Studies on Selected Transformations of Some Fluoromethanephosphonate Esters

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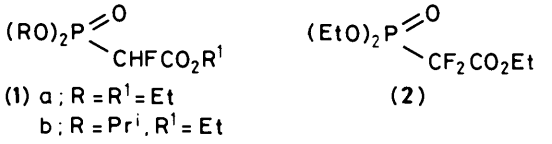
The thermal stability of α-fluoromethanephosphonate carbanions decreases in the series CHF > CF_2 > CFCl. Acylation products of the difluoromethanephosphonate carbanion show high electrophilic reactivity which results in the immediate formation of secondary products. This behaviour is not observed for the monofluoromethanephosphonate carbanion. Attempts to acylate or phosphorylate the chlorofluoromethanephosphonate carbanion unexpectedly provide esters of fluoromethylenebisphosphonic acid as products. Some physical characteristics of fluoromethanephosphonic acids are described.

Among the analogues of biological phosphate monoesters, $ROPO_3H_2$, the alkanephosphonic acids, $RCH_2PO_3H_2$, have proved to possess the greatest stability to scission of the phosphoryl group.[1] While such species have been used widely to mimic a variety of natural phosphate esters,[2] especially nucleotides,[3] considerations of their electronegativity and other factors[4] have led to the suggestion that α-monofluoro- and α,α-difluoroalkanephosphonates should have a greater potential for biological activity as analogues bearing both an isopolar and an isosteric resemblance to the parent phosphate ester.

Syntheses of such materials by a variety of routes are now well established.[5–12] In particular, the discovery of the potency of phosphonoacetic acid as an inhibitor for the replication of herpes simplex virus in animals[13] (and the even greater activity for phosphonoformic acid *in vivo*[14]) coupled with the known herbicidal activity for phosphonoacetic acid[15] stimulated a more detailed examination of the chemistry of fluoro- and difluoro-phosphonoacetic acids.

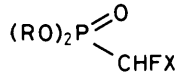
Hitherto, esters of phosphonofluoroacetic acid (**1**) have been prepared using Michaelis-Becker[16] or Arbuzov[17] reactions between phosphites and chlorofluoro-or bromofluoro-acetate esters respectively and also by the action of perchloryl fluoride on tetraethyl 2-oxo-3-phosphonobutanedioate[5] while the triethyl ester of phosphonodifluoroacetic acid (**2**) has been obtained from reaction of tetrafluoroethylene oxide with triethyl phosphite.[18] Such processes have left much to be desired and have been superseded by improved methods of synthesis.

The availability of the α-fluoromethanephosphonate esters (**3**) and (**4**) has promoted investigations of the reactions of their α-lithio derivatives with aldehydes and ketones, alkyl halides, and acyl halides,[9,10,19,20] while their reaction with carbon dioxide, carbonyl sulphide, and carbon disulphide has provided a direct and economical synthesis for a wide range of fluorinated derivatives of phosphonoacetic acid and its esters.[21] As a continuation of that work, we here describe some further transformations of the fluoromethanephosphonate esters (**3**)—(**5**) and some physical properties of salts of the parent acids.



(**1**) a; R = R^1 = Et
b; R = Pr^i, R^1 = Et

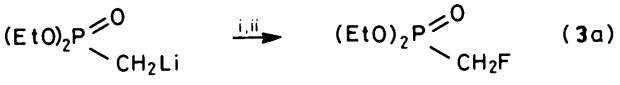
(**2**)



(**3**) X = H
(**4**) X = F
(**5**) X = Cl
a, R = Et ; b, R = Pr^i

Results and Discussion

The mono- and di-fluoromethanephosphonate esters (**3**) and (**4**) were prepared from the toxic chlorofluoromethane[22] and chlorodifluoromethane[23] by established methods using the Michaelis Becker reaction.[21] In the same way, the reaction between di-isopropyl sodiophosphite and the readily available Freon 21, dichlorofluoromethane, afforded di-isopropyl chlorofluoromethanephosphonate (**5**) in good yield.[9] Recent difficulties in obtaining a supply of chlorofluoromethane, Freon 31, made us seek an alternative route for the synthesis of (**3**). While we have found useful the selective reduction[24] of (**5**) using tributyltin hydride, the direct fluorination of diethyl lithiomethanephosphonate with perchloryl fluoride at −100 to −80 °C gives good yields of the monofluoromethanephosphonate (**3**) with no evident formation of the difluoromethanephosphonate ester (**4**) (Scheme 1).

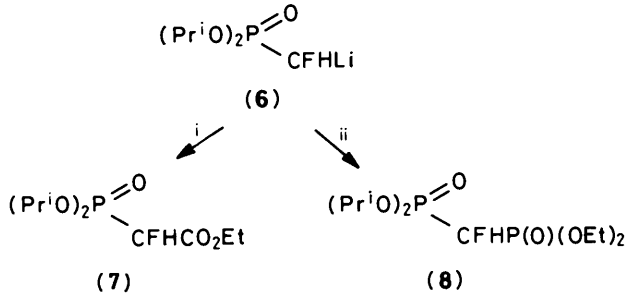


Scheme 1. *Reagents:* i, $FClO_3$, toluene, −80 °C; ii, KH_2PO_4(aq.), 20 °C

The carbanions of the three fluoromethanephosphonate esters (**3**)—(**5**) were generated conveniently using lithium diisopropylamide, LDA, at low temperature. In order to assess the thermal stability of these species, solutions of the lithio anions in tetrahydrofuran (THF) were quenched with an excess of aqueous potassium dihydrogen phosphate at either 20, 0 or −70 °C and the mixed products examined by ^{31}P and ^1H n.m.r. spectroscopy. The monofluoromethanephosphonate (**3**) was recovered unchanged in good yield (≥70%) after quenching at ≤20 °C. Neither the diethyl (**4a**) nor the di-isopropyl (**4b**) esters of difluoromethanephosphonic acid survived this procedure when quenching was carried out at ≥0 °C, though they were recovered substantially unchanged from reactions quenched at −70 °C. This result constrasts with the behaviour of [(diethoxyphosphoryl)difluoromethyl]zinc bromide, which appears to be quite stable at ambient temperature.[20]

The most labile of the carbanions proved to that derived from the chlorofluoromethanephosphonate (**5**), which exhibited variable (up to 75%) decomposition after 2 h at −70 °C. We thus conclude that these carbanions show decreasing stability in the series $PCFH^- > PCF_2^- > PCFCl^-$.

Acylation of the anion (**6**) of di-isopropyl fluoromethanephosphonate with ethyl chloroformate gave the expected ethyl (di-isopropoxyphosphonyl)fluoroacetate (**7**) in satisfactory yield. In the same fashion, phosphorylation of (**6**) with diethyl phosphorochloridate provided an adequate yield of *P,P*-diethyl *P',P'*-di-isopropyl fluoromethylenebisphosphonate (**8**) (Scheme 2). In the light of subsequent results, it would appear likely that both products (**7**) and (**8**) are converted immediately after their formation into their conjugate bases by further interaction with the basic anion (**6**), and thereby stabilised against subsequent transformations, as in the Claisen ester condensation.[25]



Scheme 2. *Reagents:* i, $ClCO_2Et$, −70 °C; ii, $(EtO)_2POCl$, −70 °C

By contrast, attempts to acylate the anion (**9**) of difluoromethanephosphonate esters with any agent other than benzoyl chloride[10] produced unexpected results. At −70 °C, acetyl chloride was insufficiently reactive while the use of ethyl oxalyl chloride resulted in the loss of starting material but no identifiable product formation. The reaction between (**9**) and ethyl chloroformate led to the isolation of a little of the desired triethyl phosphonodifluoroacetate (**2**) while the major isolated products were tetraethyl difluoromethylenebisphosphonate[7] (**10**) and a novel compound, identified as tetraethyl 1,1,3,3-tetrafluoro-2,2-dihydroxypropane-1,3-bisphosphonate (**11**) (Scheme 3). The absence of any C=O vibration in the i.r. spectrum of (**11**) favours its representation as the geminal diol, though the ammonia c.i. mass spectral data do not distinguish between the diol and the oxo formulation. However, covalent hydrates such as (**11**) are characteristic of α-fluoro ketones[26] and this proclivity of the PCF_2CO group may have important consequences for the biological activity of 2-oxo-1,1-difluoroalkanephosphonic acids as analogues of phosphate carboxylate anhydrides.

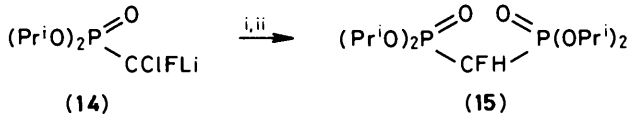
Regarding the mechanism of formation of (**10**) and (**11**), it seems most probable that the phosphonodifluoroacetate ester (**2**) is the initial product of reaction between (**9**) and ethyl chloroformate but it immediately experiences further reaction with (**9**), showing a 4:1 preference for reaction at the P=O centre, leading to (**10**), rather than at the carbonyl group, giving (**11**). It must be inferred that in Burton's efficient synthesis of (**2**), *via* the zinc bromide[12] salt of (**4a**), the metal must diminish the reactivity of the carbanion (**9**) and/or stabilise the product (**2**) against further reaction.

An attempt to acylate (**9**) using *S*-methyl (di-isopropoxyphosphonyl)dithioformate[27] failed to produce the desired α-difluoro thioketone but gave a modest yield of di-isopropyl 1-(diethoxyphosphonodifluoromethylthio)-1-methylthiomethane phosphonate (**12**). Reverse polarity reactions of the thiocarbonyl group of this sort have adequate precedent[28] (Scheme 3).

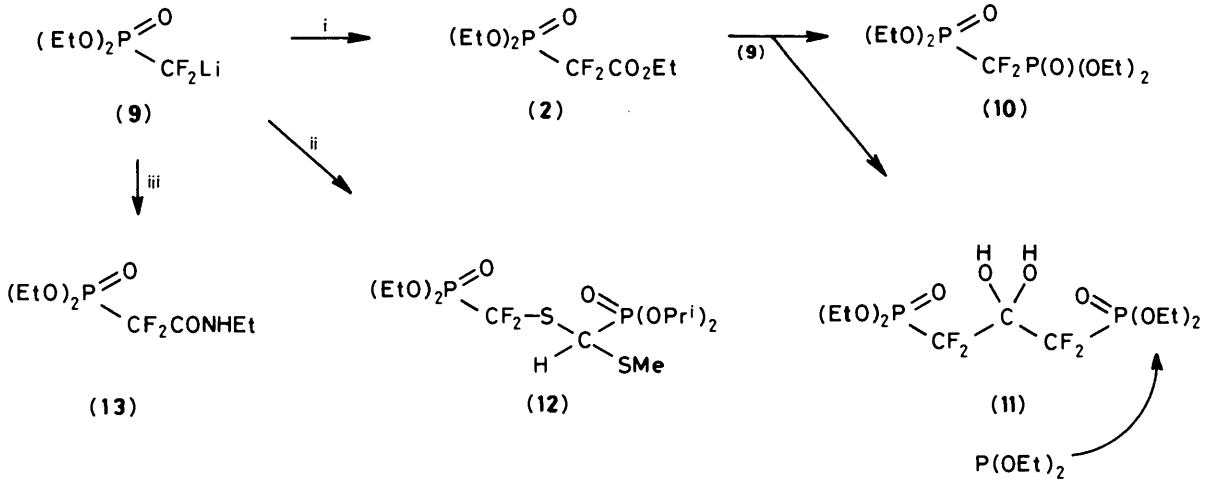
Happily, acylation of the anion (**9**) using ethyl isocyanate gave the desired diethyl *N*-ethylphosphonodifluoroacetamide (**13**) in satisfactory yield. Once again, it would appear important that the product is able to be stabilised as the amide anion and thereby resist further transformation.

Attempts to bring into reaction the anion (**9**) with other electrophiles which have proved active towards phosphonate and other carbanions, including sulphur,[29] *N,N*-dimethylformamide,[30] and Walborsky's reagent, 1,1,3,3-tetramethylbutyl isonitrile,[31] led only to recovery of difluoromethanephosphonate. The reaction of (**9**) with perchloryl fluoride or with ethyl nitrate gave complex mixtures of products, among which the reactant (**4a**) and the difluoromethylenebisphosphonate (**10**) could be identified by ^{31}P n.m.r. spectroscopy as significant components. It would thus appear that, if formed, the desired trifluoromethanephosphonate or difluoronitromethanephosphonate esters must have immediately reacted further with (**9**) to form (**10**).

All attempts to bring the anion (**14**) of chlorofluoromethanephosphonate esters (**5**) into reaction with electrophiles, including D_2O, Me_3SiBr, $ClCO_2Et$, *etc.*, and whether performed at −70 °C or at −20 °C, gave the same result. The sole product, isolated in yields up to 40%, proved to be the unexpected tetraisopropyl fluoromethylenebisphosphonate (**15**), identical with authentic material[7] (Scheme 4).



Scheme 4. *Reagents:* i, Electrophile (*e.g.* $ClCO_2Et$, Me_3SiBr), −70 °C; ii, KH_2PO_4(aq.), 0 °C

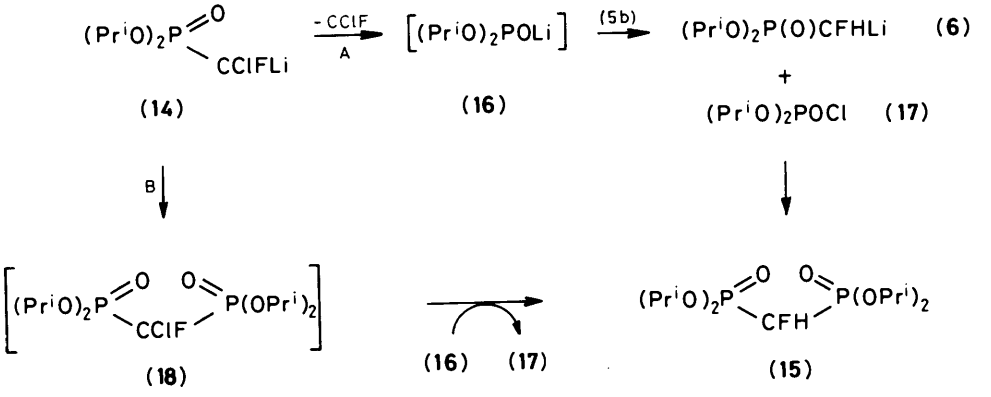


Scheme 3. *Reagents:* i, $ClCO_2Et$, −70 °C; ii, $(Pr^iO)_2P(O)CS_2Me$, − 70 °C; iii, EtNCO, −70 °C

The formation of this product (**15**) poses a significant mechanistic problem. By analogy with the production of difluoromethylenebisphosphonate esters from bromodifluoromethanephosphonates and a dialkyl phosphite anion,[7] we first considered the possible generation of the di-isopropyl lithiophosphite (**16**) by fragmentation of (**14**) with the loss of chlorofluorocarbene. This phosphorus anion (**16**) could abstract a chlorine atom from the ester (**5**) to generate the anion (**6**) which, as we have already shown (Scheme 2) can be phosphorylated by the co-product, a dialkyl phosphorochloridate (**17**), producing tetra-alkyl fluoromethylenebisphosphonate (**15**). This mechanism (Scheme 5A) was disproved when we found that the lithium salt of di-isopropyl phosphite did not react with the chlorofluoromethanephosphonate (**5a**).

product (**15**) (Scheme 6). Such displacement of a trihalogenomethyl anion from a phosphonate has been demonstrated by Hall and Inch.[33] Whatever the mechanism, this route from (**5**) to (**15**) merits further development as a potentially useful and economical means for the synthesis of esters of fluoromethylenebisphosphonic acid.

The present availability of the fluoromethanephosphonate esters (**2**)—(**5**) provided the opportunity for examination of the properties of the parent phosphonic acids, readily obtained by transesterification using bromotrimethylsilane,[34] which provides access to a range of fluoromethanephosphonic acids which are analogues of phosphoric acid itself. We have shown elsewhere[4] that α-halogenation of alkanephosphonic acids reduces their second acidic dissociation constant and we have



Scheme 5.

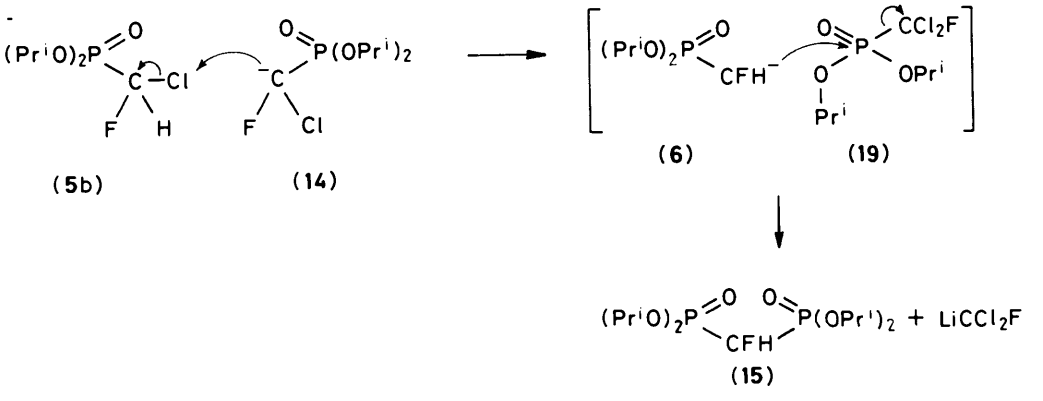
In the light of Hutchinson's work on the mono-dechlorination of tetra-alkyl dichloromethylenebisphosphonate,[32] we considered that a reasonable route to (**15**) might involve the formation of a tetra-alkyl chlorofluoromethylenebisphosphonate (**18**), from reaction between (**14**) and (**17**), which could then be dechlorinated by an appropriate anion to generate (**15**) (Scheme 5B). However, analysis of this proposal shows that any reasonable process which might be invoked for the formation of the phosphorochloridate (**17**) necessarily generates the anion (**6**) which should directly lead to the formation of (**15**). Scheme 5B therefore also fails. Moreover, it has proved impossible to detect even traces of (**18**) in the final product mixture using ammonia c.i. mass spectrometry.

Finally, we are left with the relatively straightforward route which requires transfer of chlorine from the phosphonate (**5**) to the anion (**14**) with the formation of the anion (**6**) and a dichlorofluoromethanephosphonate ester (**19**). A displacement reaction by the former on the latter would give the observed

argued[6] that the ^{31}P n.m.r. chemical shift provides a useful experimental parameter for gauging the extent of comparability between phosphonic acids and monoalkyl phosphates. It is therefore particularly gratifying to discover that there exists a good linear relationship between these two physical parameters for six methanephosphonic acids (Table) which is well fitted by the expression $\delta_P = 9.6_1$ ($pK_{a^2} - 4.5_9$) p.p.m., with a correlation coefficient of 0.996.

This relationship appears valid only for halogen-substituted methanephosphonic acids. Marked (negative) deviations are observed for three phosphonoacetic acids and esters (Figure). It seems likely that for these compounds, intramolecular hydrogen bonding between the carbonyl group and the P–O–H hydrogen has an acid-weakening effect on pK_{a^2} of some 1—1.5 pK_a units.

In conclusion, this investigation has shown that the acylation of anions of α-fluoromethanephosphonates can provide a useful route for the synthesis of a variety of analogues of phosphate esters and anhydrides. However, care must be exercised in those



Scheme 6.

Table. Elemental composition data and physical constants for some fluoromethanephosphonic acid salts and related compounds.

Compound	Composition: Found (Calc.) C	H	N	pK_{a2}	M.p. (°C)	$\delta_P(D_2O)$/p.p.m.
$CH_3PO_3Na_2$[a]	—	—	—	7.70 ± 0.1	—	30.0
$CFH_2PO_32C_6H_{14}N$	49.75 (50.00)	9.40 (9.62)	8.74 (8.97)	6.20 ± 0.1	185—186	14.2
$CF_2HPO_32C_6H_{14}N$	47.08 (47.26)	8.67 (8.85)	8.21 (8.48)	5.10 ± 0.1	193—195	4.8
$CClFHPO_32C_6H_{14}N$	45.00 (45.02)	8.57 (8.43)	7.85 (8.08)	5.20 ± 0.1	206—208	6.18
$CCl_2HPO_32Me_4N$[b]	—	—	—	5.61[b]	—	11.3[c]
$BrCF_2PO_32C_6H_{14}N$	38.15 (38.35)	6.90 (7.18)	6.84 (6.73)	4.80 ± 0.1	162—163	1.27
$EtO_2CCFHPO_32C_6H_{14}N$	49.86 (50.00)	8.93 (8.85)	7.04 (7.29)	6.20 ± 0.1	165—167	4.31
$EtO_2CCH_2PO_3C_6H_{14}N$	44.98 (45.11)	8.05 (7.89)	5.35 (5.26)	7.30 ± 0.1	188—189	11.88
$^-O_2CCF_2PO_33Na$	—	—	—	6.1[d]	—	5.56

[a] P. C. Crofts and G. M. Kosolapoff, *J. Am. Chem. Soc.*, 1953, **75**, 3379. [b] P. C. Crofts and G. M. Kosolapoff, *J. Am. Chem. Soc.*, 1953, **75**, 5738; L. B. Friedman and G. O. Doak, *Chem. Rev.*, 1957, **57**, 479. [c] J. Reiss, J. R. Van Wazer, and J. H. Letcher, *J. Phys. Chem.*, 1967, **71**, 1925. [d] Ref. 20.

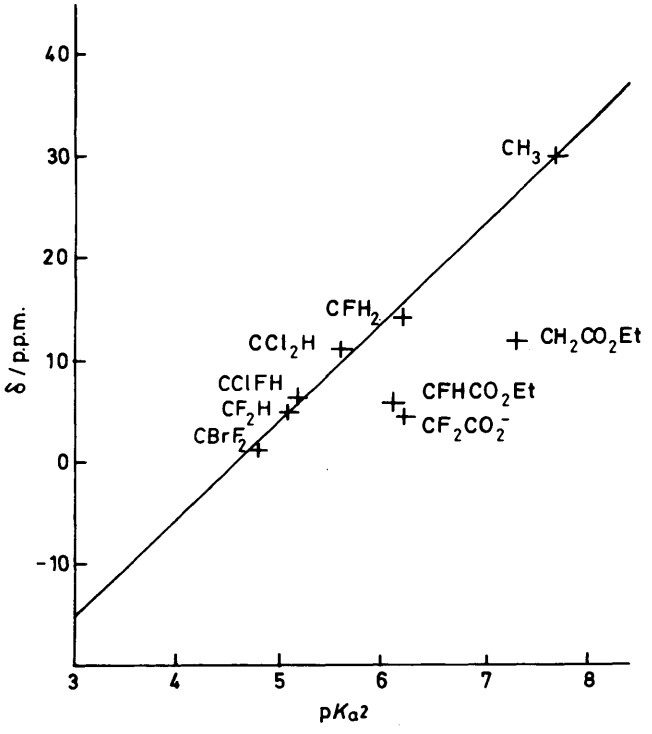


Figure. Relationship between the second dissociation constant, pK_{a2}, and the ^{31}P n.m.r. chemical shift, δ, for some substituted methanephosphonic acids, RPO_3^{2-} $2M^+$, in D_2O (pH 8.5)

cases where the first-formed product contains a good leaving group attached to phosphorus. From these results, it seems unlikely that a good synthesis of trifluoromethanephosphonic acid could be achieved by the fluorination of dialkyl difluorolithiomethanephosphonate.

Experimental

M.p.s were measured on a Kofler hot-stage micro melting point apparatus and are uncorrected. Low-resolution mass spectra were run on the Kratos MS25 using ammonia chemical ionisation.[35] I.r. spectra were recorded on a Perkin-Elmer 157G grating i.r. spectrophotometer as neat oils on sodium chloride plates. ^1H N.m.r. spectra were recorded on a Perkin-Elmer R34 instrument at 220 MHz with tetramethylsilane as internal reference. ^{31}P and ^{19}F N.m.r. spectra were recorded in the proton decoupled mode, except as indicated, on a Bruker WP80 n.m.r. spectrometer. Measurement of pK_a was carried out by titration at 25 °C and ionic strength 0.1 using a Radiometer Autoburette ABU12, Titrator 11, pH Meter 28, and recorded on a Titrograph SBR2c instrument.

Diethyl Fluoromethanephosphonate (**3a**).—Diethyl methanephosphonate (1.22 g, 8 mmol) was dissolved in dry toluene and treated with butyl-lithium (8 mmol) in hexane at −50 °C under nitrogen. Perchloryl fluoride (1 g, 10 mmol) was condensed at −196 °C and then slowly bubbled into the solution in a stream of nitrogen at −100 to −80 °C with stirring. After 1 h, the solution was allowed to warm to ambient temperature, quenched with saturated aqueous KH_2PO_4, and extracted into ether (3 × 30 ml). The combined extracts were dried and evaporated under reduced pressure. ^{31}P N.m.r. analysis of the crude reaction product indicated the presence of monofluorinated and unfluorinated species only. Flash column chromatography on silica gel using light petroleum–ethyl acetate (1 : 1) as eluant gave the *title compound* as a colourless liquid (0.62 g, 46%) (Found: C, 35.6; H, 7.4. $C_5H_{12}FO_3P$ requires: C, 35.5; H, 7.1%); $\nu_{max.}$ 1 265 cm^{-1} (P=O); $\delta_H(CDCl_3)$ 1.36 (6 H, t, *J* 7 Hz, OCH_2CH_3), 4.22 (4 H, dq, $^3J_{HP}$ 7 Hz, $^3J_{HH}$ 7 Hz, $POCH_2CH_3$), 4.70 (2 H, dd, $^2J_{HP}$ 5 Hz, $^2J_{HF}$ 47 Hz, PCH_2F); $\delta_P(CDCl_3)$ 16.3 (d, $^2J_{PF}$ 63.3 Hz); $\delta_F(CDCl_3)$ −250.4 (dt, $^2J_{FP}$ 63.3 Hz, $^2J_{FH}$ 47 Hz); *m/z* 171 ($M + H^+$, 100%).

Di-isopropyl Fluoromethanephosphonate (**3b**).—This compound was prepared according to the method of Gryszkiewicz-Trochimowski[22] from chlorofluoromethane and di-isopropyl sodiophosphite.

Diethyl Difluoromethanephosphonate (**4a**) *and Di-isopropyl Difluoromethanephosphonate* (**4b**).—These compounds were prepared from chlorodifluoromethane, Freon 31, and the sodium derivative of the appropriate dialkyl phosphite.[23]

Di-isopropyl Chlorofluoromethanephosphonate (**5b**).—This compound was prepared from dichlorofluoromethane, Freon 21, and di-isopropyl sodiophosphite.[8] The diethyl ester (**5a**) was likewise prepared using diethyl sodiophosphite.

General Procedure for the Preparation and Reaction of Halogenomethanephosphonate Carbanions.—Butyl-lithium (4.2 mmol) in dry THF (1 mmol/ml) and di-isopropylamine (4.2 mmol) were stirred at −20 °C for 20 min and then the dialkyl fluoromethanephosphonate (4.0 mmol) in THF (1 mmol/ml) was added dropwise under nitrogen at −70 °C. After 0.5 h at this temperature, the appropriate electrophile (4.0 mmol) in THF was added at −70 °C and the mixture stirred at −70 °C for 1 h; it was then warmed to 0 °C. The solution was quenched

with saturated, aqueous KH_2PO_4 and extracted (3×) with ethyl acetate. The organic layers were combined, dried, and evaporated under reduced pressure.

Tests of the Thermal Stability of Fluoromethanephosphonate Carbanions.—(*a*) Diethyl difluorolithiomethanephosphonate (**9**) (1 mmol) was stirred in THF at −70 °C for 1 h; the mixture was then brought to room temperature and quenched as above. ^{31}P and ^{1}H N.m.r. analysis of the crude product showed that only a trace of (**4a**) was present in a mixture of products of P–C bond cleavage.

(*b*) The above experiment was repeated using di-isopropyl difluorolithiomethanephosphonate with the same result.

(*c*) Di-isopropyl fluorolithiomethanephosphonate (**6**) was subjected to the same procedure. Work-up after the mixture had been stirred for 1 h at 20 °C gave a crude product, shown by ^{1}H n.m.r. spectroscopy to contain (**3b**) in not less than 70% yield.

(*d*) Di-isopropyl chlorofluoromethanephosphonate (**5b**) (0.93 g, 4 mmol) was treated with lithium di-isopropylamide as above and the solution quenched at −70 °C after 2 h. The crude product (0.71 g) was shown by ^{31}P n.m.r. spectroscopy to contain tetraisopropyl fluoromethylenebisphosphonate (**15**), δ_P 9.4 (d, $^{2}J_{PF}$ 65 Hz) (60%), along with reactant (**5b**) (35%) and no other significant phosphorus-containing products.

Ethyl (Di-isopropoxyphosphono)fluoroacetate (**7**).—Di-isopropyl fluorolithiomethanephosphonate (**6**) (20 mmol) was prepared and treated with ethyl chloroformate (2.17 g, 20 mmol) as described above. Kugelrohr distillation of the crude product gave the *title compound* as a colourless liquid (2.15 g, 40%) b.p. (oven temp.) 130—145 °C/0.5 mmHg (Found: C, 44.6; H, 7.5. $C_{10}H_{20}FO_5P$ requires: C, 44.45; H, 7.45%); $\nu_{max.}$ 1 763 (C=O) and 1 265 cm^{-1} (P=O); $\delta_H(CDCl_3)$ 1.38 [15 H, m, $POCH(CH_3)_2$ and $CO_2CH_2CH_3$], 4.35 (2 H, q, *J* 7 Hz, $COCH_2Me$), 4.86 (2 H, m, $POCHMe_2$), 5.17 (1 H, dd, $^{2}J_{HF}$ 46 Hz, J_{HP} 13 Hz, PCFHC); $\delta_P(CDCl_3)$ 8.1 (d, $^{2}J_{PF}$ 72 Hz); $\delta_F(CDCl_3)$ −210.6 (dd, $^{2}J_{PF}$ 72.5 Hz, $^{2}J_{FH}$ 47.1 Hz); *m*/*z* 288 ($M + NH_4^+$, 50%), 271 ($M + H^+$, 60%), and 246 (288 − C_3H_6, 100%).

P,P-*Diethyl* P′,P′-*Di-isopropyl Fluoromethylenebisphosphonate* (**8**).—Di-isopropyl fluorolithiomethanephosphonate (20 mmol) was treated with freshly distilled diethyl phosphorochloridate (3.45 g, 20 mmol) as above. Purification of the crude product by flash chromatography on silica using ethyl acetate–methanol (20:1) followed by Kugelrohr distillation gave the *title compound* as a colourless liquid (2.45 g, 37%), b.p. (oven temp. 120—140 °C/0.01 mmHg (Found: C, 40.2; H, 7.55. $C_{11}H_{25}FO_6P_2$ requires C, 39.55; H, 7.55%); $\nu_{max.}$ 1 256 cm^{-1} (P=O); $\delta_H(CDCl_3)$ 1.35 [18 H, m, $POCH_2CH_3$ and $POCH(CH_3)_2$], 4.30 (4 H, dq, $^{3}J_{HP}$ 7 Hz, $^{3}J_{HH}$ 7 Hz, $POCH_2Me$), 4.85 (2 H, m, $POCHMe_2$), 4.96 (1 H, dt, $^{2}J_{HF}$ 47 Hz, $^{2}J_{HP}$ 13 Hz, PCFHP′); $\delta_P(CDCl_3)$ 8 line ABX spectrum from which was calculated:[36] 9.2 (dd, $^{2}J_{PF}$ 63 Hz, $^{2}J_{PP'}$ 19 Hz), 11.4 (dd, $^{2}J_{PF}$ 65 Hz, $^{2}J_{PP'}$ 19 Hz); $\delta_F(CDCl_3)$ −227.8 (dt, $^{2}J_{FH}$ 47.0 Hz, $^{2}J_{FP}$ 64.1 Hz); *m*/*z* 335 ($M + H^+$, 100%) and 293 (335 − C_3H_6, 100%).

Reaction between (**9**) *and Ethyl Chloroformate.*—Diethyl difluoromethanephosphonate (**4a**) (10 mmol) was treated with pure ethyl chloroformate (10 mmol) using the general procedure. ^{31}P N.m.r. analysis of the crude product showed three components having the PCF_2 group along with minor products. Kugelrohr distillation gave a major fraction b.p. (oven temp.) 100—120 °C/0.1 mmHg, further purified by flash chromatography on silica using ethyl acetate–light petroleum (1:1) into compounds (**2**), (**10**), and (**11**).

Triethyl phosphonodifluoroacetate (**2**) (75 mg, 3%); $\delta_H(CDCl_3)$ 1.4 (9 H, t, *J* 7 Hz, $CO_2CH_2CH_3$ and $POCH_2CH_3$) and 4.1—4.4 (6 H, m, CO_2CH_2Me and $POCH_2Me$); $\delta_P(CDCl_3)$ 2.8 (t, $^{2}J_{PF}$ 97 Hz); $\delta_F(CDCl_3)$ −116.9 (d, $^{2}J_{FP}$ 96.7 Hz); *m*/*z* 278 ($M + NH_4^+$, 100%) and 261 ($M + H^+$, 95%).

Tetraethyl difluoromethylenebisphosphonate (**10**) (630 mg, 39%) was further purified by flash chromatography on silica using ethyl acetate–light petroleum (3:2) to give the title compound as a colourless liquid (580 mg, 36%) (Found: C, 33.6; H, 5.95. Calc. for $C_9H_{20}F_2O_6P_2$: C, 33.35; H, 6.2%); $\nu_{max.}$ 1 285 cm^{-1} (P=O); $\delta_P(CDCl_3)$ 3.6 (t, $^{2}J_{PF}$ 86 Hz); $\delta_F(CDCl_3)$ −121.2 (t, $^{2}J_{FP}$ 85.5 Hz); *m*/*z* 342 ($M + NH_4^+$, 10%) and 325 ($M + H^+$, 70%).

Tetraethyl 1,1,3,3-*tetrafluoro*-2-*oxopropane*-1,3-*bisphosphonate* (**11**) (200 mg, 9.5%), crystallised with time, m.p. 55—58 °C (Found: C, 31.55; H, 5.5. $C_{11}H_{22}F_4O_8P_2$ requires C, 31.45; H, 5.3%); $\nu_{max.}$(Nujol) 3 340 (br, OH) and 1 248 cm^{-1} (P=O); $\delta_H(CDCl_3)$, 1.40 (12 H, t, *J* 7 Hz, $POCH_2CH_3$), 4.38 (8 H, dq, $^{3}J_{HP}$ 7 Hz, $^{3}J_{HH}$ 7 Hz, $POCH_2Me$), 6.26 [2 H, br s, $C(OH)_2$]; $\delta_P(CDCl_3)$ 6.3 (t, $^{2}J_{PF}$ 95 Hz); $\delta_F(CDCl_3)$ −122.4 (d, $^{2}J_{FP}$ 94.6 Hz); *m*/*z* 420 ($M - 18 + NH_4^+$, 15%) and 403 ($M + H^+ - 18$, 100%).

Reaction between (**9**) *and* S-*Methyl Di-isopropoxyphosphonyldithioformate.*—The above standard conditions were used (3 mmol scale) to combine *S*-methyl di-isopropoxyphosphonyl dithioformate with diethyl difluoromethanephosphonate (**9**). Flash chromatography of the crude product on silica using ethyl acetate–light petroleum (1:2) as eluant gave *di-isopropyl* 1-(*diethoxyphosphonodifluoromethylthio*)-1-*methylthiomethanephosphonate* (**12**) as a colourless liquid (450 mg, 34%) (Found: C, 35.5; H, 6.55. $C_{13}H_{28}F_2O_6P_2S_2$ requires C, 35.15; H, 6.35%); $\delta_H(CDCl_3)$ 1.36 [12 H, d, *J* 7 Hz, $POCH(CH_3)_2$], 1.39 (6 H, t, *J* 7 Hz, $POCH_2CH_3$), 2.38 (3 H, s, SCH_3), 4.35 (4 H, dq, *J* 7 Hz, *J* 7 Hz, $POCH_2Me$), 4.48 (1 H, d, *J* 18 Hz, PCH), and 4.83 (2 H, m, $POCHMe_2$); $\delta_P(CDCl_3)$ 2.7 (dt, $^{4}J_{PP}$ 4 Hz), 15.4 (d, $^{4}J_{PP}$ 4 Hz); $\delta_F(CDCl_3)$ −85.5 (dd, $^{2}J_{FP}$ 99 Hz, *F*′, *F*″); *m*/*z* 445 ($M + H^+$, 100%).

N-*Ethyl* (*Diethoxyphosphonyl*)*difluoroacetamide* (**13**).—Diethyl difluorolithiomethanephosphonate (**9**) 10 mmol) was brought into reaction with ethyl isocyanate (0.71 g, 10 mmol) as above. The crude product was purified by flash chromatography on silica using ethyl acetate–light petroleum (3:1) as eluant to give the *title compound* as a colourless, viscous liquid (1.1 g, 42%) (Found: C, 37.3; H, 6.05; N, 5.5. $C_8H_{16}F_2NO_4P$ requires C, 37.05; H, 6.2; N, 5.4%); $\nu_{max.}$ 3 285 (NH), 1 690 (C=O), and 1 262 cm^{-1} (P=O); $\delta_H(CDCl_3)$ 1.20 (3 H, t, *J* 7 Hz, NCH_2CH_3), 1.40 (6 H, t, *J* 7 Hz, $POCH_2CH_3$), 3.40 (2 H, dq, $^{3}J_{HH}$ 7 and 7 Hz, simplified to q after D_2O shake, $NHCH_2Me$), 4.34 (4 H, dq, $^{3}J_{HP}$ 7 Hz, $POCH_2Me$), 7.0 (1 H, br s, disappeared on D_2O shake, NH); $\delta_P(CDCl_3)$ 3.6 (t, $^{2}J_{PF}$ 97 Hz); $\delta_F(CDCl_3)$ −117.6 (d, $^{2}J_{FP}$ 96.7 Hz); *m*/*z* 277 ($M + NH_4^+$, 40%) and 260 ($M + H^+$, 100%).

Reaction between (**9**) *and* 1,1,3,3-*Tetramethylbutyl Isonitrile* (*Walborsky's Reagent*).—The lithio carbanion (**9**) was prepared as before and treated with 1,1,3,3-tetramethylbutyl isonitrile (1 equiv.)[31] at −70 °C and the reaction solution stirred 1 h. Dimethyl sulphate (1 equiv.) was added dropwise and the mixture allowed to warm to −40 °C before work-up. Analysis of the crude product by ^{31}P n.m.r. and ^{1}H n.m.r. showed it to contain mainly diethyl 1,1-difluoroethanephosphonate, identical with a sample prepared by the reaction between dimethyl sulphate and (**9**) (see above) and unchanged isonitrile.

Diethyl 1,1-*Difluoroethanephosphonate.*—The anion (**9**) (60 mmol) was treated with dimethyl sulphate (7.56 g, 60 mmol) in the usual way. Kugelrohr distillation of the crude product gave

the *title compound* as a colourless liquid (7.57 g, 63%), b.p. (oven temp.) 95—100 °C/13 mmHg (Found: C, 35.85; H, 6.4. $C_6H_{13}F_2O_3P$ requires: C, 35.65; H, 6.45%); $\nu_{max.}$ 1 274 cm^{-1} (P=O); $\delta_H(CDCl_3)$ 1.33 (6 H, t, *J* 7 Hz, OCH_2CH_3), 1.78 (3 H, dt, $^3J_{HF}$ 22 Hz, $^3J_{HP}$ 9 Hz, PCF_2CH_3), and 4.27 (4 H, dq, $^3J_{HP}$ 7 Hz, $POCH_2Me$); $\delta_F(CDCl_3)$ −105.1 (dq, $^2J_{FP}$ 108.6 Hz, $^3J_{FH}$ 21.1 Hz); *m/z* 220 ($M + NH_4^+$, 40%), 203 ($M + H^+$, 35%), and 183 (203 − HF, 100%).

Experiments with Di-isopropyl Chlorofluoromethanephosphonate (**5b**).—(*a*) Lithium di-isopropylamide (5 mmol) and diethyl phosphite (0.69 g, 5 mmol) were admixed at −60 °C and stirred for 10 min. Di-isopropyl chlorofluoromethanephosphonate (1.16 g, 5 mmol) was then added dropwise at −70 °C under nitrogen and the solution stirred for 1 h before being worked up. Analysis of the crude reaction mixture by ^{31}P, ^1H, and ^{19}F n.m.r. spectroscopy showed the presence of both unchanged reactants and no trace of tetra-alkyl fluoromethylenebisphosphonate (**8**).

(*b*) Lithium di-isopropylamide (11 mmol) was treated dropwise with (**5b**) (2.33 g, 10 mmol) followed by pure diethyl phosphorochloridate (1.73 g, 10 mmol) in dry THF (5 ml) at −70 °C. After 1 h, the solution was quenched and worked up. ^{31}P and ^{19}F N.m.r. analysis of the crude product showed the presence of approximately equal amounts of *P,P*-diethyl *P',P'*-di-isopropyl fluoromethylenebisphosphonate (**8**) and (**5b**) with no trace of (**18**).

(*c*) Di-isopropyl phosphite (1 equiv.) was added dropwise to lithium di-isopropylamide and stirred for 1 h at −20 °C. This solution was then added dropwise at −70 °C to (**5b**) (1 equiv.). After 2 h, the solution was allowed to warm gradually to ambient temperature and worked up. Both starting materials were recovered unchanged.

(*d*) Di-isopropyl fluorolithiomethanephosphonate (**6**) was prepared as before and treated dropwise with the chlorofluoromethanephosphonate (**5b**) (3 mmol, 1 equiv.) in a little THF at −70 °C. After 2 h at this temperature, the solution was warmed gradually to 0 °C, quenched, and worked up as usual. A ^{31}P n.m.r. spectrum of the crude product mixture showed the presence of di-isopropyl fluoromethanephosphonate (**3b**), di-isopropyl chlorofluoromethanephosphonate (**5b**), and tetraisopropyl fluoromethylenebisphosphonate (**15**) in the approximate ratio 3:2:1.

Chlorofluoromethanephosphonic Acid.—Bromotrimethylsilane (1.65 g, 10.76 mmol) was added to diethyl chlorofluoromethanephosphonate (1.00 g, 4.89 mmol) and the mixture stirred at ambient temperature under nitrogen for 18 h; it was then evaporated under reduced pressure. Methanol (5 ml) was added and the solution evaporated again to give the *title compound* as a colourless, viscous oil (0.70 g, 96%); $\delta_H(CD_3OD)$ 6.35 (dd, $^2J_{HF}$ 46 Hz, $^2J_{PH}$ 9 Hz); $\delta_P(CD_3OD)$ 6.18 (d, $^2J_{PF}$ 77.8 Hz).

This product was dissolved in methanol, treated with cyclohexylamine (0.93 g, 9.43 mmol), and the resulting precipitate recrystallised from methanol to give biscyclohexylammonium *chlorofluoromethanephosphonate* m.p. 206—208 °C (Table).

In the same way, the esters (**1a**), (**3a**), (**4a**), triethyl phosphonoacetate, and diethyl bromodifluoromethanephosphonate[37] were de-esterified to give the corresponding acids as their cyclohexylammonium salts (see Table).

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References

1 R. Engel, *Chem. Rev.*, 1977, **77**, 349.
2 R. Engel, 'The Role of Phosphates in Living Systems,' ed. R. L. Hildebrand, CRC Press, Boca Raton, Florida, 1983, pp. 93—138.
3 K.-H. Scheidt, 'Nucleotide Analogues,' J. Wiley & Sons, New York, 1980, pp. 96—141.
4 G. M. Blackburn, *Chem. Ind.* (*London*), 1981, 134.
5 W. Grell and H. Machleidt, *Justus Liebigs Ann. Chem.*, 1966, **693**, 134.
6 G. M. Blackburn and D. E. Kent, *J. Chem. Soc., Chem. Commun.*, 1981, 511; *J. Chem. Soc., Perkin Trans. 1*, 1986, 913.
7 G. M. Blackburn, D. E. England, and F. Kolkmann, *J. Chem. Soc., Chem. Commun.*, 1981, 830; D. J. Burton and R. M. Flynn, *J. Fluorine Chem.*, 1980, **15**, 263; D. J. Burton, T. Ishihara, and R. M. Flynn, *ibid.*, 1982, **20**, 121.
8 G. M. Blackburn and M. J. Parratt, *J. Chem. Soc., Chem. Commun.*, 1982, 1270; *J. Chem. Soc., Perkin Trans. 1*, 1986, 1413.
9 G. M. Blackburn and M. J. Parratt, *J. Chem. Soc., Chem. Commun.*, 1983, 886; *J. Chem. Soc., Perkin Trans 1*, 1986, 1425; M. J. Parratt, Ph.D Thesis, Sheffield Univ., 1983.
10 M. Obayashi, E. Ito, K. Matsui, and K. Kondo, *Tetrahedron Lett.*, 1982, 2323.
11 C. E. McKenna and P. Shen, *J. Org. Chem.*, 1981, **46**, 4573.
12 D. J. Burton, T. Ishihara, and M. Maruta, *Chem. Lett.*, 1982, 755.
13 N. L. Shipkowitz, R. R. Bower, R. N. Appell, C. W. Nordeen, L. R. Overby, W. R. Roderick, J. B. Schleicher, and A. M. von Esch, *Appl. Microbiol.*, 1973, **26**, 264.
14 B. Öberg, *Pharm. Ther.*, 1983, **19**, 387.
15 Ger. Offen. 2318254 (*Chem. Abstr.*, 1974, **81**, 46379).
16 A. V. Fokin, V. I. Zimm, Yu. N. Studnev, and A. I. Rapkin, *Zh. Org. Chem.*, 1971, **7**, 249 (*Chem. Abstr.*, 1971, **74**, 124736).
17 H. Machleidt and R. Wessendorf, *Justus Liebigs Ann. Chem.*, 1964, **674**, 1.
18 V. A. Ginsburg and M. N. Vasil'eva, *J. Gen. Chem. USSR* (*Engl. Transl.*), 1967, **37**, 2371.
19 M. Obayashi and K. Kondo, *Tetrahedron Lett.*, 1982, **23**, 2327.
20 D. J. Burton, L. G. Sprague, D. J. Pietrzyk, and S. H. Edelmuth, *J. Org. Chem.*, 1984, **49**, 3437.
21 G. M. Blackburn, D. Brown, and S. J. Martin, *J. Chem. Res.* (*S*), 1985, 92.
22 E. Gryskiewicz-Trochimowski, *Bull. Soc. Chim. Fr.*, 1967, 4289.
23 L. Z. Soborowski and N. F. Baina, *J. Gen. Chem. USSR* (*Engl. Transl.*), 1959, **29**, 1115.
24 G. M. Blackburn, A. Bushell, and T. W. Maciej, unpublished results.
25 C. R. Hauser and B. E. Hudson, *Org. React.*, 1942, **1**, 266.
26 A. L. Henne, J. W. Shepard, and E. J. Young, *J. Am. Chem. Soc.*, 1950, **72**, 3577.
27 D. W. Grisley, *J. Org. Chem.*, 1961, **26**, 2544.
28 P. Beak and J. W. Wortley, *J. Am. Chem. Soc.*, 1970, **92**, 4142; 1972, **94**, 597.
29 M. Mikolajczyk, S. Grzejszczak, and A. Chefcznska, *J. Org. Chem.*, 1979, **44**, 2967.
30 E. E. Aboujaoude, N. Collignon, and P. Savignac, *Synthesis*, 1983, 634.
31 G. E. Niznik, W. H. Morrison, and H. M. Walborsky, *J. Org. Chem.*, 1974, **39**, 600.
32 D. W. Hutchinson and G. Semple, *Phosphorus Sulphur*, 19 4, **21**, 1.
33 C. R. Hall, T. D. Inch, G. Peacock, C. Pottage, and N. E. Williams, *J. Chem. Soc., Perkin Trans. 1*, 1984, 669.
34 G. M. Blackburn and D. Ingleson, *J. Chem. Soc., Perkin Trans. 2*, 1980, 1150; C. E. McKenna, M. T. Higa, N. H. Cheung, and M.-C. McKenna, *Tetrahedron Lett.*, 1977, 155.
35 D. A. Cload and D. W. Hutchinson, *Org. Mass Spectrom.*, 1983, **18**, 57.
36 D. H. William and I. Fleming, 'Spectroscopic methods in Organic Chemistry,' McGraw-Hill, London, 2nd edn., 1973.
37 D. J. Burton and R. M. Flynn, *J. Fluorine Chem.*, 1977, **10**, 329.

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