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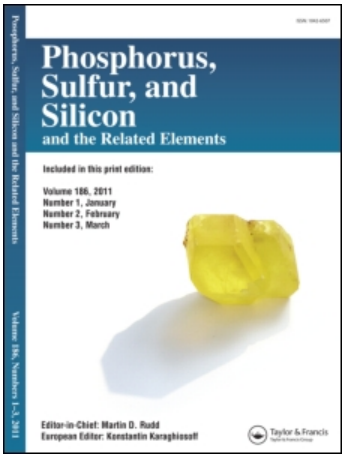

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Isotopically Labelled Phosphorus Compounds: Some Deuterated Methyl and Ethyl Derivatives

Joanna L. Mundy[a]; John M. Harrison[a]; Peter Watts[a]; Christopher M. Timperley[a]
[a] Defence Science and Technology Laboratory, Porton Down, Salisbury, Wiltshire, United Kingdom

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Isotopically Labelled Phosphorus Compounds: Some Deuterated Methyl and Ethyl Derivatives

Joanna L. Mundy
John M. Harrison
Peter Watts
Christopher M. Timperley
Defence Science and Technology Laboratory, Porton Down, Salisbury, Wiltshire, United Kingdom

The synthesis of fifteen phosphylated compounds having P—OCD_3, P—CD_3, or P—OCD_2CH_3 groups is described. Selective chemistry for the precise placement of the deuterated groups was devised, and the products were isolated in a high purity in generally good yields. The compounds were required to study their behavior after electrospray ionization in an ion trap mass spectrometer.

Keywords Arbuzov rearrangement; ethanol-1,1-d_2; iodomethane-d_3; methanol-d_4; methanol-d_3; organophosphorus compounds

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In recent years, this laboratory has studied the synthesis of derivatives of methylphosphonic acid $MeP(O)(OH)_2$ by solution[1] and solid-phase methodology[2] and their analysis in environmental matrices.[3] These compounds are hydrolysis and decontamination products and sometimes precursors of nerve agents, such as sarin (Figure 1). Deuterium and carbon-13 labelled dialkyl methylphosphonates **A**–**C** have been prepared to enable their fragmentation and reactions to be studied in the ion trap mass spectrometer,[4,5] and molecules with P—CD_3 groups have been of interest in the search for biomarkers of poisoning by nerve agents.

In this article, we describe routes to fifteen novel compounds having P—OCD_3, P—CD_3, and P—OCD_2CH_3 groups. Selective chemistry for

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Address correspondence to Christopher M. Timperley, Defence Science and Technology Laboratory, Porton Down, Salisbury, Wiltshire SP4 0JQ, UK. E-mail: cmtimperley@dstl.gov.uk

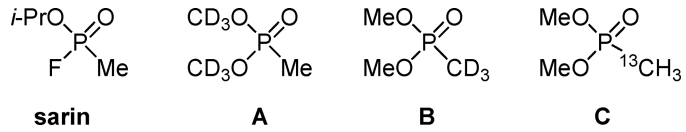


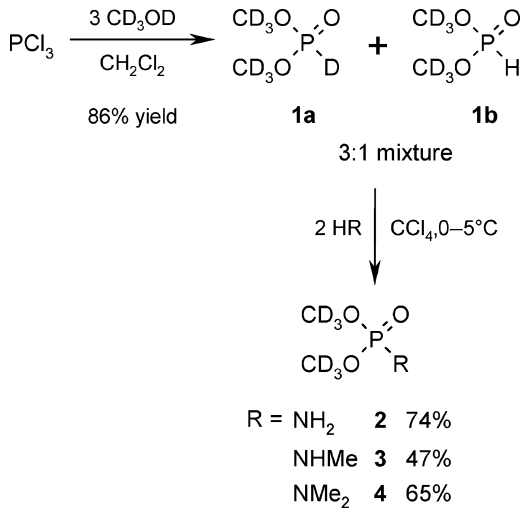
FIGURE 1

the precise placement of deuterated groups had to be devised for their synthesis. The compounds are useful for spectroscopic and biological studies of derivatives of nerve agents and organophosphorus pesticides.

RESULTS AND DISCUSSION

The Synthesis of Compounds With P–OCD_3 Groups

The reaction of phosphorus trichloride with three molar equivalents of methanol-d_4 resulted in a 3:1 mixture of *D*/*H*-phosphonates **1a,b**. The unexpected formation of the *H*-phosphonate **1b** presumably arose from the production of HCl in the reaction mixture due to a deuterium exchange with the solvent dichloromethane (the mechanism remains obscure). The treatment of the *D*/*H*-phosphonate mixture with an excess of ammonia, methylamine, or dimethylamine in carbon tetrachloride gave phosphoramidates **2**–**4** (Scheme 1). Such chemistry, developed by Atherton and Todd,[6] proceeds via an intermediate chloridate, in this case $(CD_3O)_2P(O)Cl$, formed by a base-catalysed reaction of



SCHEME 1

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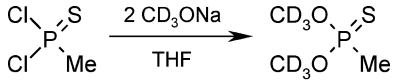
phosphonates with carbon tetrachloride.[7] The byproducts, chloroform and amine hydrochloride salt, are easily removed.

The reaction between methylphosphonic dichloride and two molar equivalents of methanol-d_3 in the presence of triethylamine in ether previously furnished $(CD_3O)_2P(O)Me$.[5] The corresponding reaction starting with methylphosphonothioic dichloride cannot be driven to completion easily with triethylamine as a base, as the thioic dichloride is less reactive than its oxygen counterpart. The use of sodium methoxide-d_3 in tetrahydrofuran did, however, allow the isolation of thiono product **5** in good yield (Scheme 2).



5 70%

SCHEME 2

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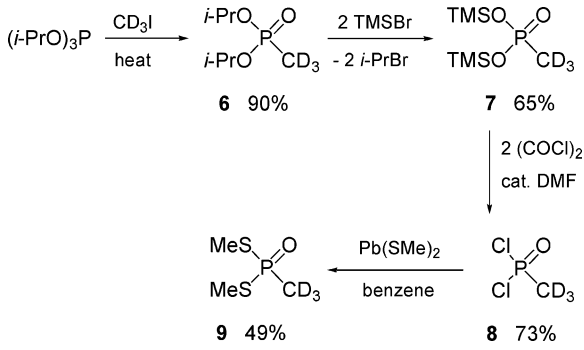
The Synthesis of Compounds With P–CD_3 Groups

An Arbuzov reaction of triisopropyl phosphite with iodomethane-d_3 gave diisopropyl d_3-methylphosphonate **6** cleanly and in excellent yield (Scheme 3). The reaction of **6** with two molar equivalents of bromotrimethylsilane[1,8–9] gave bis(trimethylsilyl) d_3-methylphosphonate **7**. This compound reacted with oxalyl chloride and a catalytic amount of *N*,*N*-dimethylformamide to give d_3-methylphosphonic dichloride **8**, which is a useful intermediate for the synthesis of deuterated nerve agents (e.g., sarin and soman). Boiling this intermediate with lead(II) methanethiolate led to the replacement of the chlorine atoms by methylthio groups, producing product **9**.[10]



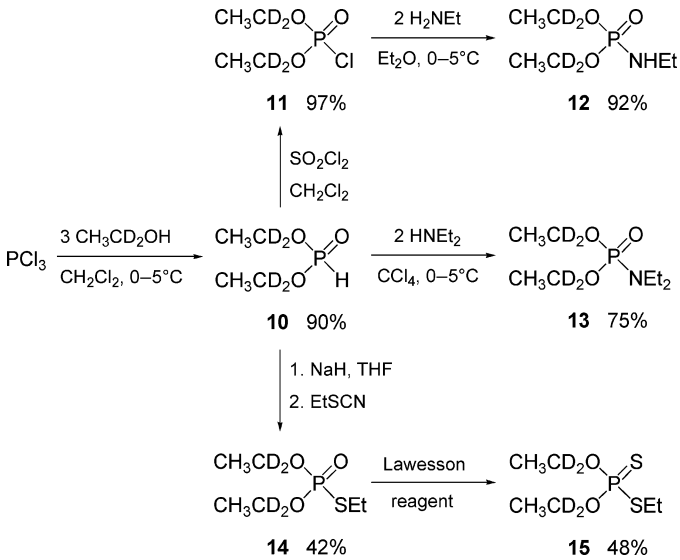
6 90% **7** 65% **8** 73% **9** 49%

SCHEME 3

The ability of a substrate with a P═O bond to undergo such a transformation depends on the groups on phosphorus: $(EtO)_2P(O)Cl$ and $(CF_3CH_2O)_2P(O)Cl$ failed to react under the same conditions.[11]

The Synthesis of Compounds With P–OCD_2CH_3 Groups

The route to these compounds initially followed the same one used for the P–OCD_3 compounds. The reaction of phosphorus trichloride with three molar equivalents of ethanol-1,1-d_2 gave *H*-phosphonate **10** in a high yield (Scheme 4). Amino derivatives were prepared from the *H*-phosphonate **10** by a chlorination with sulfuryl chloride followed by a treatment of the chloridate with ethylamine (**10**→**11**→**12**) or by a Todd–Atherton reaction with diethylamine (**10**→**13**). Thio derivatives were made by deprotonating the *H*-phosphonate **10** using sodium hydride and treating the resulting sodium salt with ethyl thiocyanate. This gave phosphorothiolate **14**, which, on thionation with a Lawesson reagent, gave the dithio species **15**.†



SCHEME 4

In summary, selective and generally high-yielding routes to fifteen novel deuterated phosphorus compounds have been devised. The

†The Lawesson reagent is 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide.

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fragmentation of some of the compounds upon electrospray ionisation in the ion trap mass spectrometer was subsequently studied.[12]

EXPERIMENTAL

Lead methanethiolate was prepared by a known procedure.[11] Reagents were purchased from Aldrich (Gillingham, UK). Triisopropyl phosphite was distilled before use (b.p. 51–52°C/10 mmHg) to remove a triisopropyl phosphate impurity produced by aerial oxidation. Anhydrous solvents were employed. Tetrahydrofuran was distilled from sodium/benzophenone and used immediately. TLC plates, MK6F silica gel 60Å (2.5 × 7.5 cm, layer thickness 250 μg), were obtained from Whatman (Maidstone, UK). Products were visualized by dipping the TLC plates into a diluted solution of potassium permanganate in acetone: Spots appeared white on a purple background. Silica gel for flash chromatography was from BDH Laboratory Supplies (Poole, UK). NMR spectra were obtained on a JEOL Lambda 500 instrument, operating at 500 and 76.7 MHz for ^{1}H and ^{2}H respectively, and at 125 MHz for ^{13}C spectra, as solutions in $CDCl_3$ with $SiMe_4$ as an internal reference. Reaction mixtures were monitored by gas chromatography-mass spectrometry using a Finnigan MAT GCQ instrument with Chemical Ionisation (CI) using methane as a reagent gas. Molecular masses of pure products were confirmed with methane +ve CI data (70 eV). All products were homogeneous by TLC, and their structures were confirmed by multiple fragmentation experiments in the ion trap mass spectrometer.[12]

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Bis(d_3-Methyl) Deuterium/hydrogen Phosphonate 1a,b

A solution of PCl_3 (8.8 g, 64 mmol) in CH_2Cl_2 (10 mL) was added dropwise to a stirred solution of CD_3OD (5 g, 139 mmol) in CH_2Cl_2 (15 mL) at 0–5°C. After the addition, the mixture was heated under reflux for 2 h to remove any residual HCl and CD_3Cl. The solvent was removed, and the product was distilled under reduced pressure to give a 3:1 mixture of $(CD_3O)P(O)D$ **1a** and $(CD_3O)P(O)H$ **1b** (6.43 g, 86%). B.p. 44°C/10 mm Hg. Compound **1a**. δ_D 3.71 (s, 6D, CD_3), 6.76 (d, 1D, $^{1}J_{PD} = 106$ Hz, P-D). δ_C 49.8–52.2 (m, CD_3). δ_P 9.0 (t, $^{1}J_{PD} = 106$ Hz, P—D). CI-MS m/z 117 (M^+, 100). Compound **1b**. δ_H 6.78 (d, 1H, $^{1}J_{PH} = 698$ Hz, P—H). δ_D 3.71 (s, 6D, CD_3). δ_C 49.8–52.2 (m, CD_3). δ_P 9.4. CI-MS m/z 116 (M^+, 32).

Bis(d_3-methyl) Phosphoramidate 2

Excess NH_3 was condensed into a solution of **1a,b** (0.8 g, 6.8 mmol) in CCl_4 (15 mL) at −78°C. On addition, a white precipitate of NH_4Cl formed. The mixture was allowed to warm to r.t. Analysis by TLC, eluting with 48:1 CH_2Cl_2—^{i}PrOH, showed a loss of starting material and formation of a product. The mixture was filtered, and the filtrate was concentrated. Column chromatography using the TLC solvent system gave the title compound as a colorless liquid (0.66 g, 74%). δ_H 2.85 (s, 2H, NH_2). δ_D 3.66 (s, 6D, CD_3). δ_C 50.1 (m, CD_3). δ_P 11.6. CI-MS *m/z* 131 (M^+, 100).

Bis(d_3-Methyl) *N*-Methylphosphoramidate 3

Excess $MeNH_2$ was condensed into a solution of **1a,b** (1 g, 8.6 mmol) in CCl_4 (15 mL) at −78°C. On addition, a white precipitate of $MeNH_2$.HCl formed. The mixture was allowed to warm to r.t. Analysis by TLC, eluting with 39:1 CH_2Cl_2—^{i}PrOH, revealed the formation of a product with R_f 0.15. The mixture was filtered, and the filtrate was concentrated. Column chromatography on silica gel using the TLC solvent system gave the title compound as a colorless liquid (0.59 g, 47%). δ_H 2.60 (dd, 3H, $^3J_{PNCH} = 12$ and $^3J_{HCCH} = 6$ Hz, CH_3), 2.89 (br s, 1H, NH). δ_D 3.64 (d, 6D, $^3J_{POCD} = 2$ Hz, CD_3). δ_C 27.4 (s, CH_3). δ_P 11.8. CI-MS *m/z* 145 (M^+, 100).

Bis(d_3-Methyl) *N,N*-Dimethylphosphoramidate 4

Excess Me_2NH was condensed into a solution of **1a,b** (1 g, 8.6 mmol) in CCl_4 (15 mL) at -78°C. On addition, a white precipitate of Me_2NH.HCl formed. The mixture was allowed to warm to r.t. Analysis by TLC, eluting with 49:1 CH_2Cl_2—^{i}PrOH, revealed the formation of a product with R_f 0.15. The mixture was filtered, and the filtrate was concentrated. Column chromatography on silica gel using the TLC solvent system gave the title compound as a colourless liquid (0.89 g, 65%). δ_H 2.70 (d, 6H, $^3J_{PNCH} = 10$ Hz, CH_3). δ_D 3.95 (br s, 6D, CD_3). δ_C 36.6 (d, $^2J_{PNC} = 4$ Hz, CH_3). δ_P 12.6. CI-MS *m/z* 159 (M^+, 100).

Bis(d_3-Methyl) Methylphosphonothionate 5

A solution of $NaOCD_3$ was prepared by adding CD_3OD (1 g, 28 mmol) in THF (10 mL) dropwise to a stirred suspension of NaH (0.73 g, 30 mmol) in THF (10 mL). The mixture was left stirring for about 30 min until H_2 evolution had ceased. $MePSCl_2$ (2.06 g, 13.8 mmol) in THF (30 mL)

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was then added dropwise at 0–5°C. After the addition, the mixture was allowed to warm to r.t. and was stirred for 2 h. Analysis by TLC, eluting with 4:1 hexane-acetone, showed two very close spots with R_f 0.5. An analysis by GC-MS showed 80% product and 20% monosubstituted analogue. The solution was heated under reflux for 1 h and then left to stir overnight. An analysis by TLC and GC-MS showed complete conversion. A few drops of water were added carefully to destroy any residual sodium hydride. About two-thirds of the volume of THF was removed by rotary evaporation. Water (30 mL) and $CHCl_3$ (30 mL) were added. The chloroform layer was separated, and the aqueous layer re-extracted with more $CHCl_3$ (2×30 mL). The organic layers were combined and dried ($MgSO_4$). The drying agent was filtered off, and the filtrate was concentrated to give a pale yellow liquid (1.8 g). Bulb-to-bulb vacuum distillation gave the title compound as a colourless liquid (1.4 g, 70%). B.p. 180°C (oven temperature) at 5 mm Hg. δ_H 1.81 (d, 3H, $^2J_{PCH} = 16$ Hz, P—CH_3). δ_D 3.61 (d, 6D, $^3J_{POCD} = 2$ Hz, CD_3). $\delta_C = 20.3$ (d, $^1J_{PC}$115 Hz, P—CH_3), 51.8–52.3 (m, CD_3). δ_P 98.5. CI-MS *m/z* 146 (M^+, 100), 111 (M—CD_3OH, 56).

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Diisopropyl d_3-Methylphosphonate 6

Iodomethane-d_3 (12.47 g, 86 mmol) was added in one portion to a stirred solution of triisopropyl phosphite (17.9 g, 86 mmol) in CH_2Cl_2 (20 mL). The reaction mixture warmed up and eventually boiled. The mixture was allowed to cool. Volatile material was removed by rotary evaporation. A fractionation of the residue under reduced pressure gave the title compound as a colourless liquid (14.27 g, 90%). B.p. 86°C/15 mmHg. δ_H 1.32 (d, 12H, $^3J_{HCCH} = 6$ Hz, CH_3), 4.66–4.73 (m, 2H, CH). δ_D 1.40 (d, 3D, $^2J_{PCD} = 2$ Hz, CD_3). δ_C 24.0 (d, $^3J_{POCC} = 4$ Hz, CH_3), 69.9 (d, $^2J_{POC} = 6$ Hz, CH). δ_P 27.5. CI-MS *m/z* 183 (M^+, 100).

Bis(trimethylsilyl)d_3-Methylphosphonate 7

Bromotrimethylsilane (27.4 g, 179 mmol) was added in one portion to **6** (14.38 g, 79 mmol) in CH_2Cl_2 (90 mL). A slight warming of the flask was observed, and the dark orange solution paled in color. The reaction mixture was stirred for 12 h. Volatile material was removed on a rotary evaporator, and the residue was distilled under reduced pressure to give the title compound as a colourless liquid (12.5 g, 65%). B.p. 80°C/10 mmHg. δ_H 0.21 (s, 18H, CH_3). δ_D 1.55 (d, 3D, $^2J_{PCD} = 3$ Hz, CD_3). δ_C 0.9 (s, CH_3), 13.1–15.4 (m, CD_3). δ_P 9.7. CI-MS *m/z* 243 (M^+, 100).

d_3-Methylphosphonic Dichloride 8

Oxalyl chloride (19 g, 150 mmol) was added over 10 min to a stirred solution of **7** (36.5 g, 150 mmol) in CH_2Cl_2 (70 mL) containing DMF (250 μL). After the addition, stirring was continued for 1 h. The solvent was removed, and the residue was distilled under reduced pressure to afford the title compound as a colourless liquid (14.8 g, 73%). B.p. 59°C/12 mmHg. δ_D 2.48 (d, 3D, $^2J_{PCD} = 2$ Hz, CD_3). δ_P 42.7. CI-MS *m/z* 136 (M^+, 100).

S,S-Dimethyl d_3-Methylphosphonodithiolate 9

Lead methanethiolate (2.4 g, 8 mmol) was added in one portion to a solution of **8** (0.54 g, 4 mmol) in benzene (20 mL), and the mixture was heated under reflux for 2 h. The dark yellow precipitate lightened. An analysis by GC-MS showed the presence of the required product. The precipitate was filtered off, and the filtrate was concentrated to give a liquid. Column chromatography on silica gel, eluting with 7:3 hexane-acetone, gave the title compound as a colourless liquid (0.31 g, 49%). δ_H 2.32 (d, 6H, $^3J_{PSCH} = 14$ Hz, CH_3). δ_D 1.93 (d, 3D, $^2J_{PCD} = 2$ Hz, CD_3). $\delta_P = 63.5$. CI-MS *m/z* 159 (M^+, 100), 111 (M^+-MeSH, 52).

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Bis(ethyl-1,1-d_2) Hydrogen Phosphonate 10

A solution of PCl_3 (4.7 g, 34 mmol) in CH_2Cl_2 (20 mL) was added dropwise to a stirred solution of CH_3CD_2OH (5 g, 104 mmol) in CH_2Cl_2 (15 mL) at 0–5°C. After the addition, the mixture was heated under reflux for 2 h to remove residual HCl and CH_3CD_2Cl. The removal of the solvent and distillation under reduced pressure gave the title compound as a colourless liquid (4.3 g, 90%). B.p. 41–42°C/5 mmHg. δ_H 1.36 (s, 6H, CH_3), 6.82 (d, 1H, $^1J_{PH} = 693$ Hz, P—H). δ_D 4.11 (br s, 4D, CD_2). δ_C 15.7 (d, $^3J_{POCC} = 6$ Hz, CH_3), 60.5–61.2 (m, CD_2). δ_P 6.3. CI-MS *m/z* 142 (M^+, 100), 112 (M^+-CH_2CD_2, 35), 82 (112-CH_2CD_2, 64).

Bis(ethyl-1,1-d_2) Phosphorochloridate 11

A solution of SO_2Cl_2 (1.12 mL, 14 mmol) in CH_2Cl_2 (10 mL) was added dropwise to a stirred solution of **10** (1.42 g, 10 mmol) in CH_2Cl_2 (15 mL) at 0–5°C. After the addition, the mixture was allowed to warm to r.t. Stirring was continued for 3 h, and the mixture then heated under reflux for 1 h to remove any dissolved HCl and SO_2. An analysis by TLC, eluting with 7:3 hexane-acetone, showed a disappearance of starting material. The solvent was removed to give the title compound

as a colourless liquid (1.7 g, 97%). δ_H 1.41 (s, 6H, CH_3). δ_D 4.23 (br d, 4D, $^3J_{POCD} = 5$ Hz, CD_2). δ_C 15.4 (d, $^3J_{POCC} = 6$ Hz, CH_3), 60.4 (m, CD_2). δ_P 3.3. CI-MS *m/z* 176 (M^+, 100), 146 (M^+-CH_2CD_2, 76), 116 (146-CH_2CD_2, 57).

Bis(ethyl-1,1-*d*$_2$)*N*-Ethylphosphoramidate 12

Ethylamine (10 mL of 2 M solution in THF, 20 mmol) was added dropwise to a stirred solution of **11** (1.76 g, 10 mmol) in ether (20 mL) at 0–5°C. A white precipitate of $EtNH_2$.HCl formed. The solution was stirred for 2 h. An analysis by TLC, eluting with 38:1 CH_2Cl_2—MeOH, showed a loss of starting material and a product with R_f 0.5. The precipitate was filtered off, and the filtrate was concentrated to give a brown liquid. Column chromatography on silica gel, eluting with the TLC solvent system, gave the title compound as a pale yellow liquid (1.71 g, 92%). δ_H 2.97 (ddq, 2H, $J = 10$, 7 and 8 Hz, CH_2), 2.47 (br s, 1H, NH), 1.15 (t, 3H, $^3J_{HCCH} = 7$ Hz, CH_3), 1.31 (s, 6H, CD_2CH_3). δ_D 4.36 (s, 4D, CD_2). δ_C 15.8 (d, $^3J_{PNCC} = 7$ Hz, CH_3), 17.1 (d, $^3J_{POCC} = 6$ Hz, $CD_2\underline{C}H_3$), 36.0 (s, CH_2), 60.2–61.0 (m, CD_2). δ_P 8.1. CI-MS *m/z* 185 (M^+, 100).

Bis(ethyl-1,1-*d*$_2$) *N,N*-Diethylphosphoramidate 13

A solution of Et_2NH (0.95 g, 13 mmol) in $CHCl_3$ (5 mL) was added dropwise to a stirred solution of **10** (0.82 g, 5.8 mmol) in CCl_4 (5 mL) at 0–5°C. A white precipitate of Et_2NH.HCl appeared immediately. After the addition, the mixture was stirred at r.t. for 12 h. An analysis by GC-MS showed the desired product to predominate. Water (10 mL) was added to dissolve the precipitate, the mixture separated, and the aqueous layer reextracted with CH_2Cl_2 (10 mL) and then ether (10 mL). The organic layers were combined and dried ($MgSO_4$), the drying agent was filtered off, and the filtrate was concentrated to reveal an orange liquid. Bulb-to-bulb distillation under reduced pressure gave pure title compound as a pale yellow liquid (0.93 g, 75%). Oven temperature 180°C/5 mmHg. δ_H 1.11 (t, 6H, $^3J_{HCCH} = 7$ Hz, CH_3), 1.29 (s, 6H, CD_2CH_3), 3.09 (dq, 2H, $^3J_{PNCH} = 11$ and $^3J_{HCCH} = 7$ Hz, CH_2). δ_D 3.95–4.03 (m, CD_2). δ_C 14.1 (s, CH_3), 15.9 (d, $^3J_{POCC} = 7$ Hz, $CD_2\underline{C}H_3$), 39.5 (d, $^2J_{PNC} = 5$ Hz, $\underline{C}H_2CH_3$), 60.9–61.3 (m, CD_2). δ_P 9.4. CI-MS *m/z* 213 (M^+, 100).

Bis(ethyl-1,1-*d*$_2$) *S*-Ethylphosphorothiolate 14

Bis(ethyl-1,1-d_2) hydrogen phosphonate **10** (2 g, 14 mmol) in THF (10 mL) was added dropwise to a stirred suspension of sodium hydride

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(0.41 g, 17 mmol) in THF (30 mL). After 30 min, when the hydrogen evolution had ceased, a solution of EtSCN (1.23 g, 14 mmol) in THF (10 mL) was added. After 12 h, an analysis by GC-MS showed an 85% conversion to the product. An analysis by TLC, eluting with 4:1 hexane:acetone, showed a product with R_f 0.5 and starting material with R_f 0.4. The solid was filtered off, and the filtrate was concentrated to give a yellow liquid. Chromatography on silica gel, eluting with the TLC solvent system, gave the title compound as a colourless liquid (1.19 g, 42%). δ_H 1.36 (s, 6H, CH_3), 1.38 (t, 3H, $^3J_{HCCH} = 7$ Hz, CH_3), 2.86 (dq, 2H, $^3J_{POCH}$ and $^3J_{HCCH} = 7$ Hz, CH_2). δ_D 4.09–4.16 (br m, CD_2). δ_C 15.4 (d, $^3J_{POCC} = 7$ Hz, CH_3), 16.0 (d, $^3J_{POC} = 6$ Hz, CH_3), 25.0 (d, $^2J_{POC} = 4$ Hz, CH_2), 62.0–62.8 (m, CD_2). δ_P 27.0. CI-MS *m/z* 202 (M^+, 100), 172 (M—CH_2CD_2, 47).

Bis(ethyl-1,1-d_2) *S*-Ethylphosphorodithioate 15

Lawesson reagent (0.99 g, 2.4 mmol) was added in one portion to a stirred solution of **14** (0.9 g, 4.4 mmol) in anhydrous MeCN (20 mL). The reaction mixture was heated under reflux and monitored periodically by GC-MS. After 20 h of reflux, 60% conversion to the product had occurred. The solvent was removed, and the residue was chromatographed on silica gel, eluting with 40:1 hexane-acetone, to give the title compound as a colourless liquid (0.46 g, 48%). δ_H 1.32–1.37 (m, 9H, CH_3), 2.84 (dq, 2H, $^3J_{HCCH} = 7$ Hz, $^3J_{PSCH} = 16$ Hz, CH_2). δ_D 4.23 (d, 4D, $^3J_{POCD} = 6$ Hz, CD_2). δ_C 14.7 (d, $^3J_{POCC} = 0.1$ Hz, $OCD_2\underline{C}H_3$), 14.9 (d, $^3J_{PSCC} = 6$ Hz, $SCH_2\underline{C}H_3$), 27.1 (d, $^2J_{PSC} = 4$ Hz, CH_2), 61.9–62.3 (m, CD_2). δ_P 95.6. CI-MS *m/z* 218 (M^+, 100).

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