A New, One-Step Transformation of Furoic Acid Derivatives to 2-Amino-3-hydroxypyridines

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2-Amino-3-hydroxypyridine and its 6-methyl derivative can be prepared in yields up to 55% by heating 2-furoic acid derivatives at 200-250° with ammonia in the presence of an acidic catalyst. The reaction is preferably conducted in an amide or a nitrile as solvent.

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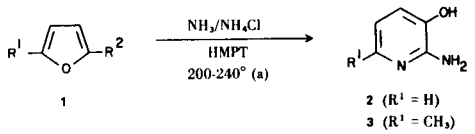
2-Amino-3-hydroxypyridine (**2**) is a valuable compound, especially as the starting material in the synthesis of highly active insecticides of low mammalian toxicity (1). Compound **2** is commonly prepared from furfural by the method of Clauson-Kaas (2,3), consisting of the following steps: 1. Oxidation of the furan ring of furfural; 2. Ring opening; 3. Reaction of the intermediate thus formed (4) with two moles of a derivative of ammonia (*e.g.*, a salt of sulfamic acid); 4. Ring closure. When considering the feasibility of interchanging any of these steps, we were curious to learn if 2-furamide (**1a**) (an "oxidation product" of furfural already containing one *N*-atom) could be transformed into **2** by incorporation of another molecule of ammonia. On a lower oxidation level, a formally analogous reaction is known, the transformation of acylfurans into 3-hydroxypyridines (5).

Indeed, it was found that heating of **1a** with gaseous ammonia in the presence of a catalyst such as ammonium chloride at 200-250° in an autoclave gave **2** (Table I). Other derivatives of 2-furoic acid, *e.g.*, **1b-d**, could also be employed as starting materials. Apparently these were transformed into **1a** under the reaction conditions. 2-

Table I



1

2 (R^1 = H)
3 (R^1 = CH_3)

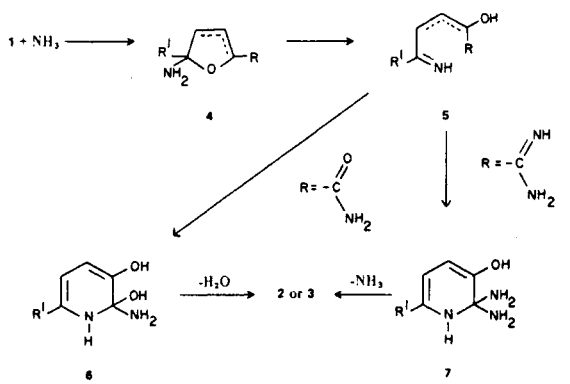
	R^1	R^2	Temperature (°C)	Time (hours)	2	% (a) or 3
1a	H	$CONH_2$	240	5	55	
1b	H	$COOC_2H_5$	240	8	50	
1c	H	COOH	240	11	45	
1d	H	$CONHCH_2C_6H_5$	240	10	20	
1e	H	CN	220	5	35	
1f	H	$C(=NH_2^+Cl^-)OC_2H_5$ (b)	200	5	35	
1g	H	CH=NOH	220	10	1-5	
1h	CH_3	$COOCH_3$	240	10		30
1i	CH_3	CN	240	8		30

(a) See experimental section. (b) No catalyst added.

Furonitrile (**1e**) or its imido ester salt (**1f**) reacted rapidly; however, yields were lower than with **1a** due to the formation of unknown side products. It is interesting to note that even furfural oxime (**1g**) (*syn-* or *anti*-isomer) can afford **2** in very low yield, probably *via* intermediate formation of **1e**. By analogy, the corresponding 5-methylfuran derivatives **1h** and **1i** were transformed into 2-amino-3-hydroxy-6-methylpyridine (**3**). Compounds **2** and **3** were obtained in pure form by the extraction technique described for **2** in the experimental section or by chromatography.

The transformation of the furan derivatives **1a-i** into the pyridines **2** or **3** is highly dependent on the solvent, the catalyst and the reaction conditions (temperature, pressure and time). The highest yields were obtained in "amidic" or related solvents (*e.g.*, nitriles). Hexamethylphosphoric triamide (HMPT) proved to be the solvent of choice, although formamide, dimethylformamide and especially acetonitrile performed almost equally well. The catalytic activity of the ammonium salts employed was found to decrease in the order ammonium iodide > ammonium bromide > ammonium chloride > ammonium fluoride ≈ diammonium hydrogen phosphate ≈ ammonium sulfate ≫ ammonium acetate. Lewis acids such as zinc chloride could also be employed (activity ≈ ammonium bromide). The reactions proceeded well in the temperature range of 200-250°, with reaction times of 0.5-15 hours, depending on the solvent and the catalyst. Care had to be taken not to "overheat", as **2**, and especially **3**, were not stable under the reaction conditions.

Although we have not conducted experiments to establish the reaction mechanism, it is reasonable to assume, that the reaction is initiated by a 1,2- or 1,4-addition of ammonia to the 5-position of the furan nucleus, which is activated by the electron withdrawing substituent in position 2. Ring opening of the intermediate **4** thus formed gives **5**, which, depending on the nature of R, will undergo ring closure to **6** or **7**. Loss of water or ammonia from **6** or **7**, respectively, leads to **2** (or **3**).



This one-step synthesis has made compounds **2** and **3** readily available. Although not yet experimentally proved, other 2-amino-3-hydroxypyridines, substituted in position 4-6, may conceivably be prepared in an analogous manner from appropriately substituted furoic acid derivatives.

EXPERIMENTAL

The furan derivatives not commercially available were prepared by known procedures: **1d** (6), **1f** (7), **1g** (8), **1h** (9), **1i** (10).

1. Transformation of **1a-i** into **2** or **3** (Table 1). General Procedure.

A furan derivative **1** (0.05 mole) was heated in a 300 ml. steel autoclave in the presence of 10 ml. of HMPT, 20 g. of gaseous ammonia and 0.5 g. of ammonium chloride (reaction temperature and time, *cf.* Table). After evaporation of excess ammonia, the reaction mixture was quantitatively transferred to a 250 ml. calibrated cylinder where it was dissolved in a 1:1 mixture of methanol and 1 *N* hydrochloric acid. Yields were determined by thin layer chromatography: spot sizes of 3 µl samples of unknown and known concentration were compared after elution with methanol/water/acetic acid/ethyl acetate (1:1:1:8) and development by spraying with potassium permaganate solution. Yields determined in this way were reproducible and agreed within 5% with yields determined by isolation procedures (*c.f.*, below).

2. 2-Amino-3-hydroxypyridine (**2**).

Compound **1b** (42 g., 0.3 mole), 3 g. (0.056 mole) of ammonium chloride and 60 ml. of HMPT were heated in a 300 ml. steel autoclave in the presence of 51 g. (3 moles) of gaseous ammonia. After heating 9 hours at 230° with stirring, the reaction mixture was cooled to 25°. Excess ammonia was evaporated. The residue was dissolved in approximately 130 ml. of 6 *N* sulfuric acid whereby a *p*H of 1.0 was attained. The dark solution was freed of HMPT and neutral products by continuous extraction with methylene chloride for 18 hours, brought to *p*H 7.4 by cautious addition of 30% sodium hydroxide solution and continuously extracted under nitrogen with ethyl acetate for 24 hours. Evaporation of the ethyl acetate extracts afforded 18.3 g. (55%) of **2** as a brown powder, m.p. 150-155°. Trituration of this material with a mixture of 50 ml. of ether and 7 ml. of methanol followed by filtration and drying at 50°/200 mm gave 15.8 g. (48%) of **2**, m.p. 165-169°. This product may be further purified by recrystallization from methanol, whereby the melting point is raised to 172° (melting points reported in the literature range from 163-165° (11) to 172-174° (2)).

3. 2-Amino-3-hydroxy-6-methylpyridine (**3**).

Compound **1i** (5.04 g., 0.05 mole) was reacted as described under 1. The reaction mixture was rapidly chromatographed on 250 g. of silicagel, eluting with methylene chloride, containing about 1-5% methanol. The pure fractions containing **3** were combined and evaporated, yield 1.53 g. (25%) of colorless crystals, m.p. 150-153° (lit. (12), 153-154.5°). The product rapidly darkened on exposure to air.

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(3) Other preparations of **2** are reviewed in (1).

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