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# Communications TO THE EDITOR

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## 3-Pyridylphosphonic Acid<sup>1</sup>

Sir:

On the basis of the apparent relation of the bacteriostatic activity of various antagonists of *p*-aminobenzoic acid to the electronegativity of sulfone and similar (XO<sub>2</sub>) groups, Bell and Roblin<sup>2</sup> predicted that compounds of the phosphanilic acid type (X = P) should show activity similar to the sulfonamides. Indeed, phosphanilic acid,<sup>3</sup> (*p*-aminophenyl)phosphonous acid<sup>4</sup> and several substituted phosphanilamides<sup>5</sup> possess significant antibacterial activity while in a series of esters and ester amidates of phosphanilic acid only slight inhibition was observed.<sup>6</sup> Since 3-pyridinesulfonic acid and its amide are niacin antagonists,<sup>7</sup> 3-pyridylphosphonic acid has now been prepared in the hope that the analogy between sulfonic and phosphonic acids would hold also in this series.

This expectation has not been fulfilled. *Lactobacillus arabinosus*, which requires niacin or niacinamide for growth, was cultured in Difco niacin assay medium.<sup>8</sup> With increasing ratios of 3-pyridylphosphonic acid to either of these essential metabolites (maximum ratio 10<sup>4</sup>:1) no inhibition or stimulation of growth was observed. This suggests that 3-pyridylphosphonic acid does not interfere with the incorporation of niacin into coenzyme systems. That the biosynthesis of niacin is not affected either was shown by experiments with two organisms which synthesize their own niacin require-

ments. *Mycobacterium smegmatis* and *M. tuberculosis* var. BCG, grown in Proskauer and Beck medium, were indifferent to concentrations up to 1,000 µg./ml. of 3-pyridylphosphonic acid.

The method of synthesis of 3-pyridylphosphonic acid was the decomposition of 3-pyridyldiazonium fluoborate<sup>9</sup> with phosphorus trichloride at a lower temperature than described for analogous cases,<sup>10</sup> and under controlled conditions of isolation. A suspension of the diazonium fluoborate<sup>9</sup> from 18.9 g. (0.201 mole) of 3-aminopyridine in 240 ml. of ethyl acetate was cooled to -10° and treated gradually with 18.9 ml. (29.6 g., 0.215 mole) of phosphorus trichloride and 3.9 g. (0.027 mole) of cuprous bromide. After the exothermic reaction was complete, 75 ml. of water was added, the mixture was concentrated under reduced pressure to 50 ml., and treated with excess saturated barium hydroxide solution. After the mixture was filtered, barium ions were precipitated with the exact amount of sulfuric acid, and the halide ions were precipitated with saturated silver lactate solution. Barium sulfate and silver halide were filtered, the filtrate was concentrated to 50 ml. and decolorized with Darco, and 800 ml. of dioxane was added to turbidity. The cloudy suspension was allowed to crystallize at 4°. The crude 3-pyridylphosphonic acid (4.4 g., 13.8%, m.p. 249–253°) was recrystallized by dissolving in a minimum of hot water, adding ethanol to turbidity, and cooling slowly. The colorless prisms (calcd. for C<sub>5</sub>H<sub>6</sub>NO<sub>3</sub>P: C, 37.74; H, 3.81; neut. equiv., 79.6. Found: C, 37.31; H, 4.04; neut. equiv., 79.5) had m.p. 258–260° (corr.).

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