Mechanism of Isomerization and Acid-Induced Transformations of 3′-Hydroxy-4,4′-dimethoxy-3′-methyl-3-oxo-7,7′-bis(piperidinocarbonyloxy)-2,2′-spirobi-[2*H*,2′*H*,3*H*,3′*H*-benzo[*b*]thiophene]. Unusual Equilibrium between the Spiro and 3-Hydroxybenzothiophene Systems

Marek T. Konieczny*[1] **and Paweł Sowiński**[2]

[1]Department of Organic Chemistry, Medical University of Gdańsk, 80-416 Gdańsk, Poland

[2]Laboratory of Nuclear Magnetic Resonance Spectroscopy, Gdańsk University of Technology, 80-952 Gdańsk, Poland

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Mechanistic investigations show that two diastereoisomers of 3′-hydroxy-4,4′-dimethoxy-3′-methyl-3-oxo-7,7′-bis(piperidinocarbonyloxy)-2,2′-spirobi[2*H*,2′*H*,3*H*,3′*H*-benzo[*b*]thiophene] (**1**) equilibrate via an open ring compound: a 3-hydroxybenzothiophene derivative. The result indicates that the spiro form is more stable than the related, aromatic benzothiophene. Acid-catalyzed transformations of **1** are also reported.

3′-Hydroxy-4,4′-dimethoxy-3′-methyl-3-oxo-7,7′-bis(piperidinocarbonyloxy)-2,2′-spirobi[2*H*,2′*H*,3*H*,3′*H*-benzo[*b*]thiophene] (**1**) was obtained from reaction of 4-acetyl-5-methoxy-1,3-benzoxathiol-2-one with piperidine or piperidine acetate in DMSO.[1] ^{1}H NMR spectra of compound **1** demonstrated that it existed as a mixture of two diastereoisomers.[1] Further studies demonstrated that in aprotic solvents (DMSO-d_6, acetone-d_6, and $CDCl_3$) the ratio between the two forms was almost constant and close to 2:1, but after addition of water or in MeOD-d_3 it changed to around 5:1.4.[2] The existence of two isomers was not surprising as there are two asymmetric carbon atoms in the molecule, however the mechanism by which the diastereoisomers equilibrated was not so obvious. Now, we wish to report some reactions which were aimed at explanation of the phenomena. Until now only three reports[1,3,4] on 1,6-dithiaspiro[4,4]nonane or its derivatives have been published and their chemistry is still unexplored, and the results could be of interest also for this reason.

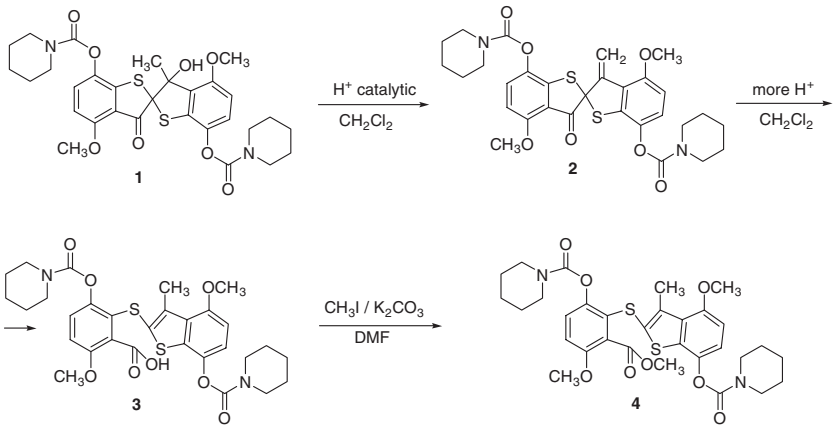
While studying the isomerization of **1** in various solvents by ^{1}H NMR, it was found that in $CDCl_3$ a slow dehydration, leading to formation of compound **2**, took place. After two days about 80% of the compound **1** was transformed into **2**. The dehydration was not observed in other solvents (DMSO, acetone, and methanol) nor in acid-free chloroform (freshly filtered through basic alumina).

Apparently, the reaction was catalyzed by traces of acids usually present in dry chloroform, and indeed, compound **2** was obtained preparatively by stirring of **1** in methylene chloride with catalytic amounts of hydrochloride or methanesulfonic acid (1×10^{-1} mmol of methanesulfonic acid per 1 mmol of **1**).

Surprisingly, reaction of **1** or **2** with a larger amount of methanesulfonic acid (10 mmol of the acid per 1 mmol of **1**) resulted in formation of the carboxylic acid **3** (Scheme 1). ^{1}H NMR of compound **3** demonstrated protons of the benzoic acid part of the molecule as a broad singlet (Figure 1) but addition of one drop of TFA transformed the broad singlet into two doublets.

Apparently, the free carboxylic acid group was involved in the line broadening, probably by hydrogen-bond formation with the nonheterocyclic sulfur atom,[5] as the corresponding ester **4**, obtained by methylation of the acid **3**, did not demonstrate any line broadening in NMR.

Based on the observed formation of compound **2**, it seemed that the interconversion of diastereoisomers of **1** took place through a reversible dehydration–hydration process, via the intermediate **2**. However, incubation of compound **1** in acetone or in acid-free chloroform with deuterated water for one week



Scheme 1. Acid-induced transformations of the spiro compound **1**.

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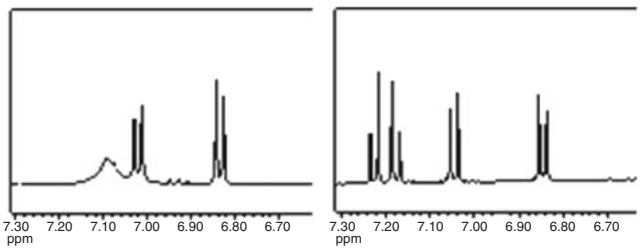


Figure 1. Influence of TFA on the shape of the aromatic protons peaks in ^{1}H NMR of **3**: DMSO-d_6 (left), DMSO-d_6 + 1 drop TFA (right) (To view the original spectra, see Supporting Information, part 1, pages 11–15).

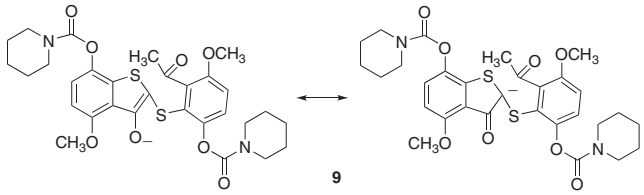
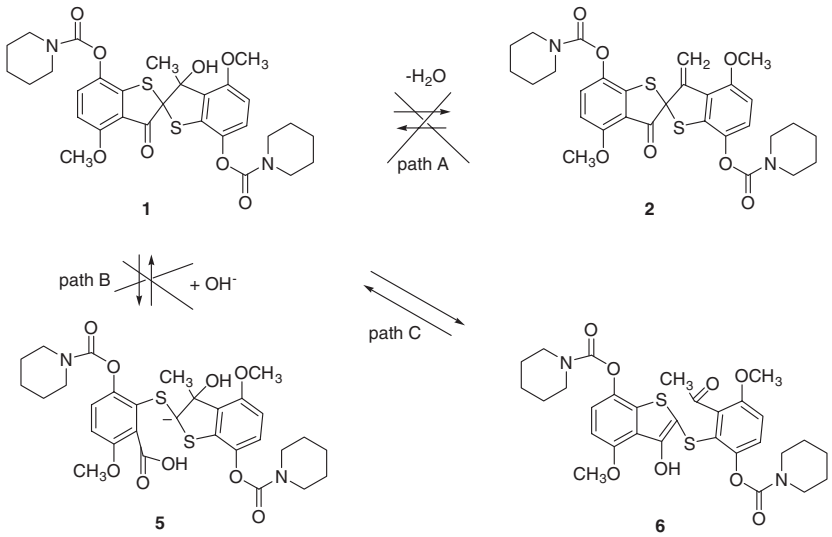
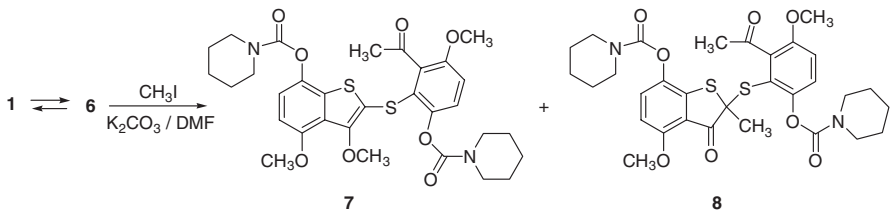


Figure 2. Mesomeric forms of anion **9**.



Scheme 2. The considered ways of isomerization of the spiro compound **1**.



Scheme 3. Methylation of the spiro compound **1**.

did not change the integration of the methyl group in NMR, which made the dehydration–hydration mechanism of isomerization improbable (Scheme 2, path A). It was then speculated that the isomerization could be due to nucleophilic attack of water on the carbonyl group, as during formation of **3**, leading to ring opening and formation of sulfur atoms stabilized carbanion **5** (Scheme 2, path B). However, after three days incubation of **1** in acetone with ^{18}O-labeled water no incorporation of the ^{18}O isotope into the molecule was found (by calculations of isotopic peaks ratios for molecular ions in MS), which made also a pathway B hardly possible.

To determine a potential participation of the free hydroxy group in the isomerization of **1**, the compound was methylated with methyl iodide in DMF in the presence of potassium carbonate. To our surprise, the reaction resulted in formation of two products of methylation, **7** and **8** in the ratio 7:1, respectively (Scheme 3).

The result suggests that two diastereoisomers of spiro compound **1** are in equilibrium, either by deprotonation–protonation or [1,5] hydrogen shift mechanism, via 3-hydroxybenzothiophene **6**. Fast changes of the equilibrium in protic solvents suggest that it is rather the ionic mechanism. In alkaline solution, the intermediate **6** forms an anion **9**, well stabilized by spreading the negative charge at the dithioacetal carbon and carbonyl group (Figure 2).

A relative distribution of the negative charge between the oxygen and carbon atoms can be estimated, based on the reported above results of methylation, as 7:1, respectively.

Concluding, it seems to be highly possible that the observed equilibration of two diastereoisomers of **1** takes place via a reversible ring opening to **6**. Noteworthy, the intermediate **6** was not observed in NMR spectra, which means that equilibrium between spiro compound **1** and aromatic compound **6** was shifted almost completely toward **1**. Similar aldol–retro-

aldol equilibrium was already proposed for isomerization of a cyclic β-keto sulfide,[6] but to the best of our knowledge it was not observed for a spiro system.

Experimental

Reaction of 3′-Hydroxy-4,4′-dimethoxy-3′-methyl-3-oxo-7,7′-bis(piperidinocarbonyloxy)-2,2′-spirobi[2*H*,2′*H*,3*H*,3′*H*-benzo[*b*]thiophene] (1) with Traces of HCl. 3′-Hydroxy-4,4′-dimethoxy-3′-methyl-3-oxo-7,7′-bis(piperidinocarbonyloxy)-2,2′-spirobi[2*H*,2′*H*,3*H*,3′*H*-benzo[*b*]thiophene] (**1**) (50 mg, 0.082 mmol) was dissolved in $CHCl_3$ (2 mL), a small amount of HCl (about 1 mL of gases from a concd hydrochloric acid bottle) was pipetted over the solution, and the mixture was stirred at rt for 24 h. The obtained product was purified on a silica gel column in $CHCl_3$–EtOAc 3:1 solution to give 4,4′-dimethoxy-3′-methylene-3-oxo-7,7′-bis(piperidinocarbonyloxy)-2,2′-spirobi(2*H*,2′*H*,3*H*,3′*H*-benzo[*b*]thiophene) (**2**) (28 mg, 57%) as a colorless glass, mp 120–122 °C. MS (MALDI TOF): 635 (M + K), 619 (M + Na), 597 (M + H). Anal. Calcd for $C_{30}H_{32}N_2O_7S_2$: C, 60.38; H, 5.41; N, 4.69; S, 10.75%. Found: C, 59.99; H, 5.38; N, 4.58; S, 10.84%. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.44 (d, 1H, $J = 8.8$ Hz), 7.11 (d, 1H, $J = 8.8$ Hz), 6.71 (d, 1H, $J = 8.8$ Hz), 6.67 (d, 1H, $J = 8.8$ Hz), 6.37 (s, 1H), 5.41 (s, 1H), 3.94 (s, 3H), 3.89 (s, 3H), 3.63–3.40 (m, 8H), 1.61 (m, 12H). IR (KBr, cm^{-1}): 2937, 2855, 1722, 1487, 1424, 1224.

Reaction of 3′-Hydroxy-4,4′-dimethoxy-3′-methyl-3-oxo-7,7′-bis(piperidinocarbonyloxy)-2,2′-spirobi[2*H*,2′*H*,3*H*,3′*H*-benzo[*b*]thiophene] (1) with Methanesulfonic Acid. 3′-Hydroxy-4,4′-dimethoxy-3′-methyl-3-oxo-7,7′-bis(piperidinocarbonyloxy)-2,2′-spirobi[2*H*,2′*H*,3*H*,3′*H*-benzo[*b*]thiophene] (**1**) (150 mg, 0.25 mmol) was dissolved in CH_2Cl_2 (5 mL), and methanesulfonic acid (0.2 mL) was added to the stirred solution. The solution was stirred for 2 h, diluted with CH_2Cl_2 (50 mL), washed with water and dried (Na_2SO_4). Evaporation of solvent gave a noncrystalline residue which was purified on silica gel column in $CHCl_3$–MeOH 10:1 solution to give 6-methoxy-2-(4′-methoxy-3′-methyl-7′-(piperidinocarbonyloxy)benzo[*b*]thiophen-2-ylthio)-3-(piperidinocarbonyloxy)benzoic acid (**3**) (130 mg, 86%) as a yellow glass, mp 139–143 °C. MS (MALDI TOF): 597 (M − OH), 614 (M), 637 (M + Na), 653 (M + K). Anal. Calcd for $C_{30}H_{34}N_2O_8S_2 \cdot 1.5H_2O$: C, 56.14; H, 5.81; N, 4.37; S, 9.99%. Found: C, 56.24; H, 5.64; N, 4.28; S, 9.70%. ^{1}H NMR (DMSO-d_6 + 1 drop TFA, 500 MHz): δ 7.22 (d, 1H, $J = 9.0$ Hz), 7.18 (d, 1H, $J = 9.0$ Hz), 7.04 (d, 1H, $J = 8.6$ Hz), 6.84 (d, 1H, $J = 8.6$ Hz), 3.87 (s, 3H), 3.80 (s, 3H), 3.60–3.25 (m, 8H), 2.56 (s, 3H), 1.65–1.35 (m, 12H). IR (KBr, cm^{-1}): 3448, 2936, 2855, 1722, 1421, 1224.

Reaction of 6-Methoxy-2-(4′-methoxy-3′-methyl-7′-(piperidinocarbonyloxy)benzo[*b*]thiophen-2-ylthio)-3-(piperidinocarbonyloxy)benzoic Acid (3) with Methyl Iodide. 6-Methoxy-2-(4′-methoxy-3′-methyl-7′-(piperidinocarbonyloxy)benzo[*b*]thiophen-2-ylthio)-3-(piperidinocarbonyloxy)benzoic acid (**3**) (123 mg, 0.2 mmol), anhydrous K_2CO_3 (138 mg, 1 mmol), and MeI (0.18 mL, 3 mmol) were stirred in anhydrous DMF (1 mL) at rt for 1.5 h. The reaction mixture was diluted with water and extracted with ether (50 mL). The ethereal layer was washed with water (3×) and brine (1×), dried (Na_2SO_4) and evaporated. The residue was purified on silica gel column in $CHCl_3$–EtOAc 5:1 solution to give 6-methoxy-2-(4′-methoxy-3′-methyl-7′-(piperidinocarbonyloxy)-benzo[*b*]thiophen-2-ylthio)-3-(piperidinocarbonyloxy)benzoic acid methyl ester (**4**) (84 mg, 67%) as a colorless, noncrystalline solid, mp 70–72 °C. MS (MALDI TOF): 597 (M − OCH_3), 628 (M), 651 (M + Na), 667 (M + K). Anal. Calcd for $C_{31}H_{36}N_2O_8S_2$: C, 59.22; H, 5.77; N, 4.46; S, 10.20%. Found: C, 59.52; H, 6.10; N, 4.19; S, 9.93%. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.17 (d, 1H, $J = 9.0$ Hz), 7.03 (d, 1H, $J = 8.6$ Hz), 6.93 (d, 1H, $J = 9.0$ Hz), 6.67 (d, 1H, $J = 8.6$ Hz), 3.88 (s, 3H), 3.84 (s, 3H), 3.80 (s, 3H), 3.63 (br s, 2H), 3.50 (br s, 2H), 3.39 (br s, 4H), 2.61 (s, 3H), 1.70–1.50 (m, 12H). IR (KBr, cm^{-1}): 2936, 2855, 1722, 1421, 1224.

Reaction of 3′-Hydroxy-4,4′-dimethoxy-3′-methyl-3-oxo-7,7′-bis(piperidinocarbonyloxy)-2,2′-spirobi[2*H*,2′*H*,3*H*,3′*H*-benzo[*b*]thiophene] (1) with Methyl Iodide. 3′-Hydroxy-4,4′-dimethoxy-3′-methyl-3-oxo-7,7′-bis(piperidinocarbonyloxy)-2,2′-spirobi[2*H*,2′*H*,3*H*,3′*H*-benzo[*b*]thiophene] (**1**) (245 mg, 0.4 mmol), anhydrous K_2CO_3 (500 mg, 3.6 mmol), and methyl iodide (0.7 mL, 11 mmol) in dry DMF (4 mL) were stirred at rt for 3 h. An excess of methyl iodide was evaporated and the residue was quenched with icy water to give a bright violet solid (200 mg). ^{1}H NMR (CD_3COCD_3, 500 MHz) of the product demonstrated a mixture of compounds **7** and **8** in a 7:1 ratio. Separation on silica gel column in $CHCl_3$–EtOAc 20:1 solution gave two products: 2-[2′-Acetyl-3′-methoxy-6′-(piperidinocarbonyloxy)phenylthio]-3,4-dimethoxy-7-(piperidinocarbonyloxy)benzo[*b*]thiophene (**7**) (100 mg, 39%) as a colorless solid, mp 154–155 °C. MS (MALDI TOF): 667 (M + K), 651 (M + Na), 628 (M). Anal. Calcd for $C_{31}H_{36}N_2O_8S_2$: C, 59.22; H, 5.77; N, 4.46; S, 10.20%. Found: C, 59.25; H, 5.63; N, 4.22; S, 10.30%. ^{1}H NMR (CD_3COCD_3, 500 MHz): δ 7.20 (d, 1H, $J = 9.0$ Hz), 7.18 (d, 1H, $J = 9.0$ Hz), 7.10 (d, 1H, $J = 8.6$ Hz), 6.88 (d, 1H, $J = 8.6$ Hz), 3.97 (s, 3H), 3.90 (s, 3H), 3.78 (s, 3H), 3.66 (br s, 2H), 3.48 (br s, 4H), 3.24 (br s, 2H), 2.50 (s, 3H), 1.74–1.48 (m, 12H). IR (KBr, cm^{-1}): 2934, 2853, 1716, 1416, 1219.

2-[2′-Acetyl-3′-methoxy-6′-(piperidinocarbonyloxy)phenylthio]-4-methoxy-2-methyl-7-(piperidinocarbonyloxy)-2*H*-benzo[*b*]thiophen-3-one (**8**) (15 mg, 6%) as cream solid, mp 74–76 °C. MS (MALDI TOF): 679 (M + 51), 667 (M + K), 651 (M + Na), 639 (M + K − CO), 627 (M − H). Anal. Calcd for $C_{31}H_{36}N_2O_8S_2$: C, 59.22; H, 5.77; N, 4.46; S, 10.20%. Found: C, 59.58; H, 6.05; N, 4.25; S, 9.87%. ^{1}H NMR (CD_3COCD_3, 500 MHz): δ 7.40 (d, 1H, $J = 8.9$ Hz), 7.19 (d, 1H, $J = 8.8$ Hz), 7.13 (d, 1H, $J = 8.8$ Hz), 6.89 (d, 1H, $J = 8.9$ Hz), 3.96 (s, 3H), 3.88 (s, 3H), 3.64–3.36 (m, 8H), 2.43 (s, 3H), 1.77 (s, 3H), 1.73–1.50 (m, 12H). IR (KBr, cm^{-1}): 2928, 2853, 1722, 1423, 1224.

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Supporting Information

^{1}H NMR spectra (aromatic region) of compound **1** in various solvents. ^{1}H NMR, ^{13}C NMR, gHMBC, gHSQC, and ROESY spectra of compounds **2**, **3**, **4**, **7**, and **8**.

References

1 M. T. Konieczny, W. Konieczny, S. Wolniewicz, K. Wierzba, Y. Suda, P. Sowiński, *Tetrahedron* **2005**, *61*, 8648.
2 Supporting Information, paragraph 1.
3 F. Weigert, *Ber. Dtsch. Chem. Ges.* **1901**, *34*, 3386.
4 F. S. Fowkes, E. W. McClelland, *J. Chem. Soc.* **1945**, 405.
5 F. H. Allen, C. M. Bird, R. S. Rowland, P. R. Raithby, *Acta Crystallogr., Sect. B* **1997**, *53*, 696.
6 R. B. Silverman, *J. Org. Chem.* **1981**, *46*, 4789.