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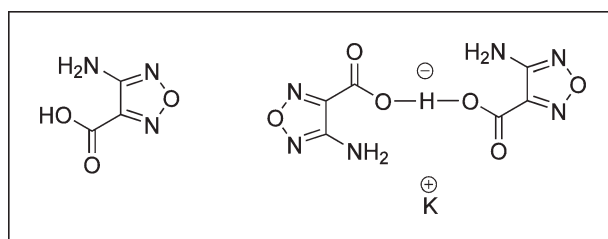
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The crystal structures of the two compounds reported to be 4-aminofurazan-3-carboxylic acid have been determined. The compound reported by Sheremetev et al. (*J Heterocycl Chem* 2005, 42, 519) is the actual 4-aminofurazan-3-carboxylic acid. The compound reported by Meyer (*Org Prep Proced Int* 2004, 36, 361) is the interesting complex formed from a molecule of the acid and a molecule of the potassium salt of the acid.

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## INTRODUCTION

In connection with several projects, we had need for a sizable quantity of 4-aminofurazan-3-carboxylic acid, **1**. There are two recent publications describing syntheses of this compound, one by Meyer [1] and one by Sheremetev et al. [2] The two syntheses are quite similar, involving the same starting compound, similar reagents, and intermediate, as outlined in Figure 1. The final neutralization step is conducted at ambient temperature in the Sheremetev procedure [2] and at 0°C in the Meyer procedure [1]. This turns out to be a critical difference between the two procedures.

When we made our first batch using Meyer's procedure, we obtained a product that seemed to match his reported properties except that the <sup>13</sup>C-NMR chemical shifts were different. Meyer reported shifts of 161.3, 157.1, and 143.3 ppm, whereas the compound we isolated had shifts of 160.7, 156.8, and 140.4 ppm. All NMR spectra were recorded in DMSO-*d*<sub>6</sub>, except as noted, as were the spectra in refs. 1 and 2. This concerned us until we noted that the <sup>13</sup>C-NMR shifts reported by Sheremetev et al. [2] (160.5, 156.8, and 140.4 ppm) were nearly identical to ours. The fact that Sheremetev et al. had transformed their product into other compounds and had obtained X-ray crystal structures on them, gave us great confidence that the com-

pound we had isolated was indeed **1**. We made several additional batches of the material over a period of about a year and always obtained the same product until, on the fifth batch, we isolated a compound, **2**, with a different crystal habit (plate for **2** vs. prism for **1**). In addition, the <sup>13</sup>C-NMR chemical shifts for **2** (161.3, 156.9, and 143.1 ppm) were nearly identical to those reported by Meyer.

Except for the differences in <sup>13</sup>C-NMR shifts, the rest of the spectral properties were quite similar. Significant differences were found in the elemental analyses and thermal properties of the two compounds. The compound with the shifts reported by Sheremetev et al. gave an almost perfect C, H, N analysis for C<sub>3</sub>H<sub>3</sub>N<sub>3</sub>O<sub>3</sub> (calculated: C, 27.92; H, 2.34; N, 32.55; found C, 27.80; H, 2.42; N, 32.63), whereas the compound with Meyer's shifts gave results that differed significantly (found C, 24.15; H, 1.62; N, 28.25). Obvious differences were observed in the DSC thermograms of the two compounds, as shown in Figures 2 and 3.

At this point, we turned to X-ray crystallography to establish the exact structure of the two compounds. A preliminary analysis of Meyer's compound showed the presence of a heavy atom. There were two possibilities, chlorine and potassium. We then reconsidered the results of the elemental analysis and found that the

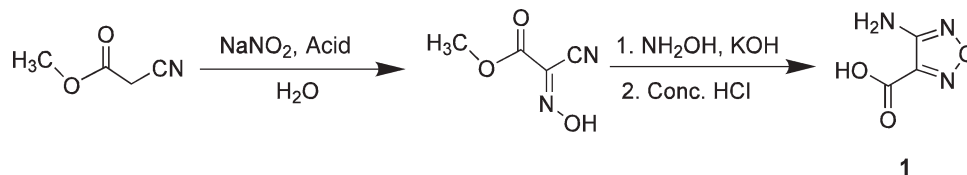


Figure 1. Generalized synthesis of **1**.

analytical results fit quite well for a molecular formula of  $C_6H_5N_6O_6K$  (calculated: C, 24.33; H, 1.70; N, 28.37; found: C, 24.15; H, 1.62; N, 28.25). An analysis of the compound for potassium gave results consistent with that molecular formula (calculated: K, 13.20; found: 13.2%). With this information in hand, the structure easily refined to the interesting complex formed between the acid and the potassium salt of the acid (Fig. 4). Similar structures have been observed previously [3,4].

Chemical confirmation of this structure comes from the fact that recrystallization of **2** from acidic water produces **1** and the fact that the treatment of **1** with 0.5 equiv of potassium hydroxide followed by recrystallization of the mixture produces **2** (Fig. 5). We also measured the  $^{13}C$ -NMR chemical shifts for the sodium salt of **1** in a mixture of  $H_2O/D_2O$  and obtained shifts of 163.8, 156.12, and 144.1 ppm. Thus, Meyer's compound has chemical shifts that are a rough average of **1** and its sodium salt.

For completeness, we determined the X-ray crystal structure for **1** (Fig. 6). The crystal data for the two compounds are summarized in Table 1.

There are several points that should be noted in the results of the X-ray diffraction of **1** (Fig. 6). At first glance, there would appear to be a center of symmetry among the four molecules in the asymmetric unit. Careful examination of the positions of the protons on O6, O6A, O6B, and O6C reveals that this is not a center of symmetry. Testing with PLATON [5] indicates that there is no missed symmetry. Further evidence on the

uniqueness of the four molecules can be seen in the hydrogen bonding (Supporting Information Table S6). In three of the molecules, N1 forms one normal H-bond and one bifurcated H-bond, whereas in the fourth molecule N1 forms only a bifurcated H-bond. O6 forms a bifurcated H-bond in one molecule while in the remaining molecules O6 forms a single H-bond with a donor-H-acceptor angle of  $152^\circ \pm 9^\circ$ . The disparity of the sizes and shapes of the displacement ellipsoids indicates possible twinning in the crystal which we were not able to resolve in the diffraction experiment. Data collection was attempted on multiple crystals of this compound and all were similarly flawed with some showing signs of severe twinning as evidenced by streaking in the diffraction pattern and broad spots.

It is somewhat puzzling that **2** would form in such acidic conditions. The best explanation would be that if the acidification process is done slowly and at a low enough temperature, **2** starts to crystallize out and once it has crystallized it is stable under the conditions. It should be noted that **2** is also completely stable to recrystallization from neutral water. It is very easy to avoid the isolation of **2** by simply heating the reaction after the acidification step to dissolve the product, insuring that the pH is still less than 1, then cooling the mixture to crystallize the product.

## EXPERIMENTAL

**4-Aminofurazan-3-carboxylic acid, 1.** A 1000-mL three-neck round-bottomed flask is equipped with a mechanical

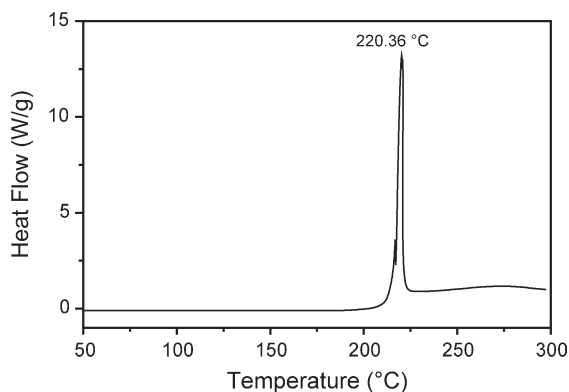


Figure 2. DSC thermogram of 4-aminofurazan-3-carboxylic acid, **1**.

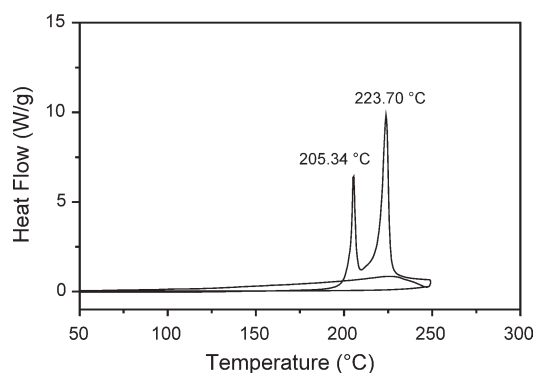
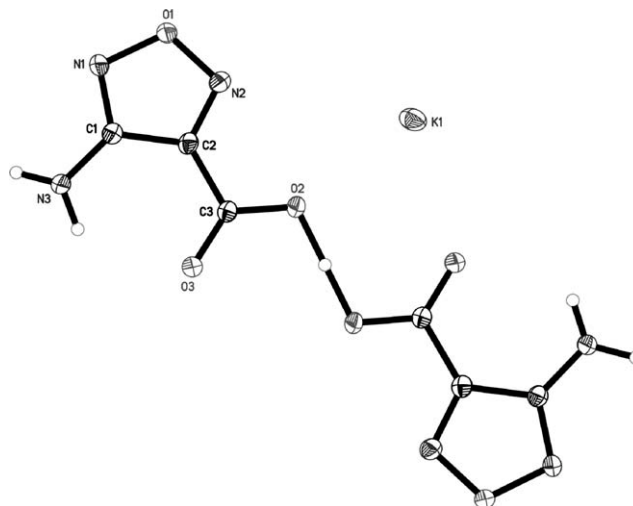


Figure 3. DSC thermogram of Meyer's compound, **2**.



**Figure 4.** X-ray crystal structure of Meyer's compound, **2**. Displacement ellipsoids are at the 50% level.

stirrer, 125-mL pressure equalizing dropping funnel, and a thermometer. Methyl cyanoacetate [59.4 g (53.4 mL, 0.60 mol)], sodium nitrite (50.0 g, 0.724 mol), and water (240 mL) are added to the flask, and the contents stirred and chilled to 0°C using a salt/ice bath. Acetic acid (46 mL, 0.80 mol) is added dropwise over 15 min. The cooling bath is removed and the mixture stirred for 4 h. The reaction is recooled to 0°C using a salt/ice bath, and the pH is adjusted to 1 using conc. HCl (~60 mL). The solution is transferred to a 1000-mL separatory funnel and extracted with ethyl acetate (3 × 150 mL). The combined ethyl acetate extracts are washed with 100 mL of brine, dried over MgSO<sub>4</sub>, and then concentrated *in vacuo* to yield the product. The yield is 76.8 g (0.60 mol).

A 1000-mL three-neck round-bottomed flask was equipped with a mechanical stirrer and thermometer. Water (150 mL) is added. This solution is stirred and potassium hydroxide (33.6 g, 0.60 mol) is added. The solution is cooled with an ice bath and 50% hydroxylamine (39.6 g, 0.60 mol) is added. Methyl 2-cyano-2-(hydroxyimino)acetate (76.8 g, 0.60 mol) is dissolved in 150 mL water and added in small portions to the stirred mixture. The cooling bath is removed. After the mixture is stirred for 1.5 h, additional KOH (67.2 g, 1.2 mol) is added portion-wise to the orange-red mixture. The mixture is heated to 100°C for 2 h using an oil bath. The mixture is cooled to 10°C using an ice bath and then acidified to pH < 1 using conc. hydrochloric acid (~125 mL). The solution is heated until all the product is in solution, and the pH is rechecked to make sure it is still below 1. Additional concentrated hydrochloric acid is added if necessary. The solution is chilled to

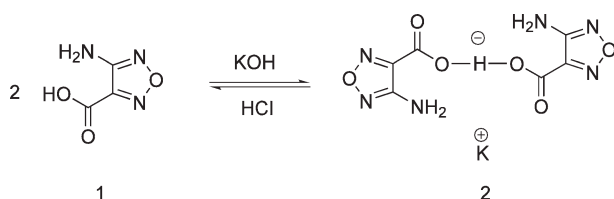
0°C using a salt-ice bath. After about 1 h, the product is collected and dried. The yield is 49.2 g (0.38 mol, 64%). The melting (decomposition) point by DSC (3°/min) is 220°C (ref. 2; 213–214°C).

**Synthesis of 2 from 1.** Authentic 4-aminofurazan-3-carboxylic acid, **1**, (1.29 g, 10 mmol), 5 mL of H<sub>2</sub>O, and 85% KOH (0.33 g, 5 mmol) are combined in a 20-mL scintillation flask equipped with a magnetic stirring bar. The contents are stirred at 100°C until the acid dissolves. The mixture is then cooled to 0°C and the product collected and dried. The yield of **2** is 1.40 g (4.7 mmol, 94%). The compound is identical in all respects to the product isolated from the Meyer's procedure.

**X-Ray Crystal Structure of Compounds 1 and 2.** Single-crystal X-ray diffraction data on **1** and **2** were collected at 100°K and 173°K, respectively, using MoK $\alpha$  radiation ( $\lambda = 0.71073$  Å) and a Bruker APEX 2 CCD area detector. The samples were prepared for data collection by coating with high viscosity microscope oil (Paratone-N, Hampton Research). The oil-coated crystal was mounted on a MicroMesh mount (MiTeGen) and transferred immediately to the diffractometer. Corrections were applied for Lorentz, polarization, and absorption effects. The structure was solved by direct methods and refined by full-matrix least squares on  $F^2$  values using the programs found in the SHELXTL suite (Bruker, SHELXTL v6.10, 2000, Bruker AXS, Madison, WI). Parameters refined included atomic coordinates and anisotropic thermal parameters for all non-hydrogen atoms. Hydrogen atoms were included using a riding model [coordinate shifts of N applied to H atoms] with N–H distance set at 0.86 Å.

The  $0.301 \times 0.224 \times 0.136$  mm<sup>3</sup> crystal of **1** was triclinic in space group  $P\bar{1}$  with unit cell dimensions  $a = 9.755(8)$  Å,  $b = 9.775(8)$  Å,  $c = 11.463(14)$  Å,  $\alpha = 108.362(12)^\circ$ ,  $\beta = 105.613(12)^\circ$ , and  $\gamma = 108.118(8)^\circ$ . Data were 92.0% complete to  $24.41^\circ$ . The asymmetric unit contains four molecules. Full information on data collection, refinement, and results of the X-ray studies are given in Supporting Information Tables S1–S6.

The  $0.64 \times 0.20 \times 0.04$  mm<sup>3</sup> crystal of **2** was monoclinic in space group  $P2_1/c$  with unit cell dimensions  $a = 10.060(4)$  Å,  $b = 4.5742(18)$  Å,  $c = 12.170(5)$  Å, and  $\beta = 107.298(6)^\circ$ .



**Figure 5.** Interconversion of compounds **1** and **2**.

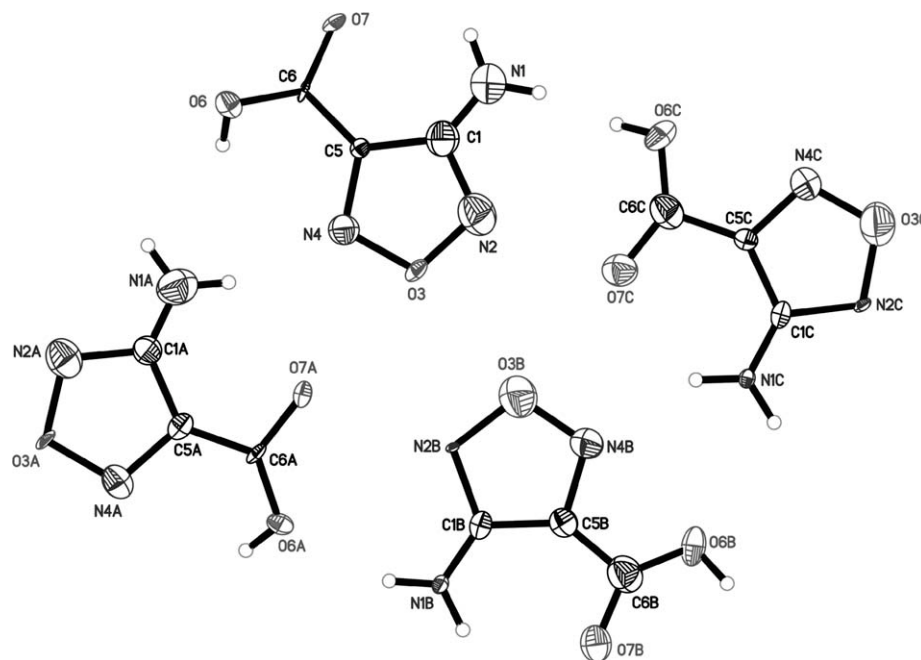


Figure 6. X-ray crystal structure of 4-aminofurazan-3-carboxylic acid, **1**. Displacement ellipsoids are at the 50% level.

Table 1

Crystal data and structure refinement for compounds **1** and **2**.

	<b>1</b>		<b>2</b>	
Empirical formula	C <sub>3</sub> H <sub>3</sub> N <sub>3</sub> O <sub>3</sub>		C <sub>3</sub> H <sub>2.50</sub> K <sub>0.50</sub> N <sub>3</sub> O <sub>3</sub>	
Formula weight	129.08		148.13	
Temperature	100(2) K		173(2) K	
Wavelength	0.71073 Å		0.71073 Å	
Crystal system	Triclinic		Monoclinic	
Space group	<i>P</i> $\bar{1}$		<i>P</i> 2/ <i>c</i>	
Unit cell dimensions (Å and °)	<i>a</i> = 9.755(8)	$\alpha$ = 108.362(12)	<i>a</i> = 10.060(4)	$\alpha$ = 90
	<i>b</i> = 9.775(8)	$\beta$ = 105.613(12)	<i>b</i> = 4.5742(18)	$\beta$ = 107.30(1)
	<i>c</i> = 11.463(14)	$\gamma$ = 108.118(8)	<i>c</i> = 12.170(5)	$\gamma$ = 90
Volume	900.6(15) Å <sup>3</sup>		534.7(4) Å <sup>3</sup>	
<i>Z</i>	8		4	
Density (calculated)	1.859 Mg/m <sup>3</sup>		1.840 Mg/m <sup>3</sup>	
Absorption coefficient	0.169 mm <sup>-1</sup>		0.537 mm <sup>-1</sup>	
<i>F</i> (000)	504		300	
Crystal size	0.301 × 0.224 × 0.136 mm <sup>3</sup>		0.64 × 0.20 × 0.04 mm <sup>3</sup>	
$\theta$ range for data collection	2.05 to 24.41°		2.12 to 28.76°	
Index ranges	-10 ≤ <i>h</i> ≤ 11		-13 ≤ <i>h</i> ≤ 13	
	-10 ≤ <i>k</i> ≤ 11		-5 ≤ <i>k</i> ≤ 6	
	-11 ≤ <i>l</i> ≤ 13		-16 ≤ <i>l</i> ≤ 16	
Reflections collected	5919		5340	
Independent reflections	2738 [ <i>R</i> (int) = 0.0415]		1385 [ <i>R</i> (int) = 0.0664]	
Completeness to $\theta = 25.00^\circ$	92.0%		99.9%	
Absorption correction			Semi-empirical from equivalents	
Max. and min. transmission	0.9773 and 0.9508		0.984 and 0.909	
Refinement method			Full-matrix least-squares on <i>F</i> <sup>2</sup>	
Data/restraints/parameters	2738/252/293		1385/3/97	
Goodness-of-fit on <i>F</i> <sup>2</sup>	0.946		1.040	
Final <i>R</i> indices [ <i>I</i> > 2 $\sigma$ ( <i>I</i> )]	<i>R</i> 1 = 0.0549, <i>wR</i> 2 = 0.0911		<i>R</i> 1 = 0.0467, <i>wR</i> 2 = 0.0989	
<i>R</i> indices (all data)	<i>R</i> 1 = 0.0777, <i>wR</i> 2 = 0.0963		<i>R</i> 1 = 0.0825, <i>wR</i> 2 = 0.1144	
Extinction coefficient			0.015(5)	
Largest diff. peak and hole	0.696 and -0.233 e Å <sup>-3</sup>		0.383 and -0.428 e Å <sup>-3</sup>	

Data were 99.9% complete to  $25.00^\circ \theta$ . The asymmetric unit contains two molecules sharing a single proton between their carboxyl groups plus one potassium ion. Full information on data collection, refinement, and results of the X-ray studies are given in Supporting Information Tables S7–S12.

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