# A Novel Synthesis of 4,6-Dimethyl- and Diphenyl-2,5-dihydro-1,3,5,2-triazaphosphorines



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The synthesis of 2,5-dihydro-1,3,5,2-triazaphosphorines *via* the intramolecular cyclization of *N,N'*-phosphinylacetamidines or benzamidines is described. These derivatives represent the sole examples of 4,6-dialkyl or diaryl substitutions of this ring system.

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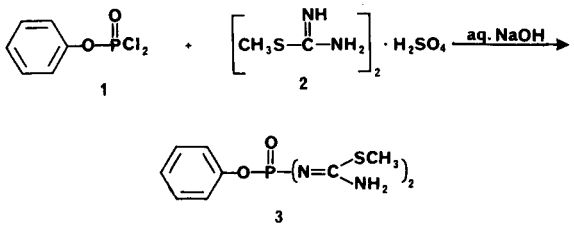
We recently synthesized a series of agents containing the P(O)N=C system as one possessing a new oncolytic moiety capable of undergoing a Michael-type addition with biologically important nucleophiles. While most of these compounds have one imido group present it was considered important to prepare diimido derivatives as possible bis-alkylators. During the synthesis of certain of these agents triazaphosphorines were serendipitously found to be the main products.

Whereas the Schotten-Baumann reaction of phenyl phosphorodichloridate (**1**) and 2-methyl-2-thiopseudourea

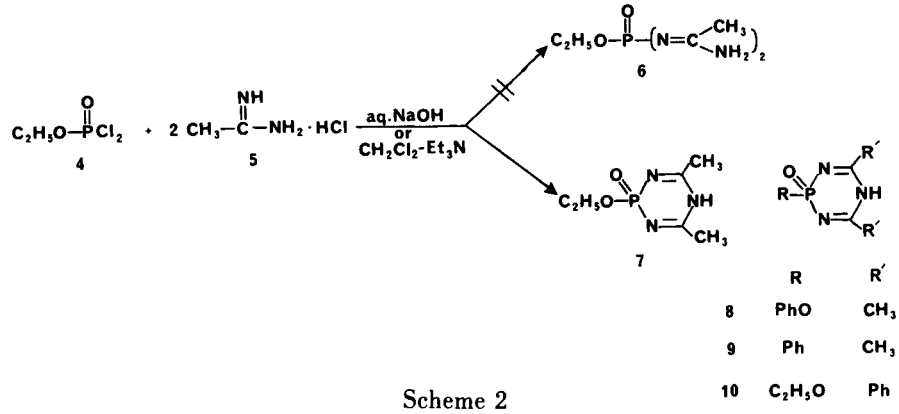


Scheme 1

sulfate (**2**), shown in Scheme 1, gave *N,N'*-(phenoxyphosphinyl)methylthiospeudourea (**3**), the same type reaction of ethyl phosphorodichloridate (**4**) with acetamidine hydrochloride (**5**) did not yield the expected diimidate (**6**), Scheme 2. After reacting **4** and **5** in methylene chloride with triethylamine as the hydrogen chloride scavenger (Scheme 2) a product was isolated and characterized as 2-ethoxy-4,6-dimethyl-2,5-dihydro-1,3,5,2-triazaphosphorine-2-oxide (**7**). This agent was identical, and its structure subsequently assigned, to the compound previously obtained under Schotten-Baumann conditions. Three additional triazaphosphorines (**8-10**) were then synthesized using the methylene chloride-triethylamine procedure. The properties of these agents and **3** are shown in Table I.

Latscha (2) indicated that he initially prepared the 2,5-dihydro-1,3,5,2-triazaphosphorine system in 1966 *via* the interesting heat mediated ring expansion of a 1,3,2-diazaphosphetidin-4-one. It was, however, first described four years earlier when Beyer, *et al.* (3), synthesized fourteen different 4,6-diamino derivatives from the reaction of a phosphorylated cyanoguanidine with amines or a phosphorochloridate with substituted biguanides. Since these earlier studies, 1,3,5,2-triazaphosphorines have primarily been synthesized from phosphorodiisocyanatidates and amines (4-7). Thus, the majority of such compounds are 4,6-diones and, provided both N-1 and N-3 possess hydrogen substituents, they can be considered to be 2,5-dihydro-1,3,5,2-triazaphosphorines. The N-1, N-3 dialkyl derivatives, like those prepared by Latscha, are, however, incapable of undergoing tautomerism to the $\Delta^3$, $\Delta^{1,6}$ enolic forms.

A search of the literature failed to reveal any 2,5-dihydro-1,3,5,2-triazaphosphorines with 4,6-dialkyl or diaryl substituents. Therefore, **7-10** represent new



Scheme 2

0022-152X/81/030503-03$02.25

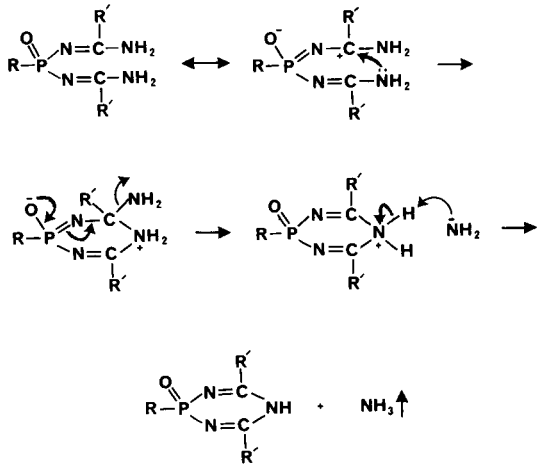
Table 1

Properties of *N,N'*-(Phenoxyphosphinyl)methylthiopseudourea and 2,5-Dihydro-1,3,5,2-triazaphosphorines

| Compound No. | M.p., °C | ν Max cm$^{-1}$ | $^1$H-Nmr, δ | Ms, m/e (%RI) |
|---|---|---|---|---|
| **3** | 114-114.5 | 3380 ($NH_2$)<br>1580 (C=C)<br>1690 (C=N)<br>1200, 1180 (P=O)<br>940 (O=POPh) | 7.20 (s, 5H, Ph)<br>6.75 (bs, 4H, $NH_2$)<br>2.34 (s, 6H, $CH_3S$) | 318 ($M^+$, 12)<br>271 (100)<br>181 (81)<br>77 (95)<br>47 (50) |
| **7** | 231-232 | 3270 (NH)<br>1630, 1660 (C=N)<br>1210 (P=O)<br>1060, 1080 (O=POEt) | 12.55 (bs, 1H, NH)<br>3.80 (m, 2H, $CH_2O$)<br>2.30 (s, 6H, $CH_3$)<br>1.25 (t, 3H, $CH_3$)<br>$^{13}$C-Nmr, δ<br>162.7 ($^2J_{CP}$ = 6.2)<br>61.5 ($^3J_{CP}$ = 5.3)<br>23.7 ($^3J_{CP}$ = 14.0)<br>16.4 ($^4J_{CP}$ = 6.0) | 189 ($M^+$, 12)<br>161 (28)<br>121 (25)<br>104 (24)<br>42 (100) |
| **8** | 303-305 | 3260 (NH)<br>1630, 1650 (C=N)<br>1590 (C=C)<br>1210 (P=O)<br>930 (O=POPh) | | 237 ($M^+$, 20)<br>103 (53)<br>65 (61)<br>42 (100)<br>39 (47) |
| **9** | 270-272 | 3260 (NH)<br>1650, 1660 (C=N)<br>1590 (C=C)<br>1190, 1210 (P=O) | 12.75 (bs, 1H, NH)<br>7.50 (bm, 5H, Ph)<br>2.30 (s, 6H, $CH_3$) | 221 (M+, 30)<br>77 (78)<br>51 (85)<br>47 (65)<br>42 (100) |
| **10** | 198-200 | 1600 (C=C)<br>1240 (P=O)<br>1040 (O=POEt) | 7.45 - 8.20 (bm, 10H, Ph)<br>4.03 (m, 2H, $CH_2O$)<br>1.30 (t, 3H, $CH_3$)<br>$^{13}$C-Nmr, δ<br>163.5<br>134.1 ($^3J_{CP}$ = 14.4)<br>132.0<br>128.0<br>61.9 ($^3J_{CP}$ = 6.4)<br>15.7 | 313 ($M^+$, 53)<br>285 (39)<br>182 (33)<br>104 (90)<br>103 (100) |

derivatives and ones produced by a novel reaction. They are considered to arise from the intramolecular nucleophilic attack on the α,β-unsaturated carbon leading to cyclization which is followed by elimination of one molecule of ammonia as shown in Scheme 3. One can speculate that the failure of **3** to undergo an intramolecular Michael-type addition is due to the lower reactivity of the imido carbons in this compound. Whether one considers the phosphorylated imine system as quasi-aromatic, because of its conjugation, or aliphatic in nature, the order of sigma values is thiomethyl > phenyl > methyl and, if σ* only is considered, the values are 1.47, 0.60 and 0.00, respectively (8). Thus, the thiomethyl group would be expected to donate electrons to the imino carbon atom to such an extent that its electrophilicity would be so lowered as to reduce nucleophilic condensation.

The synthetic method herein reported provides a new route to the 2,5-dihydro organophosphorus cyclic system and a preparative means to analogues of the postulated



Scheme 3

cyclophosphamide metabolite, iminophosphamide (9).

## EXPERIMENTAL

All solvents used were spectranalyzed or reagent grade. Melting points were determined on a Thomas-Hoover Unimelt capillary apparatus in open capillary tubes and are corrected to reference standards. Infrared spectra were taken on a Perkin-Elmer Model 283 spectrophotometer as potassium bromide pellets. Low resolution mass spectra were obtained on a Hewlett-Packard Model 5930 GCMS system with a Model 5933A data system at an ionizing energy of 70 eV. $^1$H-nmr spectra were recorded on a Varian T-60 or Varian XL-100 (for **8**) spectrometer in deuteriochloroform (for **3**, **7** and **9**) or methanol-$d_4$ (for **8** and **10**) using tetramethylsilane as an internal standard. $^{13}$C-nmr spectra (for **7** and **10**) in hexadeuteriodimethylsulfoxide were taken at 25.2 MHz on the latter apparatus equipped with a Nicolet-100 data system, an NT-440 frequency synthesizer and a NT-760 decoupler operating at a power of 20 watts centered at $\sigma$ = 6.0 in the proton spectral window with $\gamma H_2/2\pi$ = 2.9 KHz. Fixed spectral parameters were: sweep width 5 KHz; pulse width 5 $\mu$sec (32° tip); interpulse delay 2.0 sec; acquisition time 0.82 sec for 4K data points.

Synthesis of *N,N'*-(Phenoxyphosphinyl)methylthiopseudourea (**3**).

According to a modification of the procedure described by Cramer and Vollmar (10), 10 g (0.25 mole) of sodium hydroxide in 50 ml of cold water was added with stirring to 22.2 g (0.08 mole) or **2** in 200 ml of water with the reaction stirred and maintained at 5-10°. A solution of 8.4 g (0.04 mole) of **1** in 100 ml of benzene (5-10°) was added in portions and stirred vigorously for 1.5 hours while the temperature was allowed to rise to 25°. The benzene layer was separated, dried with anhydrous sodium sulfate and filtered. The filtrate was stirred while cyclohexane was added dropwise to yield 5.5 g (43%) of lustrous white crystals.

*Anal.* Calcd. for $C_{10}H_{15}N_4O_2PS$: C, 37.73; H, 4.75; N, 17.60; S, 20.14. Found: C, 37.79; H, 4.77; N, 17.58; S, 20.14.

Synthesis of 2,5-Dihydro-1,3,5,2-triazaphosphorines (**7-10**). General Procedure.

To a chilled mixture of acetamidine or benzamidine hydrochloride (0.1 mole) and triethylamine (0.22 mole, 10% excess) in 200 ml of methylene chloride, was added a solution of ethyl phosphorodichloridate, phenyl phosphorodichloridate or phenylphosphonic dichloride (0.05 mole) in 50 ml. of methylene chloride. After addition was complete the reaction was stirred at room temperature for two hours and then heated overnight at gentle reflux under static nitrogen. The solvent was removed under vacuum and the dried residue extracted with anhydrous acetone. Removal of acetone gave a solid which, in the case of **7** and **9**, was chromatographed on 70-230 mesh silica gel, eluted with chloroform -methanol (4:1). Compound **8** was purified by washing with chloroform and methanol and recrystallization from ethanol. Compound **10** was stepwise eluted from the previously described column with 0-10% methanol in chloroform. All compounds were white, crystalline solids. The analytical data for each respective compound is given below.

Compound **7**.

*Anal.* Calcd. for $C_6H_{12}N_3O_2P$: C, 38.07; H, 6.39; N, 22.21. Found: C, 38.13; H, 6.39; N, 22.19.

Compound **8**.

*Anal.* Calcd. for $C_{10}H_{12}N_3O_2P$: C, 50.61; H, 5.10; N, 17.71. Found: C, 50.80; H, 5.15; N, 17.84.

Compound **9**.

*Anal.* Calcd. for $C_{10}H_{12}N_3OP$: C, 54.27; H, 5.47; N, 18.99. Found: C, 54.35; H, 5.51; N, 19.01.

Compound **10**.

*Anal.* Calcd. for $C_{16}H_{16}N_3O_2P$: C, 61.34; H, 5.15; N, 13.41. Found: C, 61.40; H, 5.16; N, 13.38.

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