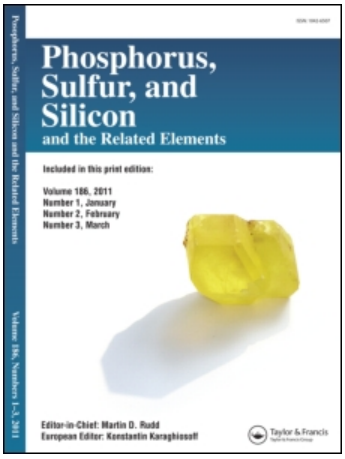

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THE AMINATION OF PHOSPHONODITHIOFORMATES; A PREPARATION OF NEW FUNCTIONALISED PHOSPHONATES

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Primary and secondary functionalised amines were successfully phosphonothiocarbonylated upon treatment with phosphonodithioformates. This method allowed the preparation of a variety of new polyfunctional thiocarbamoylphosphonates and phosphonyl substituted heterocycles.

Key words: Amination; phosphonodithioformates; functionalised phosphonates; thiocarbamoylphosphonates.

INTRODUCTION

In addition to their use as synthetic intermediates, phosphonates are of interest due to their biological activity[1] resulting from their structural analogy with phosphates. Several functionalised phosphonates such as glyphosate [N-(dihydroxyphosphonylmethyl)-glycine],[2–8] clodronate [dichloromethylenebisphosphonic acid],[9] foscarnet [phosphonoformic acid],[10,11] fosfomycin[12] [phosphonomycine] are widely used in agriculture or medicine.

The synthesis and properties of thiocarbamoylphosphonates have however been the subject of limited study and only two methods have been used for their preparation. The first was by reaction of a dialkylphosphite with an isothiocyanate in a basic medium[13,14] and the second was by an Arbuzov-type reaction between trialkylphosphite and a dialkylthiocarbamoyl chloride (Figure 1). The N,N-diethylthiocarbamoylphosphonate has been shown to have corrosion inhibitor and pesticide properties.[15]

Among the methods described for the preparation of simple thioamides the amination of dithioesters is one of the milder and easier methods[16] occurring *via* a carbophilic addition of the amine followed by elimination of an alkanethiol (Figure 2). However with a dithioester substituted by an electron-withdrawing group such as a phosphonyl substituent which often favors the thiophilic addition of nucleophiles,[17–19] the regioselectivity of the amine addition might be modified.

We therefore undertook to study, starting from phosphonodithioformates,[20] the phosphonothiocarbonylation of a variety of both simple and functionalised amines including alkyl and aryl-substituted amines, diamines, aminoalcohols, aminothiols, a bromoamine, aminoacids and semicarbazides.

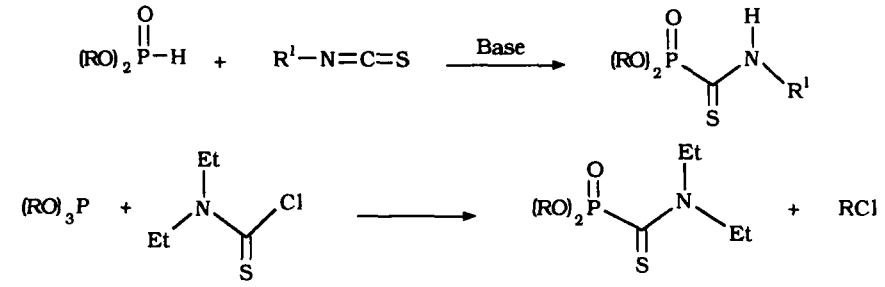


FIGURE 1

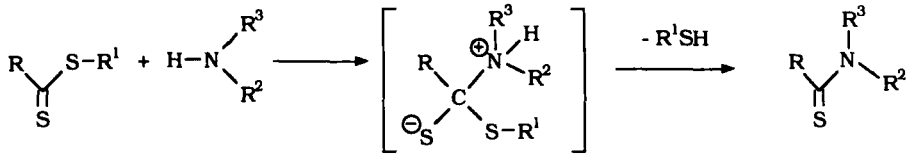


FIGURE 2

RESULTS

The S-methyl-dialkylphosphonodithioformates **1** (red oils) are prepared in high yield according to a literature procedure[20] whereby carbon disulfide is condensed onto the sodium salt of a dialkylphosphite and the resulting phosphonodithioate is alkylated with methyl iodide. Upon treatment with a variety of amines in THF at ambient temperature, the phosphonodithioesters are totally consumed as noted by decoloration of the red solution. In most cases, the decoloration is immediate however longer reaction periods are sometimes necessary due to the insolubility or lower reactivity of certain functionalised amines in THF.

If the reaction is then worked up directly after the decoloration, thiocarbamoylphosphonates **3** to **21** resulting from a carbophilic addition of the amines (hard nucleophiles), are obtained together with a phosphonodithioacetaldisulfide **2** resulting from a thiophilic addition of the methanethiolate (soft nucleophile, liberated during the reaction) to the starting dithioester **1** (Figure 3). For example, with methylamine, when the reaction was quenched after fifteen minutes, the thioamide **3** and the disulfide **2** were obtained in 70% and 30% yield, respectively. Fortunately, the base catalysed thiophilic addition of thiols to phosphonodithioformates **1**, which was the subject of a previous study,[21] has been shown to be a reversible reaction. The phosphonothiocarbonylation of amines, on the other hand, is irreversible and therefore when the mixture of **2**, the thiocarbamoylphosphonate and the unconsumed amine, is stirred at ambient temperature for fifteen hours or more, the equilibrium is gradually shifted and the phosphonothioamides **3** to **21** become the major and often sole products of the reaction. For the reactions with aminoacids and for those amines which are commercialised as hydrochlorides, it is necessary to add one equivalent of tertiary amine (triethylamine) to the reaction mixture.

The thiocarbamoylphosphonates **3** to **21** prepared from **1** by this method, are listed in Table I together with their respective yields and characteristic NMR data.

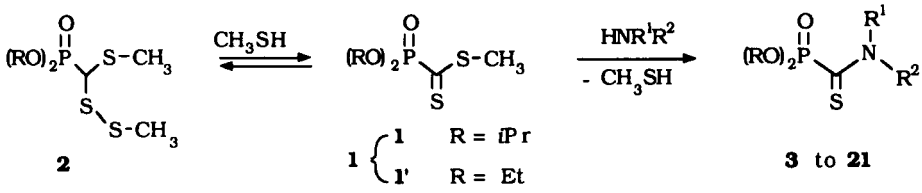
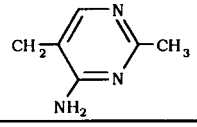


FIGURE 3

TABLE I

NMR characteristics ($CDCl_3$) of thiocarbamoylphosphonates (R = *i*Pr)

N°	R^1	R^2	^{31}P NMR ppm	^{13}C NMR* ppm (J in Hz)**	Yield (%)
3	H	CH_3	-3.00	194.75 (J=182)	82
4	CH_3	CH_3	-1.49	193.81 (J=189)	91
5	H	CH_2-C_6H_5	-3.06	194.68(J=181)	87
6	H	CH_2CH_2OH	-3.33	194.73 (J=183)	94
7	H	CH_2CH_2SH	-3.32	195.77 (J=182)	60
8	H	$CH_2CH(OH)CH_2OH$	-3.58	194.98 (J=184)	91
9	CH_3	CH_2CH_2OH	-6.60(*Syn*) -1.50(*Anti*)	194.03 (J=186)	92
10	H	CH_2CO_2Et	-3.57	196.22 (J=183)	83
11	H	CH_2CO_2H	-4.08	194.4 (J=184)	95
12	H	(S)-$CH(CH_3)CO_2H$	-4.41	193.47 (J=185)	53
13	H	(S)-$CH(CO_2H)CH_2CH_2SCH_3$	-5.62	194.12 (J=186)	78
14	H	(S)-$CH(CO_2H)CH_2Ph$	-4.08	193.78 (J=183)	63
15	H	(S)-$CH(CO_2H)CH(CH_3)2$	-3.80	194.88 (J=184)	80
16	H	(S)-$CH(CO_2H)CH_2CH_2CO_2H$	-4.54	194.33 (J=186)	44
17	(S)-$CH_2CH_2CH_2CH(CO_2H)$		-3.11(*Anti*) -4.48(*Syn*)	191.67 (J=187)	44
18	H	C_6H_5	-3.04	192.29 (J=182)	49
19	H	*o*-Br-C_6H_4	-3.62	192.95 (J=184)	62
20	-$CH_2CH_2NHCH_2CH_2$-		-1.80	192.92 (J=190)	75
21	H		-3.94	194.67 (J=181)	80

*chemical shift of the C=S.

**coupling constant ^1J between the carbon of the thiocarbonyl and the phosphorus.

When, however, the reaction was carried out with aminoethanethiol, a mixture of three compounds was isolated after the customary fifteen hours reaction time (Figure 4). These were the expected thioamide **7** (28%), the disulphide **2** (21%) and a thioamide-disulphide **22** (37%) resulting from both a carbophilic amination and a thiophilic thiolation between one molecule of the difunctional aminoethanethiol and two molecules of the starting phosphonodithioester **1**.

When the reaction was repeated, but left to stir for five days, the desired thioamide **7** was isolated in 60% yield along with a new thioamide-disulfide **23** in 18% yield. Disulfide **23** unlike disulfides **2** and **22** does not contain an acidic proton on the carbon α to the S—S bond. Given this structural difference and the relative stability of disulfide **23** even after extended periods in a basic medium, we would therefore suggest that a deprotonation step initiates the disulfide cleavage of **2** and **22** (Figure 4).

Very good yields of the corresponding thiocarbamoylphosphonates **6**, **8** and **9** were obtained by reaction of **1** with aminoethanol, aminopropane-1,2-diol and N-methylaminoethanol respectively. However, when N-methylaminoethanol was treated with the diethyl-substituted phosphonodithioformate **1'**, the expected thiocarbamoyl **9'** was isolated in only 39% yield due to an intramolecular transesterification which gave the heterocycle **24** as the major product in 47% yield. This cyclisation had not been observed during the equivalent reaction with the diisopropyl-substituted phosphonodithioformate **1** (Figure 5).

The addition of natural aminoacids to the phosphonodithioformate **1** was effected in THF/water in the presence of one equivalent of triethylamine. The reaction was

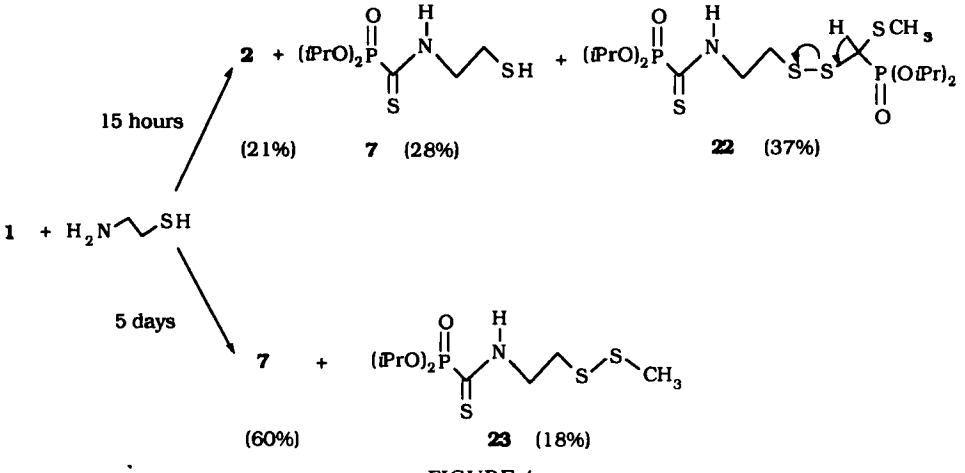


FIGURE 4

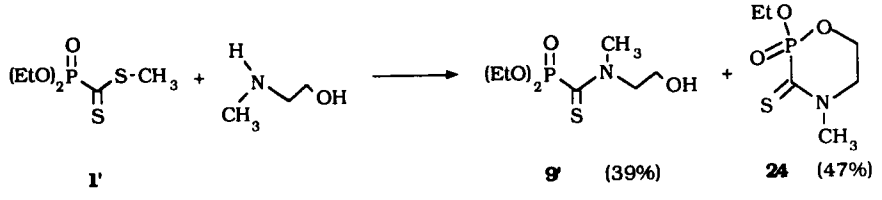


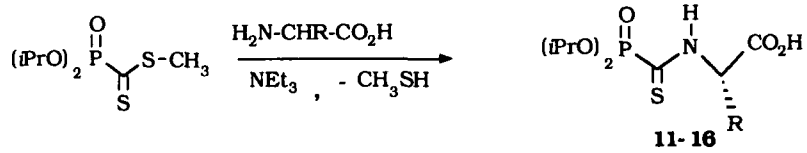
FIGURE 5

complete after 4 or 5 days as monitored by the disappearance of disulfide **2**. The thiocarbamoylphosphonates **11–17** obtained from the L-aminoacids are yellow crystalline solids (Figure 6). Thiocarbamoyl phosphonate **10** was also prepared from ethyl glycinate.

With less reactive aromatic amines such as aniline and bromoaniline, prolonged refluxing in THF is necessary to get the corresponding thioamide in satisfactory yield.

In order to confirm that phosphonothiocarbonylation of the enantiomerically pure aminoacids was not accompanied by any racemisation of the chiral centre, we synthetised compound **32** by treating the thiocarbamoylphosphonate **12** with (-)-ephedrin. Only one epimer could be detected in the ^{13}C NMR spectra (Figure 7).

Upon reaction with diamines, thiocarbamoyl- and bis-thiocarbamoylphosphonates were formed. The ratios of which were dependent on the stoichiometry of the starting materials involved. This was the case with piperazine (Figure 8) and ethylenediamine (Figure 9). However, with the latter, the main product formed with



R = H	glycine	**11**
R = CH_3	L-alanine	**12**
R = $CH_2CH_2SCH_3$	L-methionine	**13**
R = CH_2Ph	L-phenylalanine	**14**
R = $CH(CH_3)_2$	L-valine	**15**
R = $CH_2CH_2CO_2H$	L-glutamic acid	**16**

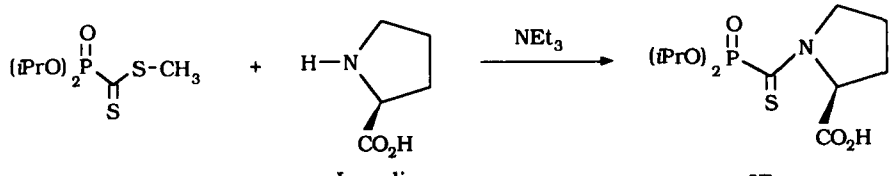


FIGURE 6

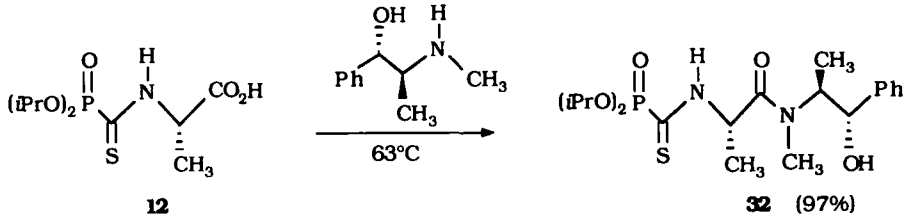


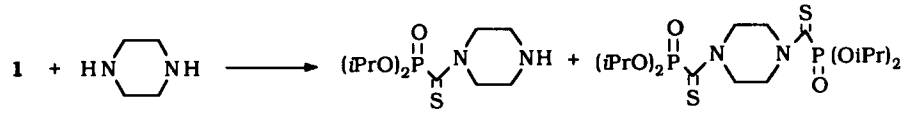
FIGURE 7

molar equivalent stoichiometry was the phosphonoimidazoline **27** resulting from an internal cyclisation with elimination of hydrogen sulfide.

With other functionalised amines, only phosphonyl substituted heterocycles were isolated. For example, with an excess of 2-bromoethylamine hydrochloride[22] in the presence of triethylamine, amination followed by an intramolecular thiophilic alkylation with the elimination of hydrobromic acid gave the thiazoline **28** (Figure 10).

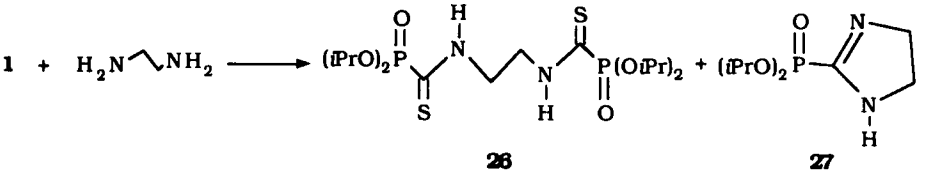
The reaction of dithioester **1** with semicarbazide (Figure 11), in the presence of triethylamine, proceeded more slowly than the other amines previously used. However cyclisation did eventually occur *via* amination and an intramolecular thiophilic acylation with elimination of ammonia to give the 5-(diisopropylphosphono)-1,3,4-thiadiazole-2(3H)-one **29**. The analogous reaction with thiosemicarbazide (Figure 11) led, after elimination of hydrogen sulfide, to the 2-amino-5-(diisopropylphosphono)-1,3,4-thiadiazole **30**. Such cyclisations are similar to those previously observed[23] with aromatic dithioesters.

With half an equivalent of hydrazine, a slow reaction occurred leading to the 2,5-bis-(diisopropylphosphono)-1,3,4-thiadiazoline **31** isolated in only 20% yield[24] (Figure 12).



	20	**25**
1 Equivalent	62%	14%
1/2 Equivalent	12%	76%

FIGURE 8



	26	**27**
1 Equivalent	-	49%
1/2 Equivalent	54%	

FIGURE 9

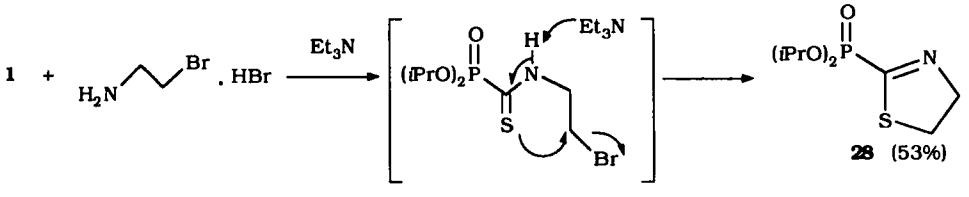


FIGURE 10

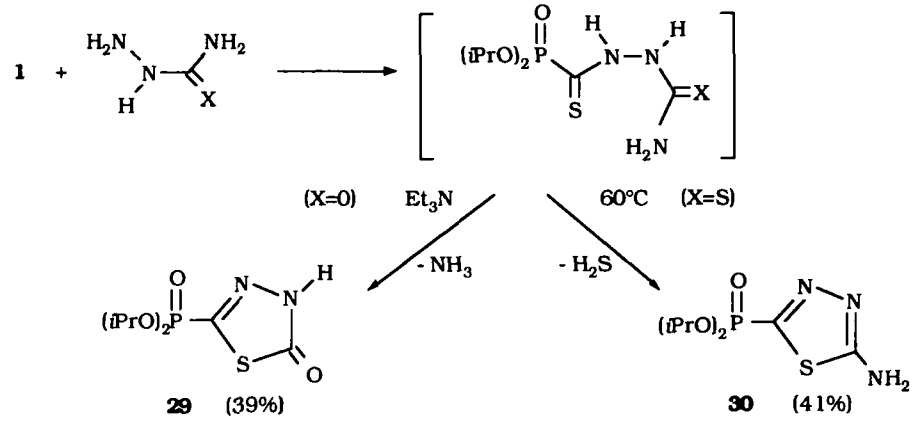


FIGURE 11

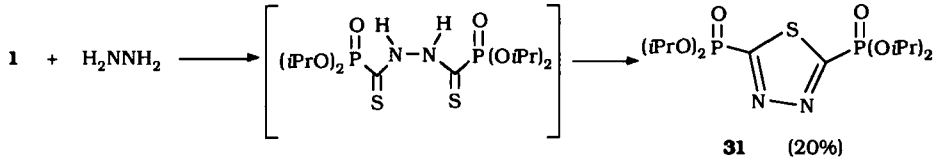
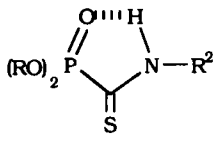
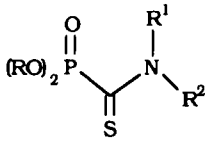


FIGURE 12

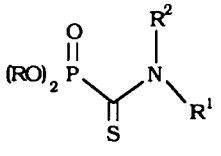


Syn isomers

FIGURE 13



(R^2>R^1) *Syn*



Anti

FIGURE 14

STRUCTURES OF THIOCARBAMOYLPHOSPHONATES

Tashma[25] has shown by X-ray crystallography that thiocarbamoylphosphonates possessing one proton on the nitrogen (secondary thioamides) have a *syn* conformation stabilised by hydrogen-bonding with the phosphonyl group. By direct correlation, we would therefore attribute a *syn* conformation to the compounds **3**, **5–8**, **10–16**, **18**, **19**, **21**, **26** isolated as a unique conformer (Figure 13).

With compounds (**4**, **9**, **17**, **20**, and **25**) ($R^1 \neq R^2 \neq H$), two conformers were detected by NMR. Again, in accordance with previous observations,[25] when R^1 and $R^2 \neq H$, the NMR signals of the carbons (and also their protons) α to the nitrogen are different depending on their *syn* or *anti* orientation relative to the sulfur atom of the thiocarbonyl group (Figure 14). These signals appear at higher field for carbons and protons *syn* to the sulfur atom. This difference was observed for the symmetrically (**4**, **20** and **25**) and the unsymmetrically (**9** and **17**) substituted thioamides and this allowed a *syn* or *anti* conformation to be proposed to each observed conformer (Table II).

TABLE II

NMR chemical shifts for *syn* and *anti* methyl or methylene groups on the nitrogen atom of thiocarbamoylphosphonates

N°	*Syn / anti* *	^{1}H NMR (ppm)	^{13}C NMR (ppm)
9	64%	3.41 (NCH_3 *Syn*)	42.18 (NCH_3 *Syn*)
	36%	3.68 (NCH_3 *Anti*)	44.40 (NCH_3 *Anti*)
9'	78%	3.44 (NCH_3 *Syn*)	41.98 (NCH_3 *Syn*)
	22%	3.73 (NCH_3 *Anti*)	44.31 (NCH_3 *Anti*)
17	43%	Complex signals	65.02 [$NCH(CO_2H)$ *Syn*]
	57%		65.90 [$NCH(CO_2H)$ *Anti*]
20		Complex signals	50.75 (NCH_2 *Syn*)
			54.93 (NCH_2 *Anti*)
4		3.37 (NCH_3 *Syn*)	44.08 (NCH_3 *Syn*)
		3.63 (NCH_3 *Anti*)	44.34 (NH_3 *Anti*)
25		4.38 (t, NCH_2 *Syn*)	48.88 (NCH_2 *Syn*)
		4.42 (t, NCH_2 *Anti*)	51.25 (NCH_2 *Anti*)

* Percentage calculated by ^{31}P NMR

CONCLUSIONS

The present study has shown that phosphonodithioformates are, *via* their reaction with amines, convenient precursors of functionalised phosphonates such as thiocarbamoylphosphonates and phosphonyl substituted heterocycles which are of interest owing to their potential biological activity.[26-29] Desulfuration of the functionalised thiocarbamoylphosphonates prepared from the amino-acids is currently under investigation as a convenient method for the preparation of novel aminomethylphosphonic acid derivatives.

EXPERIMENTAL

Flash liquid chromatography was carried out on Merck 60 (63-200 microns) silica gel. The ^{1}H NMR spectra were recorded at 60 MHz and 250 MHz. The chemical shifts (δ) are referenced against an internal TMS standard and the coupling constants (J) are given in Hertz. The ^{13}C and ^{31}P NMR spectra were recorded at 20.15 MHz and 32.44 MHz respectively, with the chemical shifts referenced against the deuterated solvent and external H_3PO_4 respectively. The mass spectra were recorded by electron impact at 70 eV. The IR spectra are given in cm^{-1} in KBr or on NaCl for solids or oil respectively. Characteristic absorptions at ~1380 (ν_{P-OiPr}), ~1240 ($\nu_{P=O}$) and ~1000 (ν_{P-OiPr}) are observed for all the compounds bearing a diisopropylphosphonyl group. Melting points are uncorrected.

Methyl diisopropoxyphosphinylmethanedithioate **1** [92659-86-4] and *Methyl diethoxyphosphinyl-methanedithioate* **1'** [55921-51-2], stable red liquids, were prepared by a method previously described[10] in 80% and 70% yields respectively.

General procedures for the phosphonothiocarbonylation of non-functionalised amines, aminoethanols, aminoethanethiol and diamines: The red solution of phosphonodithioformate **1** (512 mg; 2 mmol) in dry THF (20 mL) was placed in a 50 mL flask. The amine (2,2 mmol) was added to the solution at room temperature. A rapid change of colour from red to pale yellow was observed. The mixture was left at ambient temperature for 15 hours and the solvent was evaporated.

Diisopropyl methyldithiomethylthiomethylphosphonate **2**[21] was obtained in approximately 30% yield along with the corresponding thiocarbamoylphosphonate when the reaction was worked up immediately after decolouration.

With methylamine or dimethylamine, a stream of methylamine or dimethylamine gas was passed through the solution. The reaction mixture was purified by chromatography on a silica gel column using ether/light petroleum (1/1) as the eluent to afford **3** and **4** respectively.

Diisopropyl-N-methylthiocarbamoylphosphonate **3** was obtained as yellow crystals (82%), m.p.: 42°C. ^{1}H (CCl_4): 1.35 [d, $(C\underline{H}_3)_2CHO$, $^3J_{HH}$ = 6]; 3.13 [dd, $NC\underline{H}_3$, $^3J_{HH}$ = 5, $^4J_{PH}$ = 2]; 4.70 [dsept, $(CH_3)_2C\underline{H}OP$, $^3J_{HH}$ = 6, $^3J_{PH}$ = 1]; 10.70 [s, $N\underline{H}CH_3$]. ^{13}C ($CDCl_3$): 23.65 and 23.86 [2d, $(\underline{C}H_3)_2CHO$, $^3J_{CP}$ = 3.4, $^3J_{CP}$ = 2.9]; 32.29 [d, $N\underline{C}H_3$, $^3J_{CP}$ = 9.4]; 74.04 [d, $CH_3)_2\underline{C}HOP$, $^2J_{CP}$ = 6.8]; 194.75 [d, $P\underline{C}(S)N$, $^1J_{CP}$ = 182.0]. MS m/z (%): 239 ($M\cdot^+$/100); 197 (17); 164 (12); 155 (39); 124 (24); 122 (46); 109 (17); 88 (17); 74 (73). Analysis (%) $C_8H_{18}NO_3PS$: calcd C 40.15; H 7.58; N 5.85; S 13.40 - found C 40.36; H 7.69; N 5.65; S 13.32.

Diisopropyl N,N-dimethylthiocarbamoylphosphonate **4** was obtained as a yellow oil (91%): ^{1}H (CCl_4): 1.37 and 1.43 [2d, $(C\underline{H}_3)_2CHO$; $^3J_{HH}$ = 6]; 3.37 [d, $NC\underline{H}_3$ *syn*, $^4J_{PH}$ = 2]; 3.63 [d, $NC\underline{H}_3$ *anti*, $^4J_{PH}$ = 2]; 4.67 [dsept, $(CH_3)_2C\underline{H}OP$, $^3J_{HH}$ = 6, $^3J_{PH}$ = 1]. ^{13}C ($CDCl_3$): 23.76 and 24.01 [2d, $(\underline{C}H_3)_2CHO$, $^3J_{CP}$ = 6.4, $^3J_{CP}$ = 3.4]; 44.08 [d, $N\underline{C}H_3$ *syn*, $^3J_{CP}$ = 4.7]; 44.34 [d, $N\underline{C}H_3$ *anti*, $^3J_{CP}$ = 4.7]; 73.53 [d, $(CH_3)_2\underline{C}HOP$, $^2J_{CP}$ = 7.6]; 193.81 [d, $P\underline{C}(S)N$, $^1J_{CP}$ = 189.0]. MS m/z (%): 253 ($M\cdot^+$/30); 210 (12); 169 (12); 168 (9); 126 (10); 89 (74); 88 (100); 73 (10); 44 (42). Analysis (%) $C_9H_{20}NO_3PS$: calcd C 42.67; H 7.96; N 5.53; S 12.67 - found C 42.96; H 8.05; N 5.45; S 12.99.

With benzylamine, *Diisopropyl N-benzylthiocarbamoylphosphonate* **5** was isolated as yellow crystals (87%), after purification by flash chromatography on a silica gel column using ether/light petroleum (4/6), m.p.: 92°C: ^{1}H (CCl_4): 1.33 and 1.34 [2d, $(C\underline{H}_3)_2CHO$, $^3J_{HH}$ = 6]; 4.75 [dsept, $(CH_3)_2C\underline{H}OP$, $^3J_{HH}$ = 6, $^3J_{PH}$ = 1]; 4.87 [dd, $NC\underline{H}_2Ph$, $^3J_{HH}$ = 5.4, $^4J_{PH}$ = 2.0]; 7.28-7.38 [m, 5H, phenyl]; 9.69 [s (br), N$\underline{H}$]. ^{13}C ($CDCl_3$): 23.69 and 23.86 [2d, $(\underline{C}H_3)_2CHO$, $^3J_{CP}$ = 5.0, $^3J_{CP}$ = 4.3]; 49.25 [d, $N\underline{C}H_2Ph$, $^3J_{CP}$ = 8.5]; 74.23 [d, $(CH_3)_2\underline{C}HOP$, $^2J_{CP}$ = 6.8]; 128.26, 128.40 and 128.94 [3s, arom $\underline{C}H$]; 135.26 [s, arom $\underline{C}N$]; 194.68 [d, $P\underline{C}(S)N$, $^1J_{CP}$ = 180.6]. I.R. (KBr): 3200 (ν_{NH}). MS m/z (%): 315 ($M\cdot^+$/49); 273 (29); 231 (100); 150 (19); 148 (80); 77 (7); 43 (83). Analysis (%) $C_{14}H_{22}NO_3PS$: calcd C 53.32; H 7.03; N 4.44 - found C 53.28; H 7.01; N 4.47.

With aminoethanol, N-methylaminoethanol, 3-aminopropan-1,2-diol the residual oil obtained from **1** or **1'** was purified by flash chromatography on silica gel using ether as the eluent. The following products were isolated as yellow oils.

Diisopropyl N-(2-hydroxyethyl)thiocarbamoylphosphonate **6** (94%): ^{1}H (CCl_4): 1.38 [d, $(C\underline{H}_3)_2CHO$, $^3J_{HH}$ = 6]; 3.87 [m, $NC\underline{H}_2C\underline{H}_2OH$]; 4.33 [s (br), O$\underline{H}$]; 4.75 [dsept, $(CH_3)_2CHOP$, $^3J_{HH}$ = 6, $^3J_{PH}$ = 1]; 9.81 [s (br), N$\underline{H}$C(S)]. ^{13}C ($CDCl_3$): 23.92 [d, $(\underline{C}H_3)_2CHO$, $^3J_{CP}$ = 5.8]; 48.34 [d, $N\underline{C}H_2CH_2$, $^3J_{CP}$ = 8.1]; 59.66 [s, $NCH_2\underline{C}H_2OH$]; 74.71 [d, $(CH_3)_2\underline{C}HOP$, $^2J_{CP}$ = 7.1]; 194.57 [d, $P\underline{C}(S)N$, $^1J_{CP}$ = 183.0]. I.R. (NaCl): 3200–3450 (ν_{OH}, ν_{NH}). MS m/z (%): 269 ($M\cdot^+$/2); 162 (7); 144 (12); 121 (16); 114 (21); 102 (56); 42 (100). Analysis (%) $C_9H_{20}NO_4PS$: calcd C 40.15; H 7.43; N 5.20; S 11.90 - found C 39.98; H 7.46; N 5.27; S 11.76.

Diisopropyl N-(2,3-dihydroxypropyl)thiocarbamoylphosphonate **8** (91%): ^{1}H (CCl_4): 1.33 [d, $(C\underline{H}_3)_2CHOP$, $^3J_{HH}$ = 6]; 3.57 [s, $CH_2O\underline{H}$]; 3.5–4.2 [m, $NC\underline{H}_2C\underline{H}(OH)CH_2OH$]; 4.67 [s, CHO$\underline{H}$]; 4.60–5.05 [m, $(CH_3)_2C\underline{H}OP$, $C\underline{H}_2OH$]; 9.93 [s (br), N$\underline{H}$]. ^{13}C ($CDCl_3$): 23.75 and 23.95 [2d, $(\underline{C}H_3)_2CHOP$, $^3J_{CP}$ = 4.2, $^3J_{CP}$ = 3.6]; 48.14 [d, NH—$\underline{C}H_2$, $^3J_{CP}$ = 8.7]; 64.63 [s, $\underline{C}H_2OH$]; 69.60 [s, $\underline{C}HOH$]; 74.63 [d, $(CH_3)_2\underline{C}HOP$, $^2J_{CP}$ = 1.8]; 194.98 [d, $P\underline{C}(S)N$, $^1J_{CP}$ = 183.7]. I.R. (NaCl): 3400 (ν_{OH}, ν_{NH}). MS m/z (%): 299 ($M\cdot^+$/5); 277 (18); 214 (24); 142 (30); 82 (29); 43 (100). Analysis (%) $C_{10}H_{22}NO_5PS$: calcd C 40.12; H 7.41; N 4.68 - found C 40.39; H 7.59; N 4.39.

Diisopropyl N-(2-hydroxyethyl) N-methylthiocarbamoylphosphonate **9** (92%): ^{1}H (CCl_4): 1.35 and 1.40 [2d, $(C\underline{H}_3)_2CHO$; $^3J_{HH}$ = 6]; 3.41 [d, $NC\underline{H}_3$ *syn*, $^4J_{PH}$ = 2]; 3.68 [d, $NC\underline{H}_3$ *anti*, $^4J_{PH}$ = 2]; 3.73–4.37 [m, $NCH_2C\underline{H}_2OH$]; 4.73 [dsept, $(CH_3)_2C\underline{H}OP$, $^3J_{HH}$ = 6, $^3J_{PH}$ = 1]. ^{13}C ($CDCl_3$): 23.78 and 24.04 [2d, $(\underline{C}H_3)_2CHO$, $^3J_{CP}$ = 6.5, $^3J_{CP}$ = 3.8]; 42.18 [s, $N\underline{C}H_3$ *syn*]; 44.40 [s, $N\underline{C}H_3$ *anti*]; 58.73 [d, $N\underline{C}H_2CH_2OH$ *syn*, $^3J_{CP}$ = 3.3]; 59.54 [s, $N\underline{C}H_2CH_2OH$ *anti*]; 59.60 [s, $NCH_2\underline{C}H_2OH$]; 73.86 and 74.39 [2d, $(CH_3)_2\underline{C}HOP$, $^2J_{CP}$ = 8.0, $^2J_{CP}$ = 7.6]; 194.03 [d, $P\underline{C}(S)N$, $^1J_{CP}$ = 185.8]. I.R. (NaCl): 3400 (ν_{OH}). MS m/z (%): 283 ($M\cdot^+$/19); 240 (12); 226 (7); 198 (34); 180 (7); 43 (100). Analysis (%) $C_{10}H_{22}NO_4PS$: calcd C 42.40; H 7.77; N 4.95; S 11.30 - found C 42.18; H 7.84; N 4.86; S 11.16.

Diethyl N-(2-hydroxyethyl) N-methyl thiocarbamoylphosphonate **9'** (39%): ^{1}H (CCl_4): 1.38 [t, $C\underline{H}_3CH_2$, $^3J_{HH}$ = 7]; 3.40 [s, $NC\underline{H}_3$ *syn*]; 3.50–4.53 [m, $NC\underline{H}_2$ *anti*, $NCH_2C\underline{H}_2OH$, $CH_3C\underline{H}_2O$]. ^{31}P ($CDCl_3$): −0.20 [$(EtO)_2\underline{P}(O)$, *syn*]; 0.59 [$(EtO)_2\underline{P}(O)$ *anti*]. ^{13}C ($CDCl_3$): 16.18 [d, $\underline{C}H_3CH_2$, $^3J_{CP}$ = 6.4]; 41.98 [d, $N\underline{C}H_3$ *syn*, $^3J_{CP}$ = 6.5]; 44.31 [s, $N\underline{C}H_3$ *anti*]; 58.04 [s, $N\underline{C}H_2CH_2OH$ *syn*]; 58.19 [s, $N\underline{C}H_2CH_2OH$ *anti*]; 59.27 [s, $NCH_2\underline{C}H_2OH$ *syn*]; 59.57 [s, $NCH_2\underline{C}H_2OH$ *anti*]; 64.54 [d, $CH_3\underline{C}H_2O$, $^2J_{CP}$ = 7.3]; 193.1; [d, $P\underline{C}(S)N$ *syn*, $^1J_{CP}$ = 167.0]; 193.5 [d, $P\underline{C}(S)N$ *anti*, $^1J_{CP}$ = 185.0]. I.R. (NaCl): 3400 (ν_{OH});

1490 ($\nu_{C=S}$); 1390 (ν_{P-OEt}); 1230 ($\nu_{P=O}$); 1060–1020 (ν_{P-OEt}). MS m/z (%): 255 ($M\cdot^+$/23); 226 (13); 182 (11); 118 (51); 109 (20); 84 (25); 74 (67); 42 (100) analysis (%) $C_8H_{18}NO_4PS$: calcd S 12.55 - found S 12.82.

N-Methyl P-ethoxy P-oxo 1,4,6-oxazaphosphorine-5-thione **24** (47%): ^{1}H (CCl_4): 1.33 [t, $C\underline{H}_3CH_2$, $^3J_{HH}$ = 7]; 3.47 [s, $NC\underline{H}_3$]; 3.63–4.00 [m, $NC\underline{H}_2CH_2OP$]; 4.43 [dq, $CH_3C\underline{H}_2O$, $^3J_{HH}$ = $^3J_{PH}$ = 7]; 4.58 [m, $NCH_2C\underline{H}_2OP$]. ^{31}P ($CDCl_3$): −7.45 [$(EtO)_2\underline{P}(O)$]. ^{13}C ($CDCl_3$): 16.39 [d, $\underline{C}H_3CH_2$, $^3J_{CP}$ = 6.1]; 41.33 [d, $N\underline{C}H_3$, $^3J_{CP}$ = 6.2]; 53.12 [d, $N\underline{C}H_2CH_2OP$, $^3J_{CP}$ = 7.4]; 63.76 [d, $NCH_2\underline{C}H_2OP$, $^4J_{CP}$ = 4.4]; 66.41 [d, $CH_3\underline{C}H_2O$, $^2J_{CP}$ = 6.8]; 193.10 [d, $P\underline{C}(S)N$, $^1J_{CP}$ = 167.0]. I.R. (NaCl): 1490 ($\nu_{C=S}$); 1385 (ν_{P-OEt}); 1270 ($\nu_{P=O}$); 1020 (ν_{P-OEt}). MS m/z (%): 209 ($M\cdot^+$/18); 117 (37); 84 (55); 73 (23); 42 (100).

When phosphonodithioformate **1** and 2-aminoethanethiol were stirred together for 15 hours, we obtained a mixture of compound **7** (yellow crystals; m.p.: 78°C) in 28% yield and the disulfides **2** (21%) and **22** (37%). When the mixture was stirred for 5 days, we obtained by chromatography the thiocarbamoylphosphonate **7** in 60% yield and the disulfide **23** in 18% yield.

Diisopropyl N-(2-mercaptoethyl)thiocarbamoylphosphonate **7** (60%): ^{1}H (CCl_4): 1.35 [d, $(C\underline{H}_3)_2CHO$, $^3J_{HH}$ = 6]; 2.40 [s, $S\underline{H}$]; 2.97 [t, $CH_2C\underline{H}_2SH$, $^3J_{HH}$ = 6]; 4.00 (dt ~ q, $NC\underline{H}_2CH_2SH$, $^3J_{HH}$ = $^3J_{HH}$ = 6]; 4.73 [dsept, $(CH_3)_2C\underline{H}OP$, $^3J_{HH}$ = 6, $^3J_{PH}$ = 1]; 11.03 [s, $N(\underline{H})CH_2$]. ^{13}C ($CDCl_3$): 23.59 and 24.06 [2d, $(\underline{C}H_3)_2CHO$, $^3J_{CP}$ = 7.5, $^3J_{CP}$ = 3.6]; 34.73 [s, $N(H)CH_2\underline{C}H_2SH$]; 43.96 [d, $N(H)\underline{C}H_2$, $^3J_{CP}$ = 8.3]; 74.33 [d, $(CH_3)_2\underline{C}HOP$, $^2J_{CP}$ = 6.6]; 190.31 [d, $P\underline{C}(S)N$, $^1J_{CP}$ = 185.2]. MS m/z (%): 285 ($M\cdot^+$/17); 253 (24); 210 (14); 194 (7); 60 (25); 43 (100). Analysis (%) $C_9H_{20}NO_3PS_2$: calcd C 37.88; H 7.06; N 4.91; S 22.47 - found C 37.93; H 6.77; N 4.84; S 22.22.

^{1}H NMR signals of the isopropylphosphonyl group of compounds **22** and **23** are similar to those observed for **7** and only characteristic signals are reported below.

Tetraisopropyl (6-aza-2,3-dithia-1-methylthio-7-thioxoheptylene)bisphosphonate **22** (37%): ^{1}H (CCl_4): 2.30 [s, $SC\underline{H}_3$]; 3.07 [t, $CH_2C\underline{H}_2SS$, $^3J_{HH}$ = 7]; 3.83 [d, $PC\underline{H}$, $^2J_{PH}$ = 16]; 4.07 [m, $NHC\underline{H}_2CH_2$]; 10.37 [s, $N(\underline{H})CH_2$]. ^{31}P ($CDCl_3$): −3.28 [s, $(i\text{PrO})_2\underline{P}(O)C{=}S$]; 15.96 [s, $(i\text{PrO})_2\underline{P}(O)CH$]. ^{13}C ($CDCl_3$): 15.42 [d, $S\underline{C}H_3$, $^3J_{CP}$ = 5.0]; 23.93 and 24.26 [2d, $(\underline{C}H_3)_2CHO$, $^3J_{CP}$ = 4.1]; 34.62 [s, $CH_2\underline{C}H_2SS$]; 43.76 [s, $N(H)\underline{C}H_2CH_2$]; 54.70 [d, $P\underline{C}H$, $^1J_{CP}$ = 149.9]; 72.33 [d, $(CH_3)_2\underline{C}HOP{-}CH$, $^2J_{CP}$ = 7.1]; 74.21 [d, $(CH_3)_2\underline{C}HOP{-}C{=}S$, $^2J_{CP}$ = 6.8]; 195.46 [d, $P\underline{C}(S)N$, $^1J_{CP}$ = 181.5].

Disopropyl (3,4-dithia-pentyl)thiocarbamoylphosphonate **23** (18%): ^{1}H (CCl_4): 2.38 [s, $SSC\underline{H}_3$]; 2.93 [t, $CH_2C\underline{H}_2SS$, $^3J_{HH}$ = 7]; 3.95 [dt ~ q, $NHC\underline{H}_2CH_2$, $^3J_{HH}$ = $^3J_{HH}$ = 7]; 10.37 [s, $N(\underline{H})CH_2$].

With piperazine, we obtained the thiocarbamoylphosphonates **20** (a yellow oil in 62% yield with one equivalent of piperazine) and **25** (yellow crystals, 76% with half an equivalent; m.p.: 110°C) after purification by flash chromatography on silica gel using ethanol/light petroleum (15/85).

Diisopropyl piperazino N-thiocarbonylphosphonate **20**: ^{1}H (CCl_4): 1.47 and 1.50 [2d, $(C\underline{H}_3)_2CHO$, $^3J_{HH}$ = 6]; 2.53 [s, $CH_2N\underline{H}C\underline{H}_2$]; 2.97 [t, $C\underline{H}_2NHC\underline{H}_2$, $^3J_{HH}$ = 5]; 4.23–4.48 [m, $C\underline{H}_2NC\underline{H}_2$]; 4.78 [dsept, $(CH_3)_2C\underline{H}OP$, $^3J_{HH}$ = 6, $^3J_{PH}$ = 1]. ^{13}C ($CDCl_3$): 23.73 and 24.08 [2d, $(\underline{C}H_3)_2CHO$, $^3J_{CP}$ = 6.2, $^3J_{CP}$ = 3.4]; 45.71 [s, $\underline{C}H_2NH$ *syn*]; 46.71 [s, $\underline{C}H_2NH$ *anti*]; 50.75 [d, $C(S)N\underline{C}H_2$ *syn*, $^3J_{CP}$ = 6.3]; 54.93 [d, $C(S)N\underline{C}H_2$ *anti*, $^3J_{CP}$ = 3.2]; 73.62 [d, $(CH_3)_2\underline{C}HOP$, $^2J_{CP}$ = 7.6]; 192.92 [d, $P\underline{C}(S)N$, $^1J_{CP}$ = 189.9]. I.R. (NaCl): 3460 (ν_{NH}). MS m/z (%): 294 ($M\cdot^+$/12); 142 (17); 129 (34); 85 (42); 56 (81); 43 (100). Analysis (%) $C_{11}H_{23}N_2O_3PS$: calcd C 44.90; H 7.82 - found C 44.88; H 8.15.

Tetraisopropyl piperazino-N,N'-bisthiocarbonylphosphonate **25**: ^{1}H (CCl_4): 1.35 and 1.42 [d, $(C\underline{H}_3)_2CHO$, $^3J_{HH}$ = 6]; 4.38 [t, $NC\underline{H}_2$ *syn*, $^3J_{HH}$ = 7]; 4.42 [t, $NC\underline{H}_2$ *anti*, $^3J_{HH}$ = 7]; 4.67 [dsept, $(CH_3)_2C\underline{H}OP$, $^3J_{HH}$ = 6, $^3J_{PH}$ = 1]. ^{31}P ($CDCl_3$): −2.30 [$(i\text{PrO})_2\underline{P}(O)$]. ^{13}C ($CDCl_3$): 23.77 and 24.10 [2d, $(\underline{C}H_3)_2CHO$, $^3J_{CP}$ = 6.4, $^3J_{CP}$ = 3.6]; 48.88 [dd, $N\underline{C}H_2$ *syn*, $^3J_{CP}$ = 35.4, $^4J_{CP}$ = 6.5]; 51.25 [dd, $N\underline{C}H_2$ *anti*, $^3J_{CP}$ = 35.4, $^4J_{CP}$ = 2.4]; 74.09 [d, $((CH_3)_2\underline{C}HO)P$, $^2J_{CP}$ = 7.6]; 194.88 [d, $P\underline{C}(S)N$, $^1J_{CP}$ = 190.0]. I.R. (KBr): 1485 ($\nu_{C=S}$); 1380 (ν_{P-OiPr}); 1240 ($\nu_{P=O}$); 1000 (ν_{P-OiPr}). MS m/z (%): 502 ($M\cdot^+$/8); 333 (15); 253 (20); 209 (17); 129 (33); 43 (100). Analysis (%) $C_{18}H_{36}N_2O_6P_2S_2$: calcd C 43.03; H 7.17; N 5.58; S 12.75 - found C 43.18; H 7.30; N 5.85; S 12.64.

With 5-aminomethyl 4-amino 2-methyl pyrimidine: *Diisopropyl N-[(4-amino-2-methyl)pyrimidyl]5-methylthiocarbamoylphosphonate* **21**: [yellow crystals purified by recrystallization in THF/light petroleum (1/1) (80% yield; m.p.: 160°C)]. ^{1}H (CCl_4): 1.30 [d, $(C\underline{H}_3)_2CHO$, $^3J_{HH}$ = 6]; 2.43 [s, $C\underline{H}_3$ pyr]; 4.7 [m, $C\underline{H}_2NH$, $(CH_3)_2C\underline{H}OP$]; 6.00 [s, $N\underline{H}$, $N\underline{H}_2$]; 8.23 [s, arom $C\underline{H}$]. ^{13}C ($CDCl_3$): 23.62 and 23.83 [2s, $(\underline{C}H_3)_2CHO$]; 25.47 [s, $\underline{C}H_3$ pyr]; 42.77 [d, $N\underline{H}C\underline{H}_2$, $^3J_{CP}$ = 9.4]; 74.97 [d, $(CH_3)_2\underline{C}HOP$, $^2J_{CP}$ = 7.3]; 167.59, 161.73, 158.17 and 108.07 [4s, $\underline{C}$ pyr]; 194.67 [d, $P\underline{C}(S)N$, $^1J_{CP}$ = 181.2]. Analysis (%) $C_{13}H_{23}N_4O_3PS$: calcd C 45.07; H 6.69; N 16.18; S 9.26 - found C 44.89; H 6.69; N 16.19; S 9.45.

With ethylenediamine: *Tetraiisopropyl ethylenebisthiocarbamoylphosphonate* **26** (a yellow oil in 43% yield obtained with half an equivalent of ethylenediamine and purified by flash chromatography on silica gel using ethyl acetate): ^{1}H (CCl_4): 1.35 [d, $(C\underline{H}_3)_2CHO$, $^3J_{HH}$ = 6]; 4.03 [s, $NHC\underline{H}_2C\underline{H}_2$]; 4.79 [dsept, $(CH_3)_2C\underline{H}OP$, $^3J_{HH}$ = 6, $^3J_{PH}$ = 1]; 9.97 [s, $N\underline{H}CH_2CH_2N\underline{H}$]. ^{31}P ($CDCl_3$): −3.74 [$(i\text{PrO})_2\underline{P}(O)$].

^{13}C ($CDCl_3$): 23.64 and 23.86 [2d, $(\underline{C}H_3)_2CHO$, $^3J_{CP}$ = 3.1]; 43.13 [d, $NH\underline{C}H_2\underline{C}H_2NH$, $^3J_{CP}$ = 8.7]; 74.30 [d, $(CH_3)_2\underline{C}HOP$, $^2J_{CP}$ = 6.9]; 196.26 [d, $P\underline{C}(S)N$, $^1J_{CP}$ = 182.5]. I.R. (NaCl): 2980, 3200 (ν_{NH}); 1370 (ν_{P-OiPr}); 1250 ($\nu_{P=O}$): 1000 (ν_{P-OiPr}). MS m/z (%): 477 (45); 297 (11); 279 (28); 252 (70); 226 (100).

2-Diisopropylphosphonoimidazoline **27** was obtained from the reaction with one equivalent of diamine, after washing with water, sodium hydrogenocarbonate and brine and extracting into ether. The organic phase was evaporated and the crude product was distilled (150°C under 2.10^{-3} mbar). We obtained a colourless oil (49% yield). ^1H (CCl_4): 1.33 [d, $(\underline{C}H_3)_2CHO$, $^3J_{HH}$ = 6]; 3.25 and 3.73 [2s (br), $NC\underline{H}_2\underline{C}H_2NH$]; 4.68 [dsept, $(CH_3)_2C\underline{H}OP$, $^3J_{HH}$ = 6, $^3J_{PH}$ = 2]; 5.42 [s (br), $CH_2N\underline{H}$]. ^{31}P ($CDCl_3$): −0.08 [$(i\underline{P}rO)_2\underline{P}(O)$]. ^{13}C ($CDCl_3$): 23.75 and 23.97 (2d, $(\underline{C}H_3)_2CHO$, $^3J_{CP}$ = 4.5, $^3J_{CP}$ = 4.2]; 49.74 and 50.48 [2s, $N\underline{C}H_2\underline{C}H_2NH$]; 73.13 [d, $((CH_3)_2\underline{C}HO)P$, $^2J_{CP}$ = 6.2]; 161.08 [d, $P\underline{C}(N)N$, $^1J_{CP}$ = 234.2]. MS m/z (%): 235 (M + 1/10); 234 ($M\cdot^+$/3); 193 (11); 176 (39); 150 (61); 134 (38); 43 (92); 41 (100). Exact Mass: $[C_9H_{20}N_2O_3P]^+$: calcd (M + 1) = 235.12113 - found 235.12375. I.R. (NaCl): 3250 (ν_{NH}); 1575 ($\nu_{C=N}$); 1385 (ν_{P-OiPr}); 1250 ($\nu_{P=O}$); 1020 (ν_{P-OiPr}).

General procedure for the phosphonothiocarbonylation of aminoacids or aminoester: The aminoacids or the aminoester (3.3 mmol): glycine, L-alanine, L-methionine, L-phenylalanine, L-valine, L-glutamic acid, L-proline and ethylglycinate hydrochloride: were placed in a 100 mL flask in THF (30 mL) and water (5 mL). Triethylamine (3.3 mmol) and phosphonodithioformate **1** (3 mmol) were added successively to the solution at ambient temperature.

After stirring for 3 days, the reaction mixture was concentrated *in vacuo*, redissolved in ether and poured into dilute HCl (5%). The organic phase was dried, concentrated and crystallised from pentane. The pure thiocarbamoylphosphonates **10–15** and **17** were obtained by recrystallisation from pentane or dichloromethane/light petroleum. Compound **16** was a yellow oil and was purified by silica gel chromatography (ethyl acetate/light petroleum) (1/1).

Ethyl N-(diisopropylphosphonothiocarbonyl)aminoethanoate **10** (83% yield; m.p.: 56°C). ^1H (CCl_4): 1.28 [t, $\underline{C}H_3CH_2O$, $^3J_{HH}$ = 7]; 1.35 [d, $(\underline{C}H_3)_2CHO$, $^3J_{HH}$ = 6]; 4.17 [q, $CH_3\underline{C}H_2O$, $^3J_{HH}$ = 7]; 4.37 [dd, $N\underline{C}H_2CO_2Et$, $^3J_{HH}$ = 7, $^4J_{PH}$ = 2]; 4.70 [dsept, $(CH_3)_2C\underline{H}OP$, $^3J_{HH}$ = 6, $^3J_{PH}$ = 1]; 10.55 [s (br), $N\underline{H}C(S)$]. ^{13}C ($CDCl_3$): 14.16 [s, $\underline{C}H_3CH_2O$]; 23.74 and 23.96 [2d, $(\underline{C}H_3)_2CHO$, $^3J_{CP}$ = 4.4]; 46.44 [d, $N\underline{C}H_2CO_2Et$, $^3J_{CP}$ = 9.3]; 74.28 [d, $(CH_3)_2\underline{C}HOP$, $^2J_{CP}$ = 7.0]; 167.51 [s, $\underline{C}O_2Et$]; 196.22 [d, $P\underline{C}(S)N$, $^1J_{CP}$ = 183.0]. I.R. (KBr): 3200 (ν_{NH}); 1750 ($\nu_{C=O}$). MS m/z (%): 311 ($\underline{M}\cdot^+$/13); 270 (6); 227 (14); 147 (37); 114 (22); 43 (100). Analysis (%) $C_{11}H_{22}NO_5PS$: calcd C 42.44; H 7.07; N 4.50 - found C 42.22; H 7.09; N 4.38.

^1H NMR signals of the isopropylphosphonyl group of compounds **11**, **12**, **16** and **17** are similar to those observed for **10** and only characteristic signals are reported below.

N-(Diisopropylphosphonothiocarbonyl)aminoethanoic acid **11** (95% yield; m.p.: 106°C): ^1H (CCl_4): 4.51 [dd, $N\underline{C}H_2CO_2H$, $^3J_{HH}$ = 6, $^4J_{PH}$ = 2]; 9.93 [s (br), $N\underline{H}C(S)$]; 10.93 [s, $CO_2\underline{H}$]. ^{13}C ($CDCl_3$): 23.63 and 23.85 [2d, $(\underline{C}H_3)_2CHO$, $^3J_{CP}$ = 3.7, $^3J_{CP}$ = 2.5]; 45.95 [d, $N\underline{C}H_2CO_2H$, $^3J_{CP}$ = 17.3]; 75.15 [d, $(CH_3)_2\underline{C}HOP$, $^2J_{CP}$ = 7.3]; 170.44 [s, $\underline{C}O_2H$]; 194.3 [d, $P\underline{C}(S)N$, $^1J_{CP}$ = 184.9]. I.R. (KBr): 3300 (ν_{NH}, ν_{OH}); 1720 ($\nu_{C=O}$). MS m/z (%): 283 ($\underline{M}\cdot^+$/4); 199 (3); 82 (3); 43 (100). Analysis (%) $C_9H_{18}NO_5PS$: calcd C 38.19; H 6.41; S 11.03 - found C 37.93; H 6.13; S 10.81.

N-(diisopropylphosphonothiocarbonyl)-2-aminopropanoic acid **12** (53% yield; m.p.: 77°C; $[\alpha]_D^{20}$ = −25.33°): ^1H (CCl_4): 1.57 [d, $C\underline{H}_3CHN$, $^3J_{HH}$ = 7]; 4.97 [q, $H_2OCC\underline{H}NH$, $^3J_{HH}$ = 7]; 9.87 [dd, $N\underline{H}$, $^3J_{HH}$ = 7, $^3J_{PH}$ = 11]; 10.83 [s, $CO_2\underline{H}$]. ^{31}P ($CDCl_3$): −4.41 [$(i\underline{P}rO)_2\underline{P}$=O]. ^{13}C ($CDCl_3$): 16.16 [s, $\underline{C}H_3CH(CO_2H)N$]; 23.37 and 23.75 [2d, $(\underline{C}H_3)_2CHOP$, $^3J_{CP}$ = 2.9, $^3J_{CP}$ = 4.3]; 52.93 [d, $CH_3\underline{C}H(CO_2H)N$, $^3J_{CP}$ = 9.0]; 74.69 and 75.02 [2d, $(CH_3)_2\underline{C}HOP$, $^2J_{CP}$ = 5.1, $^2J_{CP}$ = 5.3]; 173.36 [s, $\underline{C}O_2H$]; 193.47 [d, P—$\underline{C}$=S, $^1J_{CP}$ = 185.5]. I.R. (KBr): 3200 (ν_{OH}, ν_{NH}); 1720 ($\nu_{C=O}$). MS m/z (%): 397 ($M\cdot^+$/27); 214 (24); 213 (53); 124 (45); 43 (100). Analysis (%) $C_{10}H_{20}NO_5PS$: calcd C 40.39; H 6.78; N 4.71; S 10.78 - found C 40.51; H 6.94; N 4.44; S 10.61.

N-(Diisopropylphosphonothiocarbonyl)-2-amino-4-methylthiobutanoic acid **13** (78% yield; m.p.: 125°C; $[\alpha]_D^{20}$ = +78.33°): ^1H (CCl_4): 2.07 [s, $SC\underline{H}_3$]; 2.43 [m, $CHC\underline{H}_2C\underline{H}_2SCH_3$]; 4.70 [dsept, $(CH_3)_2C\underline{H}OP$, $^3J_{HH}$ = 6, $^2J_{PH}$ = 3]; 5.23 [dt ~ q, $(H_2OC)C\underline{H}NH$, $^3J_{HH}$ = 8]; 9.83 [dd, $N\underline{H}$, $^3J_{HH}$ = 8, $^3J_{PH}$ = 10]; 10.80 [s, $CO_2\underline{H}$]. ^{13}C ($CDCl_3$): 15.47 [s, $S\underline{C}H_3$]; 23.59 and 23.81 [2d, $(\underline{C}H_3)_2CHOP$, $^3J_{CP}$ = 5.0, $^3J_{CP}$ = 3.9]; 23.91 [s, $CH\underline{C}H_2CH_2$]; 30.24 [s, $\underline{C}H_2SCH_3$]; 56.36 [d, $NH\underline{C}H(COOH)$, $^3J_{CP}$ = 9.3]; 75.31 [d, $(CH_3)_2\underline{C}HOP$, $^2J_{CP}$ = 2.2]; 172.56 [s, $\underline{C}O_2H$]; 194.12 (d, P$\underline{C}$=S, $^1J_{CP}$ = 185.6). I.R. (KBr): 3190 (ν_{NH}, ν_{OH}); 1730 ($\nu_{C=O}$). MS m/z (%): 358 (19); 357 ($M\cdot^+$/5); 199 (38); 61 (100). Analysis (%) $C_{12}H_{24}NO_5PS_2$: calcd C 40.32; H 6.77; N 3.92; S 17.94 - found C 40.23; H 6.56; N 3.76; S 17.85.

N-(Diisopropylphosphonothiocarbonyl)-2-amino-3-phenylpropanoic acid **14** (63% yield; m.p.: 129–130°C; $[\alpha]_D^{20}$ = +104.30°): ^1H (CCl_4): 1.21, 1.28 and 1.33 [3d, $(\underline{C}H_3)_2CHOP$, $^3J_{HH}$ = 6]; 3.3 [m, Ph—$C\underline{H}_2$—CH]; 4.51 and 4.78 [2 dsept, $(CH_3)_2C\underline{H}OP$, $^3J_{HH}$ = 6, $^2J_{HP}$ = 1]; 5.35 [m, $(H_2OC)C\underline{H}NH$]; 7.10 [s, arom

CH]; 9.73 [dd, NH, $^3J_{HH}$ = 8, $^3J_{PH}$ = 10]; 11.13 [s, CO_2H]. ^{13}C ($CDCl_3$): 23.59 [d, $(CH_3)_2CHOP$, $^3J_{CP}$ = 5.2]; 36.08 [s, Ph—CH_2—CH]; 57.88 [d, NHCH(CO_2H), $^3J_{CP}$ = 9.0]; 74.67 [d, $(CH_3)_2CHOP$, $^2J_{CP}$ = 7.4]; 127.08 [s, *para* arom CH]; 128.57 and 129.37 [2s, *meta* and *ortho* arom CH]; 136.03 [s, arom CH_2—C]; 172.25 [s, CO_2H]; 193.78 [d, P—C=S, $^1J_{CP}$ = 183.0]. I.R. (KBr): 3220–3240 (ν_{NH}, ν_{OH}); 1715 ($\nu_{C=O}$). MS m/z (%): 373 ($M\cdot^+$/5); 330 (13); 288 (23); 91 (37); 43 (100). Analysis (%) $C_{16}H_{24}NO_5PS$: calcd C 51.46; H 6.48; N 3.75; S 8.59 - found C 51.62; H 6.48; N 3.52; S 8.58.

N-(Diisopropylphosphonothiocarbonyl)-2-amino-3-methylbutanoic acid **15** (80% yield; m.p.: 89°C; $[\alpha]_D^{20}$ = +1.33°); ^1H (CCl_4): 1.02 and 1.08 [2d, $(CH_3)_2CHCH$, $^3J_{HH}$ = 6]; 1.37 and 1.38 [2d, $(CH_3)_2CHOP$, $^3J_{HH}$ = 6]; 4.33–5.1 [m, $(CH_3)_2CHCH$, $(CH_3)_2CHOP$]; 9.47 [dd, NH, $^3J_{HH}$ = 8, $^3J_{PH}$ = 12]; 9.8 [s, CO_2H]. ^{13}C ($CDCl_3$): 18.62 [s, $(CH_3)_2CH$]; 23.66 and 23.89 [2d, $(CH_3)_2CHOP$, $^3J_{CP}$ = 5.0, $^3J_{CP}$ = 4.2]; 30.73 [s, $(CH_3)_2CHCH$]; 62.04 [d, $(CH_3)_2CHCH$, $^3J_{CP}$ = 8.6]; 74.60 [d, $(CH_3)_2CHOP$, $^2J_{CP}$ = 6.5]; 171.45 [s, CO_2H]; 194.88 [d, P—C=S, $^1J_{CP}$ = 184.0]. I.R. (KBr): 3300 (ν_{NH}, ν_{OH}); 1725 ($\nu_{C=O}$). MS m/z (%): 325 ($M\cdot^+$/28); 282 (16); 240 (100); 128 (39); 43 (92). Analysis (%) $C_{12}H_{24}NO_5PS$: calcd C 44.29; H 7.44; N 4.31 - found C 44.36; H 7.65; N 4.32.

N-(Diisopropylphosphonothiocarbonyl) 2-aminopentan-1,5-dioic acid **16** (44% yield): ^1H (CCl_4): 2.43 [m, $CH_2CH_2CO_2H$]; 4.5–5.23 [m, CH(NH)CO_2H]; 9.73–11.10 [m, NH, 2 CO_2H]. ^{13}C ($CDCl_3$): 23.64 and 23.86 [2d, $(CH_3)_2CHOP$, $^3J_{CP}$ = 5.2, $^3J_{CP}$ = 4.0]; 25.64 [s, $CHCH_2CH_2CO_2H$]; 30.68 [s, $CH_2CH_2CO_2H$]; 57.00 [d, CH(CO_2H)CH_2, $^3J_{CP}$ = 8.5]; 75.1 and 75.46 [2d, $(CH_3)_2CHOP$, $^2J_{CP}$ = 7.2, $^2J_{CP}$ = 6.8]; 173.09 and 177.39 [2s, CO_2H]; 194.3 [d, P—C=S, $^1J_{CP}$ = 185.9]. Analysis (%) $C_{12}H_{22}NO_7PS$: calcd S 9.01 - found S 9.14.

1-(Diisopropylphosphonothiocarbonyl)pyrrolidine-2-carboxylic acid **17** (44% yield; m.p.: 99°C, $[\alpha]_D^{20}$ = −95.00°): ^1H (CCl_4): 2.10 [m, $NCH_2CH_2CH_2CH$]; 4.87 [m, $NCH_2CH_2CH_2CH$]; 9.03 [s, CO_2H]. ^{13}C ($CDCl_3$): 21.29 [s, $NCH_2CH_2CH_2CH$ *syn*]; 23.58, 23.89 and 24.09 [3d, $(CH_3)_2CHOP$, $^3J_{CP}$ = 6.1, $^3J_{CP}$ = 4.2, $^3J_{CP}$ = 2.9]; 25.24 [s, NCH_2CH_2 *anti*]; 28.65 [s, $CH_2CH(CO_2H)$ *syn*]; 31.43 [s, $CH_2CH(CO_2H)$ *anti*]; 53.69 [s, NCH_2CH_2 *syn*]; 55.38 [d, NCH_2CH_2 *anti*, $^3J_{CP}$ = 14.10]; 65.02 [s, CH(CO_2H) *syn*]; 65.90 [d, CH(CO_2H) *anti*, $^3J_{CP}$ = 7.5]; 74.18, 74.43 and 74.85 [3d, $(CH_3)_2CHOP$, $^2J_{CP}$ = 9.7, $^2J_{CP}$ = 5.5, $^2J_{CP}$ = 2.6]; 172.68 [s, CO_2H]; 191.67 [d, P—C=S, $^1J_{CP}$ = 186.8]. I.R. (KBr): 1730 ($\nu_{C=O}$). MS m/z (%): 323 ($M\cdot^+$/18); 279 (11); 238 (14); 159 (29); 158 (13); 114 (91); 70 (99); 43 (100). Analysis (%) $C_{12}H_{22}NO_5PS$: calcd C 44.57; H 6.86; N 4.33 - found C 44.73; H 6.87; N 4.29.

Diisopropyl 2,5-(N-methyl)aza-7-hydroxy-3,6-methyl-4-oxo-7-phenyl-1-thioxoheptylene phosphonate **32**. A reported method[30] was employed whereby a solution of thiocarbamoylphosphonate **12** (104 mg; 0.35 mmol) and (−)-ephedrin were refluxed in THF (10 mL) for 15 minutes and then the solvent was removed. The residual oil was washed into pentane (97%). ^{31}P ($CDCl_3$): −3.10 [$(iPrO)_2P(O)$]. ^{13}C ($CDCl_3$): 10.14 [s, $CH_3CHN(CH_3)C=O$]; 16.79 [s, $CH_3CHNHC=S$]; 23.60, 23.68, 23.80 and 23.87 [4d, $(CH_3)_2CHO$, $^3J_{CP}$ = 1.8, $^3J_{CP}$ = 2.5, $^3J_{CP}$ = 2.0, $^3J_{CP}$ = 2.4]; 31.68 [s, NCH_3]; 55.32 [d, $CH(CH_3)NH$, $^3J_{CP}$ = 8.0]; 60.88 [s, $CH(CH_3)NCH_3$]; 71.00 [s, CH(OH)]; 74.12 and 74.51 [2d, $(CH_3)_2CHOP$, $^2J_{CP}$ = 7.0, $^2J_{CP}$ = 7.1]; 125.81 and 127.39 [2s, *ortho* and *para* arom CH]; 128.30 [s, *meta* arom CH]; 140.47 [s, arom C]; 176.72 [s, C=O]; 191.40 [d, C=S, $^1J_{CP}$ = 182.0]. MS m/z (%): 444 ($M\cdot^+$/0.5); 339 (9); 254 (16); 166 (27); 77 (33); 41 (100). Analysis (%) $C_{20}H_{33}N_2O_5PS$: calcd S 7.20 - found S 7.17.

General procedure of phosphonothiocarbonylation of anilines: A solution of phosphonodithioformate **1** (1.28 g; 5 mmol) in THF (50 mL) was placed in a 100 mL two-necked flask and the aromatic amines: aniline (0.5 mL; 5.5 mmol) or 2-bromoaniline (0.95 g; 5.5 mmol) were added to the solution. The mixture was refluxed for 5 days and the solvent was removed. Yellow crystals were obtained by chromatography on a silica gel column using ethyl acetate/light petroleum (15:85).

Diisopropyl N-phenyl-thiocarbamoylphosphonate **18** (49% yield; m.p.: 55°C): ^1H ($CDCl_3$): 1.38 and 1.40 [2d, $(CH_3)_2CHO$, $^3J_{HH}$ = 6]; 4.85 [dsept, $(CH_3)_2CHOP$, $^3J_{HH}$ = 6, $^3J_{PH}$ = 1]; 7.29 [m, arom 3H]; 8.01 and 8.02 [2s, arom 2H]; 10.55 [s, C(S)NH]. ^{13}C ($CDCl_3$): 23.71 and 23.84 [2d, $(CH_3)_2CHO$, $^3J_{CP}$ = 6.4, $^3J_{CP}$ = 5.5]; 74.43 [d, $(CH_3)_2CHOP$, $^2J_{CP}$ = 8.7]; 122.08, 127.35 and 128.99 [3s, arom C]; 138.19 [d, arom NC, $^3J_{CP}$ = 19.7]; 192.29 [d, PC(S)N, $^1J_{CP}$ = 181.9]. I.R. (KBr): 3280 (ν_{NH}); 1590 ($\nu_{C=C}$); 1500 ($\nu_{C=C}$). MS m/z (%): 301 ($M\cdot^+$/5); 179 (3); 105 (100); 77 (92); 43 (63). Analysis (%) $C_{13}H_{20}NO_3PS$: calcd C 51.81; H 6.69; N 4.65; S 10.64 - found C 51.57; H 6.86; N 4.42; S 10.74.

Diisopropyl N-(2-bromophenyl)thiocarbamoylphosphonate **19** (62% yield; m.p.: 59°C): ^1H (CCl_4): 1.33 [d, $(CH_3)_2CHO$, $^3J_{HH}$ = 6]; 3.85 [d (br), C(S)NH, $^3J_{PH}$ = 5]; 4.70 [dsept, $(CH_3)_2CHOP$, $^3J_{HH}$ = 6, $^3J_{PH}$ = 1]; 7.77 [~AB system for aromatic protons, ν_A = 7.47, ν_B = 8.09, J_{AB} = 8.4]. ^{13}C ($CDCl_3$): 23.62 and 23.85 [2d, $(CH_3)_2CHO$, $^3J_{CP}$ = 2.8, $^3J_{CP}$ = 2.0]; 74.33 [d, $(CH_3)_2CHOP$, $^2J_{CP}$ = 6.7]; 119.95 [s, CBr]; 124.27 [s, *ortho* and *para* arom C]; 131.77 [s, *meta* arom C]; 137.60 [d, CNH, $^3J_{CP}$ = 16.1]; 192.95 [d, PC(S)N, $^1J_{CP}$ = 184.1]. I.R. (KBr): 3150 (ν_{NH}); 1485 ($\nu_{C=C}$); MS m/z (%): 381 ($M\cdot^+$/7); 379 (7); 306 (5); 304 (4); 264 (8); 262 (8); 215 (25); 213 (18); 124 (33); 109 (40); 43 (100).

Syntheses of Phosphonosubstituted Heterocycles

2-Diisopropylphosphonothiazoline **28**: A solution of 2-bromoethylamine hydrochloride (2.048 g, 10 mmol) dissolved in THF (25 mL) was added to a solution of the phosphonodithioformate **1** (512 mg; 2 mmol) in THF (20 mL) at room temperature. The addition of triethylamine (1.4 mL; 10 mmol) resulted in the immediate decoloration of the mixture. The solution was stirred for a further 24 hours before the solvent was removed. The mixture was poured into brine and extracted with ether. The organic phase was dried and concentrated. Purification on a silica gel column using ethanol/light petroleum (1:9) afforded the phosphonothiazoline **28** as a colourless oil (53%). ^{1}H (CCl_4): 1.35 [d, $(C\underline{H}_3)_2CHO$, $^3J_{HH}$ = 6]; 3.28 [t, $SC\underline{H}_2CH_2$, $^3J_{HH}$ = 8]; 4.40 [td, $NC\underline{H}_2CH_2$, $^3J_{HH}$ = 8, $^4J_{PH}$ = 4]; 4.65 [dsept, $(CH_3)_2C\underline{H}O$, $^3J_{HH}$ = 6, $^2J_{PH}$ = 2]. ^{31}P ($CDCl_3$): −1.43 [$(i\text{PrO})_2\underline{P}(O)$]. ^{13}C ($CDCl_3$): 23.75 and 24.0 [2d, $(\underline{C}H_3)_2CHO$, $^3J_{CP}$ = 5.3, $^3J_{CP}$ = 4.9]; 33.07 [s, $S\underline{C}H_2CH_2$]; 67.35 [d, $N\underline{C}H_2CH_2$, $^3J_{CP}$ = 31.6]; 72.90 [d, $(CH_3)_2\underline{C}HOP$, $^2J_{CP}$ = 6.4]; 166.55 [d, $P\underline{C}(N)S$, $^1J_{CP}$ = 230.0]. I.R. (NaCl): 1575 ($\nu_{C=N}$). MS m/z (%): 252 ($M\cdot^+$/5); 251 (2); 209 (34); 194 (36); 193 (44); 151 (43); 60 (100). Analysis (%) $C_6H_{18}NO_3PS$: calcd C 42.24; H 7.16; N 5.48 - found C 42.03; H 7.29; N 5.58.

5-Diisopropylphosphono-1,3,4-thiadiazol-2(3H)-one **29**: The phosphonodithioformate **1** (768 mg; 3 mmol) was added to a solution of semicarbazide hydrochloride (558 mg; 5 mmol) and triethylamine (0.7 mL; 5 mmol) in THF (30 mL) and water at room temperature. The decoloration was slow (~1 h). The mixture was stirred for 5 days and then the solvent removed. The mixture was poured into sodium hydrogenocarbonate solution and overlaid with methylene dichloride. The organic phase was dried with sodium sulfate and the solvent removed. The mixture was purified by chromatography on a silica gel column using a graded eluent of 50%–100% ethyl acetate in light petroleum to afford the thiocarbamoylphosphonate **29** (white crystals in 39% yield; m.p.: 160°C). ^{1}H (CCl_4): 1.40 [d, $(C\underline{H}_3)_2CHO$, $^3J_{HH}$ = 6]; 4.75 [dsept, $(CH_3)_2C\underline{H}OP$, $^3J_{HH}$ = 6, $^3J_{PH}$ = 2]; 5.93 [s (br), $N\underline{H}$]. ^{31}P ($CDCl_3$): +7.34 [$(i\text{PrO})_2\underline{P}(O)$]. ^{13}C ($CDCl_3$): 23.87 and 24.09 [2d, $(\underline{C}H_3)_2CHO$, $^3J_{CP}$ = 4.8, $^3J_{CP}$ = 3.9]; 71.58 [d, $(CH_3)_2\underline{C}HOP$, $^2J_{CP}$ = 6.7]; 156.57 [d, $\underline{C}{=}N$, $^1J_{CP}$ = 225.7]; 157.80 [s, $C{=}O$]. MS m/z (%): 266 ($M\cdot^+$/3); 250 (3); 245 (2); 208 (3); 166 (11); 150 (15); 43 (100). Analysis (%) $C_8H_{15}N_2O_4PS$: calcd S 12.03 - found S 12.36.

2-Amino-5-diisopropylphosphono-1,3,4-thiadiazole **30**: Thiosemicarbazide (200 mg, 2.2 mmol) was added to a solution of phosphonodithioformate **1** (512 mg, 2 mmol) in THF (10 mL) and ethanol (10 mL). The mixture was refluxed for 3 days. The solvent was removed and the thiosemicarbazide was crystallised from ethanol. The product was recrystallised from dichloromethane to obtain white crystals (41% yield; m.p.: 170°C). ^{1}H (CCl_4): 1.33 and 1.38 [2d, $(C\underline{H}_3)_2CHO$, $^3J_{HH}$ = 6]; 4.83 [dsept, $(CH_3)_2C\underline{H}OP$, $^3J_{HH}$ = 6, $^3J_{HP}$ = 2]; 6.88 [s (br), $N\underline{H}_2$]. ^{31}P ($CDCl_3$): +0.37 [$(i\text{PrO})_2\underline{P}(O)$]. ^{13}C ($CDCl_3$): 23.73 and 23.97 [2d, $(\underline{C}H_3)_2CHO$, $^3J_{CP}$ = 6.7, $^3J_{CP}$ = 5.6]; 73.36 [d, $(CH_3)_2\underline{C}HOP$, $^2J_{CP}$ = 7.9]; 149.97 [d, $\underline{C}{=}N$, $^1J_{CP}$ = 258.0]; 172.45 [s, $N{=}\underline{C}(S)NH_2$]. I.R. (KBr film): 3120–3310 (ν_{NH}); 1620 ($\nu_{C=N}$); 1500 ($\nu_{N=N}$). MS m/z (%): 265 ($M\cdot^+$/2); 208 (10); 165 (48); 74 (29); 60 (37); 43 (100). Analysis (%) $C_8H_{16}N_3O_3PS$: calcd S 12.07 - found S 11.86.

2,5-Bisdiisopropylphosphono-1,3,4-thiadiazole **31**: Hydrazine hydrochloride (69 mg, 1 mmol) was added to a solution of phosphonodithioformate **1** (512 mg, 2 mmol) in THF (20 mL). The mixture was stirred for 6 days at ambient temperature. The solvent was removed and the mixture was purified by chromatography on a silica gel column using ethyl acetate/light petroleum (1/1). We obtained a colourless oil (20%). ^{1}H (CCl_4): 1.37 and 1.42 [2d, $(C\underline{H}_3)_2CHO$, $^3J_{HH}$ = 6]; 4.96 [dsept, $(CH_3)_2C\underline{H}OP$, $^3J_{HH}$ = 6, $^3J_{PH}$ = 2]. ^{31}P ($CDCl_3$): −1.39 [$(i\text{PrO})_2\underline{P}(O)$]. ^{13}C ($CDCl_3$): 23.86 and 24.13 [2d, $(\underline{C}H_3)_2CHO$, $^3J_{CP}$ = 10.6, $^3J_{CP}$ = 14.5]; 74.21 [dd, $(CH_3)_2\underline{C}HOP$, $^2J_{CP}$ = 20.3, $^6J_{CP}$ = 6.3]; 164.45 [dd, $\underline{C}{=}N$, $^1J_{CP}$ = 221.6, $^3J_{CP}$ = 3.5]. I.R. (NaCl): 1450 ($\nu_{C=N}$); 1370 ($\nu_{N=N}$). MS m/z (%): 414 ($M\cdot^+$/4); 246 (11); 208 (4); 108 (16); 84 (6); 43 (100). Analysis (%) $C_{14}H_{28}N_2O_6P_2S$: calcd S 7.73 - found S 8.05.

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