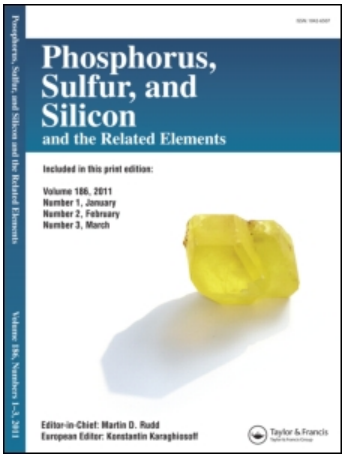


**Phosphorus, Sulfur, and Silicon and the Related Elements**
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

# SYNTHESIS AND PROPERTIES OF NOVEL α-PHOSPHORYL(THIO)UREIDOALKANEPHOSPHONATE DERIVATIVES

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**To cite this Article** Zhou, Jia and Chen, Ru-Yu(1996) 'SYNTHESIS AND PROPERTIES OF NOVEL α-PHOSPHORYL(THIO)UREIDOALKANEPHOSPHONATE DERIVATIVES', Phosphorus, Sulfur, and Silicon and the Related Elements, 118: 1, 247 — 256
**To link to this Article: DOI:** 10.1080/10426509608038816
**URL:** http://dx.doi.org/10.1080/10426509608038816

*Phosphorus, Sulfur, and Silicon*, 1996, Vol. 118, pp. 247–256
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# SYNTHESIS AND PROPERTIES OF NOVEL α-PHOSPHORYL(THIO)UREIDO ALKANEPHOSPHONATE DERIVATIVES

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*(Received 2 July 1996; Revised 21 August 1996; In final form 21 August 1996)*



Two series of novel α-phosphoryl(thio)ureido alkanephosphonate derivatives (**5**,**6**) have been synthesized by a convenient, multistep route involving the addition reaction of phosphoryl isothiocyanides with α-aminoalkanephosphonates and a homogeneous desulphurisation utilizing $Ag^{+}$-$H_2O$ system as key steps. The carbodiimide intermediate **8** in the conversion of compounds **5** into **6** was trapped to afford regioselectively the corresponding imino-ether **9** instead of its isomer **10**. All the compounds prepared were confirmed by $^{1}H$ NMR, IR, MS, $^{31}P$ NMR and elemental analysis. Preliminary bioassays indicate that compounds **5** and **6** have potent antiphytoviral activities against the tobacco mosaic virus (TMV). In addition, some of **5** possess selective herbicidal activities and some of **5** and **6** exhibit good fungicidal activities against wheat leaf rust and cucumber grey blight.

*Keywords:* α-Phosphoryl(thio)ureido alkanephosphonates; α-aminoalkanephosphonates; synthesis; desulphurisation; antiphytoviral chemicals

## INTRODUCTION

The biological activity of α-aminophosphonic acid derivatives as phosphonic analogues of naturally occurring α-amino acids and of phosphonopeptides has stimulated a great deal of interest and therefore a large number of the related compounds have been synthesized in the past two decades.[1] In particular, their N-substituted derivatives represent a class of compounds which tend to exhibit

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superior biological activities, such as antibacterial[2], herbicidal[3], antitumor[4], and inhibitory activity to enzymes[5].

We have recently found that some thioureido phosphordiamide and phosphoramidate derivatives possess significant antivirus and antitumor activities[6,7]. For the purpose of further searching for new, effective antiphytoviral chemicals and antitumor drugs, we designed and synthesized a number of novel α-phosphoryl(thio)ureido alkanephosphonates **5** and **6**. The mechanism of desulphurisation of **5** has also been studied and the possible intermediate was trapped using $Ag^+$-ROH reaction system. All of the compounds prepared were confirmed by microanalyses and spectroscopic methods, and their biological activities were preliminarily tested.

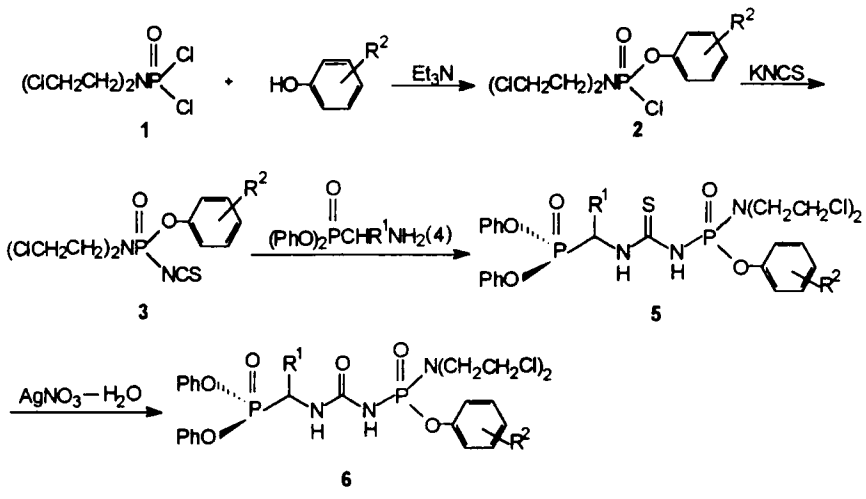


## RESULTS AND DISCUSSION

### A. Synthesis of the Title Compounds 5 and 6

Despite a variety of approaches to the synthesis of N-substituted α-aminoalkanephosphonate derivatives are available[8], to the best of our knowledge, only one general method for the preparation of (thio)ureido alkanephosphonates has been developed by a three-component mannich-type reaction involving an aldehyde, a phosphite and a compound bearing a (thio)ureido function[9]. Our synthetic strategy to yield the target compounds **5** and **6** involves the addition reaction of phosphoryl isothiocyanides with α-aminoalkanephosphonates and a homogeneous sulfur extrusion reaction under mild conditions as key steps shown in Scheme I. Significantly, the sequence as outlined has a great deal of flexibility, providing a new convenient general method for the preparation of a wide scope of structurally related (thio)ureido alkanephosphonate derivatives.

Preparation of the free α-aminoalkanephosphonates **4** was readily accomplished in a two-step sequence (36–54% overall yield) starting from aldehydes, benzyl carbamate and triphenylphosphite[10]. Bis(2-chloroethyl)aminophosphoryl dichloride **1** was allowed to react with phenols in the presence of triethylamine to give the phosphoramidates **2** in 75–78% yield. Then, **2** was treated with excess potassium thiocyanate in anhydrous acetonitrile to afford the intermediates **3** in nearly quantitative yield. The reaction of isothiocyanato phosphoramidates **3** with **4** was carried out under mild conditions to give products **5a–h** in a yield of 54–73%. It must be pointed out that the aminophosphonates **4** should be freshly prepared. Otherwise, their poor solubility might result in a weak reactivity and a disadvantage to the purification of **5**.



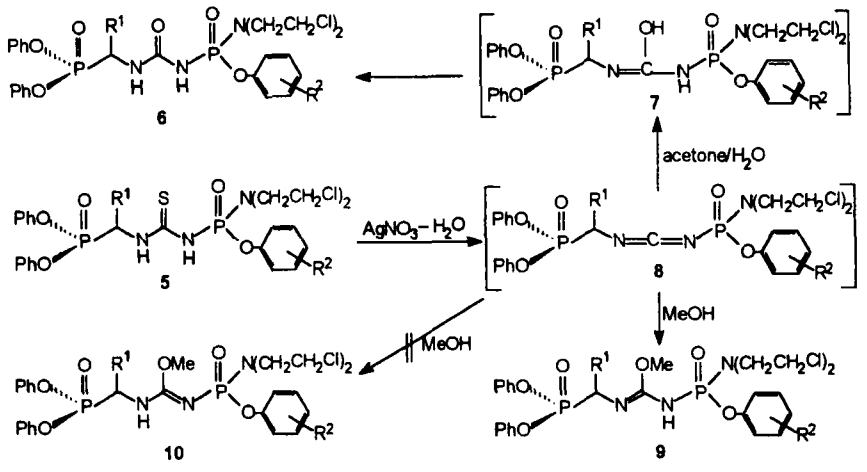
SCHEME I For **5a–h** and **6a–g**: $R^1$ = Me, n-Pr, n-Bu; $R^2$ = H, o-Cl, p-Cl, o-Me.

Compounds **6** were synthesized by a mild protocol for desulphurisation of compounds **5** *via* the corresponding tautomers **7** in excellent yields (93–97%). Penn[11] has suggested the carbodiimide might be an intermediate in O-urea formation from S-urea under the condition of $AgNO_3$-$H_2O$, but he did not provide sufficient evidence. In order to confirm the existence of carbodiimide **8**, **5a** was allowed to react with $AgNO_3$-anhydrous methanol, and the expected imino-ether **9** was obtained without formation of its isomer **10**. Compound **9** and **10** can be distinguished by the spectroscopic method (See section B). The results demonstrate that water or methanol regioselectively attacks the C=N bond linked to the phosphoramidate moiety in the desulphurisation procedure. The possible mechanism is depicted in Scheme II.

## B. Spectral Properties and Structures of 5, 6 and 9

All the compounds prepared were confirmed by $^1$H NMR, $^{31}$P NMR, IR, MS spectroscopy and elemental analysis (See Table I and Table II).

In the $^1$H NMR spectra of **5** and **6**, the methyl protons of $R^1$ = Me appear as two doublets due to the existence of the $C_\alpha$-H coupling ($^3J_{HCCH}$ = ≈ 7.2 Hz) and the phosphorus coupling ($^3J_{PCCH}$ = ≈ 17.9 Hz). The two NH protons of the thioureido group and the α-methylidyne proton in compounds **5** exhibit two broad peaks (δ 7.58–8.12, 8.72–9.16 ppm) and multiplets (δ 5.50 ppm) respectively. For compounds **6**, however, the signals of the counterparts mentioned above move upfield by about 1 ppm and appear as a broad peak or a doublet



SCHEME II For **9** and **10**: $R^1$ = Me, $R^2$ = p-Cl.



(one overlapped in Ar-H signals, the other δ 7.67–8.08 ppm, J = 8.1–9.0 Hz) and multiplets (δ 4.58–4.72 ppm), respectively. The $^{31}$P NMR spectra of **5** and **6** exhibit two signals with compound **6c** as an exception. In contrast to **5**, the $^{31}$p signals of **6** move slightly downfield by about 1–3 ppm. The presence of two stereocenters, namely the carbon substituted by $R^1$ and one of the phosphorus atoms in compounds **5a–h** and **6a–g** would lead to the generation of two diastereoisomers. However, the difference of properties between the isomers is so little that the diastereoisomerism can not be clearly detected by spectroscopic methods except compound **6c**. The $^1$H signals of methyl and methylene protons in the n-Bu group of **6c** appear as broad peaks instead of a triplet and multiplets, and the $^{31}$P NMR spectrum of **6c** exhibits three signals instead of two peaks. A separation of the diastereoisomers is not possible by the TLC method, and an attempt by HPLC is currently under investigation.

In the $^1$H NMR spectrum of **9**, the NH proton appears as a doublet with a larger coupling constant (J 10.43 Hz) which accords with the phosphorus coupling ($^2J_{P\text{-}N\text{-}H}$ 10–20 Hz) instead of the $C_\alpha$-H coupling ($^3J_{H\text{-}C\text{-}N\text{-}H}$ 2–3 Hz). We can imagine that in the $^1$H NMR of **10**, however, the NH proton should appear as two doublets coupled by both the $C_\alpha$-H ($^3J_{HCNH}$) and the phosphorus atom ($^3J_{PCNH}$).

The IR spectra of compounds **5**, **6** and **9** show normal stretching absorption bands, indicating respectively the existence of the >C=S (~1320 cm$^{-1}$), >P=O (~1197 cm$^{-1}$, ~1229 cm$^{-1}$) groups in **5a–h**, the existence of the

TABLE I Preparation of α-phosphoryl(thio)ureido alkanephosphonates **5** and **6**

| NO | $R^1$ | $R^2$ | Yield[a] (%) | m.p.[b] (°C) | Molecular formular | Cacld./Found(%) | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | C | H | N |
| **5a** | Me | p-Cl | 73.1 | 165–166 | $C_{25}H_{28}Cl_3N_3O_5P_2S$ | 46.13 | 4.34 | 6.46 |
| | | | | | (650.9) | 46.28 | 4.30 | 6.45 |
| **5b** | n-Pr | p-Cl | 68.9 | 134–135 | $C_{27}H_{32}Cl_3N_3O_5P_2S$ | 47.76 | 4.76 | 6.19 |
| | | | | | (679.0) | 47.50 | 4.60 | 6.18 |
| **5c** | Me | H | 71.2 | 93–94 | $C_{25}H_{29}Cl_3N_3O_5P_2S$ | 48.70 | 4.75 | 6.82 |
| | | | | | (616.5) | 48.73 | 4.53 | 6.66 |
| **5d** | n-Bu | H | 54.2 | 97–98 | $C_{28}H_{35}Cl_2N_3O_5P_2S$ | 51.06 | 5.37 | 6.38 |
| | | | | | (658.6) | 51.33 | 5.37 | 6.18 |
| **5e** | n-Bu | o-Cl | 62.7 | 126–128 | $C_{28}H_{34}Cl_3N_3O_5P_2S$ | 48.53 | 4.96 | 6.06 |
| | | | | | (693.0) | 48.54 | 4.90 | 5.79 |
| **5f** | n-Pr | o-Cl | 61.3 | 128–129 | $C_{27}H_{32}Cl_3N_3O_5P_2S$ | 47.76 | 4.76 | 6.19 |
| | | | | | (679.0) | 47.80 | 5.03 | 6.01 |
| **5g** | Me | o-Cl | 64.5 | 131–132 | $C_{25}H_{28}Cl_3N_3O_5P_2S$ | 46.13 | 4.34 | 6.46 |
| | | | | | (650.9) | 46.16 | 4.68 | 6.46 |
| **5h** | n-Pr | o-Me | 58.3 | 126–127 | $C_{28}H_{35}Cl_2N_3O_5P_2S$ | 51.06 | 5.37 | 6.38 |
| | | | | | (658.6) | 50.83 | 5.17 | 6.14 |
| **6a** | n-Pr | p-Cl | 96.5 | 114–115 | $C_{27}H_{32}Cl_3N_3O_6P_2$ | 48.92 | 4.88 | 6.34 |
| | | | | | (662.9) | 48.96 | 4.80 | 6.27 |
| **6b** | Me | p-Cl | 94.9 | 168–169 | $C_{25}H_{28}Cl_3N_3O_6P_2$ | 47.30 | 4.45 | 6.62 |
| | | | | | (634.8) | 46.99 | 4.17 | 6.40 |
| **6c** | n-Bu | o-Cl | 93.9 | 123–124 | $C_{28}H_{34}Cl_3N_3O_6P_2$ | 49.68 | 5.07 | 6.21 |
| | | | | | (676.9) | 49.68 | 4.83 | 6.19 |
| **6d** | Me | H | 97.4 | 144–145 | $C_{25}H_{29}Cl_3N_3O_6P_2$ | 50.01 | 4.88 | 7.00 |
| | | | | | (600.4) | 50.11 | 4.60 | 6.99 |
| **6e** | Me | o-Cl | 93.1 | 112–113 | $C_{25}H_{28}Cl_3N_3O_6P_2$ | 47.30 | 4.45 | 6.62 |
| | | | | | (634.8) | 47.27 | 4.36 | 6.61 |
| **6f** | n-Bu | H | 95.2 | 115–116 | $C_{28}H_{35}Cl_2N_3O_6P_2$ | 52.34 | 5.50 | 6.54 |
| | | | | | (642.5) | 52.27 | 5.47 | 6.36 |
| **6g** | n-Pr | o-Me | 96.6 | 159–160 | $C_{28}H_{35}Cl_2N_3O_6P_2$ | 52.34 | 5.50 | 6.54 |
| | | | | | (642.5) | 52.23 | 5.63 | 6.53 |

[a]Yield of isolated product, for **5a–h** based on **2** and for **6a–g** based on **5**.
[b]Uncorrected, after recrystallization from proper solvents.



>C=O (~1684 $cm^{-1}$), >P=O (~1183 $cm^{-1}$, ~1218 $cm^{-1}$) groups in **6a–g**, and the existence of the >C=N (1638 $cm^{-1}$), >P=O (1183 $cm^{-1}$, 1207 $cm^{-1}$) groups in **9**. The other all can be rationalized.

The EI-MS spectra of **5**, **6** and **9** demonstrate that fragmentations occur by a number of routes and no molecular ion peaks are obtained. All fragmentation ions are consistent with their structures and can be clearly assigned.

TABLE II Spetroscopic data of α-phosphoryl(thio)ureido alkanephosphonates **5** and **6**

| m- and | IR(KBr pellet) ν ($cm^{-1}$) | $^1$H-NMR($CDCl_3$, TMS)[a] δ (ppm), J(Hz) | $^{31}$P-NMR ($CDCl_3$) δ (ppm) |
|---|---|---|---|
| | 3395, 3200, 2958, 1589, 1534, 1507, 1484, 1320(m, C═S), 1235(s, P═O), 1192(s, P═O), 1158, 1085, 932, 900, 833, 773 | 1.48–1.82(dd, 3H, $CH_3$, J = 7.2 and 17.9), 3.4–3.9(m, 8H, $2ClCH_2CH_2$), 5.52(m, 1H, CH), 7.14–7.60(m, 14H, 2Ph and $C_6H_4$), 9.16 (br, 1H, NH) | 17.7765, 1.3 |
| | 3388, 3249, 2949, 1617, 1506, 1484, 1323(m, C═S), 1229(s, P═O), 1197(s, P═O), 1154, 1085, 921, 899, 846, 766 | 0.95(t, 3H, $CH_3$), 1.4–2.2(m, 4H, $2CH_2$), 3.39–3.82(m, 8H, $2ClCH_2CH_2$), 5.50(m, 1H, CH), 7.10-7.4(m, 14H, 2Ph and $C_6H_4$), 7.96(br, 1H, NH), 9.12 (br, 1H, NH) | 17.2919, 1.6 |
| | ---- | 1.445–1.571(dd, 3H, $CH_3$, J = 7.26 and 18.0), 3.38–3.62(m, 8H, $2ClCH_2CH_2$), 5.417(m, 1H, CH), 6.958–7.333(m, 15H, 3Ph), 7.917(br, 1H, NH), 9.002 (br, 1H, NH) | 16.0719, −0 |
| | 3397, 3237, 2946, 1612, 1507, 1486, 1382, 1324(m, C═S), 1225(s, P═O), 1182(s, P═O), 1156, 1084, 763, 685 | 0.868(t, 3H, $CH_3$), 1.20–2.16(m, 6H, $3CH_2$), 3.40–3.74(m, 8H, $2ClCH_2CH_2$), 5.42(m, 1H, CH), 7.02–7.24(m, 15H, 3Ph), 7.80(br, 1H, NH), 9.14(br, 1H, NH) | 15.48, 0.26 |
| | ---- | 0.829(t, 3H, $CH_3$), 1.292(m, 4H, $2CH_2$), 1.562(br, 2H, $CH_2$), 3.334– 3.458(m, 8H, $2ClCH_2CH_2$), 5.458(m, 1H, CH), 7.12–7.50(m, 14H, 2Ph and $C_6H_4$), 7.87(br, 1H, NH), 8.83(br, 1H, NH) | 17.09, 2.15 |
| | 3394, 3235, 3066, 1587, 1506, 1486, 1382, 1320(m, C═S), 1216(s, P═O), 1180(s, P═O), 1155, 1096, 1020, 763, 717, 687 | 0.90(t, 3H, $CH_3$), 1.12–1.98(m, 4H, $2CH_2$), 3.34–3.78(m, 8H, $2ClCH_2CH_2$), 5.50(m, 1H, CH), 7.08–7.58(m, 14H, 2Ph and $C_6H_4$), 8.12(br, 1H, NH), 8.72(br, 1H, NH) | 15.21, −0.13 |
| | ---- | 1.50(dd, 3H, $CH_3$, J = 7.2 and 17.9), 3.44–3.80(m, 8H, $2ClCH_2CH_2$), 5.50(m, 1H, CH), 6.96–7.62(m, 14H, 2Ph and $C_6H_4$), 8.08 (br, 1H, NH), 9.0(br, 1H, NH) | 16.15, 0 |
| | 3371, 3245, 3066, 1585, 1507, 1484, 1381, 1320(m, C═S), 1215(s, P═O), 1171(s, P═O), 1105, 1082, 948, 926, 761, 702 | 0.837(t, 3H, $CH_3$), 1.25(m, 2H, $CH_2$), 1.67(br, 2H, $CH_2$), 2.309(s, 3H, $CH_3$), 3.38–3.68(m, 8H, $2ClCH_2CH_2$), 5.458(m, 1H, CH), 7.12–7.38 (m, 14H, 2Ph and $C_6H_4$), 7.58(br, 1H, NH), 9.12 (br, 1H, NH) | 16.28, −0.13 |
| | 3299, 3136, 2946, 1685(s,C═O), 1588, 1523, 1484, 1396, 1215(s,P═O), 1182 (s,P═O), 1156, 1085, 928, 831, 766 | 0.898(t,3H,$CH_3$), 1.30–1.86(m,4H,$2CH_2$), 3.26–3.72(m,8H,$2ClCH_2CH_2$), 4.58(m,1H,CH), 6.75–7.32(m,15H,2Ph,$C_6H_4$ and NH), 7.72(d,1H,NH,J = 8.1) | 16.55, 1.07 |
| | 3389, 3144, 2978, 1684(s,C═O), 1589, 1526, 1485, 1452, 1306, 1218(s,P═O), 1183 (s,P═O), 1150, 1009, 937, 916, 831, 775 | 1.33–1.46(dd,3H,$CH_3$,J = 8.3 and 18.0), 3.29–3.69(m,8H,$2ClCH_2CH_2$), 4.61(m,1H,CH), 6.88–7.32(m,15H,2Ph,$C_6H_4$ and NH), 7.67(d,1H,NH,J = 8.3) | 19.25, 3.50 |

TABLE II Continued

| n-nd | IR(KBr pellet) ν ($cm^{-1}$) | $^1$H-NMR($CDCl_3$, TMS)[a] δ (ppm), J(Hz) | $^{31}$P-NMR ($CDCl_3$) δ (ppm) |
|---|---|---|---|
| | 3295, 3060, 2940, 1694(s,C═O), 1587, 1541, 1483, 1450, 1272(s,P═O), 1200(s,P═O), 1176, 1153, 943, 909, 765 | 0.826(br,3H,$CH_3$), 1.23(br,2H,$CH_2$), 1.50(br,2H, $CH_2$), 1.87(br,2H,$CH_2$), 3.37–3.72(m,8H,2ClCH$_2$CH$_2$), 4.58(m,1H,CH), 6.76–7.72(m,16H,14Ar-H and 2NH) | 18.71, 3.76, |
| | 3374, 3073, 1675(s,C═O), 1588, 1525, 1484, 1459, 1381, 1220(s,P═O), 1196(s,P═O), 1157, 923, 899, 767, 685 | 1.28–1.64(dd,3H,$CH_3$,J = 7.2 and 17.9), 3.40–3.82(m,8H,2ClCH$_2$CH$_2$), 4.7(m,1H,CH), 6.92–7.48(m,16H,15Ar-H and NH), 7.86(d,1H,NH,J=9.0) | 18.98, 2.69 |
| | 3406, 3165, 2917, 1671(s,C═O), 1588, 1524, 1485, 1455, 1382, 1222(s,P═O), 1186(s,P═O), 1155, 932, 757, 685 | 1.24–1.66(dd,3H,$CH_3$,J = 7.2 and 17.9), 3.36–3.82(m,8H,2ClCH$_2$CH$_2$), 4.72(m,1H,CH), 7.0–7.72(m,15H,14Ar-H and NH), 7.84(d,1H,NH,J = 9.0) | 18.71, 2.96 |
| | 3402, 3205, 3094, 1678(s,C═O), 1590, 1521, 1505, 1471, 1383, 1219(s,P═O), 1196(s,P═O), 1158, 927, 902, 765, 689 | 1.0(br,3H,$CH_3$), 1.5(br,4H,2$CH_2$), 1.92(br,2H,$CH_2$),3.52–3.84(m,8H,2ClCH$_2$CH$_2$), 4.68(m,1H,CH),7.04–7.52(m,16H,15Ar-H and NH), 8.08(d,1H,NH,J = 9.0) | 18.30, 2.96 |
| | 3389, 3086, 2955, 1691(s,C═O), 1587, 1539, 1483, 1455, 1382, 1246(s,P═O), 1197(s,P═O), 1175, 1085, 955, 935, 775, 691 | 0.84(br,3H,$CH_3$), 1.20(br,2H,$CH_2$), 1.76(br,2H,$CH_2$), 2.28(s,3H,$CH_3$), 3.32–3.88(m,8H,2ClCH$_2$CH$_2$), 4.62(m,1H,CH), 6.98–7.60(m,15H,14Ar-H and NH), 8.04(d,1H,NH,J = 9.0) | 18.03, 2.15 |

[a] NMR spectra of **5a**, **5f**, **5g** and **6d–g** were recorded at 90 MHz with a JEOL-FX-90Q spectrometer, others at 200 MHz with a BRUKER AC-P200 spectrometer. [b] $^{31}$P tra of **5a–c** were recorded at 80.96 MHz with a BRUKER AC-P200 spectrometer, others at 36.19 MHz with a JEOL-FX-90Q spectrometer.

### C. Biological Activities

Preliminary bioassays indicate that compounds **5** and **6** have potent antiphytoviral activities against the tobacco mosaic virus (TMV). The results are listed in Table III. In contrast, the inhibition rate of NS-83, one commercially used virucide, is 30–50%. Furthermore, it was found that **5** possess selective herbicidal activities by soil treatment against barnyard grass (**5f**: the inhibition rate for 1.5 Kg/ha is 67%), but not against sorghum, oats, rape, cassava and amaranth. Some of **5** and **6** exhibit fungicidal activities against wheat leaf rust (**6b**: IR for 500 ppm is 50%) and cucumber grey blight (**5c**, **5d** and **6b**: IR for 500 ppm are 78%, 86% and 56% respectively).

## EXPERIMENTAL



Elemental analysis was performed with a CHNCORDERED MT-3 elementary analyzer. Mass spectra were recorded with a VG-7070E spectrometer using the GAB method. NMR spectra were recorded with a JEOL-FX-90Q spectrometer and BRUKER AC-P200. TMS was used as an internal standard for $^{1}H$ NMR, and 85% $H_3PO_4$ was used as an external standard for $^{31}P$ NMR. IR spectra were measured by using a SHIMADZU-435 instrument. Melting points were determined with a model YANACO MP-500 apparatus and are uncorrected. Column chromatography was performed on silica gel H(10–40 μ, Haiyang Chemical Factory of Qingdao).

Bis(2-chloroethyl)aminophosphoryl dichloride **1**[6], O-aryl N,N-bis(2-chloroethyl)aminophosphoryl chloride **2**[7], and the free α-aminoalkanephosphonates **4**[10] were prepared as described. The other reagents and solvents were obtained commercially and purified according to conventional methods before use.

TABLE III The antivirus activity of some of compounds **5** and **6** against TMV

| *Compounds* | ***5a*** | ***5c*** | ***5e*** | ***5f*** | ***5g*** | ***5h*** | ***6b*** | ***6f*** |
|---|---|---|---|---|---|---|---|---|
| Concentration (ppm) | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| Inhibition rate (%) | 50 | 20 | 30 | 25 | 35 | 60 | 50 | 15 |

***O,O-Diphenyl α-(3-Phosphorylthioureido) Alkanephosphonates* (5a–h).** (General procedure):

To a solution of 4.0 mmol of O-aryl N,N-bis(2-chloroethyl)aminophosphoryl chloride (**2**) in 40 mL of anhydrous acetonitrile was added 8.2 mmol of potassium thiocyanate at 12–20°C. The reaction mixture was kept stirring at this temperature for 8–12 hrs until the phosphoryl chloride **2** disappeared, this being monitored by TLC. After vacuum evaporation, the residue was extracted with anhydrous benzene and the extract was rotarily evaporated under reduced pressure, and then 15 mL of acetonitrile was added. The mixture was reacted with an equimolecular amount of the free α-aminoalkanephosphonate (**4**) at 30–35°C for 12–18 hrs to provide the target compounds **5** as white solids. Then the mixture was filtered, and the filter liquor was concentrated under reduced pressure. The residue was crystallized from acetone-ethyl ether-petroleum ether in the refrigerator overnight to give another crop of product **5**. All the solid products were combined and recrystallized (54–73%). The physical and chemical data are listed in Table I and II.



***O,O-Diphenyl α-(3-Phosphorylureido) Alkanephosphonates* (6a–g).** (General procedure):

To a vigorously stirred solution of **5** (0.6 mmol) in acetone (10 mL) was added dropwise (r.t.) a solution of silver nitrate (1.2 mmol) in deionized water (4 mL). After stirring at room temperature for 4–5 hrs, 25 mL of water was added, and the resulting mixture was filtered and the black precipitate was extracted with DMF (5 mL × 3). To the extract was added a large amount of water, yielding compounds **6** that were recrystallized from proper solvents (93–97%). The physical and chemical data are also given in Table I and II.

***Trapping of the Carbodiimide Intermediate 8 and Preparation of the Imino-ether Derivative* 9:**

Similarly, 0.6 mmol of **5a** was allowed to reacted with 1.2 mmol of silver nitrate in 20 mL of anhydrous methanol at room temperature for 10 hrs, then filtered, and after removal of the solvent from the filter liquor under reduced pressure, a small amount of water was added to the residue. The organic product was extracted with chloroform (25 mL × 3) and the layers were separated. Combined organic extracts were dried ($MgSO_4$), and the solvent was removed under reduced pressure to produce the crude imino-ether **9**, which was purified by flash chromatography (silica gel H, ethyl ether-petroleum ether, v/v 1:2) (92%). Anal.

Cacld for $C_{26}H_{30}Cl_3N_3O_6P_2$: C, 48.11; H, 4.63; N, 6.48. Found: C, 48.23; H, 4.57; N, 6.62. $^1H$ NMR (200 MHz, $CDCl_3$, δ, ppm): 1.45–1.58 (dd, 3H, $CH_3$, J = 7.2 and 17.9 Hz), 3.32–3.59 (m, 8H, $2ClCH_2CH_2$), 3.52 (s, 3H, $CH_3$), 4.3530 (m, 1H, CH), 6.82–7.28 (m, 14H, $2C_6H_5$ and $C_6H_4$), 7.6634 (d, 1H, NH, J = 10.43 Hz). $^{31}P$ NMR (80.96 MHz, $CDCl_3$, δ, ppm): 17.0840(s), 11.2393(s). IR (film, $\nu$, $cm^{-1}$): 1183 (s, P═O), 1207 (s, P═O), 1638 (s, C═N). MS(EI): 611 ($M^+$-HCl, 2%), 507 (15%), 317 (100%), 217 (26%), 94(31%).

### *Acknowledgements*

The authors would like to thank the National Natural Science Foundation of P.R. China for financial support. We also wish to express many thanks to Associate Prof. D. W. Qiu, who is currently doing research in Department of Plant Pathology, Cornell University, for conducting the prelimilary test of antiphytoviral activities.



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