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Preparation and Oxidation of Dihydrothiophenes*[1]

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The preparation and oxidation of 3,4-disubstituted 2,5- and 4,5-dihydrothiophenes are described. The oxidation of these dihydrothiophenes with 30% hydrogen peroxide in acetic acid gave the corresponding thiophene derivatives. However, the oxidation of the same compounds with perbenzoic acid in chloroform gave the corresponding sulfone derivatives. The mechanisms for these oxidation are discussed.

During the course of our studies of the chemistry of dihydrothiophenes, we happened to find that 2,5-dihydrothiophene-3,4-dicarboxylic acid (Ia_1, R=H)[1] is oxidized to thiophene-3,4-dicarboxylic acid (IIa_1, R=H)[1] by 30% hydrogen peroxide in acetic acid. This fact is not consistent with the previously-reported findings that the oxidation of 2,5-dihydrothiophene[2] and 2-methyl-4,5-dihydrothiophene-3-carboxylic acid[3] with the same reagent gives the corresponding sulfones. These observations prompted us to study the oxidation of

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1) Suffix 1 represents R=H and suffix 2 represents $R=CH_3$.

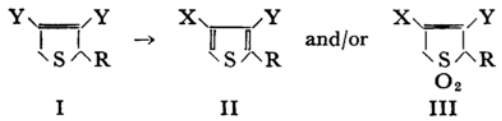
2) S. F. Birch and D. T. McAllan, *J. Chem. Soc.*, **1951**, 2556.

3) F. Korte and K. Löhmer, *Chem. Ber.*, **90**, 1290 (1957).

several 3,4-disubstituted 2,5- or 4,5-dihydrothiophenes in detail.

Results and Discussion

Oxidation of 3,4-Disubstituted 2,5-Dihydrothiophenes. When 3,4-disubstituted 2,5-dihydrothiophenes (I) were treated with 30% hydrogen peroxide in acetic acid, the corresponding thiophene (II) and/or sulfone derivatives (III) were obtained, depending on the nature of the substituents. The results are summarized in Chart 1 and in Table 1.



I II III

These results suggest that: 1) when both of the two substituents are electron-withdrawing groups, the oxidation tends to produce the corresponding thiophene derivatives, II; 2) when one substituent is an electron-releasing group and the other is an electron-withdrawing group, the oxidation tends to produce the sulfone derivatives, III; and 3) 3,4-dimethoxycarbonyl-2,5-dihydrothiophene (Ic_1, R=H) and its 2-methyl derivative (Ic_2, R=CH_3) are exceptional. Upon oxidation the former produced a mixture of $IIIc_1$ and IIc_1 in an approximate molar ratio of 7 : 3, and the latter, a mixture of $IIIc_2$ and IIc_2 in an approximate molar ratio of 8 : 2.

The oxidation of 3,4-disubstituted 2,5-dihydrothiophenes, I, was also carried out with perbenzoic acid in chloroform. The products obtained in this oxidation are summarized in Table 1. The results show that the oxidation of 3,4-disubstituted 2,5-dihydrothiophenes with perbenzoic acid in chloroform produces the corresponding sulfone derivatives irrespective of the nature of the substituents, except that 2,5-dihydrothiophene-3,4-dicarboxylic acid, Ia_1, forms the corresponding sulfoxide (V). The exceptional formation of this compound may be due to its insolubility in chloroform. In fact, this compound precipitated out during the reaction.

The structure of the products obtained by the above oxidations was confirmed as follows. The thiophene derivatives were identified by comparison with the respective authentic samples which had been obtained by the oxidation of the corresponding dihydrothiophenes with chloranil. The sulfone derivatives were identified from the results of elemental analyses and from the presence of the absorption bands corresponding to the sulfone group in

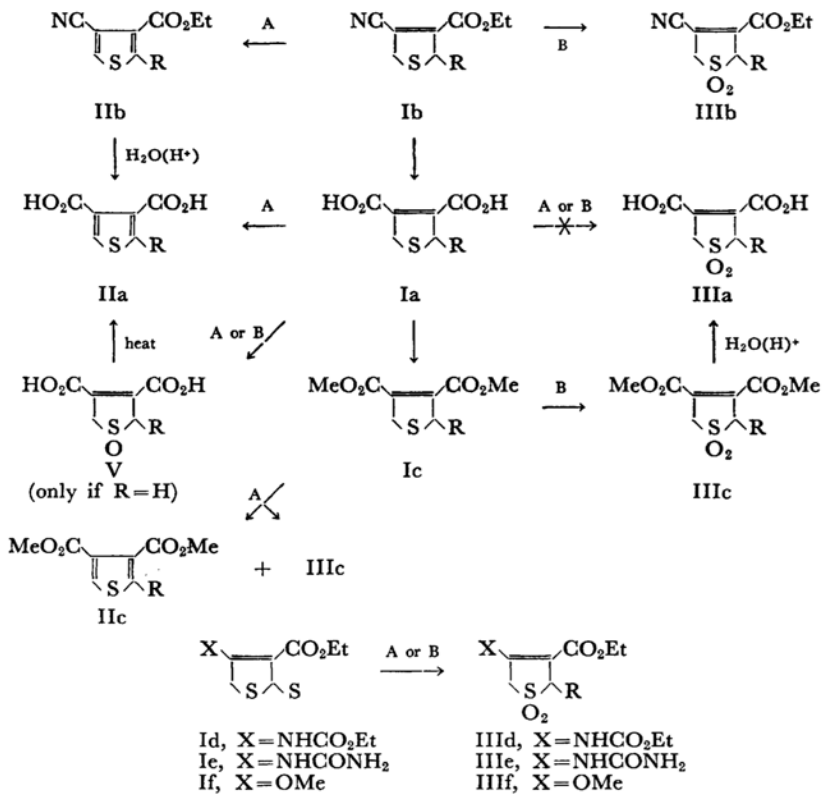
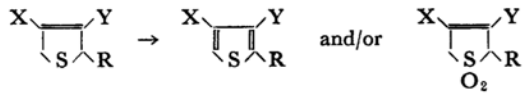


Chart 1

TABLE 1. OXIDATION OF 2,5-DIHYDROTHIOPHENES



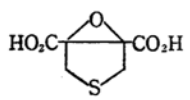
I II III

Starting material	Substituents X	Y	R	Procedure*	Product	Yield %
Ia_1	COOH	COOH	H	A	IIa_1	68
Ia_1	COOH	COOH	H	A	V	83
Ia_2	COOH	COOH	Me	A	IIa_2	90
Ib_1	CN	CO_2Et	H	A	IIb_1	92
Ib_1	CN	CO_2Et	H	A	IIb_1**	88
Ib_2	CN	CO_2Et	Me	A	IIb_2 $IIIb_2$	92 trace
Ic_1	CO_2Me	CO_2Me	H	A	IIc_1 $IIIc_1$	23 53
Ic_2	CO_2Me	CO_2Me	Me	A	IIc_2 $IIIc_2$	13 53
Id_1	$NHCO_2Et$	CO_2Et	H	A	$IIId_1$	69
Ie_1	$NHCONH_2$	CO_2Et	H	A	$IIIe_1$	67
Ie_2	$NHCONH_2$	CO_2Et	Me	A	$IIIe_2$	78
If_1	OMe	CO_2Et	H	A	$IIIf_1$	52
Ia_1	COOH	COOH	H	B	V	84
Ib_1	CN	CO_2Et	H	B	$IIIb_1$	84
Ib_2	CN	CO_2Et	Me	B	$IIIb_2$ IIb_2	77 trace
Ic_1	CO_2Me	CO_2Me	H	B	$IIIc_1$	95
Ic_2	CO_2Me	CO_2Me	Me	B	$IIIc_2$	75
Id_1	$NHCO_2Et$	CO_2Et	H	B	$IIId_1$	86
If_1	OMe	CO_2Et	H	B	$IIIf_1$	82

* A, the oxidation with 30% hydrogen peroxide - acetic acid; B, the oxidation with perbenzoic acid - chloroform. See Experimental for the detailed procedure.

** The reaction was conducted by standing the reaction mixture for 90 min at 100°C.

their infrared spectra. The structure of 3,4-dicarboxy-2,5-dihydrothiophene-1-oxide, V, was confirmed on the bases of the following observations: a) the elemental analysis, $C_6H_6O_5S$ (MW 189), shows that this compound contains one more oxygen atom than Ia_1, b) the infrared spectrum has no characteristic absorption bands in the sulfone and thiophene regions, and c) this compound produces the pyrazoline derivative (VI) when V is treated with diazomethane. The first two pieces of evidence, a) and b), suggest that either the sulfoxide V or the epoxide (IV) is a possible structure. However, the third piece of evidence, c), indicates that the most probable structure is the sulfoxide V. It is of interest to note here that when the sulfoxide V was heated for several minutes in a protic solvent such as aqueous ethanol or glacial acetic acid, it was converted into thiophene-3,4-dicarboxylic acid, IIa_1.[4]



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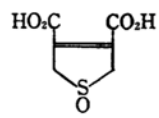
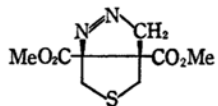
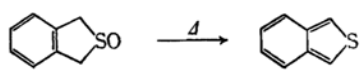


V



VI

A similar dehydration reaction has recently been found by Cava and Pollack[5] in 1,3-dihydrobenzo[*c*]-thiophene (VII); the pyrolysis of VII on neutral alumina afforded isothianaphthene (VIII) in a 94% yield.



VII VIII

4) This compound was kindly provided by Professor S. Oae.

5) M. P. Cava and N. M. Pollack, *J. Am. Chem. Soc.*, **88**, 4112 (1966).

These facts suggest that the transformation of dihydrothiophenes to the corresponding thiophene derivatives proceeds through the corresponding sulfoxide derivatives, even though attempts to isolate sulfoxides of 3,4-disubstituted dihydrothiophenes other than Ia_1 have been unsuccessful.

A probable mechanism for the transformation of the 2,5-dihydrothiophene Ia_1 to the thiophene IIa_1 *via* the sulfoxide V is illustrated in Chart 2. The

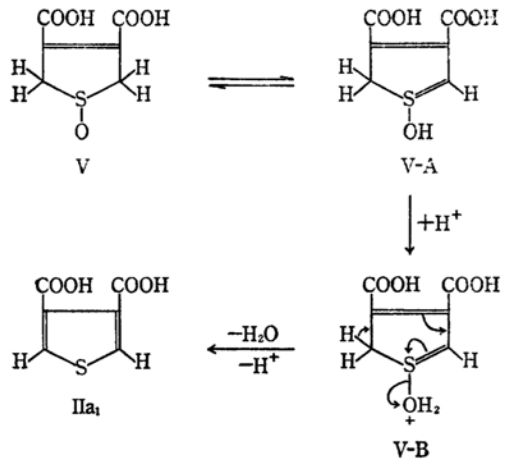
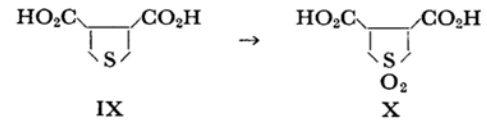


Chart 2

first step of this transformation is the oxidation of the sulfide to the sulfoxide. Since the hydrogen atom of the methylene group adjacent to the sulfoxide group is acidic, and since its acidity is also enhanced by two carboxyl groups, the electron-withdrawing groups at the 3- and 4-positions, the sulfoxide V may take a tautomeric form (V-A). The V-A tautomer would be dehydrated under acidic conditions to produce the thiophene derivative IIa_1 *via* V-B. A similar mechanism would hold for the other 2,5-dihydrothiophene which has electron-withdrawing groups at the 3- and 4- positions. In fact, in these cases the thiophene derivatives were produced. However, when one substituent is an electron-releasing group and the other is an electron-withdrawing group in 3,4-disubstituted 2,5-dihydrothiophenes, the hydrogen atom of the methylene group placed between the sulfoxide and the carbon atom bearing the electron-withdrawing group will not be acidic enough to be removed as a proton. In these cases a tautomeric equilibrium of the V⇌V-A type can not exist and the mechanism shown in Chart 2 can not be applied. As a result, the subsequent oxidation of the sulfoxide to the sulfone will take place. The proposed mechanism was further supported by the observation that tetrahydrothiophene-3,4-dicarboxylic acid (**IX**) afforded the corresponding sulfone (X) exclusively when **IX** was treated with 30% hydrogen peroxide in acetic acid.



In this case, the hydrogen atoms of the methylene group adjacent to the sulfur atom are not acidic enough to be removed as a proton. Consequently, the compound IX can not undergo the subsequent reaction indicated in Chart 2, and the sulfone derivative X is produced.

Oxidation of 3,4-disubstituted 4,5-Dihydrothiophenes. The oxidation of 3,4-disubstituted 4,5-dihydrothiophenes (XI) with 30% hydrogen peroxide or perbenzoic acid was carried out in a manner similar to that of 3,4-disubstituted 2,5-dihydrothiophenes I. The results are summarized in Table 2.

As may be seen in Table 2, 4,5-dihydrothiophene-3,4-dicarboxylic acid (XIa_1, R=H) and its 5-methyl derivative (XIa_2, $R=CH_3$) were, with 30% hydrogen peroxide in acetic acid, oxidized to the corresponding thiophene derivatives, IIa_1 and IIa_2. However,

Table 2. Oxidation of 4,5-dihydrothiophenes

Starting material	Substituents X	Y	R	Procedure*	Product	Yield %
XIa_1	COOH	COOH	H	A	IIa_1	97
XIa_2	COOH	COOH	Me	A	IIa_2	83
XIb_1	CO_2Me	CO_2Me	H	A	IIc_1	10
					$XIIb_1$	60
XIb_1	CO_2Me	CO_2Me	H	B	$XIIb_1$	97

* A, the oxidation with 30% hydrogen peroxide-acetic acid; B, the oxidation with perbenzoic acid-chloroform. See Experimental for the detailed procedure.

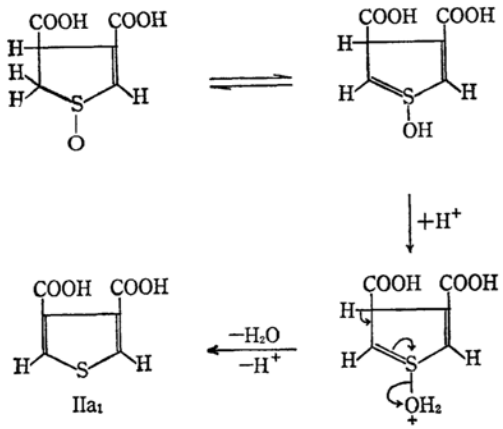
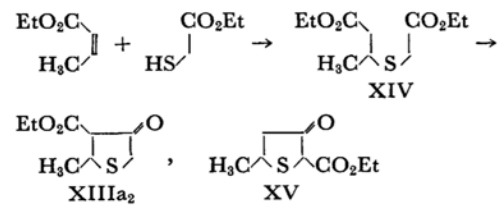


Chart 3

with the same reagent 2-methyl-4,5-dihydrothiophene-3-carboxylic acid[3] was not oxidized to the thiophene derivative, but to the corresponding sulfone derivative, in a 90% yield. These facts can probably be explained in terms of the mechanism outlined in Chart 3. Since the methylene group in XIa_1 is placed between an electron-withdrawing substituent and the sulfoxide group, one of the hydrogen atoms of the methylene group will be acidic enough to be removed as a proton*2 and the thiophene derivatives can be formed; otherwise, the dihydrothiophenes would be further oxidized to the corresponding sulfone derivatives.

The dissociation of the hydrogen atom of the methylene or methine group to a proton in the 3,4-disubstituted 2,5- or 4,5-dihydrothiophene would be much more favored in a protic solvent than in an aprotic solvent. This assumption would explain why the thiophene derivatives were produced in a protic solvent such as acetic acid, while sulfone derivatives were produced in an aprotic solvent such as chloroform. However, no explanation can be given of the fact that the oxidation of 3,4-dimethoxycarbonyl-2,5-dihydrothiophene, Ic_1, and its 2-methyl derivative, Ic_2, and 3,4-dimethoxycarbonyl-4,5-dihydrothiophene (XIb_1, R=H) with 30% hydrogen peroxide in a protic solvent such as acetic acid gave the corresponding sulfone derivative as the main product.

Preparation of Dihydrothiophenes. All of the dihydrothiophenes used in this paper, except for Ia_1, Ib_1, and XIa_1, were new compounds; they were synthesized by the following routes (see Chart 4). The starting compound ($XIIIa_2$, R=CH_3) was obtained by refluxing a solution of ethyl β-mercaptopropinate and ethyl crotonate in benzene in the presence of sodium ethoxide, ethyl β-ethoxycarbonylmethylmercaptobutyrate (XIV) was supposed to be an intermediate in this cyclization reaction. However, Larsson and Dahlström[6] have reported that, in contrast to our product, $XIIIa_2$, 2-ethoxycarbonyl-5-methyl-3-ketotetrahydrothiophene (XV) is produced by warming XIV in toluene in the presence of sodium ethoxide on a water bath. Although the reason for this inconsistency is not clear at the present time, it might be due to the differences in the reaction conditions employed.



The structures of the compounds $XIIIa_2$, Ib_2, Ia_2, Ic_2 and XIa_2 obtained in our experiments were confirmed by a comparison of their spectroscopic

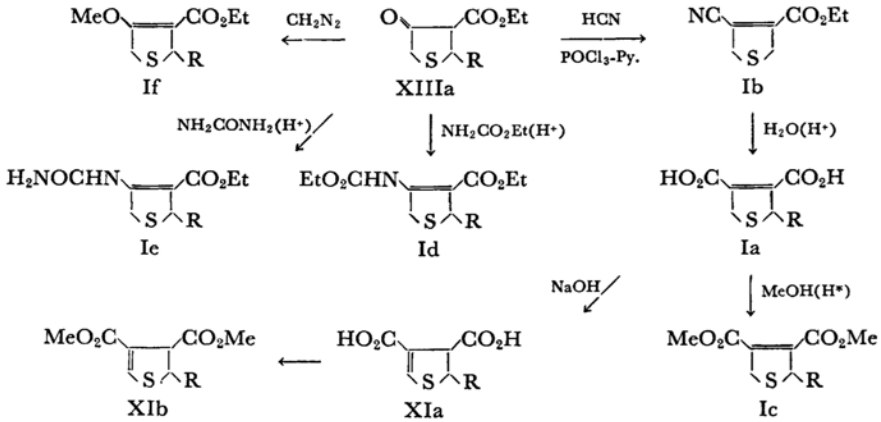


Chart 4

*2 In the case of the compound XIa_2, the hydrogen atom of the methine group to which the methyl group is attached will still be acidic enough to be removed as a proton. Thus, compound XIa_2 gave the IIa_2 thiophene upon oxidation.

6) E. Larsson and H. Dahlström, *Svensk. Kem. Tid.*, **37**, 248 (1945); *Chem. Abstr.*, **40**, 2444 (1946).

TABLE 3. SPECTROSCOPIC DATA FOR 2-METHYL-3-ETHOXYCARBONYL-4-KETOTETRAHYDROTHIOPHENE AND ITS RELATED COMPOUNDS

		$XIIIa_1$***	Ib_1	Ia_1	Ic_1	XIa_1
UV* (mμ)	λ_{max}	249	228	223	212	293
	ε	2700	7600	10000	—	9900
IR** (cm^{-1})	$\nu_{C=C}$	1625	1635	1640	1655	1570
		$XIIIa_2$***	Ib_2	Ia_2	Ic_2	XIa_2
UV* (mμ)	λ_{max}	251	225	224	212	291
	ε	1900	7100	9000	8000	9200
IR** (cm^{-1})	$\nu_{C=C}$	1620	1630	1655	1660	1570

* Measured in 99% EtOH.

** Measured in CCl_4 for $XIIIa_1$, $XIIIa_2$, Ib_1, Ib_2, Ic_1, and Ic_2: measured in a KBr disk for Ia_1, Ia_2, XIa_1, and XIa_2.

*** The infrared spectra of $XIIIa_1$, and $XIIIa_2$ showed the following absorptions: $XIIIa_1$; 1760 (ester carbonyl), 1735 (ketone), 1670 (ester carbonyl after chelation to the enolic hydroxyl group), and 1625 cm^{-1} (C=C linkage); $XIIIa_2$; 1750 (ester carbonyl), 1730 (ketone), 1660 (ester carbonyl after chelation to the enolic hydroxyl group), and 1620 cm^{-1} (C=C linkage).

TABLE 4. THE COMPOUNDS OBTAINED BY THE OXIDATION OF 2,5- AND 4,5-DIHYDROTHIOPHENE DERIVATIVES

Compound	Mp (Bp, °C/mmHg)	Recryst. solvent	Formula	Analytical data: Calcd % C	H	N	Found % C	H	N
IIa_1	225—227[a]	Water							
IIa_2	204—205	10% Ethanol	$C_7H_6O_4S$	45.17	3.25		45.38	3.54	
IIb_1	96— 97	Cyclohexane	$C_8H_7O_2NS$	53.04	3.90	7.73	53.18	4.03	7.67
IIb_2	82— 83	Petroleum ether-chloroform	$C_9H_9O_2NS$	55.38	4.65	7.18	55.16	4.57	7.22
IIc_1	59— 60[b]	Petroleum ether							
IIc_2	(123—124)		$C_9H_{10}O_4S$	50.47	4.71		50.70	4.78	
$IIIb_1$	111—113	Petroleum ether-chloroform	$C_8H_9O_4NS$	44.66	4.22	6.51	44.67	4.52	6.67
$IIIc_1$	104—105	Petroleum ether-chloroform	$C_8H_{10}O_6S$	41.03	4.30		40.91	4.18	
$IIIc_2$	70— 71.5	Petroleum ether-ether	$C_9H_{12}O_6S$	43.55	4.87		43.32	4.98	
$IIId_1$	90— 91	Chloroform-ligroin	$C_{10}H_{15}O_6NS$	43.32	5.45	5.05	43.56	5.20	4.81
$IIIe_1$	186—187	95% Ethanol	$C_8H_{12}O_5N_2S$	38.71	4.87	11.29	38.58	4.77	11.21
$IIIe_2$	189—190	95% Ethanol	$C_9H_{14}O_5N_2S$	41.22	5.38	10.68	41.50	5.17	10.38
$IIIf_1$	72— 74	Petroleum ether-ether	$C_8H_{12}O_5S$	43.64	5.49		43.85	5.42	
V	216—220		$C_6H_6O_5S$	37.90	3.18		37.79	3.29	
$XIIa_1$	125—126	Ether	$C_8H_{10}O_6S$	41.03	4.30		40.91	4.18	

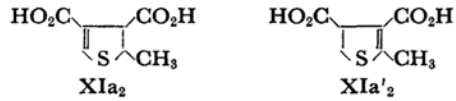
a) Lit. mp 230—231°C, J. Sice, *J. Org. Chem.*, **19**, 70 (1954).

b) Lit. mp 60—61°C, E. C. Kornfeld and R. G. Jones, *ibid.*, **19**, 1671 (1954).

properties with those of the related compounds. The spectroscopic data are summarized in Table 3.

First, note that the compounds Ib_1, Ia_1, Ic_1, and XIa_1 have been derived from $XIIIa_1$, and that the structures of all of these compounds have been confirmed. (Although Ic_1 was first obtained in our experiment, the structure of this compound should be correct since Ic_1 was prepared simply by the esterification of Ia_1.) In addition, note also that the compounds Ib_2, Ia_2, Ic_2, and XIa_2 were experimentally derived from $XIIIa_2$ by the same methods as those employed for the derivation of Ib_1, Ia_1 Ic_1, and XIa_1 from $XIIIa_1$. This means that Ib_2, Ia_2, Ic_2, and XIa_2 have structures corresponding to those of Ib_1, Ia_1, Ic_1, and XIa_1 respectively. An inspection of the spectroscopic data in Table 3 indicates that the compound XIa_1, in which the double bond in the ring is in conjugation with the sulfur atom, shows the absorption band at the longer-wavelength side both in the ultraviolet and the infrared ($\nu_{C=C}$) spectra as compared with those for the compounds Ib_1, Ia_1 and Ic_1, in which no such

a conjugation is involved. The similarity of the spectroscopic data of compounds $XIIIa_2$, Ib_2, Ia_2 Ic_2, and XIa_2 to those of the corresponding compounds, $XIIIa_1$, Ib_1, Ia_1, Ic_1 and XIa_1, strongly suggests that the structures for the compounds $XIIIa_2$, Ib_2, Ia_2, Ic_2, and XIa_2 shown in Chart 4 are all correct. For the compound XIa_2, the above arguments lead to the structure of either XIa_2 or XIa'_2. The NMR spectrum of the compound showed, however, that the XIa_2 structure is also correct (see Experimental Section).



XIa_2 XIa'_2

The preparation of the compounds which have an electron-releasing and an electron-withdrawing group in 3,4-disubstituted 2,5-dihydrothiophenes was carried out as follows. 3-Ethoxycarbonyl-4-ethoxycarbonylamino-2,5-dihydrothiophene (Id_1, R=H) and its 2-methyl derivative (Id_2, R=CH_3) were prepared by the condensation of $XIIIa_1$ or $XIIIa_2$ with urethan in the presence of *p*-toluenesulfonic acid. The position of the double bond in Id_1 was confirmed from the fact that the NMR spectrum of Id_1 showed two protons at C-2 and two protons at C-5. 3-Ethoxycarbonyl-4-ureido-2,5-dihydrothiophene (Ie_1, R=H) and its 2-methyl derivative (Ie_2, R=CH_3) were also synthesized by the condensation of $XIIIa_1$ or $XIIIa_2$ with urea. 3-Methoxy-4-ethoxycarbonyl-2,5-dihydrothiophene (If_1, R=H) was obtained by treating $XIIIa_1$ with an excess ethereal diazomethane by a method similar to that of Blake and his co-workers.[7]

Experimental

All the melting points are uncorrected. The infrared spectra were recorded with a Hitachi EPI-S_2 infrared spectrophotometer. The ultraviolet spectra were obtained with a Hitachi EPS-20 recording spectrophotometer. The NMR spectra were obtained with a Nihondenshi JNM-3H-60 high-resolution nmr spectrometer in a 10% carbon tetrachloride solution of the samples, using a TMS reference at 22°C.

Materials. 3-Cyano-4-ethoxycarbonyl-2,5-dihydrothiophene Ib_1, 3,4-dicarboxy-2,5-dihydrothiophene Ia_1, and tetrahydrothiophene-3,4-dicarboxylic acid IX were prepared by the method of Baker and his co-workers from 3-ethoxycarbonyl-4-ketotetrahydrothiophene $XIIIa_1$.[8]

2-Methyl-3-ethoxycarbonyl-4-ketotetrahydrothiophene ($XIIIa_2$, R=CH_3). Eighty-seven grams of ethyl thioglycolate in 250 m*l* of dry benzene was added to dry sodium ethoxide prepared from 23 g of sodium and absolute ethanol. To the reaction mixture there was then added, drop by drop and with shaking, 82 g of ethyl crotonate over a period of 10 min. After being refluxed for 3 hr, the benzene solution was extracted with ice water. The aqueous layer was acidified with acetic acid and then extracted with benzene. The benzene extract was washed successively with water, dilute aqueous sodium bicarbonate, and water. The distillation of the benzene extract gave 5.1 g (41%) of $XIIIa_2$ boiling at 107—108°C/6 mmHg, n_D^{25} 1.497. This compound was used for the preparation of Ib_2 without further purification. The semicarbazone of $XIIIa_2$ was prepared by the usual method. Three recystallizations from aqueous ethanol gave an analytical sample, mp 149—150°C.

Found: C, 43.90; H, 6.01; N, 17.15%. Calcd for $C_9H_{15}N_3O_3S$: C, 44.08; H, 6.17; N, 17.14%.

2-Methyl-3-ethoxycarbonyl-4-cyano-2,5-dihydrothiophene (Ib_2, R=CH_3). This compound was prepared in a 70% yield from $XIIIa_2$ by applying the method of Baker and his co-workers,[8] who prepared Ib_1 from $XIIIa_1$, bp 106—108°C/1 mmHg.

Found: C, 54.74; H, 5.90%. Calcd for $C_9H_{11}NO_2S$: C, 54.82; H, 5.62%.

2-Methyl-2,5-dihydrothiophene-3,4-dicarboxylic Acid (Ia_2, R=CH_3). This compound was obtained in a 67% yield by the acid hydrolysis of Ib_2 according to the method of Baker and his co-workers,[8] mp 145—147°C (from acetone-benzene).

Found: C, 44.95; H, 4.43%. Calcd for $C_7H_8O_4S$: C, 44.70; H, 4.29%.

5-Methyl-4,5-dihydrothiophene-3,4-dicarboxylic Acid (XIa_2, R=CH_3). A solution of 1 g of Ia_2 in 5 m*l* of ethanol was refluxed for 5 hr with 1 g of potassium hydroxide in 5 m*l* of water. The solution was then acidified with dilute hydrochloric acid and extracted three times with ethyl acetate. The extracts were dried over anhydrous sodium sulfate and evaporated to dryness *in vacuo*. The residue (0.4 g, mp 124—132°C) was recrystallized from acetone-benzene-petroleum ether to give 0.2 g (20%) of colorless crystals, mp 161—162°C. The infrared spectrum showed bands at 1570 cm^{-1} (double bond conjugated with a sulfur atom), 1705 cm^{-1} (carboxylic acid), 1660 cm^{-1} (α,β-unsaturated carboxylic acid) and 3050 cm^{-1} (olefinic proton), and the nmr spectrum of the dimethyl ester of XIa_2 showed a characteristic vinyl proton at 2, 6 τ (doublet, J=1.5 cps; a long-range coupling with a proton at C-3).

Found: C, 44.50; H, 4.32%. Calcd for $C_7H_8O_4S$: C, 44.69; H, 4.29%.

2-Methyl-3,4-dimethoxycarbonyl-2,5-dihydrothiophene (Ic_2, R=CH_3). A solution of 3.76 g of Ia_2 in dry ether containing a small amount of absolute methanol was treated with an excess of ethereal diazomethane. After the evaporation of the solvent, the distillation of the residue gave 3.1 g (70%) of a yellow liquid, bp 118—124°C/4 mmHg, n_D^{23} 1.502.

Found: C, 50.20; H, 5.34%. Calcd for $C_9H_{12}O_4S$: C, 50.00; H, 5.60%.

3,4-Dimethoxycarbonyl-2,5-dihydrothiophene (Ic_1, R=H). A mixture of 10.5 g of Ia_1, 1.0 g of *p*-toluenesulfonic acid, 80 m*l* of chloroform, and 60 m*l* of methanol was refluxed for 50 hr in a Soxhlet apparatus containing anhydrous sodium sulfate in a thimble. After the mixture had then been distilled through a Vigreux column at an atmospheric pressure in order to remove the solvent, the distillation of the residue gave 7.7 g (70%) of a colorless liquid, bp 130—131°C/3 mmHg, n_D^{23} 1.516.

Found: C, 47.68; H, 5.01%. Calcd for $C_8H_{10}O_4S$: C, 47.53; H, 4.99%.

7) J. Blacke, C. D. Willson and H. Rapoport, *J. Am. Chem. Soc.*, **86**, 5294 (1964).

8) B. R. Baker, M. V. Querry and A. F. Kadish, *J. Org. Chem.*, **13**, 123 (1948).

3,4-Dimethoxycarbonyl-4,5-dihydrothiophene (XIb$_1$, R=H). 4,5-Dihydrothiophene-3,4-dicarboxylic acid (XIa$_1$, R=H) was prepared by the method of Baker and his co-workers.[9] Recrystallization from acetone-benzene gave XIa$_1$, mp 180—181°C. A solution of 4.5 g of XIa$_1$ in dry ether containing a small amount of absolute methanol was terated with an excess of ethereal diazomethane. After the evaporation of the solvent, the residue was distilled to give 4.1 g (90%) of XIb$_1$, bp 122—124°C/3 mmHg, n_D^{30} 1.525. The infrared spectrum showed bands at 1730 cm^{-1} (ester C=O), 1700 cm^{-1} (α,β-unsaturated ester C=O), and 1575 cm^{-1} (double bond conjugated with a sulfur atom), and the nmr spectrum showed a characteristic vinyl proton at 2.55 τ (doublet, J=1.5 cps; a long-range coupling with a proton at C-3).

Found: C, 47.53; H, 4.99%. Calcd for $C_8H_{10}O_4S$: C, 47.65; H, 5.21%.

2-Methyl-3-ethoxycarbonyl-4-ethoxycarbonylamino-2,5-dihydrothiophene (Id$_2$, R=CH$_3$). A mixture of 11 g of the β-ketoester XIIIa$_2$, 6 g of urethane, 1 g of *p*-toluenesulfonic acid, and 200 m*l* of dry benzene was refluxed for 15 hr in a Soxhlet apparatus containing anhydrous sodium sulfate in a thimble. The mixture, was then washed thoroughly with water to remove the *p*-toluenesulfonic acid and the excess urethane. The evaporation of the solvent gave 14 g (93%) of the product, Id$_2$. This crude product was purified by chromatography using an alumina column and chloroform as an eluent, or by recrystallization from methanol-water, to give an analytical sample, mp 68—69.5°C.

Found: C, 50.72; H, 6.44; N, 5.17%. Calcd for $C_{11}H_{17}O_4NS$: C, 50.96; H, 6.61; N, 5.40%.

3-Ethoxycarbonylamino-4-ethoxycarbonyl-2,5-dihydrothiophene (Id$_1$, R=H). A mixture of 3.5 g of XIIIa$_1$, 1.8 g of urethane, 300 mg of *p*-toluenesulfonic acid, and 70 m*l* of dry benzene was refluxed for 15 hr in a Soxhlet apparatus. The mixture was then worked up in the manner described above to give 4.10 g (83%) of Id$_1$ (mp 70—71.5°C (from methanol-water)). The NMR spectrum of Id$_1$ ($CHCl_3$) showed a triplet at 8.7 τ (6H) (J=7.5 cps), a triplet at 6.3 τ (2H) (J=3 cps), a quartet at 4.85 τ(2H) (J=7.5 cps), a quartet at 5.75 τ(2H) (J=7.5 cps), a triplet at 5.6 τ(2H) (J=3 cps), and a singlet at 4.45 τ(1H).

Found: C, 49.13; H, 5.95; N, 5.53%. Calcd for $C_{10}H_{15}O_6NS$: C, 48.97; H, 6.17; N, 5.71%.

3-Ethoxycarbonyl-4-ureido-2,5-dihydrothiophene (Ie$_1$, R=H). A) A mixture of 5.0 g of finely-ground urea, 13 g of XIIIa$_1$, 1.5 m*l* of absolute ethanol, and three drops of concentrated hydrochloric acid was placed in an evaporating dish covered loosely with a watch glass, and then evacuated continuously by an aspirator in a desiccator containing concentrated sulfuric acid as a drying agent. After about a week, the dried mixure was recrystallized from 95% ethanol to give 12.9 g (80%) of Ie$_1$, mp 198—203°C. Repeated recrystallizations from 99% ethanol gave crystals melting at 201—203°C.

B) A mixture of 3.48 g of XIIIa$_1$, 1.20 g of urea, 40 m*l* of absolute ethanol, 90 m*l* of dry benzene, and 0.3g of *p*-toluenesulfonic acid was refluxed for 48 hr in a Soxhlet apparatus containing anhydrous sodium sulfate in a thimble. The mixture was then evaporated to dryness, and the residue was recrystallized from 95% ethanol to give 3.56 g (82%) of Ie$_1$, mp 201—203°C.

Found: C, 44.52; H, 5.27; N, 12.91%. Calcd for $C_8H_{12}O_3N_2S$: C, 44.44; H, 5.60; N, 12.96%.

2-Methyl-3-ethoxycarbonyl-4-ureido-2,5-dihydrothiophene (Ie$_2$, R=CH$_3$). By treating 4.70 g of XIIIa$_2$ and 1.65 g of urea such as has been described above in the case of Id$_1$ (method A), 3.0 g (78%) of crude Ie$_2$, mp 180—184°C, were obtained. Three recrystallizations from 95% ethanol gave pure Ie$_2$, mp 187—188.5°C.

Found: C, 47.20; H, 6.26; N, 12.18%. Calcd for $C_9H_{14}O_3N_2S$: C, 46.95; H, 6.13; N, 12.17%.

3-Ethoxycarbonyl-4-methoxy-2,5-dihydrothiophene (If$_1$, R=H). To a solution of 7 g of XIIIa$_1$ in dry ether there was added an excess of dry ethereal diazomethane. The resultant solution was kept in a refrigerator for 16 hr, and then evaporated; the residue was fractionally distilled to give 6 g of If$_1$, bp 118—120°C/5 mmHg.

Found: C, 50.95; H, 6.28%. Calcd for $C_8H_{12}O_3S$: C, 51.06; H, 6.43%.

Direct Conversion of Ia$_1$ to IIa$_1$. To a solution of 0.87 g of Ia$_1$ in 5 m*l* of acetone and 10 m*l* of acetic acid 1.5 m*l* of 30% hydrogen peroixde were added while the mixture was being cooled to prevent the temperature from rising above 50°C. The reaction mixture was then allowed to stand for 24 hr at 50°C. After the evaporation of the solvent under reduced pressure, the residue was recrystallized from water to give 585 mg (68%) of IIa$_1$.

Oxidation of the Cyanoester Ib$_1$ with 30% Hydrogen Peroxide in Acetic Acid (Procedure A). A mixture of 3.0 m*l* of 30% hydrogen peroxide and 20 m*l* of acetic acid was allowed to stand at 40°C for 3 hr. To the above cooled solution there was then added, in portions, a solution of 1.83 g of the Ib$_1$ cyanoester in 10 m*l* of acetone at a temperature below 25°C. The reaction mixture was allowed to stand for 38 hr at 25°C. The solvent was then removed under reduced pressure below 50°C. The residue was triturated with a mixture of petroleum ether and acetone to give 3-cyano-4-ethoxycarbonylthiophene (IIb$_1$, R=H).

Oxidation of Id$_1$, If$_1$, XIa$_1$ and XIa$_2$ with 30% Hydrogen Peroxide in Acetic Acid. This was carried out in a manner similar to that described for Ib$_1$.

Oxidation of the Cyanoester Ib$_2$ with 30% Hydrogen Peroxide in Acetic Acid. The oxidation of the Ib$_2$ cyanoester (1.970 g) in acetone (1.5 m*l*) with 30% hydrogen peroxide (3.0 m*l*) in acetic acid (20 m*l*) was carried out according to the procedure A. The reaction mixture was then worked up in a manner similar to that described for Ib$_1$, and the residue was chromatographed on alumina. The corresponding thiophene, IIb$_2$ (1.9 g), was eluted with a mixture of petroleum ether and chloroform (9 : 1), and a small amount of the corresponding sulfone, IIIb$_2$ (*ca.* 10 mg), was eluted with a mixture of petroleum ether and chloroform (4 : 6).

Oxidation of the Diester, Ic$_1$, Ic$_2$ and XIb$_1$ with 30% Hydrogen Peroxide in Acetic Acid. This oxidation was carried out in a manner similar to that described for Ib$_1$ (Procedure A). When the reaction mixture was worked up according to the procedure A, the residue gave a mixture of the corresponding thiophene and sulfone derivatives. The approximate molar ratio of the two derivatives in the mixture was estimated by a

9) G. B. Brown, B. R. Baker, S. Bernstein and S. R. Safir, *J. Org. Chem.*, **12**, 155 (1947).

comparison of the infrared spectra of the reaction mixture and those of a mixture of the authentic samples, IIc and IIIc, the relative concentrations of IIc and IIIc being varied correspondingly. The approximate molar ratio of the sulfone and the thiophene derivative in the oxidation products was : (70% $IIIc_1$: 30% IIc_1), (80% $IIIc_2$: 20% IIc_2), and (85% $XIIb_1$: 15% IIc_1), respectively. Attempts to separate the mixture completely by chromatography using an alumina or a silica gel column were unsuccessful.

Oxidation of Ie_1 and Ie_2 with 30% Hydrogen Peroxide in a Mixture of Acetic Acid and Acetic Anhydride. A mixture of 1.5 m*l* of 30% hydrogen peroxide, 4.5 m*l* of acetic anhydride, and 9.0 m*l* of acetic acid was allowed to stand at 45°C for 3 hr (or at 25°C for 12 hr). To the cooled solution there was then added, in portions, 1.08 g of Ie_1, with occasional cooling to prevent the temperature from rising above 45°C. Then the reaction mixture was kept at 45°C for 17 hr. After the evaporation of the solvent under reduced pressure below 45°C, the residue was recrystallized from 95% ethanol to give the product, mp 174—179°C. The infrared spectrum of the product showed a weak absorption band at 1020 cm^{-1} in the sulfoxide region. This product was presumed to be a mixture of the corresponding sulfoxide and sulfone derivative, but it was not separated by fractional recrystallizations. The product was refluxed with Raney nickel in ethanol for 1 hr, and the residue, after the evaporation of the solvent, was recrystallized to give 0.63 g (53%), of the $IIIe_1$ sulfone.

The 2-methyl derivative, Ie_2 was treated in a manner similar to that described for Ie_1 to give the corresponding sulfone, $IIIe_2$.

Oxidation of the Cyanoester Ib_1 with Perbenzoic Acid in Chloroform (Procedure B). To 46.8 m*l* (0.01 mol) of a solution of perbenzoic acid in dry chloroform there was added, portion by portion, a solution of 0.916 g (0.005 mol) of Ib_1 in 2 m*l* of acetone, while the temperature was maintained at 25°C. The mixture was then allowed to stand at 25°C for 24 hr. The reaction mixture was washed successively with two 15-m*l* portions of 5% sodium thiosulfate, with 10% aqueous sodium carbonate, and with three 20-m*l* portions of water, and then dried overnight over anhydrous sodium sulfate. After the removal of the solvent, 1.05 g of the corresponding sulfone, $IIIb_1$ was obtained. The characteristic infrared absorptions in the sulfone region were at 1343 and 1160 cm^{-1}.

Oxidation of the Cyanoester Ib_2 with Perbenzoic Acid in Chloroform. After a mixture of the Ib_2 cyanoester (591 mg, 3 mmol) and perbenzoic acid (6 mmol) in chloroform (23 m*l*) had been worked up as has been described for Ib_1 (Procedure B), the residue was chromatographed on alumina; a small amount of the corresponding thiophene, IIb_2 (*ca.* 20 mg), was eluted with a mixture of petroleum ether and chloroform (9 : 1), and 0.43 g of the corresponding sulfone, $IIIb_2$[10], with a (4 : 1) mixture of petroleum ether and chloroform.

Oxidation of Ic_1, Ic_2, Id_1, If_1, and XIb_1 with Perbenzoic Acid in Chloroform. This oxidation was carried out according to the procedure B to give the corresponding sulfones. The infrared spectra of these sulfone derivatives showed characteristic absorption bands in the sulfone region.

Oxidation of 2,5-Dihydrothiophene-3,4-dicarboxylic Acid Ia_2 to 2,5-Dihydrothiophene-3,4-dicarboxylic Acid-1-oxide (V). With 30% Hydrogen Peroxide-Acetic Acid. A mixture of 70 m*l* of acetic acid and 9.0 m*l* of 30% hydrogen peroxide was allowed to stand at 40°C for 3 hr. To this solution there was then added, portion by portion, 5.22 g of the Ia_1 diacid dissolved in 20 m*l* of acetone, while the temperature was maintained below 20°C; the reaction mixture was then kept at 20°C for 24 more hours. The colorless precipitate which was gradually formed was collected by filtration, washed with cold acetone, and then dried to give 4.70 g (83%) of the sulfoxide V, λ_{max}^{EtOH} 226 mμ (ε=11900), ν_{max}^{KBr} 1870 w, 1710 s, 1674 s, 1645 s, 1295 s, 1225 s, 1010 s, 955 m and 730 cm^{-1} (m), neut. equiv. 190 (calcd 190). A second crop of the product (0.62 g) was obtained by the concentration of the mother liquor under reduced pressure. This minor product was identical in infrared and ultraviolet spectra with the authentic sample of thiophene-3,4-dicarboxylic acid.[4] The melting point of an admixture with the authentic sample was also undepressed.

With Perbenzoic Acid-Chloroform. To a solution of 4.4 g of perbenzoic acid in 10 m*l* of dry chloroform, there was added, portion by portion, a solution of 1.74 g of the Ia_1 diacid in 3 ml of acetone, while the temperature was kept below 25°C. A colorless precipitate soon appeared from the mixture. The reaction mixture was kept at 20°C for 24 hr. The precipitate was collected by filtration, washed with cold acetone, and dried to give 1.60 g (84%) of the sulfoxide V, which was identical in infrared and ultraviolet spectra with the product obtained by the treatment of Ia_1 with hydrogen peroxide-acetic acid.

Conversion of the Sulfoxide V to Thiophene-3,4-dicarboxylic Acid IIa_1. Two grams of the V sulfoxide were dissolved in 20 m*l* of water by warming the solution on a hot-plate. After the mixture had been cooled, long colorless, needles crystallized out. The crystals were collected by filtration and dried to give 1.6 g (89%) of IIa_1. Its mixed melting point with the authentic sample showed no depression. When acetic acid or aqueous ethanol was used as the solvent, the solvent was evaporated to dryness *in vacuo*, and then the residue was recrystallized from water.

Reaction of the Sulfoxide V with Diazomethane in Ether. A solution of 570 mg of the V sulfoxide in 1 m*l* of dry methanol was treated with an excess of diazomethane in ether. The reaction mixture, after standing for 24 hr at room temperature, was dried over anhydrous sodium sulfate. After the removal of the solvent, the residue was recrystallized from benzene-chloroform to yield 390 mg (56%) of VI, mp 155—156°C. A characteristic infrared spectrum in the sulfoxide region was at 1045 cm^{-1}.

Found: C, 41.61; H, 4.65; N, 10.86%. Calcd for $C_9H_{12}O_5N_2S$: C, 41.54; H, 4.65; N, 10.77%.

Oxidation of Tetrahydrothiophene-3,4-dicarboxylic Acid (IX). Compound IX (0.82 g) was oxidized to X in a 80% yield, by a mixture consisting of 30% hydrogen peroxide (1.35 m*l*) and acetic acid (12 m*l*), in a manner similar to that described for Ib_1 except that the reaction was carried out at 50°C. The compound X had a mp of 201—203°C after recrystallization from acetic acid.

10) The structure of the sulfone $IIIb_2$ was confirmed by hydrolysis of $IIIb_2$ to $IIIa_2$ because of an unsuccessful purification of $IIIb_2$.

Found: C, 34.68; H, 3.74%. Calcd for $C_6H_8O_6S$: C, 34.62; H, 3.87%.

Dehydrogenation of the Ib_1 Cyanoester with Chloranil to the IIb_1 Thiophene. A mixture of 550 mg of the Ib_1 cyanoester and 787 mg of chloranil in 20 m*l* of dry toluene was refluxed for 6 hr. The mixture was then concentrated to a small volume under a stream of nitrogen. When the residue was diluted with 20 m*l* of dry chloroform, yellow crystals (chloranil) precipitated immediately. After filtration, the chloroform solution was concentrated to a small volume (*ca.* 5 m*l*), which was then chromatographed on alumina (20 g) using a mixture of chloroform and petroleum ether (5 : 1) as an eluent. After the evaporation of the solvent, the residue was triturated with petroleum ether to give 158 mg of the IIb_1 thiophene, which was identical in all respects (infrared, ultraviolet spectrum, and mixed melting point) with the prodct prepared from Ib_1 by the procedure A.

2-Methyl-3,4-dimethoxycarbonylthiophene (IIc_2, R=CH_3). Prepared by treating the IIa_2 diacid with diazomethane in ether, showed a bp of 123—124°C/3 mmHg, n_D^{15} 1.526.

Found: C, 50.70; H, 4.78%. Calcd for $C_9H_{10}O_4S$: C, 50.47; H, 4.71%.

Acid Hydrolysis of IIb_1 to IIa_1. A mixture of 180 mg of IIb_1, 1.5 m*l* of acetic acid, and 1 m*l* of concentrated hydrochloric acid was refluxed for 22 hr. The solvent was then evaporated to dryness *in vacuo*. Recrystallization from water gave 105 mg of IIa_1, mp 214—216°C, identical in all respects with thiophene-3,4-dicarboxylic acid, IIa_1.

Hydrolysis of $IIIc_1$ to 2,5-Dihydrothiophene-3,4-dicarboxylic Acid-1,1-dioxide ($IIIa_1$, R=H). A mixture of 2.0 g of $IIIc_1$ and 100 m*l* of saturated hydrobromic acid was stirred at 60°C for 20 hr. The reaction mixture was then concentrated to dryness under reduced pressure below 60°C. The residue was recrystallized from ether - petroleum ether to give 1.50 g (85%) of colorless crystals, mp 172—176°C. Found: C, 32.05; H, 3.58%. Calcd for $C_6H_6O_6S$: C, 32.15; H, 3.60%. The dehydration of the crystals over phosphorus pentoxide at 100°C *in vacuo* gave $IIIa_1$, mp 180—181°C.

Found: C, 34.94; H, 2.91%. Calcd for $C_6H_6O_6S$: C, 34.96; H, 2.93%.

Hydrolysis of $IIIc_2$ to 2-Methyl-2,5-dihydrothiophene-3,4-dicarboxylic Acid-1,1-dioxide ($IIIa_2$, R=CH_3). By refluxing a mixture of 592 mg of $IIIc_2$ and 10 m*l* of saturated hydrobromic acid in the manner described above for $IIIc_1$, 387 mg (72%) of $IIIa_2$ was obtained; mp 172—174°C (from ether-petroleum ether).

Found: C, 38.06; H, 3.68%. Calcd for $C_7H_8O_6S$: C, 38.19; H, 3.66%.

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