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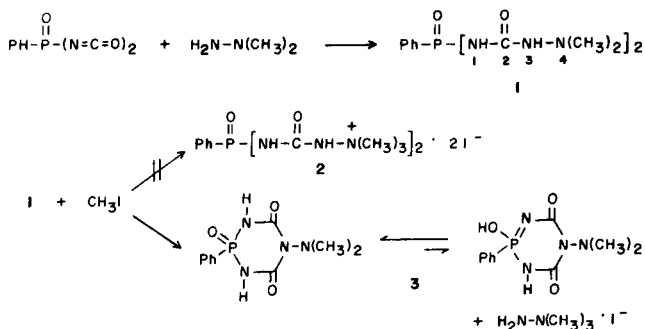
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Heating *N*⁴-phenylphosphinyl-bis-(*N*¹-dimethyl)semicarbazide in the presence, but not in the absence, of iodomethane gave 2-phenyl-5-dimethylamino-4,6-dioxo-1,3,5,2-triazaphosphorine 2-oxide and a mechanism for this reaction is proposed. The compound was also prepared by the addition of 1,1-dimethylhydrazine to phenylphosphonic diisocyanate. Treatment of the product with excess iodomethane gave a polymeric material and 1,1,1-trimethylhydrazinium iodides.

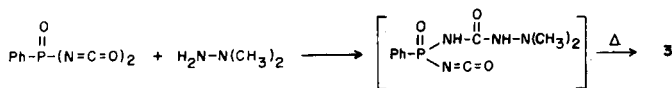
J. Heterocyclic Chem., **22**, 1559 (1985).

During an investigation of aminimides as agents affecting nerve transmission we undertook the synthesis of phosphorylated semicarbazinium inner salts. An approach to a precursor involved the methylation of *N*⁴-phenylphosphinyl-bis-(*N*¹-dimethyl)semicarbazide (**1**) which was prepared by the addition of phenylphosphonic diisocyanate to an excess amount of 1,1-dimethylhydrazine. The resulting product was not the expected carbazinium iodide (**2**) but the cyclized product, 2-phenyl-5-dimethylamino-4,6-dioxo-1,3,5,2-triazaphosphorine 2-oxide (**3**) (Scheme 1). For

Scheme 1



Scheme 2

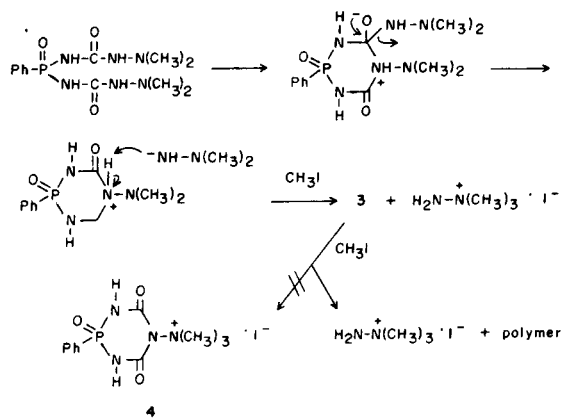


comparison purposes **3** was also synthesized by the addition of 1,1-dimethylhydrazine to phenylphosphonic diisocyanate in a 1:1 ratio (Scheme 2). Compound **3** was previously prepared *via* this method by Tomaschewski and Kühn [3] who purified by crystallization and reported only the melting point and carbonyl frequencies of the free form. We herein report the complete ir absorptions, the nmr and mass spectra and elemental analyses for the methanol complex which was synthesized by two routes, one of which is novel, and which was purified by chroma-

tography.

Similar compounds, in which the 5-substituents are alkyl groups or phenyl, have been synthesized by Tomaschewski *et al.* [4] and Shokol *et al.* [5]. The former investigators heated phosphinyl-bis-*N*³-alkylureides to produce 1,3,5,2-triazaphosphorines and the reaction was considered to proceed by the deamination of one ureido moiety to an isocyanate with subsequent intramolecular condensation with the N¹-H of the second ureido group. Shokol *et al.* also suggested that such a ureido-isocyanate intermediate is involved when aniline is added to phosphorodiisocyanate esters to form 4,6-dioxo-1,3,5,2-triazaphosphorine 2-oxides. We herein propose an alternate mechanism for the preparation of this heterocyclic system in the presence of iodomethane. This involves a nucleophilic attack by the *N*²-nitrogen of one semicarbazide moiety on the carbonyl carbon of the second with the loss of 1,1-dimethylhydrazine and equilibrium shift to product through methylation of the latter agent to the quaternary amine salt (Scheme 3). Credence is lent to this hypothesis by the failure, in the absence of iodomethane, of an attempt to produce **3** by the thermolysis of **1** in acetonitrile at 80° or in *n*-butyl ether at 140°, the same conditions employed by Thomaschewski *et al.* [4], with only starting material being recovered from the former reaction.

Scheme 3



An attempt to methylate **3** to the corresponding trimethylhydrazinium iodide (**4**) using excess iodomethane and prolonged heating with monitoring of the reaction by tlc gave only unidentified decomposition products and 1,1,1-trimethylhydrazinium iodide (Scheme 3). This result is not unexpected since the 5-dimethylamino nitrogen is deactivated toward electron acceptor species by two carbonyl groups situated adjacent to the 5-position amide nitrogen. Nielsen *et al.* [6] incorrectly applied this reasoning to the N^2 -nitrogen of phosphorohydrazides, which possess a single electron-attracting phosphinyl group, and as we have demonstrated [1], does undergo methylation.

Compounds **1** and **3** possess multiple binding sites for noncovalent interaction with solvent molecules and these two agents form 1:1 complexes with a molecule of chloroform and methanol, respectively. Treatment of **1** with ether-acetone instead of chloroform gave this compound associated with a half molecule of water, an indication that the complexation of **1** with solvent molecules is selective. The structures of **1**: CHCl_3 and **3**: CH_3OH complexes were verified by ir, nmr and gc-ms (for the latter) spectrometry and elemental analyses. A P-OH vibration frequency of 2790 cm^{-1} , associated with the $\text{P}(\text{OH})=\text{N}$ tautomer of this cyclic system and shown by Tomaschewski *et al.* [4] to occur in the range of $2700\text{--}2800\text{ cm}^{-1}$, was noted. The weak nature of this absorption, as compared to that shown by the $\text{P}=\text{O}$ moiety, indicates that equilibrium heavily favors the $\text{P}(\text{O})\text{NH}$ form.

EXPERIMENTAL

Melting points were taken on a Thomas-Hoover apparatus and are uncorrected to reference standards. The ^1H -nmr spectra were determined on a Varian FT-80A spectrometer using tetramethylsilane as the internal standard and deuterated dimethylsulfoxide as the solvent. The ir (potassium bromide) spectra were recorded on a Perkin-Elmer 283 spectrometer. The mass spectrum was determined at 70 eV on a Finnigan 1020 gc/ms spectrometer equipped with a solid sample probe and molecular ion mass and relative intensities (RI) are given. Silica gel 60 (70-230 mesh) and 2-10% methanol in chloroform were used for column chromatography with monitoring of eluants and reaction mixtures by use of silica gel 60 F254 (EM reagents) tlc plates.

N^4 -Phenylphosphinyl-bis- $(N^1$ -dimethyl)semicarbazide (**1**).

Phenylphosphinic diisocyanate [7] (6.6 g, 32 mmoles) in ether (50 ml) was added to an excess amount of 1,1-dimethylhydrazine (5.8 g, 96.5 mmoles) in ether (100 ml) with stirring under nitrogen at -5 to 0° and then at 25° for 18 hours. The ether was evaporated and the resulting white solid was washed with ether on a filter and dried *in vacuo*. The crude material was chromatographed twice to give a glassy mass which, upon trituration with chloroform, produced 6.0 g (41%) of white, crystal-

line **1** complexed with one molecule of chloroform and a half molecule of water, mp $163\text{--}164^\circ$; ir 3450 (OH), 3200 (NH), 1700 (C=O), 1600 (C=C), 1250 (P=O) cm^{-1} ; nmr: δ 2.44 (s, 12H, 4CH_3), 7.41-7.94 (m, 7H, 2NH, Ph), 8.31 (s, 1H, CHCl_3), 8.38-8.51 (bd, 2H, 2NH).

Anal. Calcd. for $\text{C}_{12}\text{H}_{21}\text{N}_6\text{O}_3\text{P}\cdot\text{CHCl}_3\cdot\frac{1}{2}\text{H}_2\text{O}$: C, 34.17; H, 5.01; N, 18.40; Cl, 23.29. Found: C, 34.07; H, 4.82; N, 18.29; Cl, 23.12.

The above compound was triturated with acetone-ether and dried to yield **1** with half molecule of water of hydration, mp $158\text{--}160^\circ$; ir: 3450 (OH), 3220 (NH), 1700 (C=O), 1600 (C=C), 1200 , 1250 (P=O) cm^{-1} ; nmr: δ 2.45 (s, 12H, 4CH_3), 7.42-7.97 (m, 7H, 2NH, Ph), 8.46 (bs, 2H, 2NH).

Anal. Calcd. for $\text{C}_{12}\text{H}_{21}\text{N}_6\text{O}_3\text{P}\cdot\frac{1}{2}\text{H}_2\text{O}$: C, 42.71; H, 6.57; N, 24.91. Found: C, 43.04; H, 6.56; N, 25.22.

2-Phenyl-5-dimethyl-4,6-dioxo-1,3,5,2-triazaphosphorine 2-Oxide (**3**). From Compound **1**.

Excess iodomethane (9.17 g, 64 mmoles) was added to a suspension of **1** (6.56 g, 20 mmoles) in acetonitrile (100 ml) and the mixture was heated to 90° to yield a solution. A second portion of iodomethane (9.12 g, 64 mmoles) was added, the mixture heated at 60° for 18 hours, cooled and filtered. The residue was washed repeatedly with acetonitrile and the washings treated with ether to give 1,1,1-trimethylhydrazinium iodide (1.3 g, 33%) with a melting point and ir and nmr spectra identical to an authentic sample. The washed residue (2.2 g, 73%) was chromatographed twice to separate the product from the remaining hydrazinium salt and yield 0.78 g (12%) of **3**, mp $149\text{--}150^\circ$; ir 3450 (OH), 3220 (NH), 2790 (P-OH), 1700 , 1740 (C=O), 1600 (C=C), 1220 , 1270 (P=O) cm^{-1} ; nmr: δ 2.47 (s, 6H, 2CH_3), 3.53 (s, 3H, CH_3), 7.52-8.02 (m, 6H, NH, Ph), 8.29 (bd, 1H, NH), 9.49 (bs, 1H, OH); ms: m/e (RI) 51 (77), 60 (90), 77 (100), 166 (88), 268 (M^+ , 37), 269 (M^+ , 12).

Anal. Calcd. for $\text{C}_{10}\text{H}_{13}\text{N}_4\text{O}_3\text{P}\cdot\text{CH}_3\text{OH}$: C, 43.98; H, 5.71; N, 18.65. Found: C, 43.97; H, 5.73; N, 18.52.

From Phenylphosphonic Diisocyanate.

Using a modification of the procedure of Tomaschewski and Kuhn [3], 1,1-dimethylhydrazine (1.0 g, 16.6 mmoles) in sodium dried toluene (50 ml) was added dropwise to phenylphosphinic diisocyanate [7] (3.45 g, 16.6 mmoles) in toluene (100 ml) with stirring at -50° . The reaction mixture was stirred at 25° for 18 hours, refluxed at 110° for 1 hour, cooled to 25° and filtered. The residue was washed with ether, dried *in vacuo* and chromatographed to yield 2.3 g (46%) of **3** whose physical properties were identical to the product obtained from **1**.

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REFERENCES AND NOTES

- [1] Preceding paper, see L. A. Cates, V.-S. Li, B. H. Saddawi and K. A. Alkadhi, *J. Med. Chem.*, **28**, 595 (1985).
- [2] To whom correspondence should be addressed.
- [3] G. Tomaschewski and G. Kühn, *Z. Chem.*, **12**, 332 (1972).
- [4] C. Tomaschewski, C. Berseck and G. Hilgetag, *Chem. Ber.*, **101**, 2037 (1968).
- [5] V. A. Shokol, L. I. Molyavko, A. G. Matyusha, N. K. Mikhailyuchenko and G. I. Derbach, *J. Gen. Chem. USSR*, **41**, 2407 (1971).
- [6] R. P. Nielsen, J. F. Vincent and H. H. Sisler, *Inorg. Chem.*, **2**, 760 (1963).
- [7] K. Utvary, E. Freundlinger and V. Gutmann, *Monatsh. Chem.*, **97**, 684 (1966).