CONDENSED HETEROAROMATIC SYSTEMS INCLUDING A THIOPHENE RING. XXXIII.*
CATALYTIC LIQUID-PHASE OXIDATION OF 3-METHYL-SUBSTITUTED THIENO[2,3-b]THIOPHENES AND THIENO[3,2-b]THIOPHENES

V. P. Litvinov. T. V. Shchedrinskaya,
P. A. Konstantinov, and
Ya. L. Gol'dfarb

UDC 547.737:541.128.
12:542.943.7

It is shown that the catalytic liquid-phase oxidation of 3-methylthieno[2,3-b]thiophene and 3-methylthieno[3,2-b]thiophene in acetic acid in the presence of cobalt acetate and sodium bromide at 90-110° gives thieno[2,3-b]thiophene-3-carboxylic acid and thieno[3,2-b]-3-formylthiophene, respectively.

We have previously studied [2] the catalytic liquid-phase oxidation of methylbenzo[b]thiophenes in order to obtain compounds containing an oxygen-containing function, which, in particular, could be used for the creation of new types of complexing systems. Continuing our research in this direction, we studied the oxidation of 3-methylthieno[2,3-b]thiophene (I) and 3-methylthieno[3,2-b]thiophene (II) with molecular oxygen at atmospheric pressure in glacial acetic acid at 90-110°C in the presence of divalent cobalt acetate or a mixture of it with manganese acetate and sodium bromide. The method used to carry out the experiments and the apparatus design were similar to those described in [2].

Methylthienothiophenes I and II were selected for the investigation because compounds of this type were detected in the distillate of sulfur-containing petroleum with bp 200-250° [3, 4]. This constitutes evidence for the presence of a natural source of thienothiophene homologs .

Starting methylthienothiophenes I and II were prepared from 3-bromothiophene in the following way. Methyl (3-thienylmercapto)acetate (III) was obtained by treatment of 3-thienyllithium, obtained by reaction of 3-bromothiophene with n-butyllithium at –70°, successively with elementary sulfur and methyl chloroacetate. Ester III, without purification, was converted to methyl (2-acetyl-3-thienylmercapto)acetate (IV), which was cyclized in the presence of sodium ethoxide to give 3-methylthieno[3,2-b]thiophene-2-carboxylic acid (V). Decarboxylation of acid V gave thienothiophene II. Similar treatment of 3-bromothiophene with n-butyllithium at –70°, dimethylacetamide (DMA), a second equivalent of n-butyllithium, sulfur, and methyl bromoacetate gave methyl (3-acetyl-2-thienylmercapto)acetate (VI). This ester was converted without purification to 3-methylthieno[2,3-b]thiophene-2-carboxylic acid (VII), from which 3-methylthieno[2,3-b]thiophene (I) was obtained by decarboxylation.

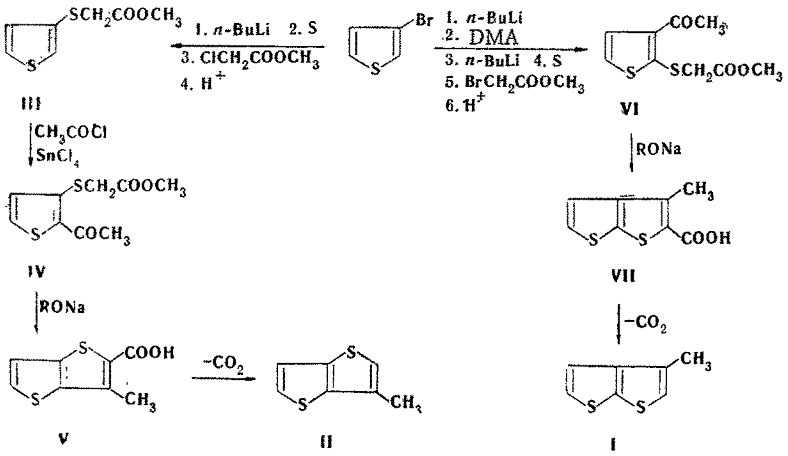
This method is an improved modification [5-7] (also see [8]) of the method for the preparation of compounds of this type. (See scheme on following page.)

In liquid-phase catalytic oxidation under identical conditions [starting thienothiophene concentration 0.081 g-mole/liter, $Co(CH_3CO_2)_2$ concentration $5 \cdot 10^{-2}$ g-mole/liter, NaBr initiator concentration $1.55 \cdot 10^{-2}$ g-mole/liter, and reaction temperature 110°] the investigated thienothiophenes I and II behave differently. This is manifested primarily in the fact that

---

*See [1] for communication XXXII.

N. D. Zelinskii Institute of Organic Chemistry, Academy of Sciences of the USSR, Moscow. Moscow Physicotechnical Institute. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 492-498, April, 1975. Original article submitted April 2, 1974.



in the case of I the chief oxidation product is thieno[2,3-b]thiophene-3-carboxylic acid (VIII), and its yield, judging from the amount of absorbed oxygen, ranges from 85 to 95%. However, the oxidation of thienothiophene II is inhibited rapidly long in advance of complete consumption of the starting thienothiophene (the degree of oxidation is ∿ 25%). In this case the chief product is thieno[2,3-b]-3-formylthiophene (IX); thieno[3,2-b]thiophene-3-carboxylic acid could not be detected in the oxidation products.

A comparison of the behavior of methylthienothiophenes I and II at various temperatures (90 and 100°) (Fig. 1) makes it possible to conclude that the rates of oxidation of both compounds are practically identical in the first few minutes. However, in the case of II the process is slowed down after 8-10 min, and oxidation ceases completely after 20 min. In addition, a continuous decrease in the rates of oxidation of I and II is seen from Fig. 1

When the behavior of thienothiophenes I and II is compared with the behavior of 2-methylbenzo[b]thiophene (X) and 3-methylbenzo[b]thiophene (XI) [2] under liquid-phase-oxidation conditions it can be seen that the degree of oxidation (to the aldehyde or the acid) is determined primarily by the mutual orientation of the ring sulfur atom and the methyl group. Thus if the methyl group is in the 3 position, which is furthest removed from the sulfur atom in the thieno[2,3-b]thiophene or benzo[b]thiophene molecule, it is oxidized to an acid. At the same time, 2-methylbenzo[b]thiophene (X) and 3-methylthieno[3,2-b]thiophene (II) are oxidized only to the corresponding aldehydes under similar conditions. The formation of a complex of the A or B type between the cobalt ion of the catalyst and the intermediate oxidation products (aldehydes or alcohols), which is capable of inhibiting further oxidation, can be proposed as a possible reason for the inhibition of the process in this case. (See scheme on following page.)

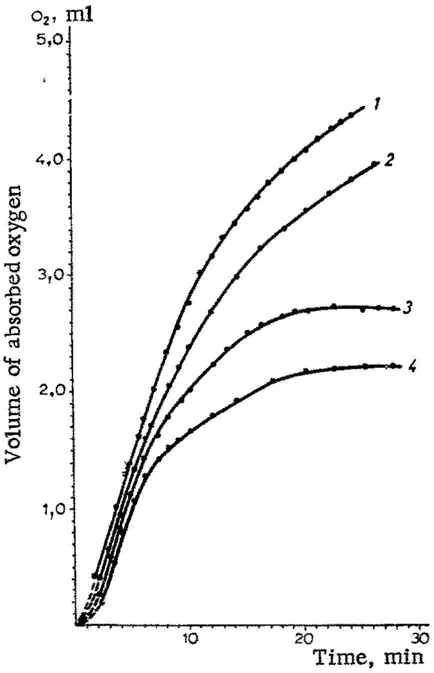


Fig. 1. Kinetic curves of oxygen absorption during the oxidation of 3-methylthieno[2,3-b]thiophene (I) and 3-methylthieno[3,2-b]thiophene (II). The concentration of I and II were $8.17\ 10^{-2}$ g-mole/liter, the $Co(CH_3CO_2)_2$ concentration was $5\cdot10^{-2}$ g-mole/liter, and the NaBr concentration was $1.55\cdot10^{-2}$ g-mole/liter. Curves 1 and 2 pertain to I at 100 and 90°C, respectively. Curves 3 and 4 pertain to II at 100 and 90°, respectively.

In this connection, let us point out the previously observed [9] inhibiting effect of some complexes of 3-hydroxy-2-iminomethylbenzo[b]thiophene, which markedly inhibit the oxidation of hydrocarbons even at a concentration of $1\cdot10^{-4}$ g-mole/liter. In particular, bis-(3-hydroxy-2-iminomethylbenzo[b]thiophenato)copper (II) can apparently be considered to be a

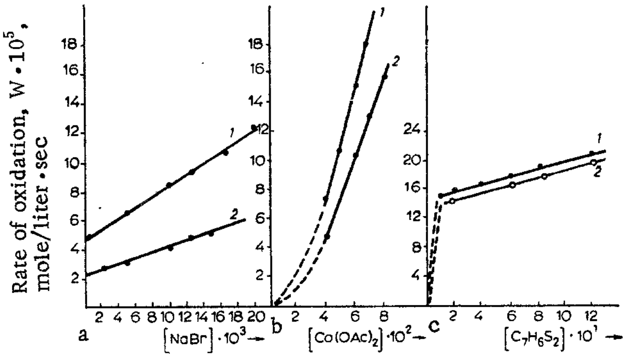
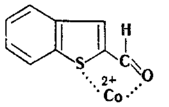
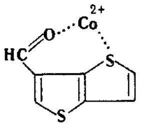


Fig. 2. Dependence of the rate of oxidation of I on the Co(OAc)$_2$ concentration at 100°: 1) [Co(OAc)$_2$] = $5 \cdot 10^{-2}$ g-mole/liter; 2) [Co(OAc)$_2$] = $3 \cdot 10^{-2}$ g-mole/liter) b) dependence of the rate of oxidation of I on the NaBr concentration at 100°: 1) [NaBr] = $1.5 \cdot 10^{-2}$ g-mole/liter; 2) [NaBr] = $1 \cdot 10^{-2}$ g-mole/liter; c) dependence of the rate of oxidation of I on its concentration at 100°: 1) [NaBr]/[Co(CH$_3$CO$_2$)$_2$] = 0.2; 2) [NaBr]/[Co(CH$_3$CO$_2$)$_2$] = 0.35.



A



B

polyfunctional inhibitor in this process, one molecule of which participates in termination of several oxidation chains.

The fact of the detection in the products of the oxidation of II, in addition to aldehyde IX, of an organic cobalt compound that we have not yet identified may serve as an indirect confirmation of this assumption. We also note that the formation of complexes of the type indicated above is impossible in the case of methyl-substituted I and XI.

As one should have expected, an increase in the temperature leads to an increase in the reaction rate and, particularly in the case of thienothiophene II, to a higher degree of oxidation.

As in the case of alkylthiophene and selenophenes [10], a synergistic effect of cobalt and manganese acetates in the presence of sodium bromide is manifested in the oxidation of methylthienothiophenes I and II. Owing to this, not only can the rate of oxidation of I and II be raised by a factor of five to six, but in the case of thienothiophene I the oxidation to acid VIII can be carried out when its concentration in solution is considerably higher (up to 5%).

We also obtained some data that provide evidence that in the absence of an initiator (NaBr) the oxidation of methylthienothiophenes I and II proceeds at barely appreciable rates. When NaBr is added, the oxidation begins almost without an induction period, and the rate increases as the concentration of not only the initiator but also the catalyst is increased (Fig. 2a). In addition, it is seen from the data obtained that the initial rate of oxidation is proportional to the square of the catalyst concentration (Fig. 2b) and that there is a linear relationship between it and the concentration of the starting compound (Fig. 2c).

In addition to a study of the kinetics of the process, certain information regarding the mechanism of the reaction can be obtained from observations of the accumulation of oxi-

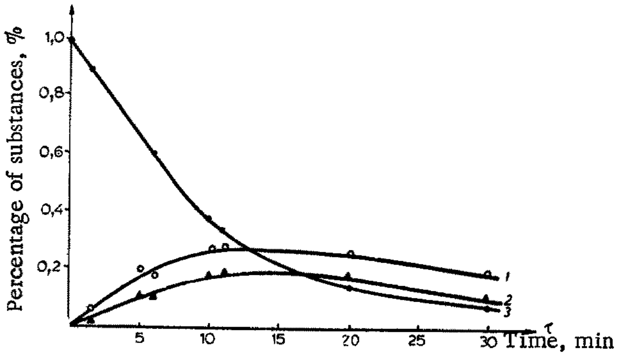
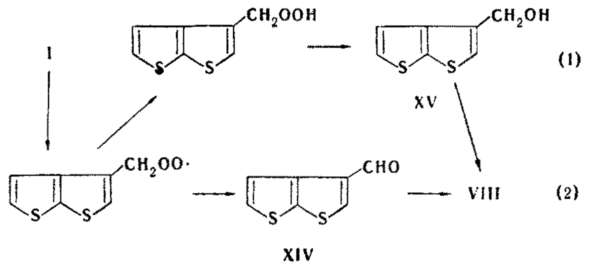


Fig. 3. Kinetic curves of the accumulation of thieno[2,3-b]-3-formylthiophene (XIV) (1) and 3-hydroxymethylthieno[2,3-b]thiophene (XV) (2) and consumption of 3-methylthieno[2,3-b]thiophene (I) (3).

dation products. The kinetic curves of the consumption of thienothiophene I and accumulation of the products of its oxidation at 100° (from gas–liquid chromatography data) are presented in Fig. 3. The results indicate that the oxidation of thienothiophene I proceeds through the intermediate formation of thieno[2,3-b]-3-formylthiophene (XIV) and 3-hydroxymethylthieno[2,3-b]thiophene (XV) (Fig. 3, curves 1 and 2). Moreover, one observes an increase up to a certain instant in the concentrations of aldehyde XIV and alcohol XV, after which they remained unchanged for a certain time and then decrease. Let us note that the instant of the decrease in the rate of oxidation coincides with the maximum percentages of XIV and XV in the catalyzate. The presence of aldehyde XIV and alcohol XV in the oxidation products in the first few minutes may constitute evidence for their parallel formation.

From a kinetic point of view, the mechanism of the oxidation of the investigated heterocyclic compounds in the early stages of the process can be represented by a scheme involving degenerately branched reactions. The rate-determining step in the process is transfer of an electron between the peroxide radical and the divalent cobalt ion, which is realized in two steps through the intermediate formation of a complex between the peroxide radical and the cobalt ion.

On the basis of the experimental data obtained it can be assumed that the formation of aldehyde XIV and alcohol XV occurs mutually independently via reaction (1), involving the decomposition of the hydroperoxide, and via reaction (2), involving disproportionation of the peroxide radicals:



Aldehyde XIV and alcohol XV are subsequently oxidized to acid VIII; they are not detected in the catalyzate after completion of the process. Acid VIII was isolated from the catalyzate. It proved to be identical to acid VIII obtained by an independent method — metallation and subsequent carbonization of 3-bromothieno[2,3-b]thiophene [11].

EXPERIMENTAL METHOD

The oxidation of thienothiophenes I and II was investigated with a gasometric apparatus [10]. The cobalt and manganese acetates and glacial acetic acid were purified in the usual way prior to the experiments.

Analysis by gas–liquid chromatography (GLC) of the starting compounds and the catalyzates was accomplished with an LKhM-8MD chromatograph (model 5). The detector was a katharometer, the column temperature was 190°, the vaporizer temperature was 200°, the carrier-gas (helium) flow rate was 36 ml/min, and the stainless steel column (300 by 0.3 cm) was filled with 5% SE-30 silicone elastomer on Chromosorb W (100-120 mesh). Diphenyl (mp 69-70°) was used as the internal standard for quantitative evaluation of the chromatograms. Inasmuch as diphenyl was not oxidized under the experimental conditions, it was added to the reaction mixture in 1.13 wt.% amounts prior to the start of the oxidation.

3-Methylthieno[2,3-b]thiophene (I). A solution of 127.2 g of 3-bromothiophene in 300 ml of absolute ether was added dropwise at –70° to 484 ml of an ether solution of n-butyllithium (0.1035 g/ml) under conditions excluding the penetration of moisture in an atmosphere of dry argon, 1 h after which a solution of 69.7 g of DMA in 300 ml of absolute ether was added at the same temperature. After 30 min, the temperature of the mixture was brought to –50°, and another 484 ml of the ether solution of n-butyllithium was added to it at –50 to –35°. The cooling bath was removed, the mixture was stirred for 30 min, and 26 g of powdered sulfur was added to it at –15°. The temperature of the mixture was raised to room temperature in the course of an hour. It was then refluxed for 30 min, after which it was cooled to –15° and treated with 119.6 g of methyl bromoacetate. The mixture was then refluxed for 30 min and acidified slightly with dilute HCl at 0°. The ether layer was separated, the aqueous layer was extracted thoroughly with ether, and the ether extracts were washed with saturated sodium carbonate solution and water and dried over $MgSO_4$. The ether was removed by distillation, and the residue was fractionated to give 74.8 g of methyl (3-acetyl-2-thienylmercapto)acetate (VI) with bp 163-168° (5 mm).

Treatment of ester VI with sodium methoxide in methanol as in [6] gave 3-methylthieno-[2,3-b]thiophene-2-carboxylic acid (VII) in 95% yield, the decarboxylation of which in quinoline in the presence of copper gave thienothiophene I (60%) with bp 122° (18 mm), n_D^{25} 1.6370, and d_4^{20} 1.5289 [bp 102-103.5° (9 mm) and n_D^{20} 1.6401 [8]]. According to GLC, thienothiophene I contained a small amount of an unidentified compound, which completely inhibited the oxidation process. Compound I was therefore subjected to two rectifications with a column with 30 theoretical plates, after which it had bp 180° (139mm) and n_D^{25} 1.6369 and did not contain any impurities, according to GLC. Found %: C 54.9; H 4.0; S 41.3. $C_7H_6S_2$. Calculated %: C 54.5; H 3.9; S 41.6.

Thieno[2,3-b]thiophene-3-carboxylic Acid (VIII). A total of 9.14 ml of an ether solution of n-butyllithium (0.085 g/ml) was added at –70° to a solution of 1.9 g of 3-bromothieno-[2,3-b]thiophene (prepared by the method in [11]) in 25 ml of absolute ether, and the mixture was stirred at this temperature for 30 min. It was then poured over dry ice in absolute ether, and the mixture was worked up to give 1.41 g (88.3%) of acid VIII with mp 185-186° (from benzene). Found %: C 45.9; H 2.3; S 34.5. $C_7H_4O_2S$. Calculated %: C 45.6; H 2.2; S 34.8.

3-Methylthieno[3,2-b]thiophene (II). A cooled (to –70°) solution of 84 g of 3-bromothiophene in 180 ml of absolute ether was added dropwise to 332 ml of an ether solution of n-butyllithium (0.0994 g/ml) at –70°, and 18.14 g of powdered sulfur was added to the mixture after 2 h. The mixture was then stirred at –70° for 1 h, after which the temperature was raised to –10°, and the mixture was treated with 45.9 g of methyl chloroacetate. The resulting mixture was refluxed for 2 h, after which the solvent was removed by distillation, and the residue was fractionated to give 47.5 g of methyl (3-thienylmercapto)acetate (II) with bp 126-140° (6 mm) and n_D^{20} 1.5627 (bp 110-111° and n_D^{20} 1.5648 [6]).

A mixture of 47.5 g of ester III, 20.4 g of acetyl chloride, and 310 ml of dry benzene was cooled to 5°, and 67.1 g of $SnCl_4$ in 50 ml of dry benzene was added to it dropwise in the course of 45 min. Workup of the resulting mixture gave 42.7 g of methyl (2-acetyl-3-thienylmercapto)acetate, which, without further purification, was treated with sodium methoxide in methanol to give 32.6 g (88.5%) of 3-methylthieno[3,2-b]thiophene-2-carboxylic acid (V) with mp 233° (dec.) (mp 228-229° [6])/

Decarboxylation of acid V gave thienothiophene II (71%) with bp 88-90° (6 mm), n_D^{20} 1.6386, and d_4^{20} 1.2526 [bp 73-74° (2 mm) and n_D^{20} 1.6370 [6]]. Found %: C 54.3; H 3.7. $C_7H_6S_2$. Calculated %: C 54.5; H 3.9. According to GLC, II did not contain impurities.

Oxidation of 3-Methylthieno[2,3-b]thiophene (I). A thermostatted cell connected to a gas burette by a system of stopcocks was charged with 16 ml of a mixture of 0.081 g-mole/liter of I, $5 \cdot 10^{-2}$ g-mole/liter of $Co(CH_3CO_2)_2$, and $1.55 \cdot 10^{-2}$ g-mole/liter of NaBr in glacial acetic acid. Oxygen was blown through the cell, and the stopcocks were closed after the pressure in the system had been equalized. The process was carried out with vigorous shaking with a high-speed rocker for 1 h at 110°. At the end of the process, the contact solution was diluted with water and extracted repeatedly with benzene. The benzene extracts were washed with saturated sodium carbonate solution and acidified with dilute HCl (1:3). Thieno[2,3-b]thiophene-3-carboxylic acid (VIII), with mp 186.5-188.5° (after recrystallization from benzene and vacuum sublimation), was obtained. Found %: C 45.4; H 2.2; S 34.2. $C_7H_4O_2S_2$. Calculated %: C 45.6; H 2.2; S 34.8

No melting-point depression was observed for a mixture of the product with acid VIII obtained by an independent method (see above). The UV spectra of the two acids were identical.

Oxidation of 3-Methylthieno[3,2-b]thiophene (II). This compound was similarly oxidized. Attempts to isolate thieno[3,2-b]thiophene-3-carboxylic acid by treatment of the benzene extract with sodium carbonate solution and subsequent acidification did not give positive results. The presence of starting thienothiophene II and a second compound with a higher retention volume in the benzene extract after drying was demonstrated by GLC. The benzene was removed by distillation, and the residue was subjected to molecular distillation. Starting compound II, with bp 73-75° (2 mm) and n_D^{20} 1.6380, was isolated. The residue was treated with hot alcohol to give a yellow crystalline precipitate of thieno[3,2-b]-3-formylthiophene (IX) with mp 67° (mp 68-69.5° [8]), which rapidly darkened in air.

LITERATURE CITED

1. V. P. Litvinov, Ya. L. Gol'dfarb, V. V. Zelentsov, L. G. Bogdanova, and N. N. Petukhova, Khim. Geterotsikl. Soedin., 486 (1975).
2. T. V. Shchedrinskaya, V. P. Litvinov, P. A. Konstantinov, Ya. L. Gol'dfarb, and É. G. Ostapenko, Khim. Geterotsikl. Soedin., 1026 (1973).
3. R. L. Hopkins, C. Y. Thompson, H. J. Coleman, and H. T. Rall, US Bureau of Mines, Rept. Juvest., No. 6795 (1969); Chem. Abstr., 65, 8619 (1966).
4. H. J. Coleman, R. L. Hopkins, and C. J. Hempson, Int. J. Sulfur Chem., 6B, 42 (1971).
5. Ya. L. Gol'dfarb and V. P. Litvinov, Izv. Akad. Nauk SSSR, Otd. Khim. Nauk, 352 (1963).
6. Ya. L. Gol'dfarb, V. P. Litvinov, and S. A. Ozolin', Izv. Akad. Nauk SSSR, Ser. Khim., 510 (1965).
7. V. P. Litvinov and G. Frénkl, Izv. Akad. Nauk SSSR, Ser. Khim., 1828 (1968).
8. A. Bugge, Acta Chem. Scand., 25, 27 (1971).
9. L. A. Smurova, T. V. Sirota, A. B. Gagarina, V. P. Litvinov, É. G. Ostapenko, Ya. L. Gol'dfarb, and N. M. Émanuél', Dokl. Akad. Nauk SSSR, 198, 1378 (1971).
10. P. A. Konstantinov, T. V. Shchedrinskaya, I. V. Zakharov, and M. N. Volkov, Zh. Organ. Khim., 8, 2590 (1972).
11. Ya. L. Gol'dfarb, I. P. Konyaeva, and V. P. Litvinov, Izv. Akad. Nauk SSSR, Ser. Khim., 1570 (1974).