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Short Communication

On the Reaction of Diethyl 3,4-Dihydroxythiophene-2,5-dicarboxylate with 1,2-Dibromoethane

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Summary. Reaction of diethyl 3,4-dihydroxythiophene-2,5-dicarboxylate (**1**) with an excess of 1,2-dibromoethane afforded a mixture of the 2,3-dihydrothieno[3,4-b] [1,4]-dioxine-derivative **3** and the 3-oxo-2,3-dihydrothiophene **4**. Compounds **3** and **4** were characterized by spectroscopic methods.

Keywords. Dihydroxythiophenes; Alkylation; NMR Spectroscopy.

Zur Reaktion von 3,4-Dihydroxythiophen-2,5-dicarbonsäurediethylester mit 1,2-Dibromethan (Kurze Mitt.)

Zusammenfassung. Die Reaktion von 3,4-Dihydroxythiophen-2,5-dicarbonsäureethylester (**1**) mit einem Überschuß an 1,2-Dibromethan führt zur Bildung des 2,3-Dihydrothieno[3,4-b] [1,4]dioxin-Derivats **3** und des 3-Oxo-2,3-dihydrothiophens **4**. Die Struktur der Verbindungen **3** und **4** wurde mit Hilfe spektroskopischer Methoden ermittelt.

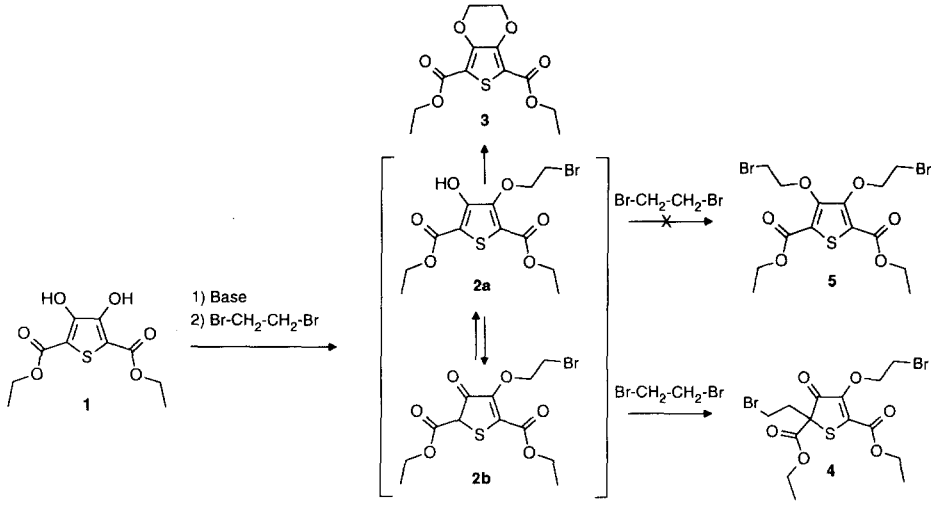
Introduction

In the course of a program directed to the synthesis of potential Thromboxane A_2 (TXA_2) synthase inhibitors we required an access to the dihalogeno compound **5**. An obvious possibility seemed to be the reaction of diethyl 3,4-dihydroxythiophene-2,5-dicarboxylate (**1**) [1, 2] with an excess of 1,2-dibromoethane. Regarding the synthesis of related compounds, it has been reported in the literature that such alkylations proceed smoothly by heating the apropriate phenol and the dihalogeno compound in the presence of anhydrous potassium carbonate [3].

Results and Discussion

The thiophene derivative **1** was refluxed with potassium carbonate and an excess of 1,2-dibromoethane in dry 2-butanone for 72 hours. From GLC/MS analysis it emerged that the reaction mixture obtained after workup (removement of the educts)

mainly consisted of two products. The far predominating component (M^+: $m/z = 286$) was found to contain no bromo atom, whereas the minor component (< 5%, M^+: $m/z = 474$) had two bromo atoms in the molecule. NMR spectroscopic investigations of the mixture revealed that the major product has to be attributed to structure **3**, which obviously results from cyclization of the initially formed *mono*-O-alkylation product **2a**. Compound **3** has already been obtained upon heating the *di*-Na salt of **1** with 1,2-dibromoethane [4, 5]. We found that the latter reaction conditions (*i.e.* refluxing the *di*-sodium salt of **1** with an excess of 1,2-dibromoethane) not only lead to the formation of compound **3**, but that again the above mentioned dibromo product (M^+: $m/z = 474$) was also present in the reaction mixture. However, in contrast to the reaction employing K_2CO_3 in 2-butanone, the two products now were detected in a *ca.* 1.5:1 ratio. They could be separated by column chromatography and were fully characterized by spectroscopic methods. The slower eluted compound was identified as the bicyclic system **3**, whereas the faster eluted component turned out to be the dibromo compound. Although elemental analysis indicated the latter to have an elemental formula of $C_{14}H_{18}Br_2O_6S$ (which corresponds with that of the desired molecule **5**), on account of its ^1H NMR spectrum which shows two non-equivalent ester functions the product could not have structure **5**. Additionally, in the ^{13}C NMR spectrum 14 different resonances were found, also indicating the molecule not to be symmetrical. The application of different NMR techniques (^1H NMR, NOE difference spectra, ^{13}C NMR, ^1H coupled ^{13}C NMR, COSY, HMQC and HMBC spectra, as well as 1D HETCOR spectra [6] and long-range INEPT experiments with selective DANTE excitation [7]) finally enabled us to assign structure **4** to this product and to perform complete assignments of all proton and carbon resonances (some of the most important criteria for assignments are diplayed in Fig. 1). A possible explanation for the formation of compound **4** is based on C-alkylation of **2b** (which represents the keto form of the *mono*-O-alkylation product of **1**). In principle, it would also be possible that under the present reaction conditions the educt **1** (or its salt) already



Scheme 1

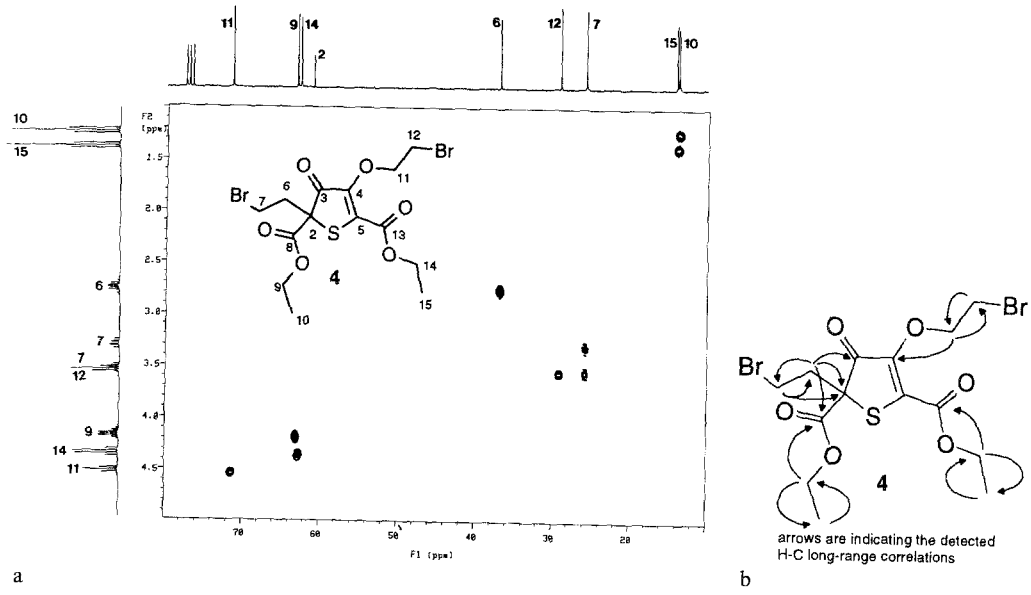


Fig. 1. **a** HMQC Spectrum of **5** ($CDCl_3$, aliphatic region): **b** long-range H–C correlations obtained from HMBC spectra and selective long-range INEPT experiments

tautomerizes to a *mono*-keto form and afterwards is C- and O-alkylated, respectively. However, ^1H and ^{13}C NMR spectra of **1** in $CDCl_3$ in *DMSO*-d_6 as well as those of its sodium salt (*DMSO*-d_6 + NaOD) prove these compounds to exist exclusively in the *di*-enol (ate) form and thus to contain an aromatic thiophene nucleus. This is in accordance with literature data [8–10] regarding tautomerism of dihydroxythiophenes. Nevertheless, the obvious occurrence of keto forms and the formation of a C-alkylation product in the course of the reaction of **1** with dibromoethane is somewhat surprising, as alkylations with 3,4-dihydroxythiophene-2,5-dicarboxylates are reported to give O-alkylation products exclusively [8].

Experimental

Elemental analyses were carried out by the Mikroanalytisches Laboratorium, Institute of Physical Chemistry, University of Vienna. IR spectra were recorded on a Perkin-Elmer FT-IR 1605 spectrometer. GLC/MS analyses were performed on a Hewlett-Packard 5890A/5970B-MSD instrument, the (high-resolution) mass spectra were obtained on a Finnigan MAT 8230 instrument (both EI, 70 eV). The NMR spectra were recorded on a Varian Unity*plus* 300 spectrometer (300 MHz for ^1H, 75 MHz for ^{13}C) at 28 °C. The center of the solvent peak was used as an internal standard which was related to *TMS* with $\delta = 7.26$ ppm (^1H, chloroform), $\delta = 2.49$ ppm (^1H, *DMSO*-d_6), $\delta = 77.00$ ppm (^{13}C, $CDCl_3$), and $\delta = 39.50$ ppm (^{13}C, *DMSO*-d_6). Column chromatography was performed on Merck Kieselgel 60 (70–230 mesh).

Diethyl 3,4-Dihydroxythiophene-2,5-dicarboxylate (**1**) [1, 2]

^1H NMR ($CDCl_3$): δ(ppm) = 9.30 (s, 2H, OH), 4.38 (q, $J = 7.1$ Hz, 4H, OCH_2), 1.38 (t, $J = 7.1$ Hz, 6H, CH_3); ^1H NMR (*DMSO*-d_6): δ(ppm) = 10.15 (broad s, 2H, OH), 4.27 (q, $J = 7.0$ Hz, 4H, OCH_2), 1.27 (t, $J = 7.0$ Hz, 6H, CH_3); ^{13}C NMR ($CDCl_3$): δ(ppm) = 165.6 (C=O), 151.8 (thiophene C-3,5), 107.3

(thiophene C-2,6), 61.7 (OCH_2), 14.1 (CH_3); ^{13}C NMR (*DMSO*-d_6): δ(ppm) = 161.9 (t, ^3J = 3.4 Hz, C=O), 149.9 (s, thiophene C-3,5), 107.9 (s, thiophene C-2,6), 60.6 (dt, ^1J = 148.4 Hz, ^2J = 4.3 Hz, OCH_2), 13.9 (dq, ^1J = 127.0 Hz, ^2J = 2.5 Hz, CH_3).

Reaction of **1** *with 1,2-Dibromoethane*

To a solution of sodium ethoxide (20 mmol, prepared from 460 mg of sodium and 20 ml of absolute ethanol) was added a solution of 2.60 g (10 mmol) of **1** in 40 ml of ethanol and the mixture was refluxed for one hour. Then the solvent was removed *in vacuo*; to the residual sodium salt were added 30 ml of 1,2-dibromoethane and the mixture was heated to 110° for 24 hours. The resulting suspension was poured onto water, the organic phase was successively washed with 2 *N* NaOH and water and evaporated *in vacuo*. The residue (1.85 g) was subjected to column chromatography. Eluting with dichloromethane gave as first component 720 mg (15%) of **4** as yellow oil. Switching to ethyl acetate as mobile phase afforded 710 mg (25%) of **3** which after recrystallization from ethanol gave colorless crystals of m.p. 151–152°.

Diethyl 2,3-Dihydro-thieno[3,4-b][1,4]dioxine-5,7-dicarboxylate (**3**)

IR (KBr): 2927 (C–H), 1695, 1676 cm^{-1} (C=O); MS (80°; *m/z* (%)): 287 (18), 286 (M^+, 96), 258 (25), 242 (23), 241 (100), 230 (15), 214 (32), 213 (59), 186 (28), 170 (15), 169 (31), 142 (17), 85 (15), 84 (18), 45 (31); high-resolution MS: calcd. for M^+: 286.0511, found: 286.0510; ^1H NMR ($CDCl_3$): δ(ppm) = 4.38 (s, 4H, O–CH_2–CH_2–O), 4.34 (q, ^3J = 6.9 Hz, 4H, ester OCH_2), 1.36 (t, ^3J = 6.9 Hz, 6H, CH_3); ^{13}C NMR ($CDCl_3$): δ(ppm) = 160.6 (C=O), 144.9 (thiophene C-3,4), 111.9 (thiophene C-2,5), 64.7 (O–CH_2–CH_2–O), 61.1 (ester OCH_2), 14.2 (CH_3).

Diethyl 4-(2-Bromoethoxy)-2-(2-bromoethyl)-3-oxo-2,3-dihydrothiophene-2,5-dicarboxylate (**4**)

IR (CH_2Cl_2): 3053, 2986 (C–H), 1738 (C=O), 1702 (C=O) cm^{-1}; MS (60; *m/z* (%)): 472/474/476 (M^+, 23/45/24), 366/368 (11/11), 356 (12), 321/323 (14/13), 276/278 (12/12), 275/277 (46/52), 251 (16), 248/250 (43/44), 249 (24), 247 (11), 227 (13), 224/226 (24/23), 173 (11), 169 (67), 168 (21), 155 (15), 151/153 (25/25), 149 (38), 145 (15), 141 (20), 117 (14), 113 (13), 109 (39), 107 (50), 100 (13), 99 (13), 85 (19), 73 (100), 71 (25), 69 (22), 55 (12), 45 (54); high-resolution MS: calcd. for M^+: 471.9191, found: 471.9194; ^1H NMR ($CDCl_3$): δ(ppm) = 4.57 (t, ^3J = 6.3 Hz, 2H, C4–OCH_2–), 4.39 (q, ^3J = 7.2 Hz, 2H, C5–$COOCH_2$–), 4.21 (m, 2H, C2–$COOCH_2$–), 3.59 (t, ^3J = 6.1 Hz, C4–OCH_2CH_2Br), 3.57 (m, 1H, C2–CH_2CH_2Br), 3.33 (m, 1H, C2–CH_2CH_2Br), 2.79 (m, 2H, C2–CH_2CH_2Br), 1.40 (t, ^3J = 7.2 Hz, 3H, C5–$COOCH_2CH_3$), 1.26 (t, ^3J = 7.2 Hz, 3H, C2–$COOCH_2CH_3$); ^{13}C NMR ($CDCl_3$): δ(ppm) = 195.4 (dd, ^3J = 3.3 Hz and 4.3 Hz, thiophene C-3), 166.7 (q, ^3J = 3.7 Hz, C2-COOEt), 160.6 (t, ^3J = 3.3 Hz, C5-COOEt), 147.5 (t, ^3J = 3.1 Hz, thiophene C-4), 141.7 (s, thiophene C-5), 71.4 (tt, ^1J = 150.8 Hz, ^2J = 2.9 Hz, C4–OCH_2–), 63.1 (qt, ^1J = 149.1 Hz, ^2J = 4.4 Hz, C2–$COOCH_2CH_3$), 62.7 (qt, ^1J = 148.8 Hz, ^2J = 4.4 Hz, C5–$COOCH_2CH_3$), 61.0 (m, thiophene C-2), 36.9 (tt, ^1J = 136.1 Hz, ^2J = 2.7 Hz, C2–CH_2CH_2Br), 29.1 (tt, ^1J = 152.7 Hz, ^2J = 2.1 Hz, C4–OCH_2CH_2Br), 25.8 (tt, ^1J = 152.7 Hz, ^2J = 5.4 Hz, C2–CH_2CH_2Br), 14.0 (tq, ^1J = 127.6 Hz, ^2J = 2.6 Hz, C5–$COOCH_2CH_3$), 13.8 (tq, ^1J = 127.6 Hz, ^2J = 2.7 Hz, C2–$COOCH_2CH_3$). Anal. calcd. for $C_{14}H_{18}Br_2O_6S$ (474.18): C 35.46, H 3.83; found: C 35.57, H 3.79.

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References

[1]. Hinsberg O. (1910) Chem. Ber. **43**: 901
[2] Overberger C. G., Lal J. (1951) J. Am. Chem. Soc. **73**: 2956
[3] For instance: Cross P. E., Dickinson R. P., Parry M. J., Randall M. J. (1985) J. Med. Chem. **28**: 1427
[4] Guha P. C., Iyer B. H. (1938) J. Indian Inst. Sci. **21A**: 115; Chem. Abstr. (1939) **33**: 2134
[5] Gogte V. N., Shah L. G., Tilak B. D., Gadekar K. N., Sahasrabudhe M. B. (1967) Tetrahedron **23**: 2437
[6] Sarkar S., Bax A. (1985) J. Magn. Reson. **62**: 109
[7] Bax A. (1984) J. Magn. Reson. **57**: 314
[8] Gronowitz S., Hörnfeldt A.-B. (1986) Synthesis, physical properties and reaction of compounds containing thiophene-oxygen bonds. In: Gronowitz S. (ed.) The chemistry of heterocyclic compounds, thiophene and its derivatives. John Wiley and Sons, New York, p. 60 and p. 76–77; and references cited therein.
[9] Hada W. A., Rusek F. W., Bordner J., Melvin, Jr. L. S. (1993) Tetrahedron Lett. **34**: 8229
[10] Mortenson J. Z., Hedegaard B., Lawesson S.-O. (1971) Tetrahedron **27**: 3839

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