CATALYZED OXIDATION OF 2-ETHYL-5-METHYLTHIOPHENE

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2-Ethyl-5-methylthiophene was subjected to liquid-phase oxidation with molecular oxygen in glacial acetic acid in the presence of cobalt acetate and sodium bromide. The effect of the concentrations of the substance undergoing oxidation, cobalt acetate, and sodium bromide on the oxidation was investigated. The chief reaction product – 2-acetyl-5-methylthiophene – was isolated. A difference in the reactivities of 2-ethylthiophene and 2-ethyl-5-methylthiophene is demonstrated.

We have previously shown [1-3] that the liquid-phase oxidation of thiophene homologs with molecular oxygen leads to oxygen derivatives of the thiophene series with ketone or acid functions. Alcohols, aldehydes, and esters were also isolated as oxidation intermediates.

It seemed of interest to investigate the behavior of other thiophene homologs, particularly 2-ethyl-5-methylthiophene (I), with respect to molecular oxygen under similar conditions and to compare its reactivity with that of 2-ethylthiophene (II).

The oxidation was carried out in glacial acetic acid at 70-110° C in the presence of cobalt acetate and sodium bromide. The thiophene I, catalyst (cobalt acetate), and initiator (sodium bromide) concentrations were varied, respectively, from 2.5 to 40 vol %, $2 \cdot 10^{-2}$ to 10^{-1} mole/liter, and $2.5 \cdot 10^{-3}$ to $2 \cdot 10^{-2}$ mole/liter. The oxidation rate was measured volumetrically from the oxygen absorption. The reaction products were analyzed by gas–liquid chromatography (GLC). The chief product of oxidation of thiophene I is 2-acetyl-5-methylthiophene (III), the yield of which with respect to the absorbed oxygen is 88%. In addition, 2-methyl-5-vinylthiophene (IV), 1-(5-methyl-2-thienyl)ethyl acetate (V), 2-acetyl-5-hydroxymethylthiophene (VI), and 2-acetyl-5-formylthiophene (VII), which are side products or intermediates, were detected.

We established that thiophene I is oxidized via the scheme

I III

When 1 mole of O_2 is absorbed per mole of I, the process, as a rule, is slowed down or stopped completely at the step involving the formation of ketone III. The accumulation of the latter and of other intermediates in the oxidation of thiophene I evidently inhibits the further development of the process.

We isolated ketone III in pure form and identified it by GLC. Its structure was confirmed by the IR and UV spectral data and by comparison with a sample obtained by an independent method. Its carbonyl derivatives with phenylhydrazine and 2,4-dinitrophenylhydrazine were obtained. The small percentages of the remaining substances detected in the contact mixture and the extremely rapid resinification of some of them did not make it possible to isolate them in pure form.

The kinetic data obtained demonstrate that the rate of oxidation of I depends on the catalyst $[Co(OCOCH_3)_2]$ and initiator (NaBr) concentrations. Oxidation commences without an induction period both when the initiator is present and when it is absent. The initial oxidation rate in the absence of bromide increases in proportion to the concentrations of cobalt acetate and starting I (Fig. 1). As the catalyst concentration is increased from $5 \cdot 10^{-2}$ to $9.75 \cdot 10^{-2}$ mole/liter, oxygen absorption increases correspondingly from 0.36 to 0.62 mole per mole

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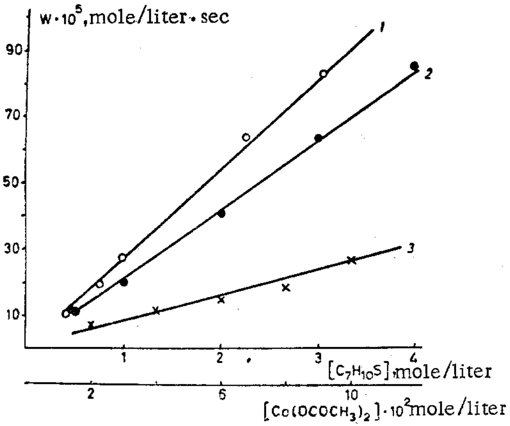


Fig. 1

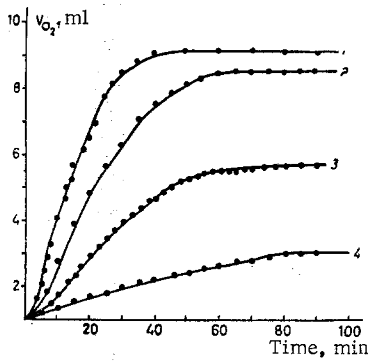


Fig. 2

Fig. 1. Relationship of the rate of oxidation of 2-ethyl-5-methylthiophene and the I and $Co(OCOCH_3)_2$ concentrations at 100°C in the absence of an initiator: 1) $[Co(OCOCH_3)_2] = 5 \cdot 10^{-2}$ mole/liter; 2) $[Co(OCOCH_3)_2] = 10^{-1}$ mole/liter; 3) $[C_7H_{10}S] = 0.382$ mole/liter.

Fig. 2. Kinetics of oxygen absorption in the oxidation of 2-ethyl-5-methylthiophene (0.19 mole/liter) and 2-ethylthiophene (0.19 mole/liter) for $[Co(OCOCH_3)_2] = 5 \cdot 10^{-2}$ mole/liter at 100°C: 1) and 3) in the presence of NaBr ($1.55 \cdot 10^{-2}$ mole/liter); 2) and 4) in the absence of NaBr; 1) and 2) 2-ethyl-5-methylthiophene; 3) and 4) 2-ethylthiophene.

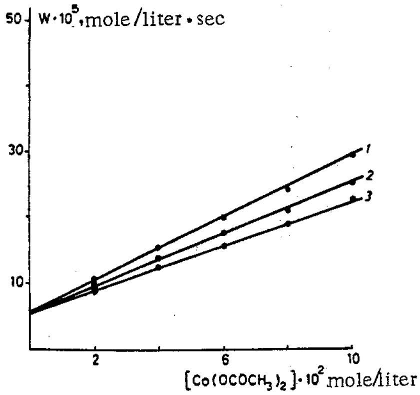


Fig. 3

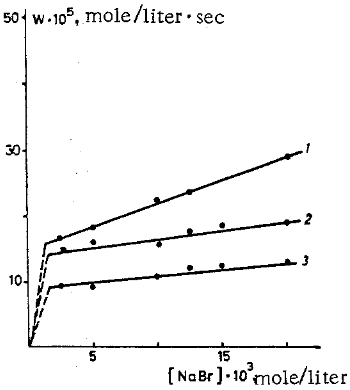


Fig. 4

Fig. 3. Relationship between the rate of oxidation of 2-ethyl-5-methylthiophene (0.382 mole/liter) and the cobalt acetate concentration at 100°C for NaBr concentrations of: 1) $1.5 \cdot 10^{-2}$; 2) 10^{-2}; 3) $5 \cdot 10^{-3}$ mole/liter.

Fig. 4. Relationship between the rate of oxidation of 2-ethyl-5-methylthiophene (0.382 mole/liter) and the NaBr concentration at 100°C for $Co(OCOCH_3)_2$ concentrations of: 1) $9 \cdot 10^{-2}$; 2) $6 \cdot 10^{-2}$; 3) $3 \cdot 10^{-2}$ mole/liter.

of oxidizable substance, and the process is inhibited for 25-28 min. In view of the limited solubility of the catalyst, the effect of higher concentrations was not investigated.

A study of the effect of the 2-ethyl-5-methylthiophene concentration on the initial reaction rate showed that the reaction is first-order in alkylthiophene; half-order in the catalyst concentration was established.

The introduction of an initiator (NaBr) made it possible to raise the overall rate and yield of the principal oxidation product. In the presence of NaBr, 0.918 mole of O_2 is absorbed per mole of thiophene I, i.e., approxi-

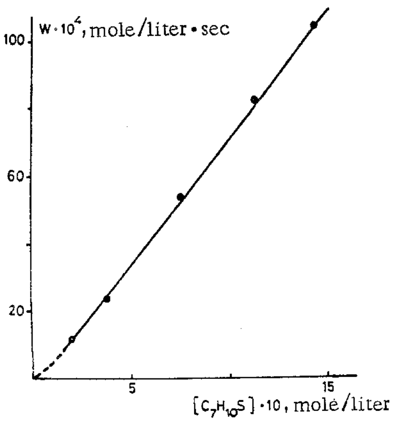


Fig. 5. Relationship between the rate of oxidation of 2-ethyl-5-methylthiophene and its concentration at 100°C when $[Co(OCOCH_3)_2] = 5 \cdot 10^{-2}$ mole/liter and $[NaBr] = 1.55 \cdot 10^{-2}$ mole/liter.

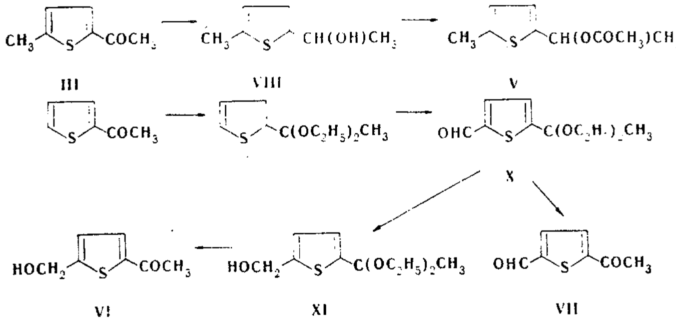
mately twice the amount that is absorbed when NaBr is absent, and oxidation proceeds selectively to ketone III. The oxidation rate has its highest value at the start of the reaction, after which it gradually falls to a constant value of 0.15 ml/min (Fig. 2).

At the start of the reaction the oxidation rate increases linearly as the initiator, catalyst, and thiophene I concentrations are increased. A study of the effects of the concentrations of these substances made it possible to determine the reaction orders, which were found to be 0.5 in NaBr, 1.0 in Co(II), and 1.0 in $C_7H_{10}S$ (I) (Figs. 3-5).

The reactivities of 2-ethyl-5-methylthiophene (I) and the previously studied 2-ethylthiophene (II) [1] differ appreciably. Under similar conditions, thiophene I is oxidized more rapidly (Fig. 2), apparently because of the effect of the electron-donor substituent (the CH_3 group). Oxidation of the methyl group of III, which is formed during the reaction, is hindered by the effect of the electron-acceptor carbonyl group and, possibly, by its capacity for complexing with the catalyst. However, in this case partial ketone-enol conversion of ketone III to the corresponding alcohol, which ties up the peroxide radicals and terminates the oxidation chain, may also be of significance. This is confirmed by the fact that the addition of ketone III and 1-(5-methyl-2-thienyl)ethanol (VIII) and its acetate V, which are formed during the reaction, to I somewhat lowers the rate of oxidation of the latter. Vinylthiophene IV, which is formed as a result of dehydration of alcohol VIII, probably does not lower the rate of oxygen absorption but, like vinyltoluene [4], lowers the degree of oxidation.

In this connection, it should also be noted that ketone III is rapidly oxidized under conditions similar to those in the oxidation of thiophene I in the presence of sodium bromide. Under the same conditions, alcohol VIII and its acetate V are oxidized to a slight degree, and the process is inhibited for 2 h with a final absorption of 0.1-0.2 mole of O_2 per mole of substance. Compound VIII is esterified and partially dehydrated to give vinylthiophene IV under the oxidation conditions.

The synthesis of the compounds necessary for the proof of the structures of the final products and intermediates in the oxidation of thiophene I was realized via the following scheme:



Proceeding from the existing theoretical concepts [5] and the results obtained in this study, the mechanism of the oxidation of thiophene I can be described by a scheme involving degenerately-branched reactions, and in this case also the rate-determining step is transfer of an electron between the peroxide radical and the divalent cobalt ion [1].

EXPERIMENTAL

The chromatographic analysis of the reaction products was carried out with an LKhM-8MD chromatograph (model 5). The carrier-gas (helium) flow rate was 50 ml/min, and detection was accomplished with a G26 catharometer and a flame-ionization detector. The columns (300 × 0.3 cm and 600 × 0.3 cm) were made of stainless steel and filled with Chromosorb W (100/120 mesh) impregnated (5%) with SE-30 silicone elastomer. The temperature-rise rate at 130-200° was 12 deg/min. The IR spectra of solutions of the substances in CCl_4 were recorded with a UR-20 spectrometer. The UV spectra of alcohol solutions of the compounds (c 10^{-3}-10^{-5} M) were recorded with an SF-4 spectrophotometer.

Oxidation was carried out in a closed system with a gasometric apparatus via the method previously described in [2]. The cobalt acetate, sodium bromide, and glacial acetic acid were purified by the methods in [3]. The starting 2-ethyl-5-methylthiophene (I) has bp 160°, d_4^{20} 0.9661, and n_D^{20} 1.5073 (bp 160°, d_4^{20} 0.9660, n_D^{20} 1.5073 [6]). 2-Ethylthiophene (II) had bp 135-137°, d_4^{20} 0.9920, and n_D^{20} 1.5123 (bp 135-136° and n_D^{20} 1.5124 [7]).

2-Acetyl-5-methylthiophene (III). This compound was obtained by the method in [8]. A 29.4-g (0.3 mole) sample of 2-methylthiophene was treated with 261 ml of a 1.15 N solution of butyllithium in ether, and the mixture was acylated by the addition of 153 g (1.5 mole) of acetic anhydride in absolute ether at −70°. Workup gave a product with bp 84-85° (2 mm) and n_D^{20} 1.5622 [bp 97-100° (8 mm)] in 30% yield. IR spectrum: 1668 (C−O) and 1360 cm^{-1} (CH_3). The 2,4-dinitrophenylhydrazone had mp 246° (from ethanol). The phenylhydrazone had mp 127-128°.

1-(5-Methyl-2-thienyl)ethyl Acetate (V). A 5.37-g (0.038 mole) sample of 1-(5-methyl-2-thienyl)ethanol (VIII) was treated with 6.66 g (0.065 mole) of acetic anhydride in 12 ml of pyridine. Workup gave a product with bp 93° (12 mm) and n_D^{25} 1.4990 in 66% yield. IR spectrum: 1742 (C−O) and 1230 cm^{-1} [bp 93-95° (12 mm) and n_D^{25} 1.4996 [9]).

1-(5-Methyl-2-thienyl)ethanol (VIII). This compound was obtained by the method in [10] by reduction of ketone III with sodium borohydride in absolute methanol. The PMR spectrum of VIII was similar to the spectrum described in [10].

2-Methyl-5-vinylthiophene (IV). This compound was isolated by decomposition of alcohol VIII by vacuum distillation. Workup gave a product with bp 30-36° (2-3 mm) and n_D^{19} 1.5623 in 64% yield. The compound decomposed on standing.

2-Acetyl-5-formylthiophene (VII). This compound was obtained by the method in [11] and had mp 104.5-105° (from hexane−benzene) [11].

2-Acetylthiophene Diethylketal (IX) and 2-Acetyl-5-formylthiophene Diethylketal (X). These compounds were obtained by the method in [11]. Diethylketal IX had bp 85-90° (10 mm) [bp 82-84° (6 mm) [12]]. Diethylketal X had bp 125-129° (2 mm) [bp 129-137° (5 mm) [11]].

2-Acetyl-5-hydroxymethylthiophene (VI). This compound was obtained by the method in [11]. A solution of 0.62 g (0.016 mole) of sodium borohydride in 12 ml of water containing one drop of 40% sodium hydroxide solution was added dropwise in the course of 12 min to a cooled (to 5-15°) solution of 7.3 g (0.032 mole) of diethylketal X in 60 ml of methanol, after which the mixture was stirred at 8-10° for 35-40 min. It was then acidified to pH 6 with acetic acid and to pH 3 with concentrated H_2SO_4, after which it was treated with water and extracted with ether. The ether was removed by distillation, and the residue (4.18 g) was dissolved in 10 ml of methanol. The methanol solution was treated with 4.5 ml of concentrated hydrochloric acid, after which the mixture was heated almost to the boiling point and poured into water. The aqueous mixture was extracted with ether, the ether extracts were dried with magnesium sulfate, and the ether was removed by distillation to give 1 g (20%) of a red-brown oil that crystallized on cooling. Found: C 53.2; 53.6; H 5.4; 5.6; S 20.2; 20.1%. $C_7H_8O_2S$. Calculated: C 53.8; H 5.2; S 20.5%.

Isolation of 2-Acetyl-5-methylthiophene (III) from the Products of Oxidation of 2-Ethyl-5-methylthiophene (I). A solution of 40 ml of cobalt acetate ($5 \cdot 10^{-2}$ mole/liter) and 24.8 ml of sodium bromide ($1.55 \cdot 10^{-2}$ mole/liter) in glacial acetic acid and 2 ml (0.19 mole/liter) of thiophene I were introduced into a flask equipped with a gasometer through drying traps filled with calcium chloride and potassium hydroxide, after which the mixture was heated to 110°, and oxygen was bubbled through it. The oxidation was carried out at 110° with vigorous stirring for 2 h. At the end of the reaction, the precipitate was separated. The reaction products were analyzed by GLC and acetic acid and I and III-VII were detected. The contact solution was diluted with water and extracted immediately with ether. The ether extracts were dried with calcined calcium chloride, the ether was removed by distillation, and the residue was vacuum distilled to give ketone III with mp 87° (4 mm) and n_D^{20} 1.5623. UV spectrum in ethanol, λ_{max}, nm (log ε): 208 (3.37), 265 (4.00), 296 (4.09). IR spectrum: 1670 (C=O), 1365 cm^{-1} (CH_3). The 2,4-dinitrophenylhydrazone had mp 246°C (from ethanol).

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REACTION OF 2,3-DICHLOROBENZO[b]THIOPHENE 1,1-DIOXIDE WITH CYCLIC AMINES

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The corresponding p-amino derivatives, which have psychotropic activity, were obtained by reaction of 2,3-dichlorobenzo[b]thiophene 1,1-dioxide with cyclic amines. Their IR and PMR spectra are presented.

Pesticides and compounds with psychotropic and cardiovascular effects have been found among benzo[b]thiophene derivatives in recent years. In order to obtain biologically active compounds – sulfones of condensed thiophene systems – and study their reactions with nucleophilic reagents [3] we investigated the reaction of 2,3-dichlorobenzo[b]thiophene 1,1-dioxide (I) with cyclic amines.

N-Aryl and N-alkyl derivatives of piperazine react with sulfone I in refluxing ethanol to give 2-chloro-3-piperazinobenzo[b]thiophene 1,1-dioxides (II) (Table 1) and the hydrochloride of the corresponding amine (reagent ratio 1 : 2). The reaction of sulfone I with excess aziridine, pyrrolidine, piperazine, and perhydroazepine, which leads to 2-chloro-3-aminobenzo[b]thiophene 1,1-dioxides (III) (Table 1), proceeds similarly.

The reaction of sulfone I with an equimolar amount of aziridine proceeds with opening of the aziridine ring to give 2-chloro-3-(β-chloroethylamino)benzo[b]thiophene 1,1-dioxide (IV) in low yield. The latter was also

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