

Oxidation of Dihydrothiophenes with Iodosobenzene*¹

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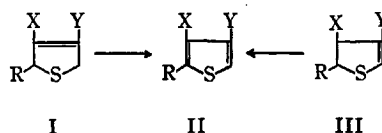
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In a previous paper,¹⁾ we have reported that the oxidation of 3,4-disubstituted 2,5- and 4,5-dihydrothiophenes with 30% hydrogen peroxide in acetic acid or with perbenzoic acid in chloroform gives the following results: 1) when both of the two substituents 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.



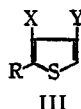
A probable mechanism for the formation of the thiophene, III, is as follows: the 3,4-disubstituted dihydrothiophenes, I or II, are oxidized by iodosobenzene²⁾ to the corresponding sulfoxide derivatives, which are then dehydrated to the thiophene derivatives, III.

*¹ 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 IODOSOBENZENE



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

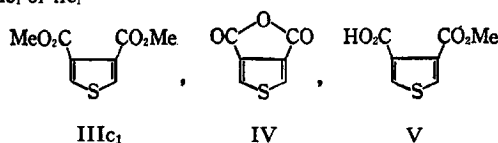
TABLE 2. PHYSICAL PROPERTIES AND ANALYTICAL DATA FOR THE THIOPHENES III

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

*1 All melting and boiling points are uncorrected.

*2 Mp 145—146.⁵⁾

The other interesting fact is that the reaction of 3,4-dimethoxycarbonyl-2,5- and 4,5-dihydrothiophene (Ic₁ and IIc₁) 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 (IIIc₁). When Ic₁ was treated in dry toluene with iodosobenzene



using a 1 : 1 ratio, two products, IIIc₁ and V, were isolated, in 81 and 14% yields respectively. The similar treatment of IIc₁ gave IIIc₁ (73%) and V (11%). When a 1 : 2 ratio of Ic₁ or IIc₁ to iodosobenzene was used in dry dioxane; a mixture of IIIc₁ and IV was obtained, along with a trace of V. The approximate ratio³⁾ of the mixture of IIIc₁ 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, IIIc₁ and IV, the relative concentrations of IIIc₁ and IV being varied correspondingly.

the reaction of IIIc_1 with iodosobenzene.

All the starting materials, 3,4-disubstituted 2,5- or 4,5-dihydrothiophenes, I or II, and the authentic samples, IIIa_1 , IIIa_2 , IIIb_1 , IIIb_2 and IIIc_1 , were prepared according to the methods described in the previous paper.¹³

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 iodosobenzene 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_1 and Ic_2 . In Toluene. A solution of 1.01 g (5 mmol) of Ic_1 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 iodosobenzene had then been carefully removed *in vacuo*, the residue was distilled to give 0.81 g (81%) of IIIc_1 , bp 125–127°C/3 mmHg. After the distillation of the IIIc_1 , 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_1 and 0.10 g (11%) of V were obtained from 1.01 g of Ic_1 and 1.21 g of iodosobenzene.

In Dioxane. A solution of 3.06 g (15 mmol) of Ic_1 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 iodosobenzene, the residue was distilled at 80–100°C/0.2 mmHg to give a mixture (2.22 g) of IIIc_1 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_1 and IV was obtained, along with a trace of V, from 3.02 g of Ic_1 and 6.6 g of iodosobenzene.

Preparation of the Authentic Samples of the Oxidation Products, IIIId_1 , IIIId_2 , IIIe_1 , IIIe_2 and IIIf_1 . The following procedure is representative of those used for the preparation of 3-ethoxycarbonyl-4-ureidothiophene (IIIId_1) and 2-methyl-3-ethoxycarbonyl-4-ureidothiophene (IIIId_2). A mixture of 3-ethoxycarbonyl-4-ureido-2,5-dihydrothiophene (Id_1 , 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_1 and IIIId_2 were 40 and 35%, respectively.

The following procedure is representative of those used for the preparation of 3-ethoxycarbonyl-4-ethoxycarbonylaminothiophene (IIIe_1), 2-methyl-3-ethoxycarbonyl-4-ethoxycarbonylaminothiophene (IIIe_2), and 3-ethoxycarbonyl-4-methoxythiophene (IIIf_1). A mixture of 3-ethoxycarbonyl-4-ethoxycarbonylamino-2,5-dihydrothiophene (Ie_1 , 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 ether⁴ (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_1 , IIIe_2 , and IIIf_1 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_1)¹³ with acetyl chloride for 4 hr according to the method of Sice.¹⁵

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_1 , IIIId_2 , IIIe_1 , IIIe_2 , IIIf_1 , IV and V are summarized in Table 2.

4) Bp 40–60°C.

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