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Structure of 3,4-Dihydroxy-2-thiophenecarboxylic Acid Ethyl Ester in the Crystal and Solution States

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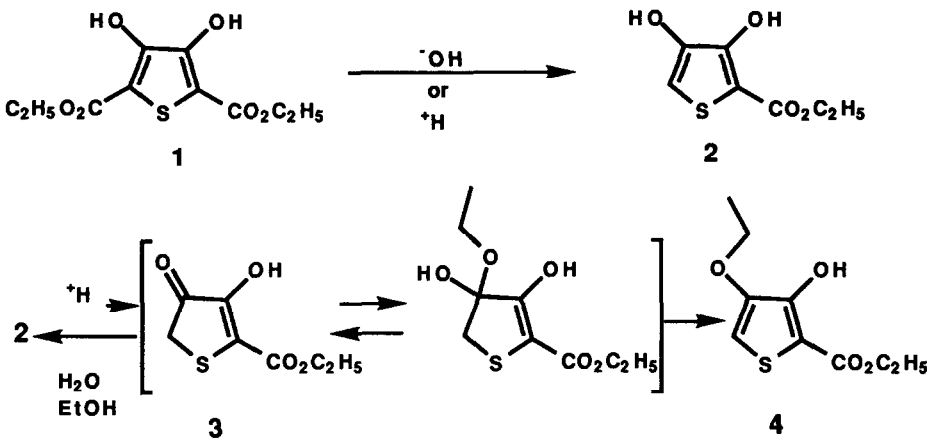
Abstract: The structure of 3,4-dihydroxy-2-thiophenecarboxylic acid ethyl ester was proven by NMR and X-ray crystallographic analysis. Under all conditions assessed, this compound existed as the dihydroxy tautomer 2.

While conducting a more complex total synthesis, we needed to prepare an intermediate, 3,4-dihydroxy-2-thiophenecarboxylic acid ethyl ester. This ethyl ester was reported twice previously in the literature[1a,b] and reviewed.[1c] The second literature report discussed tautomerism in this structural class and described a



spectral analysis of the ethyl ester that assigned the structure as the keto tautomer 3.[1b] Based on our initial spectroscopic analysis of this thiophene derivative, we fully characterized the compound and reassigned the structure as 2, a true dihydroxythiophene.

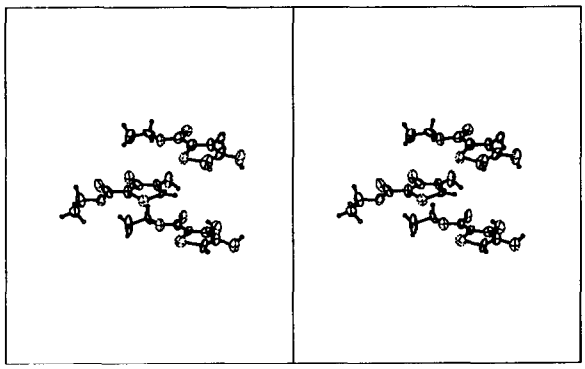
The reported syntheses of 2 utilized mono saponification and decarboxylation of the dicarboxylic acid diethyl ester 1 with NaOH; in both cases without exact experimental details and yields but giving products of similar melting points 76-78°C[1a] and 77-78°C.[1b] Attempts to reconstruct these syntheses led to the following unoptimized base catalyzed conditions for conversion of 1 to 2: 3,4-dihydroxy-2,5-thiophene-dicarboxylic acid diethyl ester, 1 (15.0g, 0.0577mol), in 225ml of 1N NaOH was heated at reflux for 5hr. The reaction was cooled to 25°C and added to ice-cold 1N HCl(225ml). The resultant mixture was stirred 1hr and filtered. The filtrate was extracted with three 500ml aliquots of EtOAc and the combined EtOAc extract dried over $MgSO_4$ and

evaporated to 6g of crude solid. The crude solid was purified via column chromatography on 300g of silica gel eluted with 9:1 hexane:EtOAc to yield 3.0g (28%) of **2** as a white solid, MP 73-74.5°C (without recrystallization), MP 76-77.5°C (recrystallized from cyclohexane).[2] The base catalyzed reactions tended to be capricious and purification of **2** was always confounded by the presence of varying amounts of unreacted **1** and the monoacid monoester intermediate, thus chromatography was a reproducible expediate for purification.

A favored and reproducible method for preparation of **2** was acid catalyzed hydrolysis/ decarboxylation: to a solution of **1** (32.5g, 0.125mol) in 750ml of dioxane was added 1l of 8N H_2SO_4. The reaction solution was heated at reflux for 15hr and then cooled to 5°C. The cold solution was extracted with three 1l aliquots of EtOAc, and the combined EtOAc extract dried over $MgSO_4$ and evaporated to 26g of crude semi-solid. The crude material was purified (1300g silica gel, 9:1 hexane:EtOAc) and recrystallized from cyclohexane to yield 11.6g (49%) of **2** as a white solid, MP 75-76°C.

The spectroscopic data for **2** that we collected[2] was inconsistent with the earlier published data which was used to support the tautomeric structure assignment of **3**.[1b] Briefly, the ^1H NMR spectrum of **2** shows a sharp aromatic C-H singlet at δ 6.65 assigned as the C-5 methine and in D_6-acetone the hydroxyl hydrogen resonances are well resolved at δ 8.65 and 9.49; no C-5 methylene resonance was detectable. The ^{13}C NMR spectrum is completely resolved with the ester C=0 resonance at 166.1ppm and no ketone resonance detectable. The ^1H NMR spectrum obtained in various solvents ($CDCl_3$, D_6-acetone, D_6-DMSO, CD_3OD, C_5D_5N) are identical except for the expected changes in the OH resonances. Since the melting point of our compound **2** appears to be identical to that previously reported[1a,1b] an ^1H NMR ($CDCl_3$) was obtained on a sample of **2** prepared immediately after it was melted. The spectrum is identical to that obtained from crystalline **2** described above. Finally, heating of the D_6-DMSO and C_5D_5N ^1H NMR samples of **2** to 100°C for 30min followed by rerecording of the spectra at RT produced unchanged spectra.

Compound **2** was further characterized with single-crystal X-ray analysis. The structure determined for the crystalline state is the dihydroxy thiophene **2** with three conformationally distinct molecules in the asymmetric unit of the refined structure **5**.[3]



5 ORTEP Projection

Two lines of evidence suggest that a less stable keto tautomer **3** may be accessible from (or in equilibrium with) the stable dihydroxy tautomer **2**. First, the C-5 hydrogen of **2** is rapidly exchanged for deuterium upon solution of **2** with NaOD-D_2O in an NMR tube. However, the C-5 hydrogen is not exchanged (at 25°C) when D_2O is added to a solution of **2** in $CDCl_3$. Secondly, following an acid catalyzed hydrolysis of **1** similar to that described above but using ethanol as cosolvent [3.00g (11.5mmol) of **1**, 115ml EtOH, 115ml 8N H_2SO_4] a 37% yield of **2** was obtained along with 20% of the monoethyl ether **4**.[6] We assume that the surprising formation of **4** under aqueous conditions is the result of reaction between ethanol and a low equilibrium concentration of the keto tautomer **3**. Once formed, **4** would be resistant to hydrolysis to **2** due to the stabilizing aromatic thiophene ring and lack of easy dearomatization such as tautomerization between **2** and **3**.

The structure of **2** in solution and the crystal state was shown to be a true 3,4-dihydroxy-thiophene. The reported keto tautomer of **2** could not be obtained or observed; however, it remains possible that the previous researchers prepared a metastable sample of the keto tautomer.

REFERENCES AND NOTES

1. (a) Hinsberg, O. *Ber. Dtsch. Chem. Ges.* **1912**, *45*, 2413. (b) Mortensen J.Z.; Hedegaard, B.; Lawesson, S.-O. *Tetrahedron* **1971**, *27*, 3839. (c) Gronowitz, S.; Hornfeldt, A.-B. Synthesis, Physical Properties and Reaction of Compounds Containing Thiophene-Oxygen Bonds. In *The Chemistry of Hetercyclic Compounds, Thiophene and its Derivatives*; Gronowitz, S. Ed.; John Wiley and Sons, Inc.: New York, **1986**; pp. 60-63.
2. Additional physical characterization data for 3,4-dihydroxy-2-thiophenecarboxylic acid ethyl ester, **2**: Anal Calcd for $C_7H_8O_4S$: C, 44.69; H, 4.28. Found: C, 44.47; H, 4.20; MS (m/e) 188(M^+) and 142 (100%, -C_2H_5OH); IR ($CHCl_3$) 3551, 3243, 2978, 1710 (w shoulder), 1658 (vs) and 1600 (w) cm-1; ^1H NMR ($CDCl_3$) δ 1.37 (t, J=7Hz, CH_3), 4.36 (q, J=7Hz, OCH_2) and 6.57 (s, CH); (D_6-Acetone) δ 1.32 (t, J=7Hz, CH_3), 4.32 (q, J=7Hz, OCH_2), 6.65 (s, CH), 8.65 (s, OH) and 9.49 (s, OH); ^{13}C NMR ($CDCl_3$) 14.3, 61.3, 102.8, 106.9, 142.4, 152.5 and 166.1ppm.
3. Single-crystal structure determination of **2** crystallized from cyclohexane-CH_2Cl_2: $C_7H_8SO_4$. group $P6_3$. Cell parameters: a=14.614(3)Å, b=14.614(3)Å, c=20.741(6)Å, α=90.00°, β=90.00°, γ=120°, V=3836(2)Å^3. Molecular weight=188.2, molecules per unit cell=18(Z=3), calculated density=1.47g/cm^3. A 1 Å data set (maximum sin θ/λ=0.5) was collected on a Nicolet R3m/μ diffractometer. Density calculations indicated that the asymmetric unit contained three molecules. Atomic scattering factors were taken from the International Tables for X-ray Crystallography[4]. All crystallographic calculations were facilitated by the SHELXTL[5] system. All diffractometer data were collected at room temperature. A trial structure was obtained by direct methods. This trial structure refined routinely. Hydrogen positions were calculated wherever possible. The methyl hydrogens and the hydrogens on oxygen were located by different Fourier techniques. The hydrogen parameters were added to the structure factor calculations but were not refined. The shifts calculated in the final cycle of least squares refinement were all less than 0.1 of their corresponding standard deviations. Refinement parameters: number of reflections=1373; nonzero

reflections ($I>3.0\sigma$)=1107; GOF=1.73; scale factor=0.7235(0.0005); secondary extinction factor=28(1)x10^{-4}. The final R-index was 0.050. A final different Fourier revealed no missing or misplaced electron density. The refined structure (**5**) was plotted using the SHELXTL plotting package. Coordinates, anisotropic temperature factors, distances and angles are available from Cambridge Crystallographic Data Centre.

4. *International Tables for X-ray Crystallography*; Kynoch Press: Birmingham. Vol. IV, **1974**; pp. 55, 99, 1439.
5. Sheldrick, G.M. SHELXTL. In *User Manual, Nicolet Instrument Co.*; **1981**.
6. Physical characterization data for 4-ethoxy-3-hydroxy-2-thiophenecarboxylic acid ethyl ester, **4**: MP 107-110°C (hexane); Anal Calcd for $C_9H_{12}O_4S$: C, 49.99; H, 5.60. Found: C, 50.15; H, 5.47; MS(m/e) 216 (M^+), 170 (-C_2H_5OH) and 142 (100%, -C_2H_5OH, -C_2H_4); IR ($CHCl_3$) 3301, 3115, 2971, 2930, 1710 (w shoulder), 1659 and 1581 (w); ^1H NMR ($CDCl_3$) δ 1.38 (t, J=7Hz, CH_3), 1.47 (t, J=7Hz, CH_3), 4.00 (q, J=7Hz, OCH_2), 4.37 (q, J=7Hz, OCH_2), 6.38 (s, CH) and 9.52 (s, OH); ^{13}C NMR ($CDCl_3$) 14.3, 14.6, 61.1, 66.2, 102.9, 103.8, 146.2, 153.9 and 166.1ppm.

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