On the Tautomerism of Some 3-Hydroxythiophene Aldehydes and Acids

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A recent communication [1] has prompted us to publish our results on the synthesis of some hydroxythiophene carboxylic acids and aldehydes and the tautomerism in these systems.**

3-Hydroxy-2-thiophene aldehyde was prepared by hydrogen peroxide oxidation of 2-formyl-3-thiopheneboronic acid.[2] Oxidation of the latter compound with silver oxide yielded 2-carboxy-3-thiopheneboronic acid, which upon hydrogen peroxide oxidation yielded the previously reported 3-hydroxy-2-thiophenecarboxylic acid.[3] The NMR-spectra of the aldehyde, the acid and its methyl ester in acetone and dimethyl sulphoxide solutions contained only bands expected for the hydroxy form. Since 2-alkyl-3-hydroxythiophenes exist as mixtures of the hydroxy form and the 4-thiolen-3-one form,[4] one would be led to suspect that intramolecular hydrogen bonding is stabilizing the enol form in the carbonyl derivatives. However, the NMR-spectrum of 3-hydroxy-5-thiophenecarboxylic acid [3] and its methyl ester also contain only bands ascribable to the enol form. It is possible, of course, that in the 3-hydroxy-2-carboxyl case the enol form is much more favoured in the equilibrium. It is, however, evident that NMR-spectroscopy is not sufficiently sensitive for determining quantitatively the stabilizing effect of intramolecular hydrogen bonding on the enol form. Methyl 3-hydroxy-5-thiophenecarboxylate was obtained through reaction of the acid with diazomethane. It is of interest to note that the esterification method of Clinton and Laskowski [5] yielded methyl 3-methoxy-5-thiophenecarboxylate. 3-Hydroxy-4-thiophene aldehyde was prepared analogously from 4-formyl-3-thiopheneboronic acid. This compound was even more unstable than the 2-formyl-3-hydroxy derivative, and elementary analyses could not be obtained before the compound decomposed. However, the NMR-spectrum in ether solution indicated that the desired compound had been obtained and that it existed in the enol form.

We have also attempted to prepare the 2-hydroxy-3-carbonyl thiophene system. Oxidation of 3-formyl-2-thiopheneboronic acid, however, gave a low yield of a crystalline compound, $C_4H_4O_2S$, m.p. 73–74°C, which is most probably 3-hydroxy-3-thiolene-2-one (the unsaturated thiolactone form of 2,3-dihydroxythiophene) as its NMR-spectrum in deuteroacetone showed a 1:2:1 triplet at 3.48 τ, and a doublet at 6.13 τ, with splittings of 3.5 c/s. These shifts and coupling are the same as those observed earlier in 3-methoxy-3-thiolene-2-one.[6] The hydroxyl resonance occurs at 1.72 τ.

Experimental. 3-Hydroxy-5-thiophenecarboxylic acid, m.p. 204°C, NMR (acetone): τ_2 3.35; τ_4 2.66; $\tau_{OH,COOH}$ 2.18; J_{24} 1.8 c/s, was prepared according to Fiesselmann and Schipprak.[3]

Methyl 3-hydroxy-5-thiophenecarboxylate was prepared in 86 % yield through reaction of 3-hydroxy-5-thiophenecarboxylic acid with ethereal diazomethane. M.p. 89.5–90.5°C after recrystallization from benzene. NMR (acetone): τ_{CH_3} 6.10; τ_2 3.19; τ_4 2.50; τ_{OH} 1.07; J_{24} 1.8 c/s. [Found: C 45.84; H 3.95; S 20.33. Calc. for $C_6H_6O_3S$ (158.2): C 45.56; H 3.82; S 20.27].

Methyl 3-methoxy-5-thiophenecarboxylate. 4.0 g (0.028 mole) of 3-hydroxy-5-thiophenecarboxylic acid, 17 ml of ethylene chloride, 4.5 ml of methanol and 0.8 ml of conc. H_2SO_4 were refluxed for 10 h and worked up in the usual manner,[5] yielding 3.5 g (73 %) of methyl 3-methoxy-5-thiophenecarboxylate, m.p. 38–39°C; identical (IR) with an authentic sample.[7]

Methyl 3-hydroxy-2-thiophenecarboxylate was prepared according to Fiesselmann *et al.*[3] B.p.$_{14}$ 100–102°C, NMR (acetone): τ_{CH_3} 6.09; τ_4 3.14; τ_5 2.25; τ_{OH} 0.34; J_{45} 5.4 c/s.

2-Carboxy-3-thiopheneboronic acid. 4.7 g (0.030 mole) of 2-formyl-3-thiopheneboronic acid,[2] dissolved in a solution of 2.4 g of sodium hydroxide in 25 ml of water, was added under ice-cooling to a suspension of silver oxide obtained from 10.6 g of silver nitrate, 4.9 g of sodium hydroxide and 50 ml of water. After stirring for 45 min the mixture was centrifugated and filtered. Adjusting the pH to about 3 with dilute hydrochloric acid caused the precipitation of 2.3 g of almost colourless crystals which

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** We have arranged with Dr. Lawesson that his group should continue the investigation on the tautomerism of carbonyl substituted hydroxythiophenes.

were recrystallized from a benzene-dioxane mixture, yielding 1.5 g (29 %) of 2-carboxy-3-thiopheneboronic acid, m.p. 159.5—162.5°C (decomp.). NMR (dimethyl sulphoxide): τ_5 2.22; τ_4 2.56; $\tau_{COOH,B(OH)_2}$ 1.98; J_{45} 5.0 c./s [Found: C 35.69; H 3.16. Calc. for $C_5H_5BO_4S$ (172.0): C 34.92; H 2.93].

3-Hydroxy-2-thiophenecarboxylic acid. 6 ml of 10 % hydrogen peroxide solution was added drop-wise to 1.48 g (0.0086 mole) of 2-carboxy-3-thiopheneboronic acid dissolved in 85.8 ml 0.1 N sodium hydroxide solution and stirred for 3 h at 36°C. After cooling, ether and 10 ml of 1 N hydrochloric acid were added. The aqueous layer was extracted three times with ether. The combined ether extracts were dried over magnesium sulphate and the ether was removed *in vacuo* under nitrogen yielding 0.77 g (62 %) of crude 3-hydroxy-2-thiophenecarboxylic acid, which was sublimed *in vacuo*, m.p. 102—110°, literature value[2] m.p. 108°. NMR (acetone): τ_4 3.25; τ_5 2.38; $\tau_{OH,COOH}$ 1.85; J_{45} 5.6 c/s.

3-Hydroxy-2-thiophenealdehyde. 30 ml of 10% hydrogen peroxide solution was added dropwise with stirring during 15 min to a suspension of 3.12 g (0.020 mole) of 2-formyl-3-thiopheneboronic acid[3] in 100 ml of ether. The mixture was refluxed for 3.5 h, the ether phase was washed four times with 20 ml of water and dried with $MgSO_4$. Removal of the ether *in vacuo* left 1.39 g (54 %) of a dark-brown crystalline residue which was sublimed *in vacuo* (10 mm Hg, 60°C), yielding colourless crystals, m.p. 88—89.5°C. NMR (acetone): τ_5 2.21; τ_4 3.18; τ_{CHO} 0.13; J_{45} 5.2 c/s; J_{CHO-5} 0.8 c/s. [Found: C 47.08; H 3.20; S 24.57. Calc. for $C_5H_4O_2S$ (128.2): C 46.86; H 3.15; S 25.02].

3-Hydroxy-4-thiophenealdehyde. 4-Formyl-3-thiopheneboronic acid[3] was treated with hydrogen peroxide and worked up as described above. However, as the product rapidly decomposed to a resin, when the ether was removed, its NMR-spectrum was run in a concentrated ether solution. NMR (ether): τ_2 3.66; τ_5 1.94; τ_{CHO} 0.14; J_{25} 4.0 c/s; J_{CHO-2} 0.8 c/s.

NMR-spectra were obtained as described earlier.[2]

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Photochemical Studies

IV. Photochemical Reactions of 2-Methylquinoline N-oxide Hydrate

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The recent report by Ishikawa, Yamada and Kaneko[1] on the photochemical transformation of 2-methylquinoline *N*-oxide (I) to a mixture of *N*-methylcarbostyril (II), 3-methylcarbostyril (III), *N*-acetylindole (IV), and 2-methylquinoline (V) in methanolic solution prompts us to report a novel type of photochemical reaction of 2-methylquinoline *N*-oxide.

In a typical run, 2-methylquinoline *N*-oxide dihydrate (5.0 g), dissolved in benzene (4.0 l), was irradiated (Hanovia 700 W, medium pressure mercury lamp, and Pyrex filter) for 15—20 h at *ca.* 20°.

Column chromatography on neutral aluminium oxide yielded as the first fraction an oil (0.86 g) which, by thin-layer chromatography, was shown to consist of largely 2-methylquinoline (V) with minor amounts of *N*-acetylindole (IV) and some other compounds which were not identified. Subsequent elution gave, as a second