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SYNTHESIS OF TWO BENZIMIDAZOLE-5-PHOSPHONIC ACIDS AND BENZOXAZOLE-6-PHOSPHONIC ACID[1]

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In connection with a study of certain organophosphorus compounds as possible materials of pharmacological interest, two benzimidazole-5-phosphonic acids and benzoxazole-6-phosphonic acid have been synthesized for the first time. These compounds were desired because of recent interest in benzimidazoles, particularly those containing substituents in the 5 position, as some of the 5-methyl derivatives have been shown to possess appreciable vitamin B_{12} activity (1). In addition, the compounds prepared here are structurally related to phosphanilic acid, a substance known to be an active antibacterial agent (2–5). It was therefore thought that these compounds might possess interesting pharmacological properties.

Benzimidazole-5-phosphonic acid and 2-methylbenzimidazole-5-phosphonic acid were prepared by refluxing a solution of 3,4-diaminobenzenephosphonic acid in hydrochloric acid with formic and acetic acids, respectively, a procedure described by Philips (6). The two acids were white solids, crystallized as needles from water. They were soluble in concentrated acid or dilute base and insoluble in organic solvents. The preparation of the previously unreported 3,4-diaminobenzene phosphonic acid was accomplished by reduction of the known (7) 3-nitro-4-aminobenzenephosphonic acid. Arnold and Hamilton (8) described the catalytic reduction at low pressure and temperature of a number of 3-nitro-4-alkylaminobenzenephosphonic acids in aqueous solution as their mono-sodium salts, using a Raney nickel catalyst. Similar conditions were employed in our work for the above reduction, except that palladium-charcoal was used as catalyst. Attempts to isolate the diamine in a pure state were unsuccessful as the compound was rapidly oxidized on contact with air. Therefore, the reduction solution was used directly for the cyclization step.

The synthesis of benzoxazole-6-phosphonic acid involved first the conversion of 3-chloro-4-nitroaniline to 3-chloro-4-nitrobenzenephosphonic acid by the method recently reported by Doak and Freedman (9), which is the reaction of phosphorus trichloride with the corresponding diazonium fluoborate. General procedure IIA of Roe (10) was used to prepare the diazonium salt. This new acid could not be obtained in a solid state; it was therefore isolated and identified as its *p*-toluidine salt. This salt was converted to the sodium salt and then re-

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fluxed with excess sodium hydroxide to effect hydrolysis of 3-hydroxy-4-nitrobenzenephosphonic acid. Acidification of the reaction solution gave the hemi-sodium salt of the acid, and attempted conversion of this to the free acid by crystallization from 6 *N* hydrochloric acid likewise gave this salt. To obtain the free acid, it was therefore necessary to remove sodium ions from the medium; this was accomplished by passing a solution of the hemi-sodium salt through a column of a cation exchange resin. The free acid was obtained from the solution from the column by evaporation. This acid was then reduced catalytically as in the previous reduction to give 3-hydroxy-4-aminobenzenephosphonic acid. This compound was also extremely readily oxidized on contact with air and was not isolated; the solution filtered from the catalyst was treated with hydrochloric acid and formic acid and refluxed to effect cyclization to benzoxazole-6-phosphonic acid. This compound was virtually insoluble in all solvents except concentrated acid; it was soluble in dilute base but immediate decomposition occurred. It was crystallized from concentrated hydrochloric acid by dilution with water.

EXPERIMENTAL[4]

Intermediates. To prepare 3-nitro-4-aminobenzenephosphonic acid, *p*-chlorobenzenephosphonic acid[5] was nitrated according to Nijk (7) to give a 73.5% yield of purified 3-nitro-4-chlorobenzenephosphonic acid, m.p. 169–170°. Reported m.p. is 166–168° (11) and 166° (7). This compound was converted to 3-nitro-4-aminobenzenephosphonic acid by reaction with aqueous ammonia at 150° (7) in a steel bomb, giving a 66.6% yield of product, m.p. 227–228° d. Nijk reported decomposition at 231°.

To prepare 3-chloro-4-nitroaniline, *m*-chloroaniline was first acetylated according to Lobry de Bruyn (12). The *m*-chloroacetanilide was nitrated with fuming nitric acid (13) to give a mixture of 3-chloro-4-nitro- and 3-chloro-6-nitroacetanilide. The isomers were readily separated by fractional crystallization from benzene (14) and the 3-chloro-4-nitroacetanilide was then hydrolyzed to 3-chloro-4-nitroaniline in 35.4% yield (from *m*-chloroaniline), m.p. 157–158°. The reported (13) m.p. is 156–157°.

3,4-Diaminobenzenephosphonic acid. A solution of 2.0 g. (0.0092 mole) of 3-nitro-4-aminobenzenephosphonic acid and 0.38 g. (0.0092 mole) of sodium hydroxide in 20 ml. of water was treated with 0.5 g. of 10% palladium-charcoal. The mixture was hydrogenated at 50 p.s.i. at room temperature for one hour. The catalyst was filtered off and the filtrate used directly in the preparation of the benzimidazoles.

Benzimidazole-5-phosphonic acid. The filtrate from the above reaction was immediately treated with 1.5 ml. of concentrated hydrochloric acid and 3 ml. of 98% formic acid and refluxed 75 minutes. The dark purple solution was treated with Norit and filtered. The filtrate was treated with 10% sodium hydroxide to *p*H 3.5 and diluted with 50 ml. of hot water. On standing, white needles of benzimidazole-5-phosphonic acid separated. They were recrystallized from water, giving 0.90 g. (49.4%) product not melting below 250°.

Anal. Calc'd for $C_7H_7N_2O_3P$: N, 14.14; P, 15.63.

Found: N, 13.88; P, 15.33.

2-Methylbenzimidazole-5-phosphonic acid. To a solution of 3,4-diaminobenzenephosphonic acid prepared as described above was added 2.0 ml. of concentrated hydrochloric acid and 5 ml. of glacial acetic acid. The mixture was refluxed 3 hours, treated with Norit, and filtered. The filtrate was brought to *p*H 3.5, diluted with water, and allowed to stand.

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[4] Melting points are corrected.

[5] From hydrolysis of diethyl *p*-chlorobenzenephosphonate, a gift of the Monsanto Chemical Company.

The product that separated was recrystallized from water, giving 0.80 g. (41.3%) of needles not melting below 320°.

Anal. Calc'd for $C_8H_9N_2O_3P$: N, 13.20; P, 14.60.

Found: N, 13.04; P, 14.39.

3-Chloro-4-nitrobenzenediazonium fluoborate. To 130 ml. of 42% fluoboric acid was added 54.2 g. (0.314 mole) of 3-chloro-4-nitroaniline. The mixture was cooled to 0° and a chilled solution of 21.7 g. (0.314 mole) of sodium nitrite in 40 ml. of water was slowly added, holding the temperature at 0–5°. The slurry was stirred 15 minutes longer and then filtered. The residue was washed with 30 ml. of cold 20% fluoboric acid, twice with 30 ml. of cold 95% ethanol, and five times with 80 ml. of dry ether. It was dried in a vacuum over phosphorus pentoxide to yield 63.7 g. (74.2%).

Di-p-toluidine 3-chloro-4-nitrobenzenephosphonate. A one-liter 3-necked flask fitted with a Hershberg stirrer, thermometer, and reflux condenser was charged with 27.2 g. (0.10 mole) of the above diazonium fluoborate, 125 ml. of ethyl acetate, and 2 g. of cuprous chloride. The flask was chilled and 13.8 g. (0.10 mole) of phosphorus trichloride was slowly added. After the vigorous exothermic reaction subsided, the mixture was stirred at room temperature for 2½ hours. It was then chilled and hydrolyzed with 30 ml. of water. A second batch of the diazonium fluoborate (36.1 g., 0.133 mole) was reacted in the same manner with 18.5 g. (0.133 mole) of phosphorus trichloride and 3 g. of cuprous chloride in 160 ml. of ethyl acetate. After hydrolysis, the two solutions were combined and steam-distilled, collecting one liter of distillate. On cooling the residual liquid, a red oil separated; the by-product of bis-(3-chloro-4-nitrophenyl)phosphinic acid could not be obtained in a crystalline state from this. The filtrate was then brought to *p*H 8.5 with 40% sodium hydroxide; the precipitated copper hydroxide was filtered off, and the filtrate, heated to 70°, was treated with a hot solution of 50 g. (0.47 mole) of *p*-toluidine in 40 ml. (0.47 mole) of concentrated hydrochloric acid. The slurry was chilled and filtered; the residue was washed with cold water, pressed dry, and then washed several times with ether. After drying in a vacuum over phosphorus pentoxide, the yield was 44.0 g. (48.7%). A small sample was recrystallized from absolute ethanol, giving yellow needles, m.p. 210–211° d.

Anal. Calc'd for $C_{20}H_{23}ClN_3O_5P$: N, 9.30. Found: N, 9.26.

3-Hydroxy-4-nitrobenzenephosphonic acid. To a solution of 8.0 g. (0.02 mole) of sodium hydroxide in 50 ml. of water was added 39.5 g. (0.0874 mole) of the above *p*-toluidine salt. The liberated *p*-toluidine was extracted three times with ether. The aqueous solution was treated with 100 ml. of 20% sodium hydroxide and refluxed 3.5 hours. Acidification with concentrated hydrochloric acid gave an orange solid. This was dissolved in the minimum amount of hot 6 *N* hydrochloric acid and on cooling, 11.8 g. of the hemi-sodium salt of 3-hydroxy-4-nitrobenzenephosphonic acid separated. This was dissolved in 400 ml. of water and passed through a column of Dowex 50 cation exchange resin. The column was washed with water until the washings were no longer yellow. The combined solutions were evaporated to 20 ml., whereupon 8.6 g. (44.9% from the *p*-toluidine salt) of orange flakes of 3-hydroxy-4-nitrobenzenephosphonic acid, m.p. 201–202° d., separated.

Anal. Calc'd for $C_6H_6NO_6P$: N, 6.39; P, 14.14.

Found: N, 6.62; P, 14.40.

Benzoxazole-6-phosphonic acid. A solution of 2.0 g. (0.00914 mole) of 3-hydroxy-4-nitrobenzenephosphonic acid and 0.37 g. (0.00925 mole) of sodium hydroxide in 15 ml. of water was treated with 0.5 g. of 10% palladium-charcoal. The mixture was hydrogenated at 50 50 p.s.i. at room temperature for one hour. The catalyst was filtered off and the filtrate added immediately to 50 ml. of 90% formic acid and 2 ml. of concentrated hydrochloric acid. The mixture was refluxed four hours. On chilling, crystals separated; they were filtered off and purified by dissolving in 2 ml. of concentrated hydrochloric acid, adding 20 ml. of water and Norit, filtering, and diluting with 80 ml. of water. Small white crystals separated on standing. The yield was 0.60 g. (32.9%). The compound darkened at 202° and had m.p. 204–205° d.

Anal. Calc'd for $C_7H_6NO_4P$: N, 7.04. Found: N, 7.24.

CHAPEL HILL, NORTH CAROLINA

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