P-N Compounds. 25. Phosphaminimides. 1. Synthesis and Bioevaluation of a Derivative of Tetrahydro-2*H*-1,3,4,2-oxadiazaphosphorinium Inner Salt [1]

Lindley A. Cates* [2], Ven-Shun Li, Jyoti P. Basrur and Bashir H. Saddawi

Department of Medicinal Chemistry, College of Pharmacy, University of Houston,
University Park, Houston, Texas 77004

Karim A. Alkadhi

Department of Pharmacology, College of Pharmacy, University of Houston,
University Park, Houston, Texas 77004

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2-Phenoxy-4,4-dimethyltetrahydro-2*H*-1,3,4,2-oxadiazaphosphorinium 2-oxide inner salt, the first known cyclic phosphaminimide, was synthesized by dehydroiodination of its hydrazinium salt. The corresponding 2-phenyl derivative was unstable and not isolated. The 2-phenoxy and 2-phenylphosphorinium iodides and their precursors produced weak inhibition of sympathetic ganglionic transmission. The phosphaminimide caused a slight potentiation and was also found to be less toxic than its corresponding hydrazinium iodide precusor.

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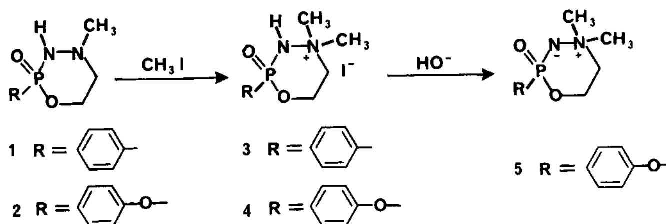
Hydrazinium inner salts, which are often referred to by their original name of aminimides, are dipolar ions containing a cationic nitrogen bonded to an anion derived from carboxyamides, sulfonamides, phosphoramides and related systems, the general formula of which can be represented as $R_nX(O)N^{-}\text{-}N^{+}R_3$. This class of compound was reviewed in 1972 [3], 1973 [4] and 1980 [5].

While numerous aminimides have been reported only about eight acyclic phosphaminimides of type $R_2P(O)N^{+}\text{-}N^{+}R_3$ have been synthesized and studied for their chemical [6] and antiseptic [7,8] properties. In this paper we describe the preparation and biological evaluation of the first cyclic phosphaminimide **5**, its intermediate **4**, the phenyl analogue **3** of **4** and its precursor **1** and discuss the differences in chemical properties between two of these compounds.

A previously reported heterocyclic, 2-phenoxy-4-methyltetrahydro-2*H*-1,3,4,2-oxadiazaphosphorine 2-oxide (**2**) [9], was considered ideally constituted for conversion to a previously unreported cyclic phosphaminimide system by means of a commonly employed route to aminimides, the intramolecular dehydrohalogenation of quaternary hydrazides. Thus, **2** was reacted with iodomethane to give the corresponding hydrazinium iodide **4** which was subsequently treated with base to yield **5**. While **5** precipitated from the reaction mixture within a few minutes as the stable pure product, the deiodination of the corresponding phenyl derivative **3** did not give a precipitate and attempts at isolation of its phosphaminimide were not successful. Material extracted from this latter reaction did not agree with the assigned structure. Acidification of its dehydroiodination product with 6*N* hydrochloric acid at 0° resulted in rapid hydrolysis to phenylphosphonic acid. It is,



therefore, likely that the phenyl group confers considerable instability on the molecule. Decomposition apparently occurs more readily in this type of compound than was found with trimethylammonium-*N*-diphenylphosphinylamine $[Ph_2P(O)N^{-}\text{-}N^{+}(CH_3)_3]$, the only phosphaminimide previously studied for its chemical properties, which was titratable with aqueous hydrochloric acid at room temperature but decomposed to trimethylhydrazinium chloride and diphenylphosphinic acid when its aqueous solution was boiled for a few minutes [6]. The increased stability of **5**, can be attributed to resonance stabilization of the anion, as has been demonstrated in aminimides derived from carboxyamides [10].

Quaternary amines are associated with several biological activities among which are antiseptic, acetylcholinesterase inhibition, curarimimetic and ganglionic blockade. The interference of such compounds in the function of the nervous system prompted an investigation of the effect of **1-5** on transmission in sympathetic ganglia. The inhibition of ganglionic transmission, as determined by the percent decrease of amplitude of the compound action potential, produced by varying concentration of **1-4** and compared to 0.2 m*M* of hexamethonium, a well established ganglionic blocking agent, is shown in Figure 1. The test compounds displayed weak activity, requiring about a 25-

fold concentration to produce inhibition compared to the standard. In addition, the nonquaternary derivatives **1** and **2** were unexpectantly more potent than the quaternary compounds **3** and **4**. The aminimide**5** caused a slight potentiation, rather than an inhibition, of ganglionic transmission, possible as a result of anticholinesterase effect but this phenomenon is one whose cause requires further study. The difference in toxicity between phosphaminimide **5** and its quaternary precursor **4** was estimated using the brine shrimp bioassay method. Compound **5** produced 32, 48 and 64% and **4** gave 0, 100 and 100% mortality at 10, 100 and 1000 μg/ml concentration, respectively. It appears, based on this single comparison, that phosphinylhydrazinium inner salts are appreciably less toxic than their corresponding quaternary salts. This property will be investigated in greater depth during subsequent studies of phosphaminimides.

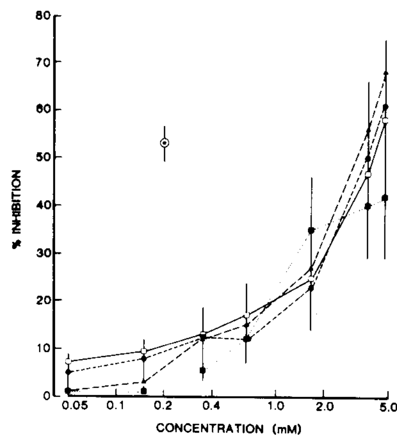


Figure 1. Inhibition of sympathetic ganglionic trnasmission in the isolated superior cervical ganglion of the rat. Key: (⊙) hexamethonium, (▲) **1**, (●) **2**, (□) **3**, (■) **4**. Each point represents the mean (± S. E.) of 4-8 experiments.

EXPERIMENTAL

Chemistry.

Melting points were taken on a Thomas-Hoover apparatus and are corrected to reference standards. The ^{1}H-nmr spectra were determined on a Varian FT-80A spectrometer using tetramethylsilane as the internal standard and either deuteriochloroform (**1**) or deuterated dimethylsulfoxide (**3-5**) as the solvents. The ir (potassium bromide) spectra were recorded on a Perkin-Elmer 282 spectrophotometer. Elemental analyses were performed by Atlantic Microlab Inc., Atlanta, GA. Silica gel 60 (70-230 mesh) and a 25 × 500 mm column was used for chromatography.

2-Phenyl-4-methyltetrahydro-2*H*-1,3,4,2-oxadiazaphosphorine 2-Oxide (**1**).

This compound was synthesized in a manner similar to that previously reported for **2** [9]. Phenylphosphonic dichloride (19.3 g, 100 mmoles) in methylene chloride (50 ml) was added to 1-(2-hydroxyethyl)-1-methylhydrazine [11] (9.0 g, 100 mmoles) and triethylamine (22.3 g, 220 mmoles) in methylene chloride (100 ml) at 0-5° with stirring. After refluxing for 18 hours the reaction mixture was filtered and the filtrate spin-evaporated. The resulting residue (30.3 g) was chromatographed using 5% methanol in chloroform (500 ml) to give a material which was rechromatographed using 2% methanol in chloroform (200 ml) and then 5% methanol in chloroform (300 ml). The solid thus obtained was recrystallized from ether-methylene chloride to yield **1** (11.2 g, 53%), mp 153-154°; ir: 3100 (NH), 1590 (C=C), 1230 (P=O) cm^{-1}; ^{1}H-nmr: δ 2.6 (d, 3H, CH_3, J = 2.2 Hz), 2.77 (bm, 2H, CH_2), 4.23-4.45 (bm, 3H, CH_2O, NH), 7.46-7.74 (m, 5H, arom).

Anal. Calcd. for $C_9H_{13}N_2O_2P$: C, 50.92; H, 6.18; N, 13.20. Found: C, 50.81; H, 6.19; N, 13.16.

2-Phenyl-4,4-dimethyltetrahydro-2*H*-1,3,4,2-oxadiazaphosphorinium 2-Oxide Iodide (**3**).

Iodomethane (7.1 g, 50 mmoles) was added to **1** (5.3 g, 25 mmoles) in acetonitrile (70 ml) and the mixture was heated to 50° to give a solution. After heating to 85° for one-half hour, iodomethane (7.1 g, 50 mmoles) was added and this solution was reacted for 18 hours at 45-50°. Cooling to 25° gave a white crystalline material which was filtered, the residue washed twice with acetonitrile, methylene chloride and ether and dried to yield **3**. Additional product was obtained from the treatment of the acetonitrile wash with ether, to give 8.2 g (93%) of total product, mp 167-169° dec; ir: 3120 (NH), 1590 (C=C), 1200, 1220, 1240 (P=O) cm^{-1}; ^{1}H-nmr: δ 3.52 (s, 3H, CH_3), 3.73 (s, 3H, CH_3), 4.20 (bm, 2H, CH_2), 4.72-5.06 (br, 2H, CH_2O), 7.83 (m, 5H, arom), 9.42 (bs, 2H, NH).

Anal. Calcd. for $C_{10}H_{16}IN_2O_2P$: C, 33.89; H, 4.55; N, 7.91. Found: C, 33.73; H, 4.60; N, 7.86.

2-Phenoxy-4,4-methyltetrahydro-2*H*-1,3,4,2-oxadiazaphosphorinium 2-Oxide Iodide (**4**).

Compound **2** was synthesized in a manner previously reported [9] with triethylamine used as the hydrogen chloride scavenger in lieu of excess hydrazine and with the use of column chromatography to yield 73% of product melting at 122-124°. Iodomethane (5.7 g, 40 mmoles) was added to **2** (4.56 g, 20 mmoles) in acetonitrile (40 ml) and the mixture was heated to 50° to give a solution. The solution was heated for 2 hours at 70°, iodomethane (5.7 g, 40 mmoles) was added and the heating was continued for 18 hours. Cooling to 25° gave a white crystalline solid which was washed twice with acetonitrile, methylene chloride and ether each and dried to yield 6.5 g of **4**. Addition of ether to the acetonitrile wash gave 0.9 g of product for a total of 7.4 g (96%), mp 158-160° dec; ir: 3030 (NH), 1590 (C=C), 1170, 1190, 1210, 1290, 1300 (P=O) cm^{-1}; ^{1}H-nmr: δ 3.75 (s, 6H, $2CH_3$), 4.20 (bm, 2H, CH_2), 4.80-5.30 (bm, 2H, CH_2O), 7.50 (m, 5H, arom).

Anal. Calcd. for $C_{10}H_{16}IN_2O_3P$: C, 32.43; H, 4.36; N, 7.56. Found: C, 32.36; H, 4.38; N, 7.52.

2-Phenoxy-4,4-dimethyltetrahydro-2*H*-1,3,4,2-oxadiazaphosphorinium 2-Oxide Inner Salt (**5**).

Compound **4** (2 g, 5.4 mmoles) was dissolved in 10% sodium hydroxide solution (10 ml) and stirred at 25° for 5 minutes. The resulting white solid was washed with acetone until it was free of sodium iodide and dried to give **5** (0.75 g, 57%), mp 212-213° dec; ir: 1590, 1600 (C=C), 1210, 1220, 1260 (P=O) cm^{-1}; ^{1}H-nmr: δ 3.33 (d, 6H, $2CH_3$, J = 8.34 Hz), 3.58 (bm, 2H, CH_2), 4.26-4.52 (bm, 2H, CH_2O), 7.22 (m, 5H, arom).

Anal. Calcd. for $C_{10}H_{15}N_2O_3P$: C, 49.56; H, 6.24; N, 11.56. Found: C, 49.48; H, 6.27; N, 11.50.

Biological Evaluations.

Using a procedure similar to that previously reported [12], superior cervical ganglia were quickly excised from Sprague-Dawley rats. The ganglia were carefully desheatheed while maintained in a cold, oxygenated (5% CO_2, 95% O_2) Locke's solution (*p*H 7.4) containing (mM): NaCl, 136; KCl, 5.6; $CaCl_2$, 2.2; $MgCl_2$, 1.2; NaH_2PO_4, 1.2; $NaHCO_3$, 16 and glucose, 11. The ganglia were immersed in this solution in a constant temperature chamber with the pre- and post-ganglionic (internal carotid) nerves drawn into stimulating and a recording suction electrodes. The

preganglionic nerve was stimulated supramaximally at 0.3 Hz. Postganglionic compound action potentials were recorded using a capacity-coupled preamplifier and the amplified potentials were displayed on an oscilloscope and permanent records made on photographic paper or film. Ganglia were selected for study only when the potsganglionic action potential was stable for at least 30 minutes. Solutions of test compounds were added to the perfusion fluid and changes in the amplitude of the action potential used as indices of effect on transmission. After the steady state condition was attained, 8-10 consecutive "control" action potentials were recorded. Dose-response relationship was obtained by testing increasing, cumulative concentrations of the compounds on the action potential. Each new concentration was left in the bath for 5-10 minutes before recording the action potential. Change in ganglionic transmission is expressed in the percent change in amplitude in the action potential.

Toxicity was determined using the brine shrimp assay procedure reported by Meyer *et al.* [13]. The only modification of this method involved sample preparation whereby filter paper was not used and the samples of test solutions were pipetted directly into the sample vials prior to drying *in vacuo.*

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