

## Oxidation of Dihydrothiophenes with Iodosobenzene\*<sup>1</sup>

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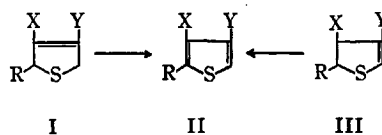
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In a previous paper,<sup>1)</sup> we have reported that the oxidation of 3,4-disubstituted 2,5- and 4,5-dihydrothiophenes with 30% hydrogen peroxide in acetic acid or with perbenzoic acid in chloroform gives the following results: 1) when both of the two substituents attached to the 3- and 4- positions are electron-withdrawing, oxidation with 30% hydrogen peroxide in acetic acid tends to produce the corresponding thiophene derivatives; 2) when one of two substituents is electron-withdrawing and the other is electron-releasing, the oxidation tends to produce the corresponding sulfone derivatives, and 3) the oxidation of 2,5- and 4,5-dihydrothiophenes with perbenzoic acid in chloroform produces mainly the corresponding sulfone derivatives.

In this paper, we will report that the oxidation of 3,4-disubstituted 2,5- and 4,5-dihydrothiophenes with iodosobenzene in dioxane gives the corresponding thiophene derivatives (III) without any

dependence on the nature of the substituent, as is shown in Table 1. This finding is in contrast with that concerning the oxidation with 30% hydrogen peroxide in acetic acid or with perbenzoic acid in chloroform.



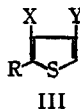
A probable mechanism for the formation of the thiophene, III, is as follows: the 3,4-disubstituted dihydrothiophenes, I or II, are oxidized by iodosobenzene<sup>2)</sup> to the corresponding sulfoxide derivatives, which are then dehydrated to the thiophene derivatives, III.

\*<sup>1</sup> Studies of the Syntheses of Heterocyclic Compounds. Part IX.

1) Part VIII: T. Takaya, S. Kosaka, Y. Otsuji and E. Imoto, *This Bulletin*, **41**, 2086 (1968).

2) a) A. H. Ford-Moore (*J. Chem. Soc.*, **1949**, 2126) has reported that iodosobenzene is a reagent for the oxidation of sulfides to sulfoxides without further oxidation to sulfones. b) For the method of preparation, see H. J. Lucas, E. R. Kennedy and M. W. Formo, "Organic Syntheses," Coll. Vol. III, p. 483 (1955).

TABLE 1. OXIDATION PRODUCTS OF DIHYDROTHIOPHENES WITH IODOBENZENE



Starting materials	Substituents			Products	Yields (%)
	X	Y	R		
Ia <sub>1</sub>	CO <sub>2</sub> H	CO <sub>2</sub> H	H	IIIa <sub>1</sub>	89
Ia <sub>2</sub>	CO <sub>2</sub> H	CO <sub>2</sub> H	CH <sub>3</sub>	IIIa <sub>2</sub>	80
Ib <sub>1</sub>	CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	CN	H	IIIb <sub>1</sub>	81
Ib <sub>2</sub>	CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	CN	CH <sub>3</sub>	IIIb <sub>2</sub>	81
Id <sub>1</sub>	CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	NHCONH <sub>2</sub>	H	IIIId <sub>1</sub>	61
Id <sub>2</sub>	CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	NHCONH <sub>2</sub>	CH <sub>3</sub>	IIIId <sub>2</sub>	53
Ie <sub>1</sub>	CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	NHCO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	H	IIIe <sub>1</sub>	72
Ie <sub>2</sub>	CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	NHCO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub>	IIIe <sub>2</sub>	73
If <sub>1</sub>	CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	OCH <sub>3</sub>	H	IIIIf <sub>1</sub>	54
IIa <sub>1</sub>	CO <sub>2</sub> H	CO <sub>2</sub> H	H	IIIa <sub>1</sub>	94
IIa <sub>2</sub>	CO <sub>2</sub> H	CO <sub>2</sub> H	CH <sub>3</sub>	IIIa <sub>2</sub>	76

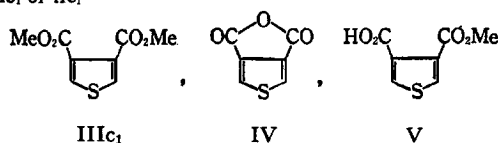
TABLE 2. PHYSICAL PROPERTIES AND ANALYTICAL DATA FOR THE THIOPHENES III

Com- pound	Mp (Bp, °C/mmHg)*1	Recryst. Solvent	Formula	Analysis			
				C	H	N	
IIIId <sub>1</sub>	171—172	Ethyl acetate	C <sub>8</sub> H <sub>10</sub> O <sub>3</sub> N <sub>2</sub> S	Found	44.95	4.67	12.76
				Calcd	44.86	4.71	13.08
IIIId <sub>2</sub>	185—186	Ethyl acetate	C <sub>9</sub> H <sub>12</sub> O <sub>3</sub> N <sub>2</sub> S	Found	47.32	5.55	12.01
				Calcd	47.37	5.30	12.28
IIIe <sub>1</sub>	34—35 (114—115/0.1)	<i>n</i> -Hexane	C <sub>10</sub> H <sub>13</sub> O <sub>4</sub> NS	Found	49.61	5.34	5.82
				Calcd	49.38	5.39	5.76
IIIe <sub>2</sub>	78—79	Methanol-water	C <sub>11</sub> H <sub>15</sub> O <sub>4</sub> NS	Found	51.21	5.78	5.37
				Calcd	51.36	5.88	5.45
IIIIf <sub>1</sub>	(73—75/0.2)		C <sub>8</sub> H <sub>10</sub> O <sub>3</sub> S	Found	51.80	5.37	
				Calcd	51.61	5.41	
IV*2	141—143	Benzene	C <sub>6</sub> H <sub>2</sub> O <sub>3</sub> S	Found	46.53	1.60	
				Calcd	46.77	1.31	
V	108—110	Benzene	C <sub>7</sub> H <sub>6</sub> O <sub>4</sub> S	Found	44.96	3.30	
				Calcd	45.17	3.25	

\*1 All melting and boiling points are uncorrected.

\*2 Mp 145—146.<sup>5)</sup>

The other interesting fact is that the reaction of 3,4-dimethoxycarbonyl-2,5- and 4,5-dihydrothiophene (Ic<sub>1</sub> and IIc<sub>1</sub>) with iodosobenzene afforded thiophene-3,4-dicarboxylic acid anhydride (IV) and 3-carboxy-4-methoxycarbonylthiophene (V) as by-products in addition to the main product, 3,4-dicarbomethoxythiophene (IIIc<sub>1</sub>). When Ic<sub>1</sub> was treated in dry toluene with iodosobenzene



using a 1 : 1 ratio, two products, IIIc<sub>1</sub> and V, were isolated, in 81 and 14% yields respectively. The similar treatment of IIc<sub>1</sub> gave IIIc<sub>1</sub> (73%) and V (11%). When a 1 : 2 ratio of Ic<sub>1</sub> or IIc<sub>1</sub> to iodosobenzene was used in dry dioxane; a mixture of IIIc<sub>1</sub> and IV was obtained, along with a trace of V. The approximate ratio<sup>3)</sup> of the mixture of IIIc<sub>1</sub> and IV was in a range from 8 : 2 to 9 : 1. Neither IV nor V was obtained in

3) The approximate molar ratio of the two derivatives in the mixture was estimated by comparing the infrared spectra of the reaction mixture with those of a mixture of the authentic samples, IIIc<sub>1</sub> and IV, the relative concentrations of IIIc<sub>1</sub> and IV being varied correspondingly.

the reaction of IIIc<sub>1</sub> with iodosobenzene.

All the starting materials, 3,4-disubstituted 2,5- or 4,5-dihydrothiophenes, I or II, and the authentic samples, IIIa<sub>1</sub>, IIIa<sub>2</sub>, IIIb<sub>1</sub>, IIIb<sub>2</sub> and IIIc<sub>1</sub>, were prepared according to the methods described in the previous paper.<sup>1)</sup>

### Experimental

**A General Procedure for the Oxidation of I and II by Iodosobenzene.** A mixture of the 3,4-disubstituted dihydrothiophene, I or II (10 mmol), and iodosobenzene (11 mmol) in dry dioxane (30 ml) was refluxed for 12 hr in a stream of nitrogen gas. After the solvent and iodobenzene had then been removed *in vacuo*, the residue was distilled under reduced pressure or recrystallized from an appropriate solvent to give the corresponding thiophene, III, whose properties were identical in every respect with those of the authentic sample.

**Reaction of 3,4-Dimethoxycarbonyl-2,5- and 4,5-dihydrothiophene, Ic<sub>1</sub> and IIc<sub>1</sub>.** *In Toluene.* A solution of 1.01 g (5 mmol) of IIc<sub>1</sub> and 1.21 g (5.5 mmol) of iodosobenzene in 20 ml of dry toluene was gently refluxed for 6 hr in a stream of nitrogen gas. After the solvent and iodobenzene had then been carefully removed *in vacuo*, the residue was distilled to give 0.81 g (81%) of IIIc<sub>1</sub>, bp 125–127°C/3 mmHg. After the distillation of the IIIc<sub>1</sub>, the residue was sublimed under a pressure of 0.2 mmHg at the bath temperature of 120°C to give 0.31 g (14%) of V, mp 105–109°C.

In a similar manner, 0.73 g (73%) of IIIc<sub>1</sub> and 0.10 g (11%) of V were obtained from 1.01 g of Ic<sub>1</sub> and 1.21 g of iodosobenzene.

*In Dioxane.* A solution of 3.06 g (15 mmol) of IIc<sub>1</sub> and 6.6 g (30 mmol) of iodosobenzene in dry dioxane (60 ml) was refluxed for 12 hr in a nitrogen stream. After the evaporation of the solvent and iodobenzene, the residue was distilled at 80–100°C/0.2 mmHg to give a mixture (2.22 g) of IIIc<sub>1</sub> and IV. A trace of V was obtained by the sublimation of the residue remaining after the distillation of the above mixture.

In a similar manner, a mixture (2.0 g) of IIIc<sub>1</sub> and IV was obtained, along with a trace of V, from 3.02 g of Ic<sub>1</sub> and 6.6 g of iodosobenzene.

**Preparation of the Authentic Samples of the Oxidation Products, IIIId<sub>1</sub>, IIIId<sub>2</sub>, IIIe<sub>1</sub>, IIIe<sub>2</sub> and IIIf<sub>1</sub>.** The following procedure is representative of those used for the preparation of 3-ethoxycarbonyl-4-ureidothiophene (IIIId<sub>1</sub>) and 2-methyl-3-ethoxycarbonyl-4-ureidothiophene (IIIId<sub>2</sub>). A mixture of 3-ethoxycarbonyl-4-ureido-2,5-dihydrothiophene (Id<sub>1</sub>, 10 mmol) and chloranil (11 mmol) was refluxed for 12 hr in dry toluene (20 ml). The reaction mixture was then cooled, washed with a dilute sodium hydroxide solution and with water, and then evaporated to dryness *in vacuo*. Several recrystallizations from ethyl acetate gave the pure product. The yields of IIIId<sub>1</sub> and IIIId<sub>2</sub> were 40 and 35%, respectively.

The following procedure is representative of those used for the preparation of 3-ethoxycarbonyl-4-ethoxycarbonylaminothiophene (IIIe<sub>1</sub>), 2-methyl-3-ethoxycarbonyl-4-ethoxycarbonylaminothiophene (IIIe<sub>2</sub>), and 3-ethoxycarbonyl-4-methoxythiophene (IIIf<sub>1</sub>). A mixture of 3-ethoxycarbonyl-4-ethoxycarbonylamino-2,5-dihydrothiophene (Ie<sub>1</sub>, 10 mmol) and chloranil (11 mmol) in dry toluene (20 ml) was refluxed for 6 hr. After the evaporation of the solvent *in vacuo*, the residue was diluted with chloroform (5 ml). The chloroform solution was chromatographed on alumina (20 g) using a mixture of chloroform and petroleum ether<sup>4)</sup> (5 : 1) as an eluent. After the evaporation of the solvent, the residue was distilled *in vacuo* to give the product. The yields of IIIe<sub>1</sub>, IIIe<sub>2</sub>, and IIIf<sub>1</sub> were 80, 65 and 40% respectively.

**Thiophene-3,4-dicarboxylic Acid Anhydride IV.** The anhydride IV was prepared in a 67% yield by refluxing thiophene-3,4-dicarboxylic acid (IIIa<sub>1</sub>)<sup>1)</sup> with acetyl chloride for 4 hr according to the method of Sice.<sup>5)</sup>

**3-Carboxy-4-methoxycarbonylthiophene V.** A solution of 1.0 g of IV in 10 ml of absolute methanol was refluxed for 1 hr. After the solvent had then been removed *in vacuo*, the residue was recrystallized to give 0.84 g (70%) of V.

The physical properties and analytical data for IIIId<sub>1</sub>, IIIId<sub>2</sub>, IIIe<sub>1</sub>, IIIe<sub>2</sub>, IIIf<sub>1</sub>, IV and V are summarized in Table 2.

4) Bp 40–60°C.

5) J. Sice, *J. Org. Chem.*, **19**, 70 (1954).