A New Method for the Preparation of Pyridine-4-phosphonic Acids

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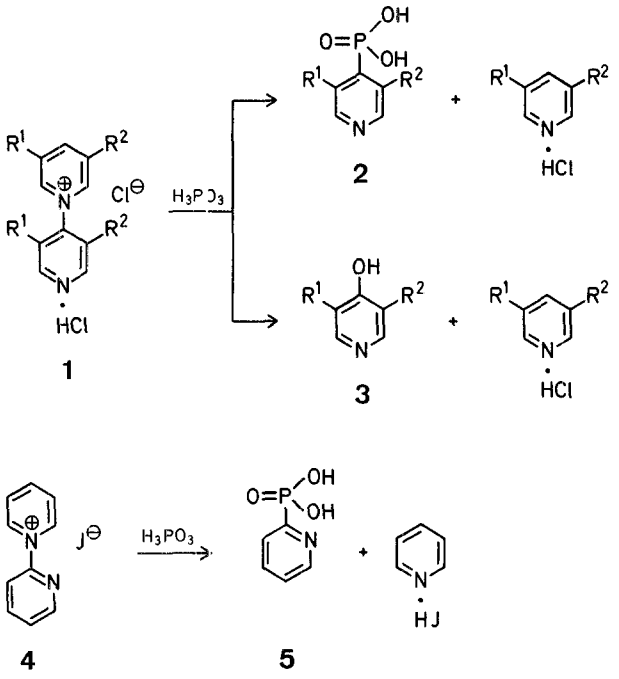
According to a recent publication[1], pyridine-4-phosphonates may be prepared by heating of 1-triphenylmethylpyridinium salts, e.g. the tetrafluoroborate, with sodium diisopropyl phosphonate in benzene. The diisopropyl pyridine-4-phosphonates so obtained, were hydrolyzed with aqueous hydrochloric acid to the corresponding pyridine-4-phosphonic acids. Recently, we have found a new method to prepare pyridine-4-phosphonic acids **2**, which involves addition of phosphorous acid to the 1-(4-pyridyl)-pyridinium salts **1**, and heating the mixture for 8–10 h at 130–140°. The main products of these reactions were 4-hydroxypyridines **3**, which were formed with good yields. The yields of pyridine-4-phosphonic acids **2**, obtained by this method were not good, but this method may be utilized to prepare these acids.

The observed reactions were simple nucleophilic substitutions of the quaternary pyridines rings of the 1-(pyridyl)-pyridinium systems by the phosphorous acid used. The quaternary pyridinium moiety was eliminated as pyridine hydrochloride. The reaction proceeds analogously to the reaction of 1-(4-pyridyl)-pyridinium chloride with hydrogen sulfide[3], or arenesulfinic acids[8]. Phosphorous acid is an ambident nucleophilic reagent so it may form pyridinephosphonic acids and hydroxypyridines with 1-(pyridyl)-pyridinium salts. Nucleophilic 1,4- or 1,2-addition is not observed in the reactions with phosphorous acid. Starting from 1-(2-pyridyl)-pyridinium iodide[5] (**4**), pyridine-2-phosphonic acid (**5**) was obtained in a small yield. Using diethyl phosphite instead of phosphorous acid in reactions with salts **1** and hydrolysing the resulting mixture with aqueous hydrochloric acid, pyridine-4-phosphonic acids were also obtained in similar yields.



The advantages of our method over the existing method[1] are as follows: the synthesis of the starting 1-(4-pyridyl)-pyridinium salts[2,3,4] from pyridines and thionyl chloride proceeds very easily. This synthesis of the title compounds is considerably simpler than the manner published[1]. In addition, this method may be used for preparation of 4-hydroxypyridines in good yields. Spectral data of the obtained products **2** (^{1}H-N.M.R., I.R.) fully support the assigned structures, with the exception of the melting points published[1]. The products **2** were additionally purified by repeated crystallizations, but show no substantial change in their melting points. Data obtained from mass spectra and molecular weights determined on the basis of potentiometric titrations were in a good agreement with the proposed structure of the acids **2**. The differences for C,H-microanalyses and melting points may be caused by the hygroscopic nature of these acids, and the possibility of a hemihydrate structure formation, which was noted by Redmore[1,6].

^{1}H-N.M.R. spectra were determined on a Tesla 487 80 MHz spectrometer. I.R. spectra were measured on a Perkin Elmer Model 621 spectrometer. Melting points were determined on a Boethius apparatus and were uncorrected.

Pyridine-4- and -2-phosphonic Acids, 2 and 5; General Procedure: A mixture of salt **1** or **4** (0.05 mol) and phosphorous acid (8.2 g, 0.1 mol) is heated in a flask for 8–10 h at 130–140°, on an oil bath. The molten mixture is cooled and dissolved in 1:1 ethanol/acetone (100 ml). The precipitated product **2** is removed by filtration and purified on an ion exchange column (Dowex 50 W). On elution of the column with pure water a few fractions with different pH are collected. Fractions with pH 1–2 contain hydrochloric acid and unreacted phosphorous acid. Fractions with pH 3–5 contain pyridine-4-phosphonic acid **2**, which is separated by evaporation of the fractions.

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Table 1. Pyridine-4- and -2-phosphonic Acids **2a–c** and **5**

Product	R^1	R^2	Yield[a] [%]	m.p. (Lit. m.p.)	Molecular formula[b]	I.R. (KBr) ν_{max} [cm^{-1}]	^{1}H-N.M.R. (D_2O) δ [ppm]	M.S. (70 eV) *m/e* (relative intensity %)
2a	H	H	25	270–275° (318°)[1]	$C_5H_6NO_3P \cdot 0.5H_2O$ (168.1)[c]	3500–3400; 3080; 3000–2400; 1620; 1150 (P=O)	9.25–9.10 (m, 2H, C-2, C-6); 8.75–8.50 (m, 2H, C-3, C-5); $J_{P-CH} = 13$ Hz	159 (M^+, 100); 141 (9); 95 (70); 82 (21); 79 (24); 78 (29); 65 (11); 52 (18); 51 (53); 50 (29); 28 (16); 18 (94)
2b	CH_3	H	28	255–261° (296°)[1]	$C_6H_8NO_3P \cdot H_2O$ (191.1)	3500–3400; 3070; 3000–2400; 1520; 1080–1020 (P=O)	9.0–8.87 (d, 2H, C-2, C-6); 8.64–8.38 (m, 1H, C-5); $J_{P-CH} = 12.5$ Hz; 3.00 (s, 3H, $ArCH_3$)	173 (M^+, 88); 155 (39); 120 (12); 109 (20); 108 (26); 93 (100); 92 (60); 45 (27); 31 (64); 27 (58)
2c	CH_3	CH_3	25	295–300° (333°)[1]	$C_7H_{10}NO_3P \cdot H_2O$ (205.2)	3500–3350; 3030; 2950–2300; 1520; 1070–1000 (P=O)	8.75 (d, 2H, C-2, C-6); 2.95 (s, 6H, $ArCH_3$)	187 (M^+, 51); 140 (28); 138 (35); 126 (52); 124 (31); 108 (28); 106 (45); 92 (41); 83 (54); 82 (39); 81 (53); 65 (100); 47 (100); 46 (91); 45 (69); 27 (63)
5	—	—	7	217–224° (224–227°)[1]	$C_5H_6NO_3P$ (159.1)	3400; 3090; 2900–2500; 1610; 1220; 1180–1150 P=O	9.20–8.80 (m, $2H_{arom}$); 8.65–8.25 (m, $2H_{arom}$)	159 (M^+, 32); 141 (3); 95 (86); 82 (10); 79 (100); 78 (33); 65 (6); 52 (26); 51 (38); 50 (21); 28 (14); 27 (8)

[a] Yields are based on salts **1** and **4** and are given for crude products. Yields of products are 5–10% after purification on an ion exchange column.

[b] The microanalyses for all compounds were in satisfactory agreement with the calculated values (C ±0.3, H ±0.3, N ±0.33, P ±0.38).

[c] M.W. = 162 (NaOH titration).

Table 2. 4-Hydroxypyridines **3a–c**

Product	R^1	R^2	Yield [%]	m.p. (Lit. m.p.)	m.p. of picrate (Lit. m.p. of picrate)	I.R. (KBr) ν_{max} [cm^{-1}]	^{1}H-N.M.R. (D_2O) δ [ppm]
3a	H	H	68	146–148° (148.5°)[2]	—	3340; 3200; 2800; 1650 (C=O); 1405; 1180; 1005; 850; 815	8.00 (d, 2H, C-2, C-6, $J = 7$ Hz); 6.60 (d, 2H, C-3, C-6, $J = 7$ Hz)
3b	CH_3	H	62	96–97° (96–98°)[7]	204–207° (205–206°)[7]	3370; 3045; 2930; 2700–2800; 1640; (C=O); 1520–1480; 1170; 1145; 830; 540	7.82 (d, 2H, C-2, C-6); 6.56 (d, 1H, C-5, $J = 6$ Hz); 2.08 (s, 3H, $ArCH_3$)
3c[a]	CH_3	CH_3	32	225–228°	180–181°	3205; 3160; 3020; 2920; 2840; 1640 (C=O); 1515; 1375; 1280; 1115; 850; 695; 495	7.68 (s, 2H, C-2, C-6); 2.07 (s, 6H, $ArCH_3$)

[a] C_7H_9NO (123.2) calc. C 68.27 H 7.37 N 11.37; found 67.69 7.14 10.75

M.S. (70 eV): *m/e* (relative intensity %) = 123 (M^+, 94); 122 (39); 108 (14); 95 (36); 94 (100); 78 (17); 67 (22); 55 (21); 39 (72); 27 (35).

The ethanolic solution (after removal of product **2**) is evaporated, and the residue separated on an ion exchange column (as above) to yield an additional amount of the product **2**, which is crystallized from aqueous ethanol. After elution of product **2**, the column is washed with normal aqueous ammonia. The fractions at pH 5–9 contain 4-hydroxypyridine **3** and pyridine and are collected. After evaporation of the solvent, 4-hydroxypyridine **3** is obtained, which is crystallized from acetone. Data for the obtained products **2** and **3** are given in Tables 1 and 2.

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Pyridine-4- and -2-phosphonic Acids 2 and 5 using Diethyl Phosphite:

A mixture of salt **1** or **4** (0.05 mol) and diethyl phosphite (13.8 g, 0.1 mol) is heated for 8–10 h at 130–140°. The dark mixture is cooled and dissolved in water (100 ml). The solution is purified with charcoal. After evaporation of the solvent, the residue is hydrolysed with 20% hydrochloric acid (50 ml) for 7 h. The products are isolated similar as described above.

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