

STUDIES IN THE THIOPHENE SERIES. V.*
ANODIC OXIDATION OF METHYL ESTERS
OF THIOPHENECARBOXYLIC ACIDS

M. JANDA, J. ŠROGL, M. NĚMEC and A. JANOUŠOVÁ

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

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Electrochemical oxidation of methyl esters of 2-thiophenecarboxylic (*I*) and 3-thiophenecarboxylic acids (*II*) on a graphite anode in methanolic solution of sulfuric acid was investigated at a constant current. From the reaction of substance *I* *cis*- and *trans*-1,3-bismethoxycarbonyl-3,3-dimethoxypropene (*III*, *IV*) have been isolated, while substance *II* gave 1,1,4,4-tetramethoxy-2-methoxycarbonyl-2-butene (*VI*) as the sole product.

During anodic oxidation of thiophene derivatives in methanolic sulfuric acid elimination of sulfur takes place under formation of derivatives of tetramethylacetal of butenedial supposedly by ECEC mechanism¹⁻⁵. In the case of alkyl and halogen derivatives of *trans*-butenedial are formed exclusively. In the case of 2-thenyl alcohol a product oxidized in the side chain was isolated; 2-thiophenecarbaldehyde was formed as the main product⁶. With the knowledge of these facts we submitted to anodic oxidation methyl esters of 2- and 3-thiophenecarboxylic acids (*I* and *II*) as representatives of derivatives with substituents of the -I, -M character. Oxidation was carried out under the same conditions as in the preceding papers, *i.e.* in methanolic sulfuric acid on a graphite anode and at a constant current.

Gas chromatographic analysis of the products of oxidation of ester *I* demonstrated that three substances are formed, A, B, and C, according to increasing retention times. Their relative representation changed slightly, as shown in Table I. Substances B and C were obtained in pure state by preparative gas chromatography. In the NMR spectrum of compound C (Table II) two signals were present, corresponding to one methoxyl, and one signal for two methoxyls shifted by 0.5 δ . No signal was found in the spectrum for the acetal proton, which should be present in the product the formation of which corresponds to the general scheme $EC_N EC_N$. Further, two signals of protons on a double bond were also present in the spectrum, which were coupled. The coupling constant indicates a *trans* arrangement at the double bond. According to these data, which also agree with the elementary analysis and the mass

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spectrum (Table III), it was possible to propose the structure of *trans*-1,3-bis(methoxy-carbonyl)-3,3-dimethoxy-propene (IV) for substance C. From the mass spectral data of substances B and C (Table III) a case of *cis-trans* isomery could be envisaged.

TABLE I
Results of Electrochemical Oxidations of Esters I and II (14.2 g)

Starting ester	Time h	Current A	Temperature °C	Products, g					
				I	II	A	III	IV	VI
I	4.5	4.3	-25	5.0	—	0.5	4.5	2.3	—
I	4.0	4.5	-50	6.0	—	1.0	5.4	1.8	—
I	8.0	4.5	-50	1.3	—	2.4	8.4	3.0	—
I ^a	6.0	4.0	-25	0.2	—	—	1.9	2.6	—
II	5.0	4.0	-50	—	4.4	—	—	—	6.8
II	8.0	4.0	-50	—	1.6	—	—	—	9.8

^a The product of a 4.5-h oxidation of ester I was oxidised.

TABLE II
PMR Spectra, Shifts δ (p.p.m.)

Substance	CH	OCH ₃
III	6.09 (s, 2 H)	3.28 (s, 6 H), 3.73 (s, 3 H), 3.82 (s, 3H)
IV	6.32 (d, 1 H, $J = 15.9$ Hz), 6.72 (d, 1 H, $J = 15.9$ Hz)	3.28 (s, 6 H), 3.75 (s, 3 H), 3.79 (s, 3 H)
VI	5.27 (s, 1 H), 5.57 (d, 1 H, $J =$ $= 8.0$ Hz), 6.71 (d, 1 H, $J =$ $= 8.0$ Hz)	3.35 (s, 12 H), 3.73 (s, 3 H)

TABLE III
Mass Spectra

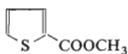
All ions of a relative intensity higher than 10% are listed, m/e (% of relative intensity).

III	218 (0.1), 187 (8), 159 (100), 113 (40), 99 (8), 85 (26), 75 (16), 59 (34), 55 (14)
IV	218 (0.1), 187 (12), 159 (100), 113 (33), 99 (24), 85 (19) 75 (12), 59 (33), 55 (12), 53 (12)
A	203 (2), 175 (7), 133 (43), 101 (21), 75 (100), 59 (14), 47 (14), 31 (10)
VI	203 (15), 187 (15), 171 (18), 143 (22), 75 (100), 41 (18)

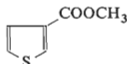
The NMR spectrum of substance B (Table II) differed from the former only in the region of signals of double bond protons. Instead of a doublet of doublets this spectrum contained only a single sharp singlet. In view of this unusual phenomenon we carried out the hydrogenation of the double bond and the addition of bromine, followed by its elimination, in order to prove the supposed structure. The NMR spectrum of the product after hydrogenation corresponds to the expected spectrum for 1,3-bis(methoxycarbonyl)-1,1-dimethoxypropane (V), and it was identical with the spectrum of this dimethyl ketal of the dimethyl α -ketoglutarate prepared from methyl 2,5-dimethoxy-2,5-dihydro-2-furancarboxylate⁷. The product of elimination of bromine with zinc had an NMR spectrum identical with that of substance IV. From these data we conclude that substance B has the structure of *cis*-1,3-bis(methoxycarbonyl)-3,3-dimethoxypropene (III). The structure of substance A can be guessed only on the basis of its mass spectrum (Table III). M/e 203 indicates that the molecular weight is 234 ($M-31$). The most abundant peak in the spectrum is m/e 75, which corresponds to the fragment $[\text{CH}(\text{OCH}_3)_2]^+$. Hence, substance A is probably the methyl ester of 2,2,5,5-tetramethoxy-3-pentenoic acid, which is the expected product of two-electron oxidation of the starting ester I.

After the oxidation of ester II the formation of a single substance was proved gas chromatographically in the reaction mixture. On the basis of the NMR spectrum (Table II), mass spectrum (Table III), and elementary analysis we assigned it the structure of 1,1,4,4-tetramethoxy-2-methoxycarbonyl-2-butene (VI). From the NMR data no conclusion can be made concerning *cis-trans* isomery on the double bond.

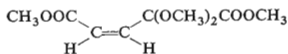
The formation of 1,1,4,4-tetramethoxy-2-methoxycarbonyl-2-butene agrees with the idea of the reaction scheme comprising a primary loss of electron in the α -position of the heterocycle under formation of a radical cation, its methanolysis, another loss of one electron, and eventual methanolysis under formation of the product ($\text{EC}_\text{N}\text{EC}_\text{N}$ mechanism). The formation of substances III and IV is not explained by this mechanism. We suppose that intermediate 2,5-dimethoxy-2,5-dihydro-2-methoxycarbonyl-



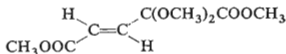
I



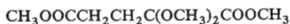
II



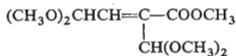
III



IV



V



VI

thiophene loses an additional electron on the anode, and that the radical cation formed is stabilised by the loss of a proton; the radical formed in this manner is again oxidised to a cation by the loss of one electron; the cation may react with the water in the reaction medium, affording the final product. The overall oxidation is therefore a four-electron reaction. In contrast to the preceding cases of oxidation in the thiophene series when *trans*-butenedials were isolated exclusively, in the case of the 2-thiophenecarboxylic acid ester both isomers were formed.

EXPERIMENTAL

The temperature data were not corrected. The NMR spectra were measured in deuteriochloroform on Tesla BS 477 (60 MHz) and JEOL 100 MHz spectrometers. The mass spectra were taken with a LKB 9000 apparatus. Gas chromatographic analyses were carried out on a Chrom II apparatus, using FID. Preparative gas chromatography was carried out with a Carlo Erba apparatus, Carbowax 20 M on Chromosorb W as stationary phase. Electrooxidations were performed in an electrolyser composed of a coaxial graphite anode and a nickel cathode, cooled externally by a mixture of butanol and solid carbon dioxide⁸.

The starting esters were prepared according to described methods. Methyl 2-thiophenecarboxylate was prepared from thiophene by acetylation⁹, haloform reaction⁹, and esterification of the acid thus formed by boiling it with methanolic hydrogen chloride. The synthesis of methyl 3-thiophenecarboxylate proceeded *via* 3-bromothiophene¹⁰ which was transformed with cuprous cyanide to nitrile¹¹. The acid obtained on hydrolysis of the nitrile¹² was esterified in the same manner as in the case of the preparation of ester I.

Anodic oxidation of esters I and II: Solutions of 14.2 g (0.1 mol) of ester and 0.5 ml of sulfuric acid in 300 ml of methanol were submitted to electrolysis. The current intensity, time of electrolysis and temperature (kept low by keeping the vessel in a cooling bath) are given in Table I for single experiments. After electrolysis the reaction mixture was neutralised with sodium methoxide (0.5 g of sodium in 20 ml of methanol), methanol was evaporated under reduced pressure, and the residue extracted with 300 ml of ether. The extract was dried over magnesium sulfate, filtered and evaporated *in vacuo*. The residue was distilled and the distillate analysed by GLC. Substances III and IV were obtained in pure state by preparative gas chromatography, while substance VI was isolated in sufficient purity by rectification of the distillate (b.p. 92°C/0.5 Torr). The results of single experiments are given in Table I, the NMR spectra in Table II, and the mass spectra in Table III. Elemental analyses: For C₉H₁₄O₆ (218.2) calculated: 49.54% C, 6.47% H, 56.89% OCH₃; found: for III: 49.61% C, 6.52% H, 57.75% OCH₃; found: for IV: 48.92% C, 6.55% H, 55.76% OCH₃. For C₁₀H₁₈O₆ (234.3) calculated: 51.28% C, 7.75% H; found: for VI: 50.64% C, 7.27% H.

1,3-Bis(methoxycarbonyl)-1,1-dimethoxypropane (V): a) Substance III (0.2 g; 0.92 mmol) and platinum oxide (0.05 g) in 10 ml of methanol were stirred under hydrogen until the consumption of hydrogen ceased (36.6 ml at 24°C). After separation of the catalyst by filtration the solvent was evaporated *in vacuo* and the residue submitted to microdistillation which afforded 90 mg of chromatographically pure substance V; NMR spectrum (in δ) CH₂ 2.26 (s, 4 H), OCH₃ 3.28 (s, 6 H), 3.68 (s, 3 H), 3.81 (s, 3 H).

b) Methyl 2,5-dimethoxy-2,5-dihydro-2-furancarboxylate (16.5 g) was mixed with 50 ml of 35% hydrochloric acid and heated at 90°C for one hour. Water was evaporated *in vacuo* and the residue boiled with 250 ml of a 5% methanolic hydrogen chloride solution for 8 h. After evapora-

tion of methanol the residue was dissolved in ether, the ethereal layer washed with water, dried over magnesium sulfate and filtered. Ether was evaporated in a vacuum and the residue distilled, affording 2.2 of substance V. b.p. 80°C/0.2 Torr. The product obtained in the described manner had the same retention time and the same NMR spectrum as the product obtained under a).

Addition of bromine: 13 g of the product of oxidation of ester I, containing 56% of substance III, were dissolved in 20 ml of tetrachloromethane and 8 g of bromine in 10 ml of tetrachloromethane were added dropwise to it. After evaporation of the solvent the distillation of the residue gave 13 g of a product which boiled at 120–130°C/1 Torr (most important ions of the mass spectrum which proved the presence of two bromine atoms in the molecule are m/e 317, 319, 321 (M - 59), 266, 268 (M - Br - 31)). Methanol (15 ml) was added to the distillate, followed by 4.5 of zinc and several crystals of mercuric chloride, and the reaction mixture was refluxed for 1 h. Methanol was evaporated and the residue extracted with dichloromethane. After drying over magnesium sulfate and evaporation of the solvent 5 g of a residue were obtained, the NMR spectrum of which coincided with that of substance IV.

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