

STUDIES IN THE THIOPHENE SERIES. VI.*

ELECTROCHEMICAL BROMINATIONS OF METHYLTHIOPHENES

M. NĚMEC, M. JANDA and J. ŠROGL

Department of Organic Chemistry,
Institute of Chemical Technology, 166 28 Prague 6

Received March 26th, 1973

The electrochemical oxidation of 2- and 3-methylthiophene has been examined in methanolic ammonium bromide as electrolyte on the carbon and platinum anode with a constant current. Thus, 2-methylthiophene affords 5-bromo-2-methylthiophene (*I*) as the main product along with 3,5-dibromo-2-methylthiophene (*II*) and 1,1,4,4-tetramethoxy-2-pentene (*III*). From 3-methylthiophene, there are obtained 2-bromo-3-methylthiophene (*V*), 2,5-dibromo-3-methylthiophene (*VI*) and 1,1,4,4-tetramethoxy-2-methyl-2-butene (*VII*).

The electrochemical bromination of thiophene¹ has been recently reported to take place when a methanolic solution of ammonium bromide is used as electrolyte. In the present paper, 2- and 3-methylthiophene are examined as suitable models in investigations on the character of the anodically generated particles. The radical bromination of methylthiophenes is known to afford as the main products the side-chain brominated derivatives². In the case of a one-electron transfer process ($\text{Br}^- \rightarrow \text{Br}^\bullet + e$), the resulting bromomethylthiophenes could be easily differentiated from products of the electrophilic bromination (cation formation by a two-electron transfer process, $\text{Br}^- \rightarrow \text{Br}^+ + 2e$).

The electrobromination of 2-methylthiophene affords 5-bromo-2-methylthiophene (*I*) as the main product. The structure of compound *I* was confirmed by NMR spectrum, mass spectrum and gas chromatography (the retention time was compared with that of an authentic sample prepared by bromination of 2-methylthiophene with dioxane dibromide. In addition to compound *I*, the reaction mixture contained three other compounds (Table I). The structure of a dibromo derivative is suggested by mass spectrum (m/e 257, 255, 253 $M-1$, 177, 175 $M-\text{Br}$, 96 $M-2\text{Br}$) for the component of the longest retention time. Consequently, the two possible dibromo derivatives have been synthesized. Thus, 3,5-dibromo-2-methylthiophene (*II*) was obtained by bromination of 2-methylthiophene with two equivalents of dioxane dibromide³. In this bromination, there was observed the presence of a product of an attack at the methyl group (NMR $\delta\text{-CH}_2\text{Br}$, 4.64 p.p.m.). 2,3-Dibromo-5-

* Part V: This Journal 38, 1221 (1973).

methylthiophene was prepared by an analogous bromination of 4-bromo-2-methylthiophene, obtained in turn from 2,4-dibromothiophene *via* the reaction with one equivalent of ethyllithium⁴ and methylation of the thus-obtained 2-lithio-4-bromothiophene with dimethyl sulfate. On the basis of the gas-chromatographic comparison with these two authentic samples, the above dibromo derivative was ascribed the structure of compound *II*. As shown by mass spectra, the other two by-products represent methoxylated compounds, lacking the sulfur atom. Furthermore, these mass spectra are identical with those of the two principal products obtained by the electrochemical oxidation of 2-methylthiophene in a methanolic solution of sulfuric acid⁵. According to NMR and mass spectrum, the compound of the shortest retention time is 1,1,4,4-tetramethoxy-2-pentene (*III*). As suggested by the coupling constant 5 Hz, the configuration at the double bond is *cis*. On the basis of the mass spectrum and in agreement with the occurrence of a strong absorption band at 1740 cm⁻¹ in infrared spectrum, the remaining component was ascribed the structure of methyl 4,4-dimethoxypentanoate (*IV*).

The electrochemical bromination of 3-methylthiophene (see Table II) affords as the main product the ring-brominated 2-bromo-3-methylthiophene (*V*), the structure of which was confirmed by NMR spectrum, elemental analysis, and comparison of the retention time with that of an authentic sample. Similarly to the electrophilic bromination (*e.g.*, with dioxane dibromide), the first bromo atom enters exclusively the position 2 and not the position 5. Compound *V* is accompanied by 2,5-dibromo-3-methylthiophene (*VI*), the structure of which was confirmed similarly, *i.e.*, by NMR spectrum, elemental analysis, and comparison of the retention time with that of an authentic specimen. In the electrobromination of 3-methylthiophene, the proportion of the dibromo derivative is higher; this finding might be explained by the presence of two unoccupied α -positions which are more favourable for the electrophilic substitution. The third component of the reaction mixture is 1,1,4,4-tetramethoxy-2-methyl-2-butene (*VII*). The NMR spectrum indicates the presence of a single geometrical isomer but can not determine whether a *cis* or *trans* compound is involved.

As suggested by the above results of the electrochemical bromination of 2- and 3-methylthiophene in a methanolic solution of ammonium bromide (see Tables I and II), a primary oxidation occurs at the anode of the bromide anion to the cation Br⁺ which then reacts with the substrate in terms of the electrophilic substitution. The one-electron transfer process accompanied by the formation of free radicals may be entirely excluded because of the absence of any derivatives brominated in the side chain. The formation of the methoxylated products *III* and *VII* might be explained by a partial simultaneous oxidation of the substrate at the anode which affords the regular products of an ECEC oxidation (*cf.* the anodic oxidation of thiophene derivatives in methanolic sulfuric acid^{5,6}). Compound *IV* is presumably formed by an additional reaction from compound *III*. The methoxylated products are formed to a greater extent at low temperatures when the chemical reaction of the

primarily formed bromide cation with the thiophene ring is slow enough to allow a simultaneous oxidation of the thiophene ring at the anode. The result of the electrobromination of 2-methylthiophene is also promising from the standpoint of a preparative application. The yield of 5-bromo-2-methylthiophene is under some conditions (see Table I) similar to those of the chemical brominations.

EXPERIMENTAL

Temperature data are uncorrected. NMR spectra were measured on a Varian XL 100 (100 MHz) apparatus in deuteriochloroform with the use of tetramethylsilane as internal standard. Mass spectra were taken on a LKB 9000 spectrometer. Gas chromatography was performed on a Chrom 31 apparatus (flame ionisation detector; Carbowax 20 M and Silicone SE 30 as the stationary phase). The electrochemical brominations were carried out in an externally cooled electrolysis apparatus⁷ with a coaxial graphite anode and nickel cathode. The platinum anode electrolysis was performed in a 250 ml beaker equipped with coaxial platinum electrodes and a stirrer.

Electrochemical Bromination of Methylthiophenes

A. A solution of the corresponding methylthiophene (4.9 g; 0.05 mol) and ammonium bromide (5 g) in methanol (150 ml) was electrolysed with constant current 1.5 A. For the bath temperatures during the electrolysis see Tables I and II. The reaction mixture after the electrolysis was concentrated to a half of the original volume and the residue poured into water (150 ml). The aqueous phase was extracted with five 40 ml portions of ether, the extracts were combined, dried over anhydrous magnesium sulfate, the ether evaporated at the ordinary pressure, and the residue distilled *in vacuo*. The composition of the distillate (b.p. 60–100°C/15 Torr) was determined by gas chromatography. In the case of 2-methylthiophene, the product *I* (b.p. 65°C/15 Torr) was obtained in the pure state by distillation. In the case of 3-methylthiophene, a rectification through a 40 cm packed column was necessary to obtain pure compounds *V* (b.p. 60°C/12 Torr), *VI* (b.p. 101°C/12 Torr), and *VII* (b.p. 90°C/12 Torr). Compound *III* was isolated by preparative gas chromatography. For experimental details and results see Table I (electrobromination of 2-methylthiophene) and Table II (of 3-methylthiophene). For compound *V*, C₅H₅BrS (177.1) calculated: 45.13% Br; found: 44.35% Br. For compound *VI*, C₅H₄Br₂S (256.0) calculated: 62.44% Br; found: 61.84% Br.

NMR spectra (δ). *I*, 2.42 (d, 3, CH₃), 6.49 (dq, 1, 3 H), 6.80 (d, 1, 4 H), $J_{\text{HH}} = 3.7$ Hz, $J_{\text{HCH}_3} = 1.0$ Hz. *III*, 1.43 (s, 3, CH₃), 3.20 (s, 12, OCH₃), 5.50 (d, 1, 2 or 3 H), 5.54 (s, 1, 4 H), 5.84 (d, 1, 2 or 3 H), $J_{\text{HH}} = 5.0$ Hz. *V*, 2.20 (s, 3, CH₃), 6.74 (d, 1, 4 H), 7.14 (d, 1, 5 H), $J_{\text{HH}} = 5.5$ Hz. *VI*, 2.16 (s, 3, CH₃), 6.76 (s, 1, 4 H). *VII*, 1.76 (d, 3, CH₃), 3.22 (s, 6, OCH₃), 3.36 (s, 6, OCH₃), 4.99 (s, 1, 1 H), 5.20 (d, 1, 4 H), 5.48 (dq, 1, 3 H), $J_{\text{HH}} = 6.5$ Hz, $J_{\text{HHC}_3} = 1.2$ Hz.

Mass spectra, m/e (% of rel. intensity). *I*, 178 (38), 176 (38), 97 (100), 53 (42), 45 (44). *II*, 257 (46), 255 (92), 253 (47), 177 (100), 175 (100), 96 (92). *III*, 159 (41), 143 (64), 111 (100), 75 (36), 43 (64). *IV*, 175 (12), 159 (80), 143 (70), 127 (80), 101 (51), 89 (61), 85 (86), 43 (100). *VII*, 159 (41), 143 (24), 127 (24), 115 (24), 85 (53), 75 (100).

B. A solution of 2-methylthiophene (9.8 g; 0.1 mol), sulfuric acid (0.8 ml), and methanol (300 ml) was electrolysed for 5 h with the current 4 A at the bath temperature of –60°C. After neutralisation with methanolic sodium methoxide (from 0.8 g of sodium and 20 ml of methanol), the reaction mixture was processed as in paragraph *A*. Distillation afforded 5.1 g of a liquid, b.p. 80–125°C/15 Torr, containing as the main products two compounds, the retention times and mass spectra of which corresponded to compounds *III* and *IV* obtained as by-products of the electrolysis in ammonium bromide as the electrolyte.

TABLE I
Electrochemical Bromination of 2-Methylthiophene

Charge <i>F</i> /mol	Anode	Temperature °C	Total yield, %	Products, rel. %			
				<i>I</i>	<i>II</i>	<i>III</i>	<i>IV</i>
2	C	-6	56.6	99.2	—	0.8	—
4	C	-7	65.1	99.0	trace	1.0	—
4 ^a	C	-5	60.7	97.8	2.0	0.2	—
2	C	30	42.6	100	—	—	—
2	Pt	5	38.2	99.0	—	1.0	—
2	C	-50	29.8	96.5	—	3.5	—
6	C	-50	50.3	87.5	3.2	6.3	3.0
8	C	-50	55.2	80.8	3.1	9.1	7.0

^a The reaction mixture contained 1.5 mol of ammonium bromide per 1 mol of 2-methylthiophene.

TABLE II
Electrochemical Bromination of 3-Methylthiophene

Charge <i>F</i> /mol	Anode	Temperature °C	Total yield, %	Products, rel. %		
				<i>V</i>	<i>VI</i>	<i>VII</i>
2	Pt	5	50.6	95.6	4.4	trace
3	C	-5	53.9	86.5	8.0	5.5
3	C	-70	37.1	57.5	17.5	25.0
6	C	-70	66.3	56.0	20.0	24.0
12	C	-70	69.0	53.0	22.5	24.5

Materials and Authentic Specimens

2-Methylthiophene. The Vilsmeier-Haack formylation of thiophene⁸ afforded 2-thiophene-carbaldehyde, the Kishner-Wolff reduction of which with 30% hydrazine hydrate led to 2-methylthiophene⁹, b.p. 112°C.

3-Methylthiophene. The intermediary 3-thienyllithium (obtained by metallation of 3-bromothiophene¹⁰ with *n*-butyllithium) was formylated at -78°C with dimethylformamide¹¹. The thus-obtained 3-thiophene-carbaldehyde was reduced with 75% hydrazine hydrate to 3-methylthiophene³, b.p. 114°C.

5-Bromo-2-methylthiophene (I). To a solution of 2-methylthiophene (4.9 g) in dioxane (25 ml), there was added dropwise under stirring bromine (8.0 g) in dioxane (50 ml) over 30 min. The reaction mixture was stirred at room temperature for additional 30 min, poured into water, and

extracted with ether. The extract was washed with aqueous sodium hydroxide and water, dried over anhydrous magnesium sulfate, and evaporated. Distillation of the residue afforded 4.6 g of compound *I*, b.p. 85°C/45 Torr.

3,5-Dibromo-2-methylthiophene (II). 2-Methylthiophene (4.9 g) was processed analogously to the preparation of compound *I*; bromine (16 g) in dioxane (100 ml) was added over 2 h and the reaction mixture was stirred at 80°C for additional 2 h. Distillation afforded 5.9 g of a liquid (b.p. 100–120°C/14 Torr) containing (as indicated by NMR spectrum) two components, one of which carried the bromomethyl group. Rectification of this liquid afforded compound *II*, b.p. 90°C/10 Torr. NMR spectrum (δ): 2.32 (s, 3, CH₃), 6.86 (s, 1, 4 H).

2,3-Dibromo-5-methylthiophene. 4-Bromo-2-methylthiophene (6.1 g) was processed analogously to the preparation of compound *I*. Distillation afforded 7.7 g of the product, b.p. 105–107°C/14 Torr. NMR spectrum (δ): 2.40 (d, 3, CH₃), 6.58 (q, 1, 4 H), $J_{\text{HCH}_3} = 1.0$ Hz.

2-Bromo-3-methylthiophene (V). 3-Methylthiophene (4.9 g) was processed analogously to the preparation of compound *I*. Distillation afforded 5.1 g of compound *V*, b.p. 85°C/45 Torr.

2,5-Dibromo-3-methylthiophene (VI). 3-Methylthiophene (2.45 g) was processed analogously to the preparation of compound *II* to afford 4.0 g of compound *VI*, b.p. 100–105°C/14 Torr.

REFERENCES

1. Němec M., Šrogl J., Janda M.: This Journal 37, 3122 (1972).
2. Campaigne E., Le Suer W. M.: J. Am. Chem. Soc. 70, 1555 (1948).
3. Reinecke M. G., Adickes H. W., Pyun Ch.: J. Org. Chem. 36, 2690 (1971).
4. Laweson S. O.: Arkiv Kemi 11, 317 (1957).
5. Šrogl J., Janda M., Valentová M.: This Journal 35, 148 (1970).
6. Janda M., Šrogl J., Janoušová A., Kubelka V., Holík M.: This Journal 35, 2635 (1970).
7. Němec M., Stibor I.: Chem. listy 66, 1310 (1972).
8. King J. W., Nord F. F.: J. Org. Chem. 13, 635 (1948).
9. King J. W., Nord F. F.: J. Org. Chem. 14, 638 (1949).
10. Gronowitz S., Raznikiewicz T.: Org. Syn. 44, 9 (1964).
11. Gronowitz S.: Arkiv Kemi 8, 441 (1956).

Translated by J. Pliml.