

P-N Compounds 14. Synthesis of *N*-Amino-1,3,2-oxazaphospholidines and a Derivative of Tetrahydro-2*H*-1,3,4,2-oxadiazaphosphorine, a Novel Ring System (1,2)

Lindley A. Cates

University of Houston, College of Pharmacy, Houston, Texas 77004

Received November 13, 1972

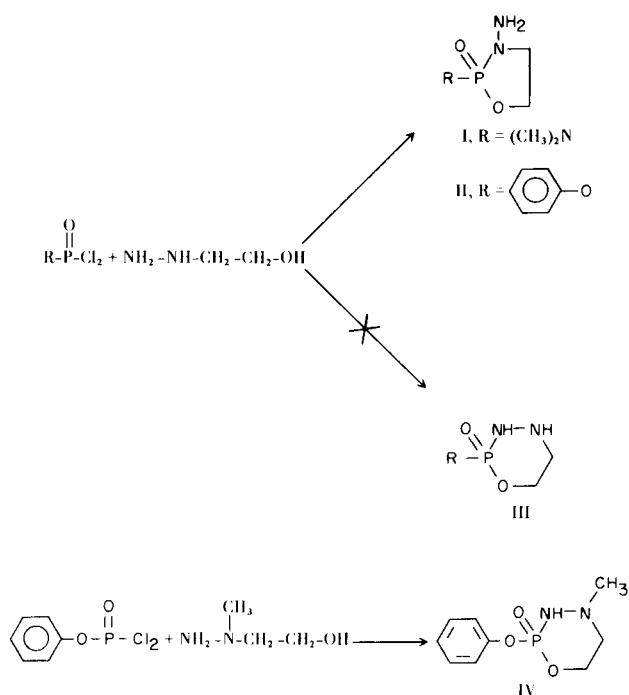
As part on an investigation involving potential oncolytic moieties it was deemed advisable to prepare heterocyclic agents containing the N-P(O)-N-N system and a nitrogen analog of tetrahydro-2*H*-1,3,2-oxazaphosphorine, the carrier grouping present in the most widely studied anti-cancer drug, cyclophosphamide. A review of the literature indicates neither tetrahydro-2*H*-1,3,4, 2-oxadiazaphosphorine nor any of its derivatives has been synthesized and that none of the numerous 1,3,2-oxazaphospholidines to be reported contain a 3-amino group.

The reaction between phosphoric dichlorides and 2-hydroxyethylhydrazine yielded the anticipated phospholidines (I and II), rather than the oxadiazaphosphorines (III), since substitution occurs at the more nucleophilic secondary nitrogen. Contrary to some previous reports this appears to be the primary phosphorylation reaction involving monosubstituted hydrazines (3). The structures

of I and II were assigned on the basis of their elemental analyses, ir, and nmr spectra. The fundamental N-H stretching mode at c.3 microns associated with primary amines (4) was observed in these two derivatives but not in the oxadiazaphosphorine. Two hydrazone derivatives of II, prepared as additional proof of structure, gave nmr spectra whose peak areas integrated for the expected number of protons.

The synthesis of IV, which appears to be a member of a new class of cyclic phosphorus derivatives, was achieved through the reaction of phenyl phosphorodichloridate and 1-(2-hydroxyethyl)-1-methylhydrazine. The latter reactant, possessing only one amino group capable of substitution, yielded the 6-membered ring. The synthesis of structurally related Δ^4 -1,3,4,2-oxadiazaphospholines has been achieved by Russian workers using tertiary phosphines and diazo compounds (5) and phosphorus trichloride and phenylhydrazines (6).

With regard to reactions yielding I, II, and IV, cyclization was the expected result since Arnold and Bourseaux, who employed closely related reactants, reported that not even with an excess of aminoalcohol could open chain products be isolated (7). Products were qualitatively, and in the case of IV quantitatively, tested for chlorine content as further evidence of composition and they all reduced silver ion. The nmr spectrum of IV showed a complex of peaks at δ 3.92 to 4.73 (3H) which was assigned to C₆ and N₃ protons since its area reduced to a ratio of two protons upon deuterium oxide addition. With both I and II the methylene protons on C₅ were sufficiently separate at δ 3.90 to 4.50 and δ 4.22 to 4.90, respectively, to permit determination of their nuclear ratios. Deuterium oxide addition reduced ratios in these compounds in the region δ 2.71 to 3.75 by two protons. Therefore, absorption by the N₃ proton in IV was shifted downfield due to deshielding by the phosphinyl group whereas the more remote amino protons in I and II give higher field signals. What appears to be a doublet occurs in the complex at δ 2.48 to 2.86. These distinct peaks



(δ 2.57, 1.3 Hz, 3H total) are somewhat unexpected since Neilsen and Sisler, working with noncyclic hydrazinophosphorus compounds, reported a singlet with an N_1 methyl derivative (8).

I has been screened for activity against L-1210 lymphoid leukemia and P388 lymphocytic leukemia (9). Preliminary results indicate a lack of activity against these tumor systems and that toxicity occurs at doses between 200-400 mg/Kg.

EXPERIMENTAL

Nmr spectra were obtained using a Varian T-60 spectrometer with tetramethylsilane as the internal reference standard and deuteriochloroform as the solvent. Ir spectra were determined in a Nujol mull on a Beckman IR-8 spectrophotometer. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, Georgia. Melting points were taken on a Fisher-Johns apparatus and are corrected.

2-Dimethylamino-3-*N*-amino-1,3,2-oxazaphospholidine, 2-Oxide (I).

N,N-Dimethylphosphoramidic dichloride (10) (16.2 g., 0.1 mole) was added dropwise with stirring to a cooled (ice-salt) solution of 2-hydroxyethylhydrazine (30.4 g., 0.4 mole) in chloroform (100 ml.). The reaction mixture was heated at 45° for 1 hour, cooled, and filtered. Spin-evaporation of the filtrate gave a clear oil which, upon treatment with benzene, developed into a solid. Repeated crystallization from benzene afforded the lustrous, water-soluble, crystalline product (2.4 g., 15% pure yield), m.p. 122-124° dec.; ir 3.03 μ (N^1); nmr δ 2.72 (d, 10 Hz, 3H each), complex of peaks δ 3.18 to 3.75 (4H, 2 of which exchange with deuterium oxide), complex of peaks δ 3.90 to 4.50 (2H).

Anal. Calcd. for $C_4H_{12}N_3O_2P$: C, 29.09; H, 7.32; N, 25.45. Found: C, 29.16; H, 7.34; N, 25.58.

2-Phenoxy-3-*N*-amino-1,3,2-oxazaphospholidine, 2-Oxide (II).

Phenyl phosphorodichloridate (10.5 g., 0.2 mole) and 2-hydroxyethylhydrazine (15.2 g., 0.2 mole) were reacted in the same manner as described for I. The chloroform layer was removed from the gelatinous portion of the reaction mixture using a separatory funnel, spin-evaporated, and the residue crystallized several times from benzene to yield II as white crystals (4.1 g., 19% pure yield); m.p. 129-130°; ir 3.01 μ (N^1); nmr complex of peaks δ 4.22 to 4.90 (2H), δ 7.43 (m, 5H). The region δ 2.71 to 3.85 (4H) reduced to 2H upon deuterium oxide addition.

Anal. Calcd. for $C_8H_{11}N_2O_3P$: C, 44.87; H, 5.18; N, 13.08. Found: C, 45.03; H, 5.38; N, 12.94.

The refluxing of a concentrated ethanolic solution of II with equal molar amounts of *p*-anisaldehyde and salicylaldehyde for

thirty minutes and allowing the reaction mixtures to remain overnight gave yellow precipitates of the corresponding hydrazones. The *p*-anisaldehyde (m.p. 167° dec.) and salicylaldehyde (m.p. 143° dec.) derivatives gave nmr spectra consistent with their structures.

2-Phenoxy-4-methyl-tetrahydro-2-*H*-1,3,4,2-oxadiazaphosphorine, 2-Oxide (IV).

Phenyl phosphorodichloridate (10.5 g., 0.05 mole) and 1-(2-hydroxyethyl)-1-methylhydrazine (11,12) (18.0 g., 0.2 mole) were reacted and the reaction mixture worked up in the same manner as II to give IV as colorless needles after several crystallizations from benzene (1.8 g., 7.9% pure yield); m.p. 118-119°; ir 3.24 μ (N^2); nmr complex of peaks δ 2.48 to 2.86 (5H) which includes δ 2.57 (d, 1.3 Hz, 3H total), complex of peaks δ 3.92 to 4.73 (3H, 1 of which exchanges with deuterium oxide), δ 7.23 (m, 5H).

Anal. Calcd. for $C_9H_{13}N_2O_3P$: C, 47.37; H, 5.74; N, 12.28; Cl, 0.00. Found: C, 47.11; H, 5.77; N, 12.32; Cl, 0.00.

Acidification of boiled, dilute sodium hydroxide solutions of I, II, and IV with nitric acid and treatment with silver nitrate solution gave negative chloride tests. Heating of these solutions produced a silver mirror.

Acknowledgment.

The technical assistance of Charles J. Johansson is gratefully acknowledged.

REFERENCES

- (1) Previous paper in this series: E. K. Ryu and L. A. Cates, *J. Med. Chem.*, **14**, 1022 (1971).
- (2) This work was supported in part by Grant E-297 from the Robert A. Welch Foundation, Houston, Texas and by Grant CA 13123-01 from the National Cancer Institute, PHS, Bethesda, Maryland.
- (3) The discussion of this reaction is the subject of a future paper in this series.
- (4) J. P. Phillips, "Spectra-Structure Correlation," Academic Press, New York, New York, 1964, p. 97.
- (5) B. A. Arbuzov, N. A. Polezhaeva, and V. S. Vinogradova, *Cf. Chem. Abstr.*, **70**, 87682r (1969).
- (6) T. L. Italinskaya, N. N. Malnikov, and N. I. Shvetsov-Shilovskii, *Cf. Chem. Abstr.*, **70**, 37737s (1969).
- (7) H. Arnold and F. Bourseaux, *Angew. Chem.*, **70**, 539 (1958).
- (8) R. P. Nielsen and H. H. Sisler, *Inorg. Chem.*, **2**, 753 (1963).
- (9) Screening data supplied by the Drug Research and Development Branch, National Cancer Institute, Bethesda, Maryland.
- (10) A. Michaelis, *Ann. Chem.*, **326**, 129 (1903).
- (11) B. Benoit, *Bull. Soc. Chim. France*, 242 (1947).
- (12) Reported n_D^{20} 1.466_. Found n_D^{20} 1.4665, see reference 11.