SYNTHESIS OF 4-BENZYL-5-(2,6-DICHLOROPHENYL)-2-ETHOXY-1,2,3,4-TETRAHYDRO -1,4,6,2-OXADIAZAPHOSPHORINE 2-OXIDE

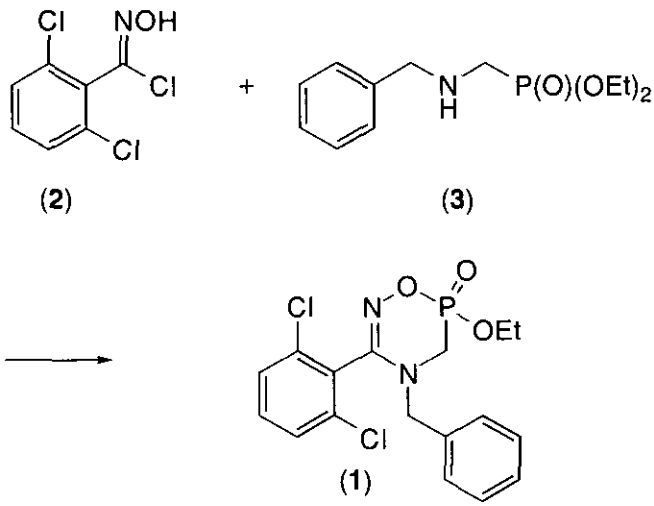
Wynona Johnson,[a*] Alan Faux,[a] and Gary Fallon[b]

[a]CSIRO, Molecular Science,
Private Bag 10, Clayton South MDC,
Victoria, Australia 3169

[b]Department of Chemistry, Monash University, Clayton, Victoria, Australia 3168

Abstract - A derivative of the novel heterocyclic ring system - 1,2,3,4-tetrahydro-1,4,6,2-oxadiazaphosphorine (**1**), was prepared by the cycloaddition of the nitrile oxide generated from hydroximoyl chloride (**2**) with aminomethylphosphonate (**3**). The structure was elucidated by NMR analysis and X-Ray crystallography. The stability of the new ring system was investigated.

As part of our investigation[1] of novel heterocyclic ring systems as potential crop protection chemicals, it was of interest to synthesize the previously unreported 1,2,3,4-tetrahydro-1,4,6,2-oxadiazaphosphorine ring system (**1**). The synthetic approach adopted for **1** involved the cycloaddition of the arylhydroximoyl chloride (**2**) with an aminomethylphosphonate (**3**) in the presence of triethylamine to give **1**.



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

(**1**)

Although reactions of hydroximoyl chlorides with nitrogen nucleophiles are well known, there is only one report of the addition of an aminoalkylphosphonate in the literature.[2] In this investigation an acyclic amidoxime, not the cyclic compound, was the product formed. We envisaged that by choosing a one carbon alkyl group for the aminoalkylphosphonate, cycloaddition to form the six-membered heterocyclic ring might be possible. Thus the aminomethylphosphonate (**3**) was reacted with 2,6-dichlorohydroximoyl chloride (**2**) in dry dichloromethane in the presence of triethylamine. After chromatography on silica gel a white crystalline material was obtained in 44% yield. The IR showed no bands for a hydroxy group but bands at 1265 and 1035 cm^{-1} for the phosphonate moiety. The ^{31}P-NMR spectrum clearly showed a resonance at 12.41 ppm. This shift is distinctly different from the starting aminomethylphosphonate (**3**) that showed a resonance at 27.03 ppm. In the ^{1}H-NMR spectrum the broad doublet due to the CH_2 next to the P in **3** became two overlapping AB quartets (J_{HH} = 14 Hz, J_{HP} = 16 Hz) in the product (**1**). The non-equivalence of the methylene protons is a strong indication of a cyclic product. No exchangeable protons were present and only one ethoxy group remained. The mass spectrum and ^{13}C-NMR were also consistent with compound (**1**) being the product formed from the addition of the aminomethylphosphonate to the intermediate nitrile oxide followed by ring closure. Confirmation of structural assignment was achieved by X-Ray analysis using crystals of **1** recrystallized from acetonitrile (Figure 1).

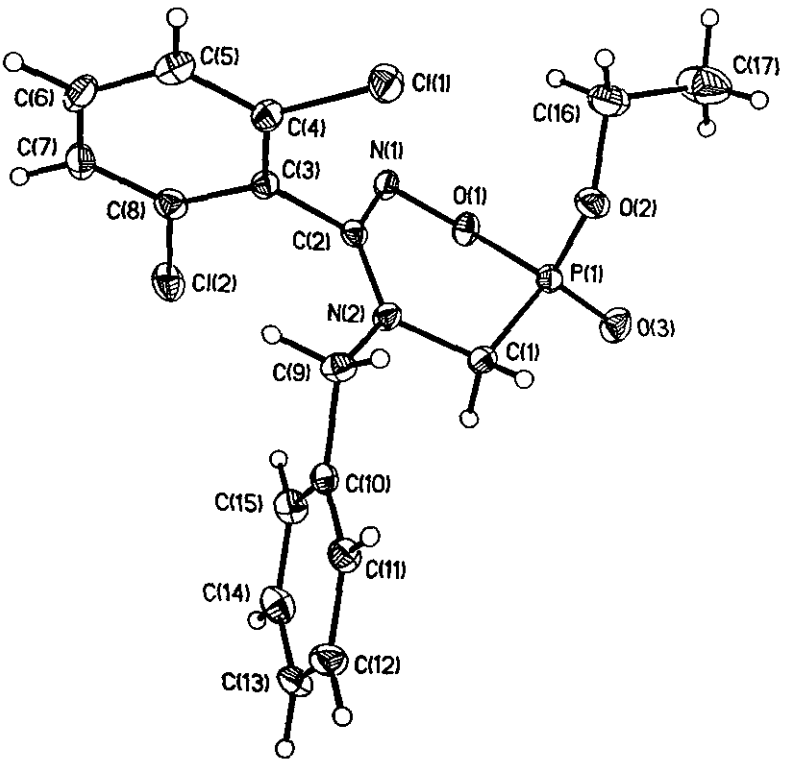
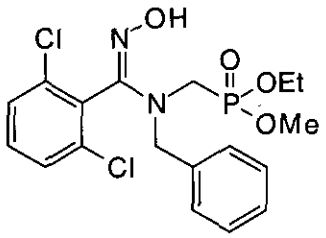


Figure 1. X-Ray crystal structure of 4-benzyl-5-(2,6-dichlorophenyl)-2-ethoxy-1,2,3,4-tetrahydro-1,4,6,2-oxadiazaphosphorine 2-oxide

Thus the structure 4-benzyl-5-(2,6-dichlorophenyl)-2-ethoxy-1,2,3,4-tetrahydro-1,4,6,2-oxadiazaphosphorine 2-oxide has been assigned to compound (**1**). Compound (**1**) is the first example of this heterocyclic ring system. Work is continuing in this area of phosphorus-containing heterocyclic compounds.

It was found that compound (**1**) remained unchanged after stirring for seven days with a tenfold excess of water in tetrahydrofuran. After stirring for seven days in dry methanol 84% remained unchanged while 16% was the ring opened compound (**4**). This material showed one peak in the ^{31}P-NMR spectrum at 25.5 ppm. The ^{1}H-NMR spectrum showed signals for one ethoxy group and one methoxy group attached to phosphorus and a doublet for the CH_2 group next to the phosphorus. The MS was consistent with the ring opened structure. In contrast to the relative stability of the ring system in the solvents reported above, compound (**1**) was completely decomposed in 6 h by 3M HCl to unidentified materials.



(**4**)

EXPERIMENTAL

Melting points were determined on a Reichert hot-stage melting point apparatus and are uncorrected. Microanalyses were performed by Campbell Microanalytical Laboratories, Dunedin, NZ. IR spectra were measured on a Perkin Elmer Spectrum 2000 FT-IR spectrophotometer. ^{1}H-, ^{31}P-, and ^{13}C-NMR spectra were recorded on a Bruker AC200, at the following frequencies 200MHz (^{1}H), 81.0 MHz (^{31}P), and 50.3 MHz (^{13}C). Chemical shifts were measured in ppm relative to H_3PO_4 as external standard(^{31}P), and the solvent ($CDCl_3$) which was related to Me_4Si at δ 0.0 ppm (^{1}H)(^{13}C). Numbering of atoms is as shown in Figure 1. High and low resolution MS were recorded on a JEOL JMS-DX303 Mass Spectrometer using methane. Column chromatography was performed using Kieselgel 40 (70-230 mesh, Merck).

4-Benzyl-5-(2,6-dichlorophenyl)-2-ethoxy-1,2,3,4-tetrahydro-1,4,6,2-oxadiazaphosphorine 2-oxide (1)

To a solution of diethyl *N*-benzylaminomethylphosphonate[3] (2.57 g, 0.01 mol) and triethylamine (1.39 mL, 0.01 mol) in dry dichloromethane (20 mL) was added dropwise a solution of 2,6-dichlorobenzohydroximinoyl chloride[4] (2.12 g, 0.09 mol) in dry methylene chloride (20 mL). The reaction was allowed to stir at rt until TLC indicated that no more

nitrile oxide remained. The solvent was removed *in vacuo* and the residue chromatographed using a gradient of CH_2Cl_2 to EtOAc. The title compound (**1**) was obtained as a thick viscous oil that crystallised on trituration with ether. Recrystallization from benzene gave 1.7 g (44% yield) of white crystals, mp 149-152°; IR (KBr) υ_{max} 2926, 1565, 1393, 1265, 1035 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.41 (t, 3H, J=7 Hz, CH_3), 3.43, 3.52 (2 x ABq, J=14, 16 Hz, 2H, CH_2P), 4.13 (d ABq, J = 2.6, 15 Hz, 2H, CH_2Ph), 4.20-4.40 (m, 2H, OCH_2), 7.21-7.46 (m, 8H, ArH). ^{13}C-NMR($CDCl_3$) δ 16.4 (J_{CP} = 6.5 Hz, CH_3), 42.0 (J_{CP} = 140 Hz, CH_2P), 57.0 (J_{CP} = 8.7 Hz, CH_2N), 62.6 (J_{CP} = 7 Hz, CH_2O), 128.4, 128.5, 128.6 (3 x s, C11-C15), 128.9 (C3), 129.1 (C5, C7), 132.1 (C6), 133.4 (C4, C8), 135.8, 136.1 (C2, C10). ^{31}P-NMR δ 12.41 ppm. Anal. Calcd for $C_{17}H_{17}N_2O_3Cl_2P$: C, 51.15; H, 4.29; N, 7.02; P, 7.76. Found: C, 51.17; H, 4.25; N, 7.08; P, 7.44. HR CIMS *m/z*: Calcd for $C_{17}H_{18}N_2O_3Cl_2P$, 399.0424. Found: 399.0428. CIMS (rel. int.): *m/z* 399 (M^{+1}, 44), 188 (41), 172 (100).

Stability Studies on Compound (1)

With water

Heterocyclic compound (**1**) (100 mg, 0.25 mmol) was stirred with a solution of water (50 mg, 2.8 mmol) and tetrahydrofuran (5 mL) at 20° for 7 days. At the end of this time TLC showed only starting material present. The solvent was removed *in vacuo* and the residue examined by spectroscopic methods. All spectra were identical to those of the starting material (**1**).

With methanol

Heterocyclic compound (**1**) (100 mg, 0.25 mmol) was dissolved in methanol (5 mL) and stirred at 20° for seven days. TLC showed the presence of two components. The solvent was removed *in vacuo* and the residue chromatographed using a gradient of CH_2Cl_2 to EtOAc. Starting material (84 mg, 84%) was recovered. A new material was recovered as an oil (16 mg). ^{1}H-NMR δ 1.32 (t, J=7 Hz, 3H, CH_3CH_2), 3.75, 3.79 (2 x d, J=9.42, 11 Hz, 5H, OMe, CH_2P), 4.03-4.22 (m, 2H, CH_2O), 4.36 (s, 2H, CH_2Ph), 7.26-7.40 (m, 8H, ArH). ^{31}P-NMR δ 25.5 ppm. CIMS (rel int): m/z 431(M^{+1}, 48), 286(42), 242(36), 172(95), 123(100), 107(75). The instability of this material did not allow an elemental analysis to be obtained.

X-Ray crystal structure analysis of 4-benzyl-5-(2,6-dichlorophenyl)-2-ethoxy-1,2,3,4-tetrahydro-1,4,6,2-oxadiazaphosphorine 2-oxide[5] (**1**): Formula $C_{17}H_{17}N_2O_3Cl_2P$, M = 399.20, colorless prismatic crystal, 0.20 x 0.15 x 0.10 mm, orthorhombic, space group $P2_12_12_1$ (No. 19), *a*=11.2912(2), *b* = 11.3315(2), *c* = 13.8290(2) Å, V = 1769.37(5) $Å^3$, ρ_{calc} = 1.499 g cm^{-3}, F(000) = 824, λ = 0.71073 Å, T= 123(2)K, μ = 0.477 mm^{-1}. Nonius Kappa CCD diffractrometer, φ scan data, 25125 data processed, corrected for Lorentz and polarization effects, 5158 unique (R_{int} = 0.036, Friedel pairs not merged) and 4672 observed [$I \geq 2\sigma(I)$], 227 refined parameters, R = 0.033, ωR^2 = 0.067, GooF = 1.035, Flack parameter 0.03(4), max. (min.) residual electron

density 0.51 (-0.27) eÅ^{-3}, hydrogens calculated and refined as riding atoms. Structure solution, SHELXS-97[6], structure refinement, SHELXL-97.[6]

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5. Crystallographic data (excluding structure factors) for the structure in this paper has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 125670. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).
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