P-N Compounds. 30. Phosphaminimides. 5. *N*-Phosphinylimino-1,2,5,6-tetrahydropyridines [1]

Lindley A. Cates* [2] and Ven-Shun Li

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

Received May 9, 1987

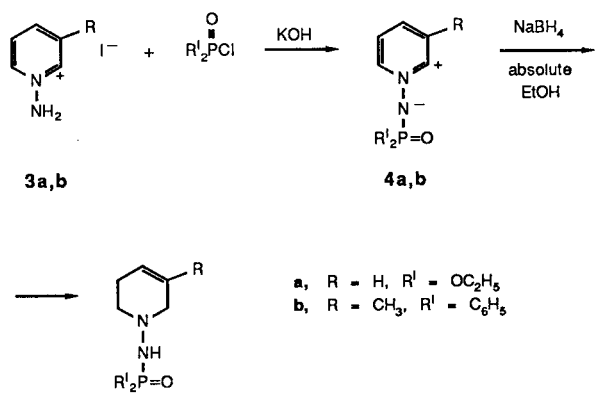
N-[(Diethoxyphosphinyl)imino] and *N*-[(diphenylphosphinyl)imino]-5-methyl-1,2,5,6-tetrahydropyridines were prepared by sodium borohydride reduction of the corresponding pyridinium and 3-methyl pyridinium inner salts. The carbonyl analog of this latter precusor was resynthesized and its structure completely verified.

J. Heterocyclic Chem., **24**, 1635 (1987).

The synthesis of *N*-carbonyl **1** and *N*-sulfonyl **2** imino-1,2,5,6-tetrahydropyridines was first reported by Knaus and Redda who obtained these compounds *via* sodium borohydride reduction of the corresponding pyridinium ylides (hyrazinium inner salts, aminimides) [3]. Certain derivatives of **1** were subsequently found to have interesting analgesic [4], antiinflammatory [5], hypoglycemic [4,5] and hyperglycemic [4,5] activities. Our interest in phosphaminimides as bioisosteres of aminimides, in which a P=O replaces a C=O or SO_2 group, led us to investigate synthetic procedures whereby phosphaminimides are converted to *N*-phosphinylimino-1,2,5,6-tetrahydropyridines as models for pharmacological studies.

Knaus and Redda originally prepared the requisite carbonyl and sulfonylaminimide precursors through the reaction of appropriate hydrazides and 2,4-dinitrophenylpyridinium chlorides [3] and later from *N*-aminopyridinium iodide [4] or *N*-iminopyridinium inner salts [5] and acyl chlorides in the presence of aqueous sodium hydroxide. The former method was previously attempted using diphenylphosphinylhydrazide and found to be unsuccessful, apparently a result of poor solubility characteristics of this reactant [1]. The *N*-aminopyridinium iodide **3a** and **3b**-phosphinyl chloride-potassium hydroxide method [1] is, however, a viable route and provided the phosphaminimide precusors **4a** and **4b** leading to the title compounds as the diethoxy **5a** and diphenyl-3-methyl **5b** derivatives, respectively (Scheme 1).

Scheme 1



We also repeated the synthesis of *N*-(phenylcarbonylamino)-5-methyl-1,2,5,6-tetrahydropyridine from *N*-[(phenylcarbonyl)imino]-3-methylpyridinium inner salt (**6**) for comparison use in biological testing. Yeung and Knaus reported a 39% yield and only the mass value and melting point of 215-217° for this compound. Using this method we obtained **6** in 82% yield with a melting point of 150-152° and verified its structure by ^{1}H-nmr and ir spectrometry and elemental analysis (C, H and N% differing by ±0.09 from their theoretical values).

The chemistry of phosphaminimide has been shown to differ in some aspects from carbonyl and sulfonyl analogs. A pertinent example is the instability of 2-diethoxyphosphinyl-1,1-dimethyl-1-(4-nitrobenzyl)hydrazinium inner salt (**7**) which gradually eliminates EtBr with the formation of a novel type of aminimide, 2-ethoxyphosphinyl-1,1-dimethyl-1-(4-nitrobenzyl)hydrazinium inner salt, in which the negative charge is centered on a P-O oxygen atom [1]. At elevated reaction temperatures **7** is obtained directly from 4-nitrobenzyl bromide and 2-diethoxyphosphinyl-1,1-dimethylhyrazide [1]. Compound **5a**, however, proved to be stable, a property that supports the proposed nucleophilic displacement of the ethyl group in **7** by bromide ion and/or proton labilization by the 4-nitrobenzyl group [1]. The ability to synthesize sufficiently stable diethoxy-containing phosphaminimides leading to the corresponding reduced forms which possess these groups is considered of importance with regard to investigations of certain biological activities of these compounds.

EXPERIMENTAL

Melting points were taken on a Thomas-Hoover apparatus and are corrected to reference standards. The ^{1}H-nmr spectra were determined on a Nicolet NT-300 spectrometer using tetramethylsilane as the internal standard and deuterated chloroform as the solvent. The ir (potassium bromide) spectra were recorded on a Perkin-Elmer 283 spectrometer. Silica gel 60 (70-230 mesh) and 1-5% methanol in chloroform were used

for column chromatography with monitoring of eluants and reactions mixtures by use of silica gel UV_{254} (Brinkmann Polygram) tlc plates. Solvents were evaporated under reduced pressure.

N-[(Diphenylphosphinyl)imino]-3-methylpyridinium Inner Salt (**4b**).

To a stirred solution of 3-methyl-1-aminopyridinium iodide (**3b**) [6] (3.54 g, 15 mmoles) in ethanol (100 ml) were added, dropwise and concurrently, potassium hydroxide (2.52 g, 45 mmoles) in ethanol (100 ml) and diphenylphophinic chloride (5.9 g, 25 mmoles) in dichloromethane (20 ml) and the reaction mixture was stirred for 16 hours at 25°. The solvent was removed at 30-40°, the residue dissolved in 10% sodium carbonate (40 ml), the solution extracted with dichloromethane (3 x 100 ml) and the extract dried over sodium sulfate. After evaporation of the solvent the oil residue was chromatographed to yield 2.0 g (43%) of crystalline **4b** ($C_{18}H_{17}N_2OP$), mp 190-192° dec; ir: 1620 (C=C), 1180, 1255 (P=O) cm^{-1}; nmr: δ 2.28 (s, 3H, CH_3), 7.20 (m, 2H, C_4-H, C_5-H, pyridinium), 7.39 (m, 6H, phenyl), 7.93 (m, 4H, phenyl), 8.59 (s, 1H, C_2-H, pyridinium), 8.61 (d, J = 5.97, 1H, C_6-H, pyridinium).

Anal. Calcd. for $C_{18}H_{17}N_2OP$: C, 70.10; H, 5.56; N, 9.08. Found: C, 69.86; H, 5.60; N, 8.97.

N-[(Diethoxyphosphinyl)imino] (**5a**) and *N*-[(Diphenylphosphinyl)imino]-3-methyl (**5b**) -1,2,5,6-tetrahydropyridine.

A solution of **4a** [1] (5.5 mmoles) or **4b** (6 mmoles) in ethanol (20 ml) was added dropwise with stirring to a solution of sodium borohydride (1.13 g, 3 mmoles) in ethanol (20 ml) at 0° and the mixture stirred at this temperature for 5 hours. Water (50 ml) was added, the mixture warmed to 25° and extracted with dichloromethane (4 x 50 ml). After drying over sodium sulfate the extracts were evaporated under high vacuum to give crystals which were chromatographed to yield the white, solid product. For **5a** (0.69 g, 54% yield), mp 65-66°; ir: 3160 (NH), 1235 (P=O), 970, 1050, 1070 (POEt) cm^{-1}; nmr: δ 1.35 (t, 6H, $2CH_3$), 2.25 (m, 2H, C_3-H), 2.91 (t, 2H, C_3-H), 3.31 (m, 2H, C_6-H), 4.08-4.21 (m, 5H, $2CH_2O$, NH), 5.57 (d, J = 10.1 Hz, 1H, C_4-H). 15.73 (d, J = 10.1 Hz, 1H, C_5-H).

Anal. Calcd. for $C_9H_{19}N_2O_3P$: C, 46.12; H, 8.17; N, 11.96. Found: C, 46.15; H, 8.18; N, 11.93.

Compound **5b** was obtained in a yield of 48% (0.9 g), mp 151-153°; ir: 3085 (NH), 1595 (C=C), 1195, 1210 (P=O) cm^{-1}; nmr: δ 1.59 (s, 3H, CH_3), 2.11 (m, 2H, C_3-H), 2.92 (t, 2H, C_2-H), 3.32 (s, 2H, C_6-H), 4.26 (d, J = 17.62, 1H, NH), 5.36 (m, 1H, C_4-H), 7.45 (m, 6H, Ph), 7.92 (m, 4H, Ph).

Anal. Calcd. for $C_{18}H_{21}N_2OP$: C, 69.19; H, 6.78; N, 8.97. Found: C, 69.18; H, 6.80; N, 8.90.

Acknowledgement.

This research was supported by the Robert A. Welch Foundation, Houston, Texas, Grant No. E-920.

REFERENCES AND NOTES

[1] Preceding paper, see L. A. Cates and V.-S. Li, *Phosphorus Sulfur*, in press.

[2] To whom correspondence should be addressed.

[3] E. E. Knaus and K. Redda, *J. Heterocyclic Chem.*, **13**, 1237 (1976).

[4] J. M. Yeung, L. A. Corleto and E. E. Knaus, *J. Med. Chem.*, **25**, 191 (1982).

[5] Y. M. Yeung and E. E. Knaus, *J. Med. Chem.*, **30**, 104 (1987).

[6] R. Gosl and A. Meuwsen, *Org. Synth.*, **43**, 1 (1963).