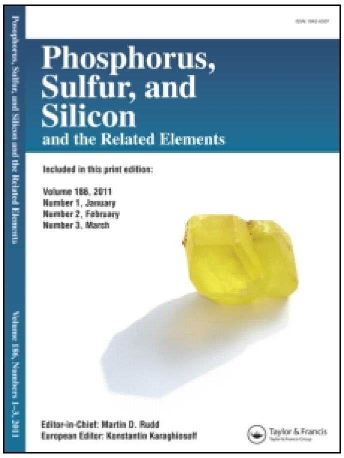

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

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To cite this Article Hudson, Harry R. , Jászay, Zsuzsa M. and Pianka, Max(2003) 'The Preparation and Properties of Some α-Acyloxy- and α-Carbamoyloxy-Phosphonothionates', Phosphorus, Sulfur, and Silicon and the Related Elements, 178: 7, 1571 — 1582

To link to this Article: DOI: 10.1080/10426500307878

URL: http://dx.doi.org/10.1080/10426500307878

Phosphorus, Sulfur, and Silicon, 178:1571–1582, 2003

ISSN: 1042-6507 print
DOI: 10.1080/10426500390212988

THE PREPARATION AND PROPERTIES OF SOME α-ACYLOXY- AND α-CARBAMOYLOXY-PHOSPHONOTHIONATES

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(Received January 28, 2003)

New α-acyloxy and α-carbamoyloxy derivatives of dimethyl 2,2,2-trichloroethyl-phosphonothionate have been prepared, characterized, and screened for activity against free-living soil nematodes. Several of the more easily hydrolysable esters, and also the N-*methylcarbamoyl derivative, were as active as the parent pesticide, dimethyl α-hydroxy-2,2,2-trichloroethylphosphonothionate, after an induction period during which the active species is assumed to be released* in vivo. *It is concluded that the 2,2,2-trichloroethyl group is essential for activity in compounds of these types and that the presence of the* N-*methylcarbamoyl group does not in itself confer activity.*

Keywords: Acyloxy; carbamoyloxy; nematicidal activity; phosphonothionate

Phosphonic acids and their derivatives are of widespread interest as biologically active molecules in the medical and agrochemical fields.[1] One important application in the control of insect pests and parasites is dependent on anticholinesterase activity for which it is a normal requirement that a suitable leaving group (Y) should be attached to phosphorus (**1**, R^1 and/or R^2 = alkyl, alkoxy, dialkylamino; X = O or S; Y = F, CN, p-$O_2NC_6H_4O$, or other good leaving group).[2] In the absence of such a leaving, group activity may depend upon molecular rearrangement

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We are grateful to British Technology Group for financial support and to Mr. Ian Cook and Dr. Richard A'Court for helpful discussions and advice. We also thank Dr. Anne Terry and Dr. Paul Matewele for biological screening.

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**The late Professor Max Pianka, to whose memory this paper is dedicated.

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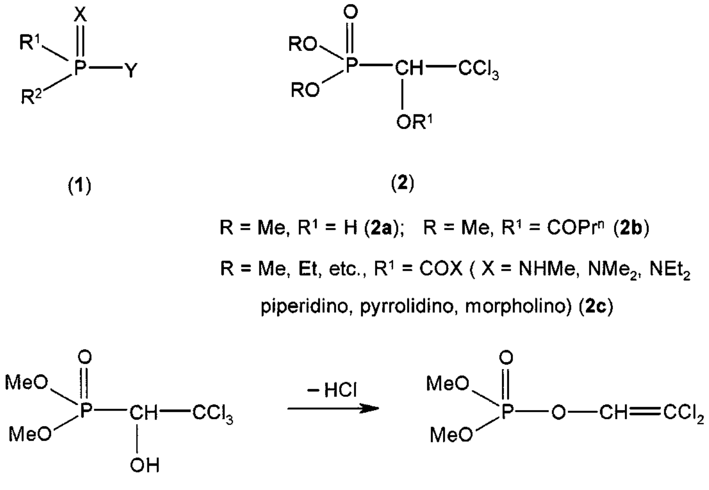
for activation or the presence in the molecule of some other source of activity, e.g., a carbamate moiety.[3] An important example involving rearrangement of the parent molecule is provided by dimethyl 2,2,2-trichloro-1-hydroxyethylphosphonate (**2a**) which finds application as a low toxicity domestic insecticide (trichlorfon),[4] and as an anthelmintic agent (metrifonate) in the control of *Schistosoma haematobium*.[5] The molecule readily rearranges with the elimination of hydrogen chloride in alkaline conditions (Scheme 1) to give dimethyl 2,2-dichlorovinyl phosphate (**3**),[6] otherwise known as the insecticide dichlorvos[7] and it is likely that a similar rearrangement occurs in vivo. The butanoic ester (butonate, **2b**)[8] has also been reported as a propesticide which may yield dichlorvos (possibly via the intermediate formation of trichlorfon) by enzymic degradation.[7]



(**1**) (**2**)

R = Me, R^1 = H (**2a**); R = Me, R^1 = $COPr^n$ (**2b**)

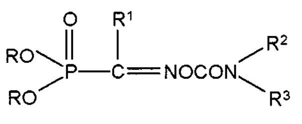
R = Me, Et, etc., R^1 = COX (X = NHMe, NMe_2, NEt_2 piperidino, pyrrolidino, morpholino) (**2c**)

(**2a**) (**3**)

SCHEME 1

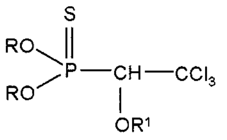
Other derivatives of trichlorfon claimed as agricultural insecticides[9] include the *N*-substituted carbamates or urethans (**2c**) which also may be expected to act as propesticides of dichlorvos, either via hydroysis to give trichlorfon and subsequent rearrangement (Scheme 1), or by direct rearrangement with concerted cleavage of the O—CO and C—Cl bonds. Although the activity of these carbamates and of other analogous dialkyl esters (R = Et, etc.)[9] might alternatively be associated with the carbamate moiety, it is normally only *N*-methyl- or (less frequently) *N*,*N*-dimethyl-carbamates which are insecticidal.[3]

The α-carbamoyloximinoalkylphosphonates (**4**) constitute another class of insecticidal phosphonates[10,11] which do not have a conventional leaving group attached directly to the phosphorus atom and for which alternative activation sequences can be envisaged. In these cases also the carbamoyl group (especially the *N*-methylcarbamoyl group or a suitable precursor of this group) might account for their activity as anticholinesterases although the possibility of intramolecular rearrangement to give an active organophosphate species cannot be excluded. There is no evidence presently available to show whether such an activation mechanism is involved in vivo but it is worth noting that α-hydroxyiminophosphonates are known to undergo Beckmann rearrangement, or to fragment with the elimination of alkyl cyanide according to conditions,[12] and that either of these processes could lead to the formation of an active phosphorylating agent.



(4)

R = alkyl, R^1 = alkyl or aryl, R^2 = alkyl, R^3 = H (**4a**);
R = alkyl, R^1 = alkyl or cycloalkyl, R^2 = Me,
R^3 = H, Me, or sulfenyl group (**4b**)

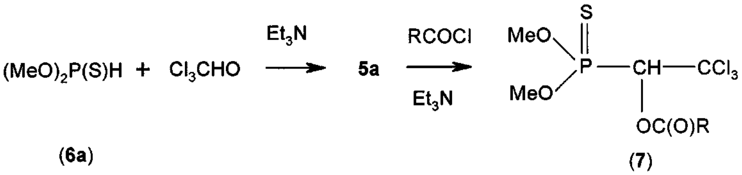


(5)

R = Me, R^1 = H (**5a**);
R = Et, R^1 = COMe (**5b**);
R = Pr^i, R^1 = COMe (**5c**)

DISCUSSION

The purpose of this article is to report the preparation and properties of some new ester and carbamoyl derivatives of the thiono analogue of trichlorfon, viz. dimethyl 2,2,2-trichloro-1-hydroxyethylphosphonothionate (**5a**).[13] Thiono compounds may have practical advantages as insecticides over the oxygen analogues (to which they are converted in vivo) because of their generally lower mammalian toxicities.[2,3] Ester derivatives may provide for the controlled release of the parent molecule in vivo. The only esters of 2,2,2-trichloro-1-hydroxyethylphosphonothionates reported in the literature are the acetates of diethyl and diisopropyl 2,2,2-trichloro-1-hydroxyethylphosphonothionate (**5b**, **5c** respectively). These compounds were obtained during a study of the chemistry of *O*,*O*-dialkyl



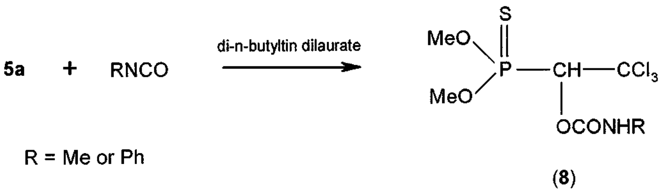
R = Me (**7a**), ClCH$_2$ (**7b**), Cl$_2$CH (**7c**),

Cl$_3$C (**7d**), F$_3$C, (**7e**), MeO (**7f**)

SCHEME 2

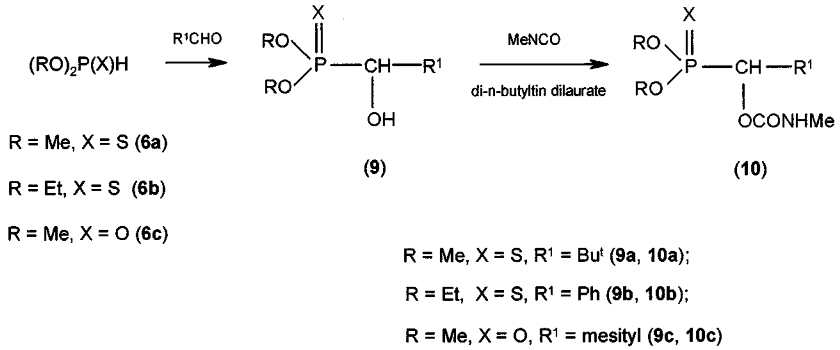
S-acetyl phosphorothioites, being formed by the interaction of the latter with chloral.[14] Their biological activity was not, however, discussed.

In the present work, dimethyl 2,2,2-trichloro-1-hydroxyethylphosphonothionate (**5a**) was prepared as described[13] by the base-catalyzed interaction of dimethyl phosphonothionate (**6a**) with chloral, and was then esterified by addition of the appropriate acyl halide (Scheme 2), to give the acetate, mono-, di-, and trichloro-acetates, the trifluoroacetate, and the mixed methyl carbonate (**7a**–**7f** respectively). The *N*-methylcarbamoyl (**8a**) and *N*-phenylcarbamoyl derivatives (**8b**) were formed by reaction of the hydroxyphosphonate (**5a**) with methyl or phenyl isocyanate in the presence of a catalytic quantity of dibutyltin dilaurate (Scheme 3), as described elsewhere for the carbamoylation of trichlorfon.[15] For purposes of comparison, *N*-methylcarbamoyl derivatives also are reported for related phosphonothionates in which the trichloromethyl group is replaced by t-butyl (**10a**) or phenyl (**10b**), and for dimethyl α-(*N*-methylcarbamoyloxy)-2,4,6-trimethylbenzylphosphonate (**10c**). Products were purified by column chromatography on Kieselgel 60 and were characterized by a combination of elemental analysis, nmr, and ir spectroscopy.



R = Me (**8a**), Ph (**8b**)

SCHEME 3



SCHEME 4

Spectroscopy

^{1}H, ^{13}C, and ^{31}P nmr data for all compounds are shown in the Experimental section. As noted previously for α-hydroxyphosphonates,[16] the two alkoxy groups attached to phosphorus are anisochronous and give rise to separate ^{1}H and ^{13}C signals by virtue of the presence of a chiral α-carbon atom. Thus, the methoxy groups for most compounds appear as two overlapping doublets ($\Delta\delta_H$ 0.01–0.02 ppm; J_{POCH} 13.8–14.7 Hz). The largest chemical shift difference ($\Delta\delta_H$ 0.32 ppm) is exhibited by the methoxy groups of the α-mesityl derivative (**10c**), while the α-phenyl derivatives (**8b**, **10b**) are exceptional in that no separation of the signals is observable. Chemical shift differences for the two methoxy groups in the ^{13}C spectra of all compounds are consistently in the range $\Delta\delta_C$ 0.3–0.6 ppm (J_{POCH} 5.8–6.7 Hz).

The presence of P=S in the compounds under investigation is confirmed by characteristic ^{31}P nmr signals in the region δ_P 80–90 ppm.[17] Infrared spectroscopy is less useful for the unambiguous identification of this group for which stretching absorptions are usually relatively weak.[18] Absorption frequencies between 584 and 632 cm^{-1} have been reported for the P=S bond in several phosphonothionates[19] and a band at 628 cm^{-1} has been assigned to P=S in diethyl and diisopropyl 1-acetoxy-2,2,2-trichloroethylphosphonothionate (**5b** and **5c**).[14] Our compounds, which are closely related to **5b** and **5c**, exhibit absorptions of weak to medium intensity between 600 and 630 cm^{-1} which may be attributed tentatively to the P=S stretching vibration. Strong carbonyl absorptions are exhibited in the range 1770–1805 cm^{-1} by the carboxylic esters (**7a**–**7f**) and 1715–1758 cm^{-1} by the carbamates (**8a**, **8b**, **10a**). The P—O—C linkage also gives rise to a characteristically strong absorption for all compounds between 1030 and 1057 cm^{-1}.

$MeSCMe_2CH{=}NOC(O)NHMe$

(11)

SCHEME 5

Biological Activity

Screening against free-living soil nematodes* showed the pesticide trichlorfon (**2a**) and its thiono analogue (**5a**) to be as active at 50 ppm as the commercial nematicide, aldicarb (**11**). Under identical conditions the acetate (**7a**) and monochloroacetate (**7b**) were inactive. However, the di- and trichloroacetates (**7c**, **7d**), the methoxycarbonyl derivative (**7e**), and the *N*-methylcarbamoyl derivative (**8a**) showed similar activity to that of the parent hydroxyphosphonate (**5a**) after an induction period of 24 h, indicating that the active species was being released gradually in vivo. The triflouroacetate (**7f**), which hydrolyzed rapidly in water, immediately showed similar activity to **5a**. The total absence of nematicidal activity in dimethyl 1-hydroxy-2,2,2-trimethylethylphosphonothionate (**9a**) and in the *N*-methylcarbamoyl derivatives **10a**, **10b**, and **10c**, confirms the requirement that the 2,2,2-trichloroethyl group should be present and shows also that the *N*-methylcarbamoyl group does not in itself give rise to activity in compounds of these types.† The *N*-phenylcarbamate (**8b**) also was inactive.

EXPERIMENTAL

Starting Materials

General reagents and research chemicals were obtained from Aldrich Chemical Company. Methyl isocyanate was kindly supplied as a gift by Glaxo Research, Ware, Herts. Dimethyl 2,4,6-trihydroxybenzylphosphonate (**9c**)[20] was available in the laboratory and was spectroscopically pure.

Analytical and Instrumental Methods

Microanalysis (for C, H, N, and S) was carried out on a Carlo Erba 1106 Elemental Analyser. ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded

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*As a convenient and simple method of preliminary screening for nematicidal activity, tests were made by visual observation under a microscope of free-living soil nematodes in an aqueous environment. (Method devised by Dr. Anne Terry of this department.)

†Similar results have been obtained in studies of a series of P=O analogues of the type $(MeO)_2P(O)CR^1R^2OCONHMe$, none of which showed activity except for the trichlorfon derivative ($R^1 = H$; $R^2 = CCl_3$) (R.O. Yusuf, unpublished).

for solutions in $CDCl_3$, using a Bruker AM250 FT spectrometer operating at 250.133 or 62.896 MHz for ^1H and ^{13}C spectra respectively. ^{31}P spectra were recorded either on the Bruker AM250 instrument operating at 101.256 MHz, or a Bruker WP80 FT spectrometer operating at 32.292 MHz. Chemical shifts are reported relative to TMS (internal reference) for ^1H and ^{13}C spectra and to 85% H_3PO_4 (external reference) for ^{31}P spectra. Infrared spectra were obtained for liquid films on a Bio-Rad FT S40 instrument. Electron impact mass spectra were run on a Kratos Profile spectrometer operating at 70 eV.

Preparation of Intermediates

Dimethyl Phosphonothionate (6a)

Trimethyl phosphite (93.1 g, 0.75 mmol) was added to an excess of liquefied hydrogen sulfide (*ca.* 40 ml) and *N*,*N*-diethylaniline (56 g, 0.38 mmol) in a stirred stainless steel autoclave and the mixture was heated for 24 h at 53–54°C (pressure 12–3 atm.).[21] After evaporation of unreacted hydrogen sulphide and removal of by-product methanol under reduced pressure, the residue was distilled to give the product (46.7 g), b.p. 66°C at 20 mmHg (lit.[22] 52–53.5°C at 16.5 mmHg), and a higher fraction (28.4 g), b.p. 66–76°C at 20 mmHg, containing some diethylaniline. The latter was removed by washing a solution in dichloromethane with dilute hydrochloric acid, followed by drying ($MgSO_4$) and redistilling to give a further quantity (17.9 g) of pure product (total yield 68.4%) (Found: C, 19.08; H, 5.57. $C_2H_7O_2PS$ requires: C, 19.04; H, 5.59%); δ_H ($CDCl_3$) 3.77 (d, 6H, MeO, J_{POCH}14.3 Hz), 7.72 (d, 1H, P—H, J_{PH}651.8 Hz); δ_C ($CDCl_3$) 52.5 (d, MeO, J_{POC}6.7 Hz); δ_P ($CDCl_3$) 75.0 (d sept, J_{PH} 652.3 Hz, J_{POCH} 14.4 Hz).

Diethyl Phosphonothionate (6b)

Hydrogen sulphide gas was passed into an ice-cold solution[23] of diethyl phosphorochloridite (prepared as described)[24] (25.8 g, 0.165 mmol) and pyridine (13.2 g, 0.167 mmol) in petroleum (b.p. 60–80°C) (160 ml). The temperature rose to 25°C. After 10 min the precipitate of pyridinium chloride was filtered off (17.5 g, 92%) and the filtrate was concentrated and distilled to give the product (i) (9.6 g, 37.8%), b.p. 73–76°C at 25 mmHg and (ii) (5.1 g, 20.0%, b.p. 76–81°C at 25 mmHg (lit.[25] b.p. 80–81°C at 20 mmHg); δ_H ($CDCl_3$) 1.35 (t, 6H, $C\underline{H}_3CH_2O$, J_{HCCH} 7.1 Hz), 4.0–4.2 (m, 4H, 2 x CH_2O), 7.75 (d, 1H, P-H, J_{PH}647.4 Hz); δ_C ($CDCl_3$) 16.2 (d, $\underline{C}H_3CH_2O$, J_{POCC} 6.7 Hz), 62.3 (d, $CH_3\underline{C}H_2O$, J_{POC} 6.6 Hz); δ_P ($CDCl_3$) 69.1 (d quintet, J_{PH} 647.8 Hz, J_{POCH} 10.8 Hz).

1-Hydroxyphosphonates and 1-Hydroxyphosphonothionates

Dimethyl 2,2,2-trichloro-1-hydroxyethylphosphonate (trichlorfon, **2a**),[6,26] δ_C ($CDCl_3$) 17.5, and the corresponding phosphonothionate (**5a**),[13] δ_C ($CDCl_3$) 92.1, were prepared as described by the condensation of dimethyl phosphonate (**6c**) or dimethyl phosphonothionate (**6a**), respectively, with chloral. Condensation of dimethyl phosphonothionate (**6a**) (0.03 mmol) and 2,2-dimethylpropanal (0.03 mmol) in the presence of alumina[27] gave *dimethyl 1-hydroxy-2,2-dimethylpropylphosphonothionate* (**9a**) as a colourless oily liquid (66% yield), δ_H ($CDCl_3$) 1.09 (s, 9H, $\underline{Me}_3C$), 2.86 (br m, OH), 3.58 (m, 1H, α-CH), 3.77 (d, 3H, MeO, J_{POCH} 13.0 Hz), 3.78 (d, 3H, MeO, J_{POCH}13.2 Hz); δ_C ($CDCl_3$) 26.8 (d, $\underline{Me}_3C$, J_{PCCC} 5.8 Hz), 35.3 (d, β-C, J_{PCC} 6.0 Hz), 53.5 (d, MeO, J_{POC} 7.9 Hz), 53.6 (d, MeO, J_{POC} 7.7 Hz), 79.9 (d, α-C, J_{PC} 116.1 Hz); δ_P ($CDCl_3$) 101.5; EI-MS m/z (%) 213 (MH^+, 43.8), 212 (M^+, 43.5). Similarly, diethyl phosphonothionate (**6b**) (0.0052 mmol) and benzaldehyde (0.0052 mmol) gave *diethyl 1-hydroxybenzylphosphonothionate* (**9b**) (62.8% yield), m.p. 41–42°C from hexane, δ_H ($CDCl_3$) 1.12 (t, 3H, $C\underline{H}_3CH_2O$, J_{HCCH} 7.1 Hz), 1.30 (t, 3H, $C\underline{H}_3CH_2O$, J_{HCCH} 7.1 Hz), 3.17 (br s, 1H, OH), 3.7–3.9 (m, 2H, $CH_3\underline{C}H_2O$), 3.9–4.2 (m, 2H, $CH_3\underline{C}H_2O$), 4.95 (d, 1H, α-CH, J_{PCH} 7.1 Hz), 7.26–7.46 (m, 5H, Ar); δ_C ($CDCl_3$) 16.0 (d, $\underline{C}H_3CH_2O$, J_{POCC} 6.6 Hz), 16.2 (d, $\underline{C}H_3CH_2O$, J_{POCC} 6.7 Hz), 63.7 (d, $CH_3\underline{C}H_2O$, J_{POC} 7.7 Hz), 64.3 (d, $CH_3\underline{C}H_2O$, J_{POC} 7.6 Hz), 74.9 (d, α-C, J_{PC} 119.8 Hz), 127–136 (Ar); δ_P ($CDCl_3$) 93.4.

General Procedure for the Preparation of O-Acyl Derivatives of Dimethyl 2,2,2-Trichloro-1-hydroxyethylphosphonothionate

The acyl chloride (0.008 mmol) was added to a stirred solution of phosphonothionate (1.36 g, 0.005 mmol) in dichloromethane (20 ml) at −10 to −20°C. Triethylamine (0.8 g, 0.008 mmol) was then added and stirring was continued at room temperature until the reaction, monitored by TLC, was complete (typically 2–3 h). Pentane was added as necessary to complete the precipitation of triethylamine hydrochloride which was filtered off. The oily residue was subjected to column chromatography using toluene/petroleum b.p. 60–80°C (95:5) to give the purified product. The following new compounds were obtained as light yellow oils:

Dimethyl 1-acetoxy-2,2,2-trichloroethylphosphonothionate (**7a**) (69.8% yield) (Found: C, 23.05; H, 3.21; S, 9.95. $C_6H_{10}Cl_3O_4PS$ requires: C, 22.83; H, 317; S, 10.15%); δ_H ($CDCl_3$) 2.28 (s, 3H, MeCO), 3.82 (d, 3H, MeO, J_{POCH} 13.8 Hz), 3.84 (d, 3H, MeO, J_{POCH} 13.9 Hz), 5.94 (d, 1H, α-CH, J_{PCH} 8.5 Hz); δ_{C} ($CDCl_3$) 20.6 ($\underline{\text{Me}}$CO) 54.0 (d, MeO, J_{POC} 6.7 Hz), 54.5 (d, MeO, J_{POC} 6.4 Hz), 79.8 (d, α-C, J_{PC} 136.4 Hz), 94.6 (d, CCl_3, J_{PCC} 7.5 Hz), 168.5 (d, C=O, J_{PCOC} 3.7 Hz); δ_{P} ($CDCl_3$) 80.5; IR (ν, cm^{-1}) 1771 (s) (C=O), 1052 (s), 1029 (s) (P—O—C), 621(m), 600(w) (P=S); EI-MS *m/z* (%) 314 (M^+ for $^{35}Cl_3$, 18).

Dimethyl 1-chloroacetoxy-2,2,2-trichloroethylphosphonothionate (**7b**) (66.7% yield) (Found: C, 20.38; H, 2.65; S, 8.95. $C_6H_9Cl_4O_4PS$ requires: C, 20.57; H, 2.57; S, 9.14%); δ_{H} ($CDCl_3$) 3.83 (d, 3H, MeO, J_{POCH} 14.0 Hz), 3.85 (d, 3H, MeO, J_{POCH} 14.1 Hz), 4.29 (s, 2H, CH_2Cl), 5.95 (d, 1H, α-CH, J_{PCH} 7.9 Hz); δ_{C} ($CDCl_3$) 40.4 (CH_2Cl) 54.0 (d, MeO, J_{POC} 6.2 Hz), 54.6 (d, MeO, J_{POC} 6.2 Hz), 80.8 (d, α-C, J_{PC} 135.1 Hz), 93.9 (d, CCl_3, J_{PCC} 6.2 Hz), 168.4 (d, C=O, J_{PCOC} 3.2 Hz); δ_{P} ($CDCl_3$) 82.7; IR (ν, cm^{-1}) 1784 (s) (C=O), 1051 (s), 1026 (sh) (P—O—C), 625 (m) (P=S).

Dimethyl 1-dichloroacetoxy-2,2,2-trichloroethylphosphonothionate (**7c**) (57.2% yield) (Found: C, 18.98; H, 2.07; S, 8.25. $C_6H_8Cl_5O_4PS$ requires: C, 18.73; H, 2.08; S, 8.32%); δ_{H} ($CDCl_3$) 3.84 (d, 3H, MeO, J_{POCH} 14.0 Hz), 3.86 (d, 3H, MeO, J_{POCH} 14.1 Hz), 5.92 (d, 1H, α-CH, J_{PCH} 8.2 Hz), 6.15 (s, 1H, $CHCl_2$); δ_{C} ($CDCl_3$) 54.2 (d, MeO, J_{POC} 6.0 Hz), 54.6 (d, MeO, J_{POC} 6.0 Hz), 63.4 ($CHCl_2$), 81.5 (d, α-C, J_{PC} 134.5 Hz), 93.6 (d, CCl_3, J_{PCC} 6.5 Hz), 162.4 (d, C=O, J_{PCOC} 3.6 Hz); δ_{P} ($CDCl_3$) 81.0; IR (ν, cm^{-1}) 1789 (s), 1772 (s) (C=O), 1050 (sh), 1036 (s) (P—O—C), 626 (m), 608 (m) (P=S).

Dimethyl 1-trichloroacetoxy-2,2,2-trichloroethylphosphonothionate (**7d**) (14.3% yield) δ_{H} ($CDCl_3$) 3.86 (d, 3H, MeO, J_{POCH} 14.0 Hz), 3.87 (d, 3H, MeO, J_{POCH} 14.2 Hz), 5.91 (d, 1H, α-CH, J_{PCH} 7.9 Hz); δ_{C} ($CDCl_3$) 54.2 (d, MeO, J_{POC} 6.3 Hz), 54.6 (d, MeO, J_{POC} 5.8 Hz), 83.1 (d, α-C, J_{PC} 134.3 Hz), 93.3 (CH$\underline{\text{C}}$$Cl_3$), 160.0 (C=O); δ_{P} ($CDCl_3$) 80.0; IR (ν, cm^{-1}) 1786(s) (C=O), 1049(sh), 1035(s) (P—O—C), 623(w), 607(m) (P=S); EI-MS *m/z(%)* 409 (0.9), 407 (4.0), 405 (8.4), 403 (10.6), 401 (5.3) ($[M\text{-}15]^+$, Cl isotope cluster).

Dimethyl 1-trifluoroacetoxy-2,2,2-trichloroethylphosphonothionate (**7e**) (94.7% yield, not chromatographed) (Found: C, 19.49; H, 2.03; S, 8.85. $C_6H_7Cl_3F_3O_4PS$ requires: C, 19.49; H, 1.89; S, 8.66%); δ_{H} ($CDCl_3$) 3.85 (d, 3H, MeO, J_{POCH} 14.0 Hz), 3.86 (d, 3H, MeO, J_{POCH} 14.0 Hz), 5.93 (d, 1H, α-CH, J_{PCH} 7.8 Hz); δ_{C} ($CDCl_3$) 54.3 (d, MeO, J_{POC} 6.4 Hz), 54.7 (d, MeO, J_{POC} 6.2 Hz), 82.1 (d, α-C, J_{PC} 133.3 Hz), 93.0 (d, CCl_3, J_{PCC} 5.5 Hz), 114.3 (quart., CF_3, J_{FC} 285.3 Hz), 155.6 (d quart., C=O, J_{FCC} 44.7 Hz, J_{PCOC} 3.3 Hz); δ_{P} ($CDCl_3$) 79.8; IR (ν, cm^{-1}) 1805 (s) (C=O), 1053(sh), 1035(s) (P—O—C), 629(w), 612(m) (P=S).

Dimethyl 1-methoxycarbonyloxy-2,2,2-trichloroethylphosphonothionate (**7f**) (42.2% yield) (Found: C, 22.08; H, 3.07; S, 9.75. $C_6H_{10}Cl_3O_5PS$ requires: C, 19.49; H, 1.89; S, 8.66%); δ_{H} ($CDCl_3$) 3.84 (d, 3H, MeOP, J_{POCH} 14.7 Hz), 3.85 (d, 3H, MeOP, J_{POCH} 14.0 Hz), 3.94 (s, 3H, MeOCO), 5.70 (d, 1H, α-CH, J_{PCH} 8.2 Hz); δ_{C} ($CDCl_3$) 54.2 (d, MeOP, J_{POC} 6.2 Hz), 54.5 (d, MeOP, J_{POC} 5.8 Hz), 56.3 ($\underline{\mathrm{Me}}$OCO)83.5 (d, α-C, J_{PC} 136.1 Hz), 94.2 (d, CCl_3, J_{PCC} 7.7 Hz), 154.3 (d, C=O, J_{PCOC} 4.7 Hz); δ_{P} ($CDCl_3$) 82.5; IR (ν, cm^{-1}) 1770(s) (C=O), 1049(sh), 1030(s) (P—O—C), 628(m), 611(m) (P=S).

Preparation of N-Methyl and N-Phenylcarbamoyl Derivatives of 1-Hydroxyphosphonates and 1-Hydroxyphosphonothionates

Dimethyl 2,2,2-trichloro-1-(N-methylcarbamoyloxy)ethylphosphonothionate (**8a**) Dimethyl 2,2,2-trichloro-1-hydroxyethylphosphonothionate (**5a**) (2.73 g, 0.01 mmol) was dissolved in toluene (2 ml). A catalytic amount (one drop) of di-n-butyltin dilaurate was added, followed by methyl isocyanate (0,63 g, 0.11 mmol), and the mixture was heated in a sealed ampoule (4 h at 95–100°C). Removal of the toluene under reduced pressure gave an oily residue [δ_{P}, 92.7 (starting material), 89.7, and 83.7 (desired product)] which was heated again (6 h at 110°C) with similar quantities of catalyst and methyl isocyanate to give further reaction). Toluene was removed and the oily residue (2.65 g) was subjected to column chromatography, using toluene/acetone (9:1) as eluent, to give a main fraction consisting of *dimethyl 2,2,2-trichloro-1-(N-methylcarbamoyloxy)ethylphosphonothionate* (**8a**) (1.3 g, 39%) as a colorless oil (Found: C, 22.09; H, 3.23; N, 4.37; S, 9.70. $C_6H_{11}Cl_3NO_4PS$ requires: C, 21.79; H, 3.33; N, 4.24; S, 9.69%); δ_{H} ($CDCl_3$) 2.92 (d, 3H, MeN, J_{HNCH} 4.9 Hz), 3.81 (d, 3H, MeO, J_{POCH} 13.8 Hz), 3.83 (d, 3H, MeO, J_{POCH} 13.9 Hz), 5.84 (d, 1H, α-CH, J_{PCH} 9.4 Hz); δ_{C} ($CDCl_3$) 28.1 (MeN), 54.0 (m, MeO), 80.3 (d, α-C, J_{PC} 138.8 Hz), 95.1 (d, CCl_3, J_{PCC} 10.9 Hz), 154.4 (d, C=O, J_{PCOC} 4.2 Hz); δ_{P} ($CDCl_3$) 83.7; IR (ν, cm^{-1}) 1750(sh), 1735(s) (C=O), 1049(s), 1027(s) (P—O—C), 624(m), 609(m) (P=S); EI-MS *m/z* (%) 335 (9), 333 (24.5), 331 (41.0), 329 (40.8) (M^+, Cl isotope cluster).

General Procedure for the Preparation of N-Methylcarbamoyl Derivatives of 1-Hydroxyphosphonates and Phosphonothionates

The 1-hydroxyphosphonate or phosphonothioate (0.01 mmol), methyl isocyanate (0.011 mmol), and di-n-butyltin dilaurate (1 drop) were dissolved in toluene (4 ml) and heated in a sealed ampoule (8–18 h at 100–110°C), the reaction being monitored by TLC and/or NMR until complete. After removal of toluene under reduced pressure, the product was purified by column chromatography using toluene/aceone (9:1) as eluent, to give:

Dimethyl 1-(N-methylcarbamoyloxy)-2,2-dimethylpropylphosphonothioate (**10a**) as a colorless oil (26% yield) (Found: C, 40.33; H, 7.76; N, 5.15; S, 12.05. $C_9H_{20}NO_4PS$ requires: C, 40.15; H, 7.43; N, 5.20; S, 11.90%); δ_H ($CDCl_3$) 1.10 (s, 9H, Me_3C), 2.85 (d, 3H, MeN, J_{HNCH} 4.9 Hz), 3.73 (d, 6H, MeO, J_{POCH} 13.4 Hz), 5.06 (d, 1H, α-CH, J_{PCH} 8.0 Hz); δ_C ($CDCl_3$) 27.0 (d, $\underline{Me}_3C$, J_{PCCC} 6.0 Hz), 27.8 (MeN), 52.9 (d, MeO, J_{POC} 6.7 Hz), 53.2 (d, MeO, J_{POC} 7.0 Hz), 79.5 (d, α-C, J_{PC} 129.5 Hz), 156.3 (d, C=O, J_{PCOC} 4.5 Hz); δ_P ($CDCl_3$) 93.1; IR (ν, cm^{-1}) 1738(sh), 1715(s) (C=O), 1057(sh), 1033(s) (P—O—C), 634(m), 615(m) (P=S); EI-MS *m*/*z* (%) 269 (M^+, 45.8).

Diethyl α-(N-methylcarbamoyloxy)benzylphosphonothioate (**10b**) as a white crystalline solid, m.p. 65–68°C (56.7% yield) (Found: C, 49.13; H, 6.62. $C_{13}H_{20}NO_4PS$ requires: C, 49.20; H, 6.35%); δ_H ($CDCl_3$) 1.17 (t, 3H, $C\underline{H}_3CH_2O$, J_{HCCH} 7.0 Hz), 1.27 (t, 3H, $C\underline{H}_3CH_2O$, J_{HCCH} 7.0 Hz), 2.79 (d, 3H, MeN, J_{HNCH} 4.9 Hz), 3.8–4.2 (m, 4H, 2 x CH_2O), 5.03 (br s, 1H, NH), 6.11 (d, 1H, α-CH, J_{PCH} 11.8 Hz), 7.3–7.5 (m, 5H, Ar); δ_C ($CDCl_3$) 16.1 (m, $\underline{C}H_3CH_2O$), 27.7 (MeN), 63.7 (m, $CH_3\underline{C}H_2O$), *ca.* 80 (α-C, overlapping solvent peaks), 128–134 (Ar), 155.5 (d, C=O, J_{PCOC} 10.2 Hz); δ_P ($CDCl_3$) 87.4.

Dimethyl α-(N-methylcarbamoyloxy)-2,4,6-trimethybenzylphosphonate (**10c**) as a white crystalline solid, m.p. 120–123°C (79.3% yield) (Found: C, 53.40; H, 7.06; N, 4.36; $C_{14}H_{23}NO_4P$ requires: Found: C, 53.33; H, 7.03; N, 4.44%); δ_H ($CDCl_3$) 2.23 (s, 2,6-Me_2), 2.58 (s, 4-Me), 2.75 (d, 3H, MeN, J_{HNCH} 2.8 Hz), 3.46 (d, 3H, MeO, J_{POCH} 10.5 Hz), 3.78 (d, 3H, MeO, J_{POCH} 10.7 Hz), 5.30 (br s, 1H, NH), 6.52 (d, 1H, α-CH, J_{PCH} 18.6 Hz), 6.8 (2H, Ar); δ_C ($CDCl_3$) 20.53 (4-Me), 20.89 (2,6-Me_2), 27.7 (MeN), 53.3 (d, MeO, J_{POC} 6.5 Hz), 53.5 (d, MeO, J_{POC} 7.2 Hz), 68.2 (d, α-C, J_{PC} 173.7 Hz), 127–138 (Ar), 155.7 (d, C=O, J_{PCOC} 12.2 Hz); δ_P ($CDCl_3$) 22.6.

Similarly, the interaction of phenyl isocyanate with dimethyl 2,2,2-trichloro-1-hydroxyethylphosphonothionate gave:

Dimethyl 2,2,2-trichloro-1-(N-phenylcarbamoyloxy)ethylphosphonothionate (**8b**) (2.4 g, 81.5%), δ_H ($CDCl_3$) 3.82 (d, 6H, MeO, J_{POCH} 13.8 Hz), 5.93 (d, 1H, α-CH, J_{PCH} 9.4 Hz), 7.3–7.5 (5H, Ar); δ_C ($CDCl_3$) 54.0 (d, MeO, J_{POC} 6.7 Hz), 54.3 (d, MeO, J_{POC} 6.4 Hz), 80.1 (d, α-C, J_{PC} 137.3 Hz), 94.8 (d, CCl_3, J_{PCC} 10.4 Hz), 154.4 (d, C=O, J_{PCOC} 4.2 Hz), 129–136 (Ar), 150.6 (C=O); δ_P ($CDCl_3$) 83.7; IR (ν, cm^{-1}) 1758(s), 1741(sh) (C=O), 1054(s), 1030(s) (P—O—C), 620(m) (P=S).

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