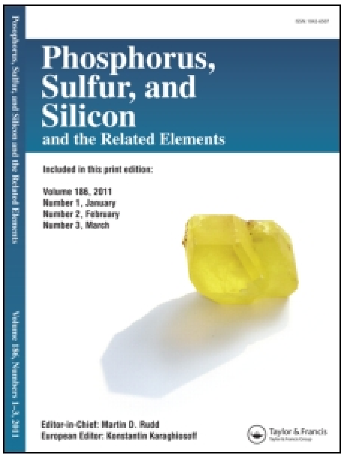

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THE SYNTHESIS AND PROPERTIES OF SOME FLUORINATED DIALKYL PHOSPHORAMIDATES

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The synthesis and physical properties of the first fluorinated dialkyl phosphoramidates of structure $(RCH_2O)_2P(O)NHCH_2R_F$*, where* $R = CH_3$*,* CF_3 *or* CCl_3 *and* $R_F = CF_3$ *or* C_2F_5*, are described. They were obtained by treatment of the respective dialkyl phosphorochloridates with trifluoroethylamine or pentafluoropropylamine in ether in the presence of triethylamine.*

Keywords: Bis(2,2,2-trichloroethyl)phosphorochloridate; bis(2,2,2-trifluoroethyl) phosphorochloridate; dialkyl phosphoramidate; dialkyl phosphorochloridate; fluorinated amine

The early foundations of organophosphorus chemistry were laid from the late 1860s by Professor Carl Arnold August Michaelis in Germany. For over 40 years, he and his students were responsible for a vast amount of synthetic work and for the development of methods of preparation still used today. Among the many compounds studied were the dialkyl phosphoramidates. In 1915, Michaelis reported the synthesis and properties of compounds **1a–b** (Figure 1).[1]

Previously we drew attention to the fact that, although phosphorus chemistry is an old subject, the possibilities offered by the introduction of fluoroalkoxy groups have been examined only recently.[2–5] The C—F system forms the basis of a new branch of organophosphorus chemistry, paralleling the well-known field arising from C—H bonds. The range of compounds capable of existence is enormous, especially as mixed fluorohydrocarbon species and derivatives are usually stable. Of interest is the selective incorporation of fluorinated groups into phosphoryl compounds. Previous work from our laboratory has resulted in the synthesis

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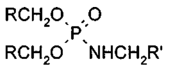

Compound	R	R'
1a	CH_3	CH_3
1b	CH_3	C_2H_5
2a	CH_3	CF_3
2b	CH_3	C_2F_5
3a	CF_3	CF_3
3b	CF_3	C_2F_5
4a	CCl_3	CF_3
4b	CCl_3	C_2F_5

FIGURE 1

of many new fluorinated phosphoryl compounds,[2–5] most of which have known hydrologues,[*] and has also led to stable compounds whose hydrologues are too unstable to permit isolation, such as bis(fluoroalkyl) phosphoroiodidates $(CF_3CH_2O)_2P(O)I$ and $[(CF_3)_2CHO]_2P(O)I$.[6] In this communication, we describe the synthesis and properties of some halogenated analogues of the phosphoramidates first prepared by Michaelis, namely compounds **2a–b**, **3a–b**, and **4a–b** (refer to Figure 1).

Phosphoramidates **2a–b** contain fluorine atoms in the amide group. Their unfluorinated analogues are usually made by phosphorylation of an amine with a dialkyl phosphorochloridate in an inert solvent. If the amine is readily available, two molar equivalents are used, one to accept the hydrogen chloride liberated during the reaction. If the amine is scarce, then common amines, such as pyridine or triethylamine, are used to remove the hydrogen chloride. Phosphorylation proceeds best when the phosphorus atom of the phosphorochloridate is electrophilic and the nitrogen atom of the amine nucleophilic. The outcome depends on a compromise between the reactivities of the two reagents. The presence of fluorine atoms in amines considerably reduces the basicity of the nitrogen atom; base dissociation (K_b) constants for $CH_3CH_2NH_2$ and $CF_3CH_2NH_2$ are 5×10^{-4} and 5×10^{-9} respectively.[7,†] Little is known

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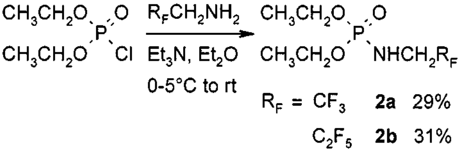
[*] The term hydrologue, derived from the Greek word *logos* meaning ratio or proportion, is used here to denote a hydrogenated analogue of a fluorinated compound. Likewise, the term fluorologue can be suggested for a fluorocarbon analogue of a hydrocarbon compound. Using this terminology, CH_4 is a hydrologue of CF_4 (and CF_4 is a fluorologue of CH_4). Its adoption saves writing, for example, "the hydrocarbon analogue of" or "the fluorinated counterpart of," which becomes cumbersome.

[†] Base dissociation constants were taken from A. L. Henne and J. J. Stewart, *J. Am. Chem. Soc.*, **77,** 1901 (1955). A CF_3 group affects the basicity of the NH_2 group adversely

about the chemistry of fluorinated amines. They react with phosgene to give isocyanates,[8,9] but their behavior toward other —X(O)Cl systems, where X is a carbon atom or a heteroatom, awaits study. We found that diethyl phosphorochloridate was reactive enough to combine with trifluoroethylamine and pentafluoropropylamine in ether in the presence of triethylamine (Scheme 1).



SCHEME 1

Compounds **2a–b** are only the second and third dialkyl *N*-(fluoroalkyl)phosphoramidates to have been synthesised. The first was prepared in 1966 by Dyatkin et al.* in two stages: treatment of triethyl phosphite with *tert*-nitrosoperfluoroisobutane gave phosphazo intermediate **5** which, on acid hydrolysis, yielded the phosphoramidate **6** as a low melting solid (Scheme 2). Our route is of more general utility and allows easy access to phosphoramidates derived from primary fluoroalkylamines.

Bis(trifluoroethyl) *N*-(fluoroalkyl)phosphoramidates were prepared similarly. Chlorination of phosphite **7** proceeded smoothly in dichloromethane and gave the bis(trifluoroethyl) phosphorochloridate **8** in excellent yield.[10,†] This chloridate is more reactive than

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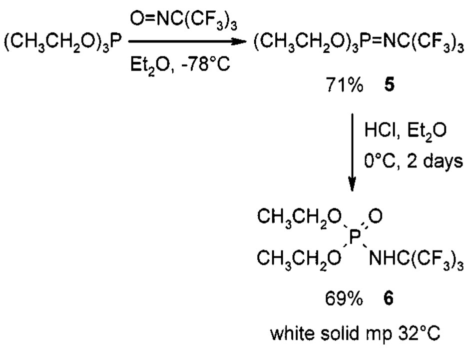
by a factor of 10^5 when separated by a single CH_2 group. The data illustrates the strong inductive effect of the trifluoroethyl group; the reduced donor ability of the nitrogen atom in $CF_3CH_2NH_2$ probably arises from some rehybridisation (greater *s* character of orbitals containing the electrons not involved in σ bonds).

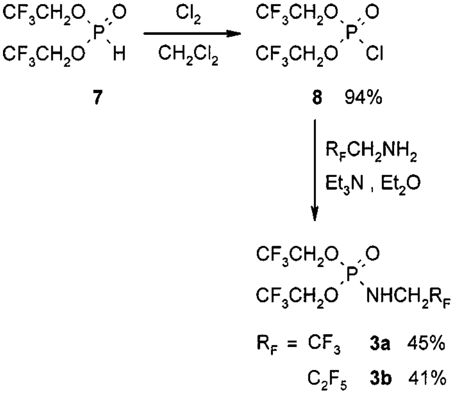
*The preparation of diethyl *N*-(perfluoro-*t*-butyl) phosphoramidate $(EtO)_2P(O)NHC(CF_3)_3$ **6** was first outlined in a short communication and reported later with experimental details. Refer to the English translations: E. P. Mochalina, B. L. Dyatkin, and I. L. Knunyants, *Izv. Akad. Nauk. SSSR, Ser. Khim.*, 2188 (1966); and B. L. Dyatkin, E. P. Mochalina, Yu S. Konstantinov, S. R. Sterlin, and I. L. Knunyants, *Izv. Akad. Nauk. SSSR, Ser. Khim.*, 2200 (1967). The related compound, diphenyl *N*-hexafluoroisopropyl phosphoramidate $(PhO)_2P(O)NHCH(CF_3)_2$, a solid with a melting point of 173–174°C, was made in 57% yield by treating $Cl_2P(O)NHCH(CF_3)_2$ with two molar equivalents of sodium phenoxide. See the *English translation* of E. S. Kozlov, A. A. Kisilenko, A. I. Sedlov, and A. V. Kirsanov, *Zh. Obshch, Khim.*, **37,** 1528 (1967).

†The synthesis of $(CF_3CH_2O)_2P(O)H$ **7** is given in D. E. Gibbs and C. Larsen, *Synthesis*, 410 (1984). Bubbling chlorine gas into a solution of the phosphite (0.2 mol) in dry dichloromethane (50 ml) until the yellow color persisted, removal of solvent and distillation of the residue gave bis(trifluoroethyl)phosphorochloridate $(CF_3CH_2O)_2P(O)Cl$ **8** in 94% as a colorless mobile liquid (bp 62°C/10 mmHg).



SCHEME 2

diethyl phosphorochloridate to nucleophiles because trifluoroethoxy groups are more electronegative than ethoxy groups. It reacted with the fluorinated amines to give compounds **3a–b** in moderate yield (Scheme 3).



SCHEME 3

Bis(trichloroethyl) phosphorochloridate **9** combined with the fluorinated amines to give the phosphoramidates **4a–b** in modest yield (Scheme 4).[11,*] It is less reactive than bis(trifluoroethyl) phosphorochloridate due to the larger size of its ester groups and their lower electronegativity. The reactions were accelerated by the addition of a catalytic amount of 4-dimethylaminopyridine (DMAP).

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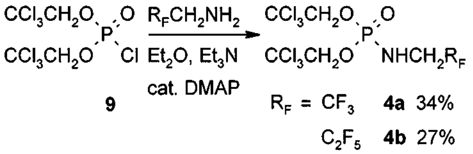
[*] The study of heavily halogenated phosphorus molecules, such as bis(trichloroethyl) phosphoramidates, has been neglected. The amidate $(CCl_3CH_2O)_2P(O)NHPh$, a white solid that melts between 135–136°C, was made by treatment of the chloridate with aniline. See L. N. Markovskii, A. V. Solov'ev, V. E. Pashinnik, and Yu G. Shermolovich, *Zh. Obshch. Khim.* (English translation), **50,** 644 (1980).



SCHEME 4

The halogenated phosphoramidates were purified by vacuum distillation in a Kugelrohr apparatus, many of them subliming in the receiver bulbs. Their physical properties, including phosphorus NMR shifts, are summarized in Table I.

Phosphoryl compounds with trifluoroethyl or pentafluoropropyl groups generally have boiling points lower than those of nonfluorinated types, but comparisons are not available when fluorine atoms are present in amide groups.[12,*] An interesting property of the fluorinated phosphoramidates is that their boiling points are much higher than those of dialkyl phosphoramidates **1a–b**. Whereas the latter are liquids at room temperature, most of the fluorinated phosphoramidates are low-melting white solids. Intermolecular NH···F-hydrogen bonding probably accounts for the differences.

In conclusion, we have developed facile routes to a range of novel dialkyl phosphoramidates. Multiple fluorine atoms in such molecules

TABLE I Physical Properties of Phosphoramidates $(RCH_2O)_2P(O)NHCH_2R'$

Compound	R	R′	δ_P (ppm)[a]	bp (°C/mm Hg)[b]	m.p. (°C)
1a	CH_3	CH_3	—	135/25	—
1b	CH_3	C_2H_5	—	112/8	—
2a	CH_3	CF_3	6.2	95/0.05	32
2b	CH_3	C_2F_5	6.4	60/0.03	—
3a	CF_3	CF_3	6.3	83/0.03	55
3b	CF_3	C_2F_5	6.5	62/0.03	40
4a	CCl_3	CF_3	3.9	92/0.03	82–83[c]
4b	CCl_3	C_2F_5	3.9	95/0.06	149–150[c]

[a] NMR shifts measured in $CDCl_3$.

[b] Approximate oven temperatures quoted except for **1a–b**—data for these compounds were taken from Reference 1.

[c] Recrystallized from hot ether-hexane.

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[*] An analysis of the effects of fluorination on the boiling points of phosphoryl compounds appears in C. M. Timperley and M. J. Waters, *J. Fluorine Chem.*, **109,** 103 (2001).

should cause their chemical behavior to differ dramatically from that of their unfluorinated couterparts and lead to some unusual phosphorus chemistry. A more detailed account of our work in this area will be reported at a later date.

EXPERIMENTAL

Diethyl phosphorochloridate and bis(2,2,2-trichloroethyl) phosphorochloridate were purchased from Aldrich Ltd., U.K. and the fluorinated amines from Apollo Scientific Ltd., U.K. Analytical information was obtained using instrumentation and techniques described in C. M. Timperley, M. Bird, I. Holden, and R. M. Black, *J. Chem. Soc., Perkin Trans.* **1**, 26 (2001). NMR data were recorded in $CDCl_3$ at 500 MHz for ^1H, 125 MHz for ^{13}C, 470 MHz for ^{19}F, and 202 MHz for ^{31}P nuclei. Products gave satisfactory microanalyses: C ± 0.14, H ± 0.12, N ± 0.11.

Typical Procedure: Preparation of Diethyl *N*-(trifluoroalkyl)phosphoramidates 2a–b

A solution of the fluorinated amine (4 mmol) and triethylamine (4 mmol) in ether (10 ml) was added dropwise by cannula to a stirred solution of diethyl phosphorochloridate (4 mmol) in ether (20 ml) at 0–5°C. After addition, the mixture was allowed to warm to room temperature and left to stand for 12 h. The precipitate was filtered off and the filtrate concentrated. Distillation of the residue under reduced pressure using a kugelrohr apparatus gave the title compounds as colourless oils.

Selected Spectroscopic Data

Compound 2a: δ_H 4.1 (2H, complex m, $J = 1$ and 9 Hz, NCH_2), 3.63 (1H, br q, $J = 8$ Hz, NH), 3.49 (4H, m, OCH_2), 1.31 (6H, dt, $J = 0.9$ and 7 Hz, CH_3); δ_C 124.5 (q, $J = 278$ Hz, CF_3), 62.8 (d, $J = 5$ Hz, OCH_2), 43.3 (q, $J = 35$ Hz, NCH_2), 15.8 (d, $J = 7$ Hz, CH_3); δ_F −73.1 (t, $J = 9$ Hz, CF_3); ν_{max}/cm^{-1} (film) 3199 (N—H), 2987, 1479, 1396, 1300, 1281, 1240 (P=O), 1151, 1032, (P—O—C), 974 (P—N), 868, 829, 800.

Compound 2b: δ_H 4.1 (2H, complex m, NCH_2), 3.77 (1H, br q, $J = 8$ Hz, NH), 3.53 (4H, m, OCH_2), 1.33 (6H, dt, $J = 0.9$ and 7 Hz, CH_3); δ_C 118.5 (tq, $J = 286$ and 35 Hz, CF_3), 113.1 (tq, $J = 254$ and 5 Hz, CF_2), 62.3 (d, $J = 5$ Hz, OCH_2), 41.5 (t, $J = 24$ Hz, NCH_2), 15.6 (d, $J = 7$ Hz, CH_3); δ_F −122.5 (m, CF_2), −83 (m, CF_3); ν_{max}/cm^{-1} (film) 3195 (N—H), 2987, 1606, 1446, 1396, 1348, 1240 (P=O), 1201, 1144, 1026 (P—O—C), 974 (P—N), 860, 798, 735.

Compound 3a: δ_H 4.4 (2H, complex m, $J = 2$ and 8 Hz, NCH_2), 4.06 (1H, br q, $J = 8$ Hz, NH), 3.5 (4H, m, OCH_2); δ_C 123.8 (q, $J = 277$ Hz, ester CF_3), 122.2 (weak m, amino CF_3), 63.1 (dq, $J = 4$ and 38 Hz, OCH_2), 43.3 (q, $J = 35$ Hz, NCH_2); δ_F −74.4 (t, $J = 9$ Hz, ester CF_3), −73.3 (t, $J = 9$ Hz, amino CF_3); ν_{max}/cm^{-1} (KBr) 3170 (N—H), 1458, 1427, 1290 (P=O), 1147, 1084, 962 (P—N), 904, 842.

Compound 3b: δ_H 4.37 (2H, complex m, $J = 2$ and 8 Hz, NCH_2), 4.13 (1H, br q, $J = 8$ Hz, NH), 3.59 (4H, ddd, $J = 2$, 5 and 8 Hz, OCH_2); δ_C 122.2 (q, $J = 278$ Hz, ester CF_3), 118.6 (tq, $J = 286$ and 35 Hz, amino CF_3), 114.6 (tq, $J = 248$ and 4 Hz, CF_2), 63 (dq, $J = 4$ and 38 Hz, OCH_2), 41.3 (t, $J = 25$ Hz, NCH_2); δ_F −122.7 (m, CF_2), −83.1 (m, amino CF_3), −74.5 (t, $J = 9$ Hz, ester CF_3); ν_{max}/cm^{-1} (KBr) 3178 (N—H), 2931, 1458, 1423, 1350, 1292 (P=O), 1255, 1171, 1078, 1032 (P—O—C), 962 (P—N), 895, 843.

Compound 4a: δ_H 4.55 (2H, dq, $J = 6$ and 9 Hz, NCH_2), 4.11 (1H, br q, $J = 8$ Hz, NH), 3.56 (4H, m, OCH_2); δ_C 124.6 (q, $J = 278$ Hz, CF_3), 95.2 (d, $J = 12$ Hz, CCl_3), 76.5 (d, $J = 4$ Hz, OCH_2), 43.9 (q, $J = 35$ Hz, NCH_2); δ_F −73.4 (t, $J = 8$ Hz, CF_3); ν_{max}/cm^{-1} (KBr) 3207 (N—H), 2951, 1450, 1392, 1296, 1279 (P=O), 1159, 1103, 1051, 1030 (P—O—C), 976 (P—N), 908, 798, 735.

Compound 4b: δ_H 4.61 (2H, dq, $J = 7$ and 11 Hz, NCH_2), 3.86 (1H, br q, $J = 8$ Hz, NH), 3.7 (4H, m, OCH_2); δ_C 120.1 (tq, $J = 286$ and 35 Hz, CF_3), 113.4 (tq, $J = 217$ and 6 Hz, CF_2), 95 (d, $J = 11$ Hz, CCl_3), 78 (d, $J = 4$ Hz, OCH_2), 42 (t, $J = 24$ Hz, NCH_2); δ_F −122.9 (m, CF_2), −83.4 (m, CF_3); ν_{max}/cm^{-1} (KBr) 3200 (N—H), 1295, 1257, 1207, 1147, 1101, 1030 (P—O—C), 908, 798, 735.

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