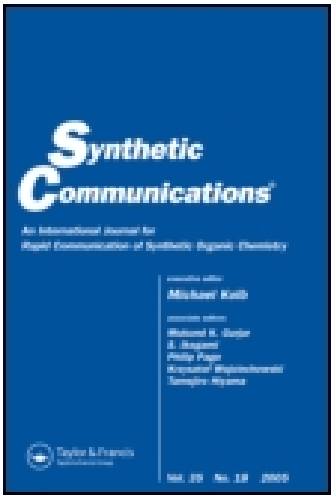

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Improved Syntheses of 5-Hydroxy-2-Pyridones (2,5-Dihydroxypyridines)

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Improved Syntheses of 5-Hydroxy-2-Pyridones (2,5-Dihydroxypyridines)

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Abstract: Improved syntheses of 5-hydroxy-2-pyridone, 6-chloro-5-hydroxy-2-pyridone, 2,5-dihydroxynicotinic acid, and three methyl-substituted 5-hydroxy-2-pyridones are reported.

Keywords: Elbs oxidation, peroxydisulfate, 2,5-dihydroxypyridines, 5-hydroxy-2-pyridones

The procedure described here for the synthesis of 5-hydroxy-2-pyridone by an Elbs oxidation of 2-pyridone (Fig. 1) has improvements over previous syntheses by this route, which include a higher yield, omission of unnecessary iron salts, a reproducible melting point, and, particularly, a detailed description in the style of Organic Syntheses.

Two reports[1,2] of the synthesis of 5-hydroxy-2-pyridone actually give the 2,3-isomer.[3] Adams and Govindachari[4] were the first to synthesize the 2,5-isomer in 1947. Two other routes were reported in 1950 and 1959.[5,6] All three are multistep, low-yielding procedures. A much simpler approach was reported by Behrman and Pitt in 1958[7] by application of the Elbs peroxydisulfate oxidation to 2-pyridone. Improvements to this procedure were made by Möhrle and Weber in 1970.[8] The intermediate sulfate ester has also been isolated.[9] The Elbs oxidation has been reviewed.[10,11] 5-Hydroxy-2-pyridone is an intermediate in the bacterial metabolism of a number of pyridine derivatives including nicotinic acid.[12]

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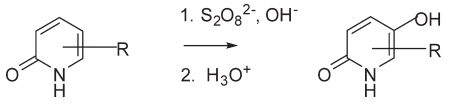

Figure 1. Synthesis of 2,5-dihydroxypyridines.

It has been linked with damage to DNA[13]and shows activity as an antitumor agent.[14]

The syntheses of five other 5-hydroxy-2-pyridones are also described. The methodology for each varies according to the solubility properties of the 2-pyridones used as starting materials and the products. 2,5-Dihydroxy-6-chloropyridine is a new compound, whereas 2,5-dihydroxynicotinic acid[15,16] and three methyl-substituted 2,5-dihydroxypyridines (3-methyl-,[17] 4-methyl-,[17] 6-methyl-[17,18]) have been reported but with few details of the syntheses or properties.

Crystals of the 6-substituted 2,5-dihydroxypyridines exhibit an unexpected property that we have explored so far in greatest detail with the 6-chloro compound. Combustion analysis showed the presence of one molecule of chloroform (used for crystallization) per eight molecules of the pyridine. The chloroform was also seen in the NMR and IR spectra. It could not be removed by heating in vacuo at 60 °C. Vacuum sublimation gave chloroform-free material. Preliminary X-ray crystallographic data show the presence of channels within the crystal that contain disordered molecules of chloroform.[19] NMR data for the 6-methyl compound suggest similar stoichiometry for crystals containing acetone or 2-propanol. This is an unusual finding that will be published separately.

EXPERIMENTAL

General Procedures

The 2-pyridones were bought from Alfa-Aesar and used as supplied. UV-visible spectra were taken on a Shimadzu Bio-mini with a resolution of about 2 nm in 5×10^{-4} M HCl. IR spectra were recorded in Nujol mulls on a Nicolet Impact 410 single-beam instrument. Melting points were determined in evacuated capillaries or under nitrogen.

5-Hydroxy-2-pyridone

2-Pyridone (14.6 g, 0.15 mol) and NaOH (16.9 g, 0.42 mol) are dissolved in 300 mL of water in a 1-L Erlenmyer flask equipped with a magnetic stirring bar and stoppered to keep out CO_2. Ice (200 g) is added to cool the solution

to about 5 °C, and then potassium peroxydisulfate (40.5 g, 0.15 mol) is added. The flask is placed in an empty ice bucket, and the mixture is stirred. Room temperature (23–25 °C) is reached in about 3 h. At this point, room-temperature water (500 mL) is added to the ice bucket to serve as a heat sink. The peroxydisulfate dissolves completely in about 2.5 h more. The homogeneous reaction mixture is allowed to stand at rt for 20 h. The clear orange solution is treated with conc. sulfuric acid (15 mL, 0.285 mol, 0.57 equiv), which is added all at once with stirring. A few boiling chips are added, and then the solution is boiled gently on a hot plate under a nitrogen atmosphere for 1 h. There is no need to reflux. The solution turns from orange to brown, and the volume is reduced by about 100 mL. The solution is cooled to about 15 °C in an ice-water bath. A solution made by dissolving 40 g of NaOH in 100 mL of water is added in 5- to 10-mL portions with stirring under nitrogen such that the internal temperature stays colder than 20 °C to bring the solution to pH 6. The pKa of the product is 8[20] (formation of the anion). The estimated pKa for formation of the cation is 0.4.

The last few mL of the NaOH solution are added 1 mL at a time so as to avoid exceeding pH 6. The total volume of NaOH added is about 50 mL (0.45 mol). Most of the water is removed from the neutral solution in two portions to form a damp solid using a rotary evaporator (ca. 23 mmHg) at 45 °C in a 1-L round-bottomed flask. Absolute ethanol (50 mL) is added and then removed on the rotary evaporator. This procedure is repeated with another 50 mL of ethanol. Note: if the salt cake is dried too thoroughly, it is difficult to remove from the flask. The damp salt cake is removed from the flask using appropriately bent spatulas, spread out in a thin layer in a pie plate, and allowed to air dry overnight at rt. The dry chocolate-brown salt cake weighing about 100 g is powdered in a mortar, placed in a 32-cm-diameter Whatman No. 1 circular filter paper, and then extracted in a Soxhlet apparatus with chloroform (250 mL in a 500-mL round-bottomed flask; the chloroform contained 0.75% ethanol) for 8 h. The Soxhlet apparatus used for this step and subsequent extractions had a 55/50 upper female joint and a 24/40 lower male joint. The joints should be greased lightly. The working volume of the chamber was about 180 mL. Note that it is impractical to try to remove all of the 2-pyridone in this way as even 45 h was insufficient.

Heating is carried out at such a rate that one cycle of the extraction takes about 12–13 min. This process removes about 90% of excess 2-pyridone (4.5 g) and all of the by-product, 3-hydroxy-2-pyridone (0.5 g) (^{1}H NMR). The extracted salt cake is removed from the Soxhlet apparatus and allowed to air dry overnight. The salt cake is re-extracted for 24 h with 2-propanol (250 mL in a 500-mL round-bottomed flask) in the Soxhlet apparatus under nitrogen saturated with 2-propanol using a gas-washing bottle equipped with a coarse frit. Nitrogen is introduced via a 5-in. piece of glass tubing inserted into the top of the condenser. The contents of the flask are cooled and allowed to stand at 5 °C overnight in a refrigerator.

The solids are filtered on a Büchner funnel and the mother liquors saved. The solids are washed (3 × 10 mL) with cold methanol (−20 °C), which removes dark-colored material without dissolving appreciable amounts of product. This process yields 4.2–4.9 g of crude product as a brown powder of about 95% purity. The impurity is largely 2-pyridone (^{1}H NMR). The salt cake is re-extracted in the Soxhlet apparatus with fresh 2-propanol (250 mL) for another 24 h. This extract is combined with the mother liquors from the first Soxhlet extraction and taken to dryness on a rotary evaporator at 45 °C. The flask and its contents are cooled to −20 °C. The solids are swirled with 12–15 mL of cold methanol. The suspended solids are filtered on a Büchner funnel and washed with cold methanol.

This yields an additional 2.2–2.7 g of crude product as a pinkish-brown powder of about 90% purity. The overall yield allowing for impurities is 6.4 g (38%). The corrected yield allowing for the recovered starting material is 56%.

Crystallization is performed from 95% ethanol. Six g of 95% purity material are combined with 2 g of 90% purity product. This mixture is dissolved in 700 mL of boiling 95% ethanol, Norite (1 g) is added, and the solution is filtered by gravity. The solution is slowly cooled to rt under nitrogen and then stored in a refrigerator overnight. The crystals are filtered on a Büchner funnel, washed with 5–10 mL of cold ethanol, and allowed to air dry. The yield is 3.2 g of a reddish-tan material.

The volume of the mother liquors is reduced to about 300 mL by boiling in a l-L Erlenmyer on a hot plate while a slow stream of nitrogen is bubbled through the solution. Approximately 0.5 g of Norite is added to the boiling ethanol, which is filtered by gravity. The solution is slowly cooled to rt under nitrogen and then stored in a refrigerator overnight, which provides an additional crop of solid (0.6 g). Reduction of the mother liquors from the second crystallization to 100 mL, addition of 0.2 g of Norite, filtration, and cooling in a refrigerator gives a third crop of solid (approximately 1 g). The three crystallizations (all of the same purity) provide a total of 4.8 g (60%) of better than 98% purity as judged by ^{1}H NMR and UV spectroscopy. A second crystallization gives almost colorless material. These crystals are stable in air at rt for at least 50 years.

An alternative method of purification is fractional sublimation. Sublimation at 0.05 mm Hg is first carried out at 100 °C to remove 2-pyridone and then at a higher temperature to sublime the product. A 0.5-g sample of 95% purity is finely ground and placed in a 40-mL Dailey sublimation apparatus available from Safety Emporium, Lexington, KY; the manufacturer is ChemGlass. Sublimation for 3 h at 100 °C gives a small white sublimate of 2-pyridone. This is removed, and then the residue is sublimed for 2.5 h while the temperature is gradually raised to 190 °C. The sublimate is a reddish powder that weighs 0.45 g and is about 98% pure. About 20 mg of dark material remains in the apparatus. Several previous reports have used sublimation for purification.[4,5,8] Tipson[21] provides a good discussion of the subject.

Physical Properties of 5-Hydroxy-2-pyridone

The literature reports of the melting behavior are not in good agreement with each other except that discoloration is reported and the decomposition point is reported over a wide range. If the melting point is taken in an evacuated capillary, little darkening occurs and a sharp melting point is observed: 261–263 °C.

IR (Nujol): 1671, 1625, 1556, 1310, 1293, 1245, 1002, 945, 842, 826, 798 cm^{-1}. Additional bands appear in a halocarbon mull: 3276, 3250, 3083, 2913, 2825, 2768, 2701, and 1448 cm^{-1}. These data are in accord with the spectrum shown in ref. [4] and in the Sadtler catalogue, no. 15057 (KBr).

^{1}H NMR (600 MHz, DMSO-d_6) δ: 6.30 (d, $J = 9.4$, H-3); 6.96 (d, $J = 3$, H-6); 7.16 (dd, $J = 9.4$, 3, H-4); 8.78 (s, OH); 10.76 (br, NH). ^{13}C NMR (151 MHz, DMSO-d_6) δ: 159.3 (C-2), 141.2 (C-5), 133.5 (C-4), 121.0 (C-6), 117.7 (C-3). These data are in accord with those given by Hunt et al.[18] UV: (5×10^{-4} M HCl), λ_{max} 230, 320 nm. ε: 6800 ± 200, 5350 ± 150 M^{-1} cm^{-1}. These data are in accord with those of Refs. [5] and [7]. The UV spectrum is a convenient way to assay the purity of a sample quantitatively; 2-pyridone has no appreciable absorption at 320 nm but absorbs strongly at 230 nm (λ_{max} 224, 294 nm). $FeCl_3$ complex: λ_{max} 510 nm. Anal. calcd. for $C_5H_5NO_2$: C, 54.05; H, 4.54; N, 12.61. Found (first crystallization from ethanol): C, 53.68; H, 4.36; N, 12.37; (second crystallization): C, 54.11; H, 4.70; N, 12.40.

General Procedures for the Substituted Pyridones

Reactions of the pyridones with peroxydisulfate and hydrolysis of the sulfate esters are all carried out in the same way as described for the parent compound but on a scale of 0.01 to 0.05 mol.

5-Hydroxy-6-chloro-2-pyridone

Unreacted starting material (6-chloro-2-pyridone, ca. 30%) is removed by extraction of the neutralized hydrolysate with chloroform. The extracted solution is dried by rotary evaporation. The dried salt cake is extracted in a Soxhlet apparatus with chloroform for 7 h with a cycle time of 9 min. Evaporation of the solvent yields the crude product in 30–40% yield (60–70% allowing for recovered starting material). The material crystallizes from chloroform or 1,2-dichloroethane. The data are for the crystals from chloroform.

Mp (under nitrogen): 151–152 °C dec. IR: 3312, 1668, 1605, 1494, 1326, 1284, 1241, 1210, 1183, 1086, 913, 812, 756 ($CHCl_3$), 692 cm^{-1}. UV: ε, λ max: 5700, 301 nm; 5500, 222 nm; sh. 340. $FeCl_3$ complex: λ max, 511 nm, sh. 545. The ortho isomer has λ_{max} at 614 nm. NMR (DMSO-d_6,

600 MHz): δ 10.53 (s, NH); 9.65 (s, OH), 7.24 (d, H4, $J = 8.5$ Hz), 6.48 (d, H3, $J = 8.5$ Hz). $CHCl_3$ at 8.30. Anal. calcd. for $C_5H_4ClNO_2 \cdot 0.125$ $CHCl_3$: C, 38.36; H, 2.59; N, 8.73. Found: C, 38.47; H, 2.63; N, 8.63.

5-Hydroxy-6-methyl-2-pyridone

Unreacted starting material (6-methyl-2-pyridone) is removed by extraction of the neutralized hydrolysate with chloroform. The extracted solution is dried and then extracted in an Soxhlet apparatus with chloroform for 5 h to yield a small quantity of 3-hydroxy-6-methyl-2-pyridone (blue color with ferric chloride, $\lambda_{max} = 590$ nm). The remaining dry salt cake is extracted with 2-propanol for 3 h to yield about 60% of crude product. The material crystallizes from ethanol–acetone mixtures or from 2-propanol. The data are for the material crystallized from ethanol–acetone.

Mp (under nitrogen): 260–262 °C dec. IR: 3260, 1709 (acetone), 1657, 1626, 1541, 1453, 1380, 1316, 1264, 1232, 1173, 940, 827, 788 cm^{-1}.

UV: ε, λ_{max}: 7050, 322 nm; 6650, 229 nm. $FeCl_3$ complex: λ_{max}, 500 nm. NMR (DMSO-d_6, 600 MHz): δ 10.95 (NH); 8.40 (OH); 7.10 (d, H-4, $J = 9.3$ Hz); 6.07 (d, H-3, $J = 9.3$ Hz), 2.08 (Me). Acetone at 2.09.

5-Hydroxy-4-methyl-2-pyridone

The crude product crystallizes directly from the neutralized hydrolysate in about 60% yield. Recrystallization from water with Norite gives almost colorless crystals. Mp (under nitrogen): 255–260 °C (dec. without melting). IR: 3486, 1670, 1623, 1312, 1243, 1007, 948, 937, 867, 833, 796 cm^{-1}. UV: ε, λ_{max}: 5190, 309 nm; sh. 227. $FeCl_3$ complex λ_{max}: 507 nm. NMR (DMSO-d_6, 800 MHz): δ 10.7 (NH); 8.68 (OH); 6.82 (H-6); 6.16 (H-3); 2.03 (Me).

5-Hydroxy-3-methyl-2-pyridone

The neutralized hydrolysate is dried and then extracted in the Soxhlet with chloroform to remove starting material (3-methyl-2-pyridone). The salt cake is redried and reextracted in the Soxhlet with 2-propanol. Removal of the solvent gives the crude product in about 50% yield as a pink powder. It can be crystallized, but in poor yield, from 2-propanol. A better procedure is to precipitate it as a powder from a 2-propanol solution by the addition of benzene. This yields material of better than 95% purity.

Mp (under nitrogen): 223–225 °C (dec.). IR: 3070, 1666, 1623, 1570, 1431, 1384, 1367, 1278, 1202, 1010, 821, 710 cm^{-1}. UV: ε, λ_{max}: 5725, 315 nm; 5200, 230 nm. $FeCl_3$ complex: λ_{max}, 532, 503 nm.

NMR (DMSO-d_6, 800 MHz): δ 10.96 (NH); 8.60 (OH); 7.05 (d, H-4, $J = 1.7$ Hz); 6.68 (d, H-6, $J = 2.2$ Hz); 1.94 (Me).

Potassium 2-Hydroxynicotinic Acid 5-Sulfate and 2,5-Dihydroxynicotinic Acid

The reaction is carried out as described in Ref. [15] except that ferrous sulfate is omitted. The precipitate that forms upon acidification contains product, inorganic salts, and the starting material, 2-hydroxynicotinic acid. Soxhlet extraction of the dried precipitate with acetone removes 2-hydroxynicotinic acid. The residue is then dissolved in hot water, filtered, and cooled to yield the potassium salt of the sulfate ester in about 30% yield (60% allowing for recovered starting material).

Mp 293–296 °C (dec.), lit.[15] 292 °C. IR: 1732, 1646, 1604, 1557, 1448, 1402, 1291, 1254, 1062, 956, 905, 856, 805, 763, 736, 717, 644 cm^{-1}. UV: ε, λ_{max}: 4400, 333 nm; 4700, 236 nm. $FeCl_3$ complex λ_{max} 400 nm (sh). NMR (DMSO-d_6, 600 MHz): δ 15.06 (COOH), 13.33 (NH), 8.27 (H-4, $J = 3$ Hz), 7.78 (H-6, $J = 3$ Hz).

Hydrolysis of the sulfate ester in boiling 5% sulfuric acid for 30 min, decolorization with Norite, and cooling gives 2,5-dihydroxynicotinic acid hemihydrate in moderate yield.

Mp 294–295 °C (dec.), lit. 306–308 °C[15]; 198–200 °C.[16] IR: 3386, 1713, 1605, 1551, 1416, 1208, 1078, 913, 840, 803, 607 cm^{-1}. UV: ε, λ_{max}: 6930, 355nm; 6680, 238nm. $FeCl_3$ complex λ_{max}: 441 nm. NMR (DMSO-d_6, 600 MHz): δ 15.57 (COOH), 13.10 (NH), 9.68 (OH), 8.03 (H-4, $J = 3.1$ Hz), 7.42 (H-6, $J = 3.1$ Hz).

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