

## The 3-Hydroxythiophene System

### II.\* The Structure of Some Oxidative Coupling Products of the 2,5-Dimethyl- and 2,5-Di-*tert*-butyl Substituted 3-Hydroxythiophene System

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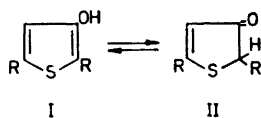
When the 2,5-dimethyl-3-hydroxythiophene system is treated with potassium ferricyanide, the racemic and meso forms of 2,2'-5,5'-tetramethyl-2,2'-dehydro-di-4-thiolen-3-one (Va) are formed. When the substituents in the  $\alpha$ -position become *tert*-butyl groups instead of methyls, the reaction follows other paths. When exposed to air the 2,5-di-*tert*-butyl-3-hydroxythiophene system gives 2-(2,5-di-*tert*-butyl-4-thiolenyl-3-one)-3-(2,5-di-*tert*-butylthienyl)-ether (VIb).

From earlier investigations it is known that unsubstituted 3-hydroxythiophene is a very unstable compound<sup>1</sup> and that the 2-methyl-3-hydroxythiophene system is the only methylsubstituted derivative that can be isolated.<sup>2</sup> Since the instability can depend on the fact that these systems easily undergo oxidative coupling reactions, two of the 2,5-dialkylsubstituted 3-hydroxythiophene systems have been subjected to oxidative couplings in connection with their preparation and structure determination.<sup>3</sup>

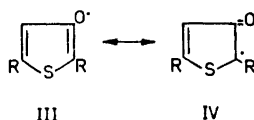
The hydroxythiophene systems are obtained by oxidation of thiophene boronic acids with hydrogen peroxide. In the preparation of the 5-*tert*-butyl-2-hydroxythiophene system, 5,5'-di-*tert*-butyl-3,3'-di-3-thiolen-2-one was formed as a by-product.<sup>4</sup> Several attempts were made to prepare this compound from the monomer. Successful results were obtained by using potassium ferricyanide; an indigo-like product, 5,5'-di-*tert*-butyl-3,3'-dehydro-di-4-thiolen-2-one, was isolated.<sup>4</sup>

The 2,5-dialkylsubstituted 3-hydroxythiophenes exist in an equilibrium between the oxo and enol forms ( $I \rightleftharpoons II$ ). The oxidative attack in phenols and naphthols seems to involve, as a first step, removal of the hydroxyl hydrogen to yield an oxy radical.<sup>5</sup> For the oxy radical of the 2,5-dialkylsubstituted 3-

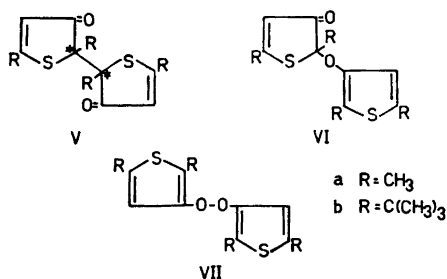
\* Part I, Ref. 2.



hydroxythiophene system two mesomeric forms are possible (III, IV), which by carbon-carbon, carbon-oxygen, and oxygen-oxygen coupling form the



products V – VII. On treatment with alkaline potassium ferricyanide the 2,5-dimethyl-3-hydroxythiophene system gave a product containing two com-



ponents, with identical mass spectra and molecular weights (254), which could be separated by column chromatography. By using a 1:1 chloroform:ligroin mixture as eluent on a silica gel column, the first fractions contained an oil, while the following were crystalline with melting point 195–196°.

NMR spectra of the two components had the same pattern with small shift differences. They contained three peaks with relative intensities of 1:3:3, a quartet in the aromatic region and two types of methyl absorptions, one as a doublet with the same splitting as in the quartet and one as a sharp singlet. The  $\tau$  values were 4.05, 7.64, and 8.34 for the oil and 4.12, 7.63, and 8.27 for the crystalline compound. This is in accord with what is expected for structures V and VII, while structure VI, an unsymmetrical molecule, would give rise to two aromatic absorptions and probably more than two types of methyl bands. However, both of the isolated forms show carbonyl stretchings in their IR spectra, which is not in agreement with structure VII, and furthermore structures V and VII would not give the same mass spectra. From the spectroscopic data it is evident that the two forms isolated are the meso and racemic

forms of 2,2',5,5'-tetramethyl-2,2'-dehydro-di-4-thiolen-2-one (Va). We have not yet been able to determine the stereochemistry of either form. However, it seems likely that the crystalline compound is the meso form.

The crystalline form was also isolated in the oxidation step in the preparation of the 2,5-dimethyl-3-hydroxythiophene system when the reaction time was prolonged. This system is prepared by hydrogen peroxide oxidation of 2,5-dimethyl-3-thiophene boronic acid.

When the substituents in the  $\alpha$ -positions become larger for example *tert*-butyl groups instead of methyls, both the reaction with potassium ferricyanide and that with hydrogen peroxide follow other paths. In the first case the initially formed product seems to be a peroxide, which decomposes to two compounds containing only one ring with a sulphur atom and with IR spectra showing both carbonyl and various types of OH stretching bands. The details of this reaction are under investigations.

In the case of the hydrogen peroxide oxidation and on exposure to air, the *tert*-butyl analogue of the carbon-oxygen coupling product, VI b, was isolated. The structure of this oxidative coupling products was demonstrated by its spectroscopic data. The mass spectrum gives a molecular weight of 422, the IR spectrum contains carbonyl stretching at  $1690\text{ cm}^{-1}$  and the five absorptions in the NMR spectrum (Fig. 1) of this substance showed that it

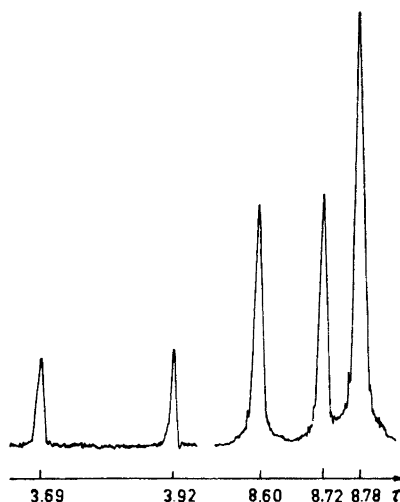


Fig. 1. NMR spectrum of VIb in deuteriochloroform.

could not be either of the symmetrical compounds Vb or VIIb. The relative intensities of the absorptions in the NMR spectrum were 1:1:9:9:18, and the assignments of the different peaks were carried out by a comparison with other 2,5-di-*tert*-butyl substituted thiophene compounds. The two peaks with the relative intensities of one are in the aromatic region at  $3.69\ \tau$  and  $3.92\ \tau$  and the one at lower field is referred to the thiolene-3-one ring. The assignments of the *tert*-butyl absorptions are more difficult, but the pair at lower field seems to be due to the substituents in the thiophene ring.

The 2,5-di-*tert*-butyl-3-hydroxythiophene system was obtained by a reaction route similar to that used for the 2,5-dimethyl-3-hydroxythiophene system. Thiophene was alkylated with isobutylene using sulphuric acid as catalyst,<sup>6</sup> and the isomeric mixture thus obtained, consisting of 2,4- and 2,5-di-*tert*-butylthiophene, was treated with ethyllithium and dry carbon dioxide. As only 2,4-di-*tert*-butylthiophene undergoes metallation, the 3,5-di-*tert*-butyl-2-thiophenecarboxylic acid could be separated from the neutral 2,5-di-*tert*-butylthiophene,<sup>7</sup> and the latter was then brominated with bromine in acetic acid.<sup>8</sup> The resulting 2,5-di-*tert*-butyl-3-bromothiophene was treated with ethyllithium and triethylborate. The boronic ester thus obtained was directly oxidized with hydrogen peroxide, as it was in this case difficult to hydrolyse the boronic ester to the acid. It was found that the use of ethyllithium instead of butyllithium improved the yield in the halogen-metal exchange step.

The enol form of the 2,5-di-*tert*-butyl-3-hydroxythiophene system thus obtained could not be detected in the NMR spectrum when either chloroform or carbon disulphide was used as solvent. In other 2,5-disubstituted 3-hydroxythiophene systems studied<sup>3</sup> the enol form was favoured in carbon disulphide solution.

#### EXPERIMENTAL

*The 2,5-di-tert-butyl-3-hydroxythiophene system.* 237 ml of ethereal 0.93 N ethyllithium was added dropwise to 55 g (0.20 mol) of 2,5-di-*tert*-butyl-3-bromothiophene<sup>8</sup> in 150 ml of dry ether under nitrogen at  $-70^{\circ}$ . When the addition was complete the reaction mixture was left with stirring for half an hour more and then treated with 36.5 g (0.25 mol) of newly distilled triethyl borate in 150 ml of dry ether. After stirring at  $-70^{\circ}$  for 4 h. the reaction mixture was allowed to warm to room temperature and 96 ml of 10 % hydrogen peroxide was added dropwise. After complete addition the reaction mixture was refluxed for an hour and cooled, whereupon the phases were separated and the water phase extracted twice with ether. The combined ethereal phases were washed with cold water until the separating water did not oxidize ferrous ammonium sulphate, dried over magnesium sulphate and distilled under nitrogen. 25 g of the 2,5-di-*tert*-butyl-3-hydroxythiophene system and small amounts of 2,5-di-*tert*-butylthiophene and 2,5-di-*tert*-butyl-3-bromothiophene, b.p.  $110-120^{\circ}/4.5$  mmHg, were obtained. The hydroxy system was purified on a column filled with silica gel and eluted with toluene saturated with nitrogen. The fractions were collected under nitrogen and analyzed by gas chromatography using an NGPS column. Distillation of the purest fractions gave 5.5 g, b.p.  $130^{\circ}/13$  mmHg. IR spectrum (film): C=O  $1680\text{ cm}^{-1}$ , OH  $3330\text{ cm}^{-1}$ . NMR spectrum ( $\text{DCCl}_3$ ):  $\tau_{2\text{-tBu}} = 8.90$ ,  $\tau_{5\text{-tBu}} = 8.68$ ,  $\tau_{\text{H}_3} = 6.50$ ,  $\tau_{\text{H}_4} = 4.05$ . (Found: C 66.3; H 9.19; M.w. 212. Calc. for  $\text{C}_{12}\text{H}_{20}\text{OS}$ : C 67.86; H 9.49; M.w. 212.35.)

*2,5-Di-tert-butyl-3-acetoxythiophene.* 3 g (0.014 mol) of the 2,5-di-*tert*-butyl-3-hydroxythiophene system was refluxed for 20 h with excess acetyl chloride. The unreacted acetyl chloride was removed *in vacuo*, and the residue gave upon distillation 2.5 g (70 %), b.p.  $110^{\circ}/11$  mmHg,  $n_D^{20} = 1.4954$ . IR spectrum (film): C=O  $1780\text{ cm}^{-1}$ . NMR spectrum ( $\text{DCCl}_3$ ):  $\tau_{2\text{-tBu}} = 8.66$ ,  $\tau_{5\text{-tBu}} = 8.68$ ,  $\tau_{\text{H}_3} = 3.49$ ,  $\tau_{\text{CH}_3} = 7.77$ . (Found: C 65.6; H 8.69; S 12.3; M.w. 254. Calc. for  $\text{C}_{14}\text{H}_{22}\text{O}_2\text{S}$ : C 66.10; H 8.72; S 12.61; M.w. 254.38.)

*2-(2,5-Di-tert-butyl-4-thiolenyl-3-one)-3-(2,5-di-tert-butyl-thienyl)-ether* was formed when the 2,5-di-*tert*-butyl-3-hydroxythiophene system was exposed to air. M.p. after recrystallisation from ethanol-petroleum ether  $152-154^{\circ}$ . IR spectrum (KBr): C=O  $1690\text{ cm}^{-1}$ . NMR spectrum ( $\text{DCCl}_3$ ):  $\tau_{2\text{-tBu}} = 8.72$ ,  $\tau_{5\text{-tBu}} = 8.78$ ,  $\tau_{\text{H}_4} = 3.69$ ,  $\tau_{2'\text{-tBu}} = 8.78$ ,  $\tau_{5'\text{-tBu}} = 8.60$ ,  $\tau_{\text{H}_4'} = 3.92$ , where the primed values refer to the thioen-3-one ring. (Found: C 67.1; H 8.83; S 15.2; M.w. 422. Calc. for  $\text{C}_{24}\text{H}_{38}\text{O}_2\text{S}_2$ : C 68.19; H 9.06; S 15.17; M.w. 422.68.)

*2,2'-5,5'-Tetramethyl-2,2'-dehydro-di-4-thiolene-3-one.* A solution of 3.81 g (0.03 mol) of the 2,5-dimethyl-3-hydroxythiophene system<sup>3</sup> in 75 ml of benzene was added dropwise

under nitrogen to a well stirred solution of 36 g (0.11 mol) of potassium ferricyanide in 150 ml of water, 300 ml of benzene and 6.0 g (0.07 mol) of potassium hydroxide. The mixture was heated to gentle reflux and stirred for 2 h, and then poured onto crushed ice. The benzene layer was separated, washed with water and dried over magnesium sulphate. The solvent was removed at reduced pressure to yield 1.25 g (32 %) of crude product consisting of two components. NMR analysis showed that it contained 50 % of the meso form and 50 % of the racemic form. The two components were separated on a column filled with silica gel and eluted with a 1:1 chloroform:ligroin mixture. The first fractions consisted of a yellow oil, which was distilled, b.p. 80–85°/0.1 mmHg. IR spectrum (film): C=O 1685 cm<sup>-1</sup>. NMR spectrum (CCl<sub>3</sub>):  $\tau_{2-\text{CH}_3} = \tau_{2'-\text{CH}_3} = 8.27$ ,  $\tau_{5-\text{CH}_3} = \tau_{5'-\text{CH}_3} = 7.63$ ,  $\tau_{\text{H}_4} = \tau_{\text{H}_4'} = 4.12$ ,  $J_{\text{H}_4-5\text{CH}_3} = J_{\text{H}_4'-5'\text{CH}_3} = 1.2$  Hz. The following fractions contained the crystalline form, which was recrystallized from 9:1 ligroin:ethanol, m.p. 195–196°. IR spectrum (film): C=O 1665 cm<sup>-1</sup>. NMR spectrum (CDCl<sub>3</sub>):  $\tau_{2-\text{CH}_3} = \tau_{2'-\text{CH}_3} = 8.34$ ,  $\tau_{5-\text{CH}_3} = \tau_{5'-\text{CH}_3} = 7.64$ ,  $\tau_{\text{H}_4} = \tau_{\text{H}_4'} = 4.05$ ,  $J_{\text{H}_4-5\text{CH}_3} = J_{\text{H}_4'-5'\text{CH}_3} = 1.2$  Hz. (Found: C 56.4; H 5.48; S 24.8; M.w. 254. Calc. for C<sub>12</sub>H<sub>14</sub>O<sub>2</sub>S<sub>2</sub>: C 56.67; H 5.50; S 25.20; M.w. 254.12.)

The NMR spectra were obtained with a Varian A-60 high resolution spectrometer. The IR spectra were recorded on a Perkin-Elmer Model 257 instrument. The mass spectra were recorded on an LKB A 9000 mass spectrometer and the ion-source voltage was 70 eV. The gas chromatographs used were a Perkin-Elmer 900 analytical instrument and a Perkin-Elmer F 21 preparative instrument. The elementary analyses were carried out at the Analytical Department at the Chemical Center.

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