtO_2CC(CH_3)XP(O)(OEt)_2$ **13** (X = Cl) and **14** (X = Br) (the α-fluoro derivative **12** is reported elsewhere[4a]). Aside from their intrinsic interest as α-methyl substituted PAA esters, these structures provide models for more lipophilic α-alkyl α-halo PAA derivatives. Comprehensive (^1H, ^{13}C, ^{31}P, (^{19}F)) NMR spectral data are provided for compounds **3**, **4**, **6–10**, **13**, and **14** (Table I, Table II).

Although the preparation of halogenated triethyl PAA derivatives has not been previously studied on a systematic basis, several authors have investigated routes to analogous tetraalkyl α-halomethanediphosphonates. Nicholson and Vaughn[6] considered three approaches proposed earlier: Michaelis–Arbuzov condensation of a trialkyl phosphite with a trihalobromomethane,[7] reaction of molecular halogen with the sodium carbanion of a methanediphosphonate ester,[8] and direct halogenation of the latter using hypohalite reagent.[8] They noted that the first two methods gave mixtures posing separation problems, while reaction with hypobromite or hypochlorite gave good yields of dibromo- or dichloromethanediphosphonates. These authors reported that NaSH reduction then provided the corresponding monobromo and monochloro compounds. A number of alternate reducing agents (NaCN/NaOH, $SnCl_2$, Et_3SiH and Na_2SO_3) were briefly explored and found to give fair to poor yields of monohalomethanediphosphonates based on ^{31}P NMR analysis; the products were not isolated. The synthesis of tetraethyl chloromethanediphosphonate by reaction of the dichloro ester with 1 equiv of *n*-butyllithium has also been described.[9] More recently, Hutchinson and Semple[10] have reported nucleophilic monodehalogenation of tetraalkyl dihalomethanediphosphonates with potassium fluoride in acetonitrile containing [18,6]-crown ether, in a reaction requiring 7 days followed by chromatographic workup. Inferior results were obtained with a number of other nucleophiles. These authors reexamined the reductive (NaSH) monodehalogenation route cited above,[6] but found it to be unsatisfactory for preparative purposes.[10]

Table II. Et_3PAA Derivatives: ^{31}P and ^{19}F NMR Spectral Data

compound	^{31}P, δ (*J* in Hz)	^{19}F, δ (*J* in Hz)
Et_3Cl_2PAA **6**	8.04 (p, $^3J_{PH}$ = 8)	
Et_3Br_2PAA **7**	8.45 (p, $^3J_{PH}$ = 8)	
Et_3ClPAA **3**	13.04 (m, $^2J_{PH}$ = 16, $^3J_{PH}$ = 8)	
Et_3BrPAA **4**	13.24 (m, $^2J_{PH}$ = 16, $^3J_{PH}$ = 8)	
$Et_3ClBrPAA$ **10**	8.41 (p, $^3J_{PH}$ = 8)	
$Et_3FClPAA$ **8**	5.55 (dp, $^2J_{PF}$ = 85, $^3J_{PH}$ = 8)	−137.0 (d, $^2J_{FP}$ = 85)
$Et_3FBrPAA$ **9**	5.62 (dp, $^2J_{PF}$ = 80, $^3J_{PH}$ = 8)	−140.9 (d, $^2J_{FP}$ = 80)
Et_3ClPPA **13**	16.65 (m, $^3J_{PH}$ = 15, $^3J_{PH}$ = 8)	
Et_3BrPPA **14**	16.95 (m, $^3J_{PH}$ = 15, $^3J_{PH}$ = 8)	

In a few cases, extension of some of these synthetic methods to preparation of halogenated phosphonoacetates has been briefly examined.[6] Thus, the simplest route to the dichloro and dibromo PAA esters **6** and **7** should be oxidative halogenation of a trialkyl phosphonoacetate by using the appropriate hypohalite reagent. Nicholson and Vaughn[6] have reported the preparation of **6** by treating **1** with aqueous alkaline hypochlorite. In our hands, this reaction was not satisfactory. A ^{31}P NMR analysis of the reaction mixture revealed the presence of two phosphorus-containing side products in addition to the dichloro PAA product ester. However, we found that by adjusting the hypochlorite reagent pH to 7 and moderating the reaction temperature, a nearly quantitative yield of **6** was obtained in an exceptionally clean reaction. The modified procedure was applied with comparable success to chlorination of triethyl PAA monosubstituted with an electron-donating (methyl, **11**) or electron-withdrawing (fluorine, **2**) substituent to form triethyl chloro PPA **13** and triethyl chlorofluoro PAA **8**, respectively. In the parallel reaction of triethyl PAA with hypobromite,[6] we were able to increase the isolated yield to 93% and improve product purity significantly by minimizing unwanted hydrolysis of the product dibromo triester **7** to diethyl dibromo PAA. This was accomplished by adjusting the organic:aqueous volume ratio in the biphasic reaction mixture and maintaining the temperature near 0 °C as specified in the Experimental Section. The resulting procedure also smoothly converted the α-fluoro, α-chloro, and α-methyl esters **2**, **3** and **11** into the corresponding α-bromo derivatives **9**, **10**, and **14** (90–98% yield).

There is some advantage in following the sequence **1** → **6** → **3** → **10** that we describe here, rather than the alternative route **1** → **7** → **4** → **10**. This arises from the fact that reduction of the dichloro ester **6** to **3** requires less

(6) Nicholson, D. A.; Vaughn, H. *J. Org. Chem.* **1971**, *36*, 1835. Cf. Nicholson, D. A. U.S. Pat. 3627842, 1971.
(7) Bunyan, P. J.; Cadogan, J. I. G. *J. Chem. Soc.* **1962**, 2953.
(8) Quimby, O. T.; Curry, J. D.; Nicholson, D. A.; Prentice, J. B.; Roy, C. H. *J. Organomet. Chem.* **1968**, *13*, 199. Cf. Quimby, O. T.; Prentice, J. B. U.S. Pat. 3772412, 1973.
(9) Seyferth, D.; Marmor, R. S. *J. Organomet. Chem.* **1973**, *59*, 237.
(10) Hutchinson, D. W.; Semple, G. *Phosphorus Sulfur* **1984**, *21*, 1.

careful control of reaction conditions to ensure a pure product than the reduction of **7** to **4**, as discussed below. Fluorination[4a,b] of **3** and **4** is possible as an alternative synthesis of the fluorohalo esters **8** and **9** but entails one more step starting from **1** than our preferred route.

The high yield and simplicity of these oxidative halogenations suggest a subsequent selective reduction to convert the dichloro or dibromo products to the corresponding monohalo esters. We confirmed sodium sulfite[6] to be efficaciously selective in the reduction of **6** to triethyl chloro PAA **3**.[11] The pure monochloro product is obtained by extraction from hexane into aqueous $NaHCO_3$, followed by reextraction into $CHCl_3$. The small amount of unreacted **6** is quantitatively retained in the hexane. However, sulfite is not useful for preparation of monobromo ester **4** from triethyl dibromo PAA **7**, which is completely debrominated. Several alternate preparations of **4** have been previously explored. Reduction of **7** with NaSH provided less than 4% of **4**, while reduction with SnF_2 resulted in a mixture from which the monobromo product could not be separated;[6] treatment of sodium triethyl PAA carbanion with bromine was reported to give a moderate yield of **4**.[14,15] We found that reduction of **7** with *nearly* 1 equiv of $SnCl_2$ in a homogeneous aqueous ethanol solution readily gave the desired monobromo ester **4** in an isolated yield of 85%. Excess reductant caused removal of both bromine atoms.

An important practical detail in the synthesis of **4** is the use of slightly less than 1 equiv of reductant, ensuring that no double debromination to **1** occurs. The small amount of unreacted dibromo starting material **7** is easily removed by partitioning between hexane and H_2O, while **1**, if formed, follows the monobromo product into the aqueous phase and cannot be easily separated by a simple extractive process.

A full discussion of the NMR spectra that we have determined for the α-halogenated phosphonoacetates will not be given here,[17] but selected aspects that are helpful in characterization of the compounds will be noted briefly. The ^1H and ^{13}C NMR data are presented in Table I. As expected, the ^1H chemical shifts of the ester alkyl groups show little variation, but the signals appear as particularly complex multiplets in the racemic esters **3**, **4**, **8**, **9**, **10**, **13**, and **14** because in these compounds all six alkyl methylene protons are diastereotopic, as are the two sets of P–O–Et methyl protons. In those PAA esters that have a methine proton, such as **3** or **4**, the diagnostic value of ^1H NMR is enhanced. The NMR spectral data in Table I also illustrate the sensitivity of the α-carbon atom ^{13}C chemical shift to α-halo substitution, although this signal tends to be weak and of variable strength, depending on the nature of the substituents.

In characterizing the α-fluoro esters, ^{19}F NMR spectra (Table II) are naturally of value. However, ^{31}P NMR is the most generally useful method in monitoring the synthesis and isolation of PAA derivatives. ^{31}P NMR chemical shifts have been previously reported[6] at low frequency (24.3 MHz) for **4** (in a crude reaction mixture), **6**, and **7**. Making allowance for slight concentration effects, our data (Experimental Section; summarized in Table II) show a trend generally consistent with predicted shielding effects of different α-halogen substituents.[18] Relative to **1**, introduction of bromine and chlorine gives similar upfield shifts, with chlorine producing the slightly greater change, while fluorine causes a more pronounced shift upfield.[4a,b,18] In the presence of an α-Me substituent, a similar trend is observed.

In conclusion, we present here simple, general,[19] rapid, and high-yield procedures that taken with a complementary fluorination method[4a,b] make available from triethyl PAA or triethyl PPA the integral family of their fluoro, chloro, and bromo α-substituted derivatives.[20]

Experimental Section

All solvents were analytical grade. Triethyl phosphonoacetate and triethyl 2-phosphonopropionate were purchased from Aldrich Chemical Co. Sodium hypochlorite (5.25%) was purchased as "Clorox bleach" from a local market. Proton (^1H, 270.13 MHz), carbon (^{13}C, 67.92 MHz), phosphorus (^{31}P, 109.35 MHz), and fluorine (^{19}F, 254.17 MHz) NMR spectra were measured on a Bruker WP-270SY spectrometer. NMR samples were 5% w/v in $CDCl_3$. Chemical shifts are reported relative to external Me_4Si (^1H), internal $CDCl_3$ (δ = 77.0; ^{13}C), external 85% H_3PO_4 (^{31}P), or external $CFCl_3$ (^{19}F). All chemical shifts upfield of the reference are given as negative values. Elemental analyses were performed by Galbraith Laboratories.

Chlorinations Using Sodium Hypochlorite. Triethyl Dichlorophosphonoacetate (6). A solution of 5.25% sodium hypochlorite (316 g, 223 mmol) was adjusted to pH 7.1 with approximately 20 mL of 3 N HCl. Triethyl phosphonoacetate (10 g, 44.6 mmol) was added dropwise at ice-bath temperature with vigorous stirring. After complete addition, the ice-bath was removed, and stirring was continued for an additional 5 min. The turbid solution was extracted with 5 × 50 mL of hexane. The combined hexane extracts were dried ($MgSO_4$), and the solvent was removed in vacuo at 50 °C to give triethyl dichlorophosphonoacetate in 95% yield (12.5 g) which was vacuum distilled to give a colorless oil, bp 84–86 °C (0.01 mm): ^{31}P NMR ($CDCl_3$) δ = 8 ppm (p) (lit.[6] 7.5 ppm). Anal. Calcd for $C_8H_{15}O_5Cl_2P$: C, 32.78; H, 5.16. Found: C, 32.78; H, 5.23 (cf. lit. value[6] found for C: −0.7%).

Extraction of the reaction mixture with 2 × 50 mL chloroform gave a residue having a single ^{31} P resonance at δ = 21 ppm, identifying it as starting material (triethyl phosphonoacetate). The recovered yield (5%) confirmed the absence of side products.

Triethyl Chlorofluorophosphonoacetate (8). In a similar reaction, triethyl chlorofluorophosphonoacetate was obtained from 5.25% sodium hypochlorite (30 g, 21.2 mmol, pH 7.1) and triethyl fluorophosphonoacetate[4a,b] (0.9 g, 3.7 mmol). The product (90%) was vacuum distilled to yield a colorless oil, bp 88–90 °C (0.01 mm): ^{31}P NMR ($CDCl_3$) δ = 5.5 ppm (dp). Anal. Calcd for $C_8H_{15}O_5PClF$: C, 34.73; H, 5.46. Found: C, 34.58; H, 5.72.

Triethyl 2-Chlorophosphonopropionate (13). In a similar reaction, triethyl 2-chlorophosphonopropionate was obtained from 5.25% sodium hypochlorite (315 g, 222 mmol, pH 7.2) and triethyl 2-phosphonopropionate (10 g, 42.0 mmol). The product was isolated in 92% yield and vacuum distilled to give a colorless oil, bp 83–85 °C (0.01 mm): ^{31}P NMR ($CDCl_3$) δ = 16.6 ppm (m). Anal. Calcd for $C_9H_{18}O_5PCl$: C, 39.64; H, 6.65. Found: C, 39.36; H, 6.74.

(11) Other reported routes to monochloro ester **3** include ethoxycarbonylation of diethyl 1,1-dichloro-1-lithiomethanephosphonate/*n*-butyllithium with ethyl chloroformate[12] and reaction of a 1,2-dichloro-2-ethoxyvinylphosphonic acid derivate with ethanol.[13]

(12) Villieras, J.; Perriot, P.; Normant, J. F. *Synthesis* **1978**, *31*.

(13) Ismailov *et al. Izv. Vyssh. Uchebn. Zaved., Khim. Khim. Tekhnol.* **1977**, *20*, 824; *Chem. Abstr.* **1977**, *87*, 748.

(14) Grinev. G. V.; Chervenyuk, G. I.; Dombrovskii, A. V. *Zh. Obshch. Khim.* **1968**, *39*, 1253.

(15) Carbanion made by reaction of **1** with Na; in a similar, in situ preparation the carbanion was prepared from **1** and NaH.[16]

(16) Wadsworth, W. S.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733.

(17) A detailed analysis of ^1H, ^{13}C, ^{19}F, and ^{31}P NMR chemical shift and coupling constant correlations in halogenated phosphonoacetates and related compounds will be presented elsewhere.[18]

(18) McKenna, C. E.; Khawli, L. A., to be submitted for publication.

(19) McKenna, C. E.; Khawli, L. A.; Bongartz, J. P.; Pham, P.; Ahmad, W. Y., to be submitted for publication.

(20) We have not discussed preparation of Et_3 *α-iodo* PAA derivatives in this note, due to their instability.[18] For corresponding acids, see: Khawli, L. A. Ph.D. Dissertation, University of Southern California, August 1986; also ref 4a,b and ref 21.

(21) McKenna, C. E.; Khawli, L. A.; Cheng, Y.-C.; Bapat, A., submitted for publication.

Brominations Using Sodium Hypobromite. Preparation of Sodium Hypobromite. A solution of sodium hydroxide (20 g, 0.5 mol) in H_2O (60 mL) was prepared in a 200-mL, three-necked, round-bottomed flask fitted with a thermometer and a dropping funnel. The solution was cooled to 0 °C in an ice–salt bath, and bromine (40 g, 12.81 mL, 0.25 mol) was slowly added with stirring over 25 min at a rate such that the temperature did not exceed 10 °C.

Triethyl Dibromophosphonoacetate (7). Triethyl phosphonoacetate (12 g, 53.5 mmol) was added over 3 min to the freshly prepared, stirred sodium hypobromite solution cooled in an ice–salt bath. The temperature was maintained below 10 °C. When addition was complete, the mixture was immediately extracted with chloroform (4 × 100 mL). The chloroform extracts were washed with water (2 × 20 mL) and dried ($MgSO_4$), and the solvent was removed in vacuo. ^{31}P NMR analysis of the residue showed that triethyl dibromophosphonoaceate (7) (δ = 8.4 ppm) made up 95% of the phosphorus-containing products; the remaining 5% was accounted for by a compound with δ = 10.5 ppm. The identity of this minor side product was not determined.

The residue was partitioned between hexane (400 mL) and H_2O (2 × 5 mL), and the hexane extracts were dried ($MgSO_4$). Removal of the solvent in vacuo left pure triethyl dibromophosphonoacetate (93%) which was vacuum distilled to give a colorless oil, bp 104–106 °C (0.01 mm): ^{31}P NMR ($CDCl_3$) δ = 8.4 ppm (p) (lit.[6] 7.0 ppm). Anal. Calcd for $C_8H_{15}O_5Br_2P$: C, 25.15; H, 3.96. Found: C, 25.20; H, 3.70.

Triethyl 2-Bromophosphonopropionate (14). In a similar reaction, a solution of sodium hypobromite was prepared by mixing NaOH (10 g, 0.25 mol) in H_2O (35 mL) with bromine (20 g, 6.4 mL, 0.125 mol). Triethyl 2-phosphonopropionate (6 g, 25 mmol) was then added over 2 min, and the resulting mixture was immediately extracted with chloroform (3 × 100 mL). The product was isolated in 98% yield; on vacuum distillation it was obtained as a colorless oil, bp 116–118 °C (0.01 mm): ^{31}P NMR ($CDCl_3$) δ = 16.9 ppm (m). Anal. Calcd for $C_9H_{18}O_5BrP$: C, 34.08; H, 5.72. Found: C, 33.83; H, 5.59.

Triethyl Bromochlorophosphonoacetate (10). The sodium hypobromite reagent was prepared by mixing a solution of 4.8 g (0.12 mol) of NaOH in 16 mL H_2O with bromine (9.76 g, 0.06 mol). Triethyl chlorophosphonoacetate (3) (3.18 g, 0.012 mol) was then added over 2 min and the resulting mixture was immediately extracted with chloroform (3 × 75 mL). The product was isolated (96%) by evaporation of the solvent at reduced pressure. It was obtained by vacuum distillation as a colorless oil, bp 103–105 °C (0.01 mm): ^{31}P NMR ($CDCl_3$) δ = 8.4 ppm (p). Anal. Calcd for $C_8H_{15}O_5BrClP$: C, 28.46; H, 4.47. Found: C, 28.14; H, 4.29.

Triethyl Bromofluorophosphonoacetate (9). The sodium hypobromite reagent was prepared as described above from 1.6 g (40 mmol) NaOH, 5.3 mL of H_2O, and 3.2 g (20 mmol) of bromine. Triethyl fluorophosphonoacetate (1 g, 4 mmol) was then added, and the resulting mixture was immediately extracted with chloroform (3 × 25 mL). The combined chloroform extracts were dried ($MgSO_4$) and evaporated at reduced pressure, yielding a residue containing 9 (δ = 5.6 ppm, 92%), starting material (2) and an unidentified minor side product (δ = –0.2 ppm). The crude product was partitioned between hexane (50 mL) and H_2O (3 × 15 mL); the organic phase was then dried ($MgSO_4$) and evaporated at reduced pressure to give 1.1 g (90%) of pure 9. Vacuum distillation provided an analytical sample as a colorless oil, bp 101–102 °C (0.01 mm): ^{31}P NMR ($CDCl_3$) δ = 5.6 ppm (dp). Anal. Calcd for $C_8H_{15}O_5BrFP$: C, 29.92; H, 4.70. Found: C, 30.08; H, 4.70.

Dehalogenation of Dihalophosphonoacetates. Triethyl Chlorophosphonoacetate (3). Triethyl dichlorophosphonoaceate (11.2 g, 38.2 mmol) was dissolved in EtOH (75 mL), and the resulting solution was cooled in an ice bath. A solution of sodium sulfite (9.64 g, 76.5 mmol) in H_2O (300 mL) was added with stirring at a rate such that the temperature could be maintained below 15 °C (15 min). During addition the reaction mixture became turbid; after 20 min of further stirring at room temperature, it was extracted with chloroform (5 × 100 mL). The chloroform extracts were dried ($MgSO_4$), and the solvent was removed in vacuo. ^{31}P NMR of the residue showed that triethyl chlorophosphonoacetate (δ = 13 ppm) made up 97% of the phosphorus-containing products, the remainder being starting material 6 (δ = 8 ppm).

The crude mixture was partitioned between hexane (200 mL) and 0.1 M $NaHCO_3$ (8 × 50 mL). The bicarbonate fractions were combined and reextracted with chloroform (6 × 50 mL). The chloroform extracts were dried ($MgSO_4$), and the solvent was removed in vacuo to give 9.4 g of pure triethyl chlorophosphonoacetate (95%). Vacuum distillation provided the product as a colorless oil, bp 93–95 °C (0.01 mm): ^{31}P NMR ($CDCl_3$) δ = 13.0 ppm (m) (lit.[5] 12.0 ppm). Anal. Calcd for $C_8H_{16}O_5ClP$: C, 37.15; H, 6.23. Found: C, 36.97; H, 6.36.

Triethyl Bromophosphonoacetate (4). To triethyl dibromophosphonoacetate (10 g, 26 mmol) dissolved in EtOH (25 mL) was added with cooling (ice bath) a solution of 5.60 g (25 mmol) of $SnCl_2 \cdot 2H_2O$ in H_2O (50 mL). The temperature was maintained below 10 °C. When addition was complete (20 min), the reaction mixture was stirred for an additional 5 min at room temperature and then extracted with chloroform (4 × 50 mL). The chloroform extracts were dried ($MgSO_4$), and the solvent was removed in vacuo. ^{31}P NMR analysis of the residue showed that triethyl bromophosphonoacetate (δ = 13.2 ppm) made up more than 95% of the phosphorus-containing products. Besides a trace of starting material, two minor side products (δ = 10.5 ppm and δ = 4.5 ppm) were present; these were not further characterized.

The desired product was isolated by partitioning the crude residue between hexane (100 mL) and H_2O (4 × 25 mL). The aqueous fractions were combined and reextracted with chloroform (3 × 50 mL). The chloroform extracts were dried ($MgSO_4$) and evaporated at reduced pressure to provide 6.7 g (85%) of pure triethyl bromophosphonoacetate. Vacuum distillation gave the product as a colorless oil, bp 93–94 °C (0.01 mm): ^{31}P NMR ($CDCl_3$) δ = 13.2 ppm (m). Anal. Calcd for $C_8H_{16}O_5BrP$: C, 31.69; H, 5.31. Found: C, 31.39; H, 5.16.

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^1H NMR Spectra of (*Z*)- and (*E*)-1,2-Di-9-anthrylethene

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In connection with our studies on molecular gearing[1] we became interested in (*Z*)-1,2-di-9-anthrylethene (1) as a potential synthetic precursor of (*Z*)-1,2-di-9-triptycylethene.[2] The markedly different splitting patterns in the ^1H NMR spectra of 1 and its *E*-isomer (2) had previously been attributed to hindered rotation around the anthryl–ethylene single bond in 2.[3] However, we find that the room temperature spectra of 1 and 2 are *both* fully con-

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