Preparation of 5-Hydroxy-2-iodopyridine: A Refutation of Earlier Reports

Peter W. Sheldrake,* Laurence C. Powling, and Pritpal K. Slaich†

Synthetic Chemistry Department, Analytical Sciences Department, SmithKline Beecham Pharmaceuticals, Old Powder Mills, Nr Leigh, Tonbridge, Kent TN11 9AN, United Kingdom

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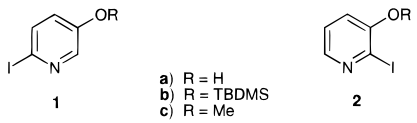
Recent work in this department needed a sample of 5-hydroxy-2-iodopyridine (**1a**). The literature reveals modern work apparently describing the preparation of **1a**, mp 188−189 °C, by iodination of 3-hydroxypyridine using sodium iodide and sodium hypochlorite in a methanol/water system.[1] Also, material prepared in this way is reported as the starting material for the preparations of L-β-(5-hydroxy-2-pyridyl)alanine[2] and a derivative[3] of this unnatural amino acid.

Electrophilic substitution reactions of 3-hydroxypyridine are well-known, and predominant reaction at the 2-position is evident.[4,5] Iodination of 3-hydroxypyridine using 1 mol of iodine in aqueous sodium carbonate gave 3-hydroxy-2-iodopyridine (**2a**), mp 203 °C, in high yield.[6] When we attempted to prepare **1a** by the literature method,[1] difficulties were encountered. Much starting material remained, and such product as was obtained (mp 189−192 °C) was identical by ^{1}H NMR and HPLC to **2a**. We then found that both the ^{13}C NMR spectrum (acetone-d_6) of authentic **2a** and its ^{1}H NMR spectrum ($CDCl_3$) coincided exactly with those presented by Edgar and Falling for what they originally claimed to be 5-hydroxy-2-iodopyridine. Of further interest to the anomaly is the report of the comparison of the melting point of their compound to literature values (191.5−192.5 °C).[7] 5-Hydroxy-2-iodopyridine is not in fact mentioned in the Broekman paper, and it is quite possible that the comparison was with **2a**.



In a further attempt to clarify the situation, authentic **2a** was converted to its *O*-TBDMS (**2b**) and *O*-methyl (**2c**) derivatives, using literature methods.[2] The NMR data obtained for **2b** and **2c** were identical to those reported[2] for what are stated by Ye and Burke to be the corresponding isomeric compounds **1b** and **1c**. We were therefore forced to conclude that 5-hydroxy-2-iodopyridine has not been prepared[1] and used[2,3] in the literature. It appears that both groups misinterpreted spectroscopic data of 3-hydroxy-2-iodopyridine and ascribed it to the desired 5-hydroxy-2-iodopyridine.

Table 1. ^{1}H and ^{13}C NMR Assignments

	compound **1a**			compound **2a**		
	^{1}H[a]			^{1}H[a]		
position	δ (ppm)	J (Hz)	^{13}C[b] δ (ppm)	δ (ppm)	J (Hz)	^{13}C[b] δ (ppm)
2			104.8			110.5
3	7.58	$^3J = 8.6$	135.7			154.6
4	6.95	$^3J = 8.6$	126.2	7.16	$^3J = 8.1$	121.8
		$^4J = 3.3$			$^4J = 1.9$	or 124.7
5			155.0	7.21	$^3J = 8.1$	124.7
					$^4J = 4.4$	or 121.8
6	7.96	$^4J = 3.3$	140.2	7.85	$^3J = 4.4$	142.7
					$^4J = 1.9$	

[a] DMSO-d_6 (400 MHz). [b] Acetone-d_6 (100.4 MHz).

Clearly the situation could only be resolved by preparing and characterizing a sample of the unknown **1a**. Directed syntheses from compounds to hand were considered, but rejected either because of length or failure of key steps. We therefore reexamined the iodination of 3-hydroxypyridine. The reaction mix obtained from iodination with iodine (1 equiv) in aqueous potassium carbonate at 20 °C was examined by LCMS and revealed only one monoiodinated product (the expected 3-hydroxy-2-iodopyridine, MW 221). However, when the reaction was carried out at 100 °C, a second peak of MW 221 was detected, albeit at a very low level. Higher levels of this new peak were found when the reaction was performed in DMF at 100 °C, but significant amounts of tar and diiodinated material also formed. Since the 2-position of 3-hydroxypyridine is more reactive than the 6-position to electrophilic substitution, we reasoned that **1a** would react faster than **2a** with iodine to give diiodinated product and decided to limit the amount of iodine used. Reaction of 3-hydroxypyridine in DMF at 60−70 °C with 0.6 equiv of iodine produced what by HPLC seemed useful amounts of the new monoiodinated product (although some of the known[6] 2,6-diiodo-3-hydroxypyridine was still formed). Conventional workup with crystallization and chromatography isolated the new iodohydroxypyridine (98.1% pure by HPLC) of melting point 149−151 °C, satisfactorily sharp yet substantially lower than that of 3-hydroxy-2-iodopyridine.

Spectroscopic evidence that the new monoiodohydroxypyridine is indeed 5-hydroxy-2-iodopyridine (**1a**) is provided by the NMR data. The chemical shifts (DMSO-d_6) $\delta = 7.96$, 7.58, and 6.95 are indicative of a pyridine with only one α-hydrogen. Thus, 3-hydroxy-4-iodo- and 3-hydroxy-5-iodopyridines are excluded. The coupling constants $J_{3,4} = 8.6$ Hz and $J_{4,6} = 3.3$ Hz are consistent with a 2,5-disubstituted pyridine; no coupling is routinely observed between H-3 and H-6. By contrast, 3-hydroxy-2-iodopyridine shows (DMSO-d_6) δ 7.85, 7.21, and 7.16 with $J_{4,5} = 8.1$ Hz, $J_{5,6} = 4.4$ Hz, and $J_{4,6} = 1.9$ Hz, consistent with the three adjacent hydrogens and distinct from the spectrum of **1a**. Proton and ^{13}C NMR data are shown in Table 1. The ^{13}C signal assignments were made by HMQC and HMBC experiments.

Chemical evidence that the new monoiodohydroxypyridine is represented by the structure **1a** comes from its further reaction with iodine. When the compound is reacted with 1 equiv of iodine in aqueous potassium carbonate, 2,6-diiodo-3-hydroxypyridine is produced, identical with authentic samples prepared from 3-hydroxypyridine or 3-hydroxy-2-iodopyridine (**2a**). The only isomer of **2a** capable of this is **1a**.

† Analytical Sciences Department.

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Experimental Section

^{1}H NMR spectra were obtained at 400 MHz and ^{13}C NMR spectra at 100 MHz. Melting points are uncorrected. Flash chromatography was performed on Matrex (Amicon Corp.) silica 60 (35−70 μm) purchased from Fisher Scientific, U.K. All solvents and reagents were used as received. Reactions and their workup were followed by HPLC using a 15 cm Waters C_8 Novapak column and a gradient over 25 min of 10−35% acetonitrile in 0.05 M ammonium acetate pH 5.0 buffer, flow rate 1 mL/min; UV detection at 285 nm. Retention times are as follows: **1a**, 10.7 min; **2a**, 6.4 min.

5-Hydroxy-2-iodopyridine (1a). Potassium carbonate (276 g, 2.0 mol) was added to a solution of 3-hydroxypyridine (95.1 g, 1.0 mol) in DMF (1400 mL). The mechanically stirred mixture was heated to 60 °C and the heater removed. Iodine (152 g, 0.6 mol) was added in portions over 5 min, the temperature rising to 72 °C. The reaction mix was allowed to cool to 40 °C and filtered. The solid was washed with DMF (2 × 100 mL) and the combined filtrates were evaporated to dryness under vacuum. Water (1500 mL) was added to the residue and the pH brought to pH 2, using concentrated sulfuric acid. The deposited tan solid (**2a**, dry weight 96.0 g), was filtered off and washed with water. The combined aqueous filtrates were extracted with ethyl acetate (3 × 200 mL). The combined organic extracts were washed with 0.2 M sulfuric acid (200 mL), 0.5 M sodium thiosulfate solution (250 ml), and water (2 × 250 mL). The ethyl acetate solution was dried over sodium sulfate, filtered, and evaporated to leave a solid (16.1 g). This was slurried in toluene (78 mL) at 90 °C for 1 h. After cooling, filtration gave a white solid (11.5 g). The solid was dissolved in ethyl acetate (100 mL) and evaporated onto flash silica (30 g). This was packed onto a dry column of flash silica (600 g). The column was eluted with 10% ethyl acetate in dichloromethane, removing 2,6-diiodo-3-hydroxypyridine. Elution with 20% ethyl acetate in dichloromethane gave first **2a** and then fractions containing both **1a** and **2a** (2.75 g dry weight) and finally 5-hydroxy-2-iodopyridine (**1a**) (dry weight 2.58 g): mp 149−151 °C; ^{1}H NMR (DMSO-d_6) δ = 10.12 (broad s, 1H), 7.96 (d, J = 3.3 Hz, 1H), 7.58 (d, J = 8.6 Hz, 1H), 6.95 (dd, J = 8.6, 3.3 Hz, 1H); ^{13}C NMR (acetone-d_6) δ 155.0, 140.2, 135.7, 126.2, 104.8; MS EI (m/z) 221, 127, 94, 39; IR (Nujol, cm^{-1}) 3049, 2573 (br), 1595, 1562, 1410, 1326, 1297, 1283, 1227, 1081, 826.

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