On the Reaction of 3,4-Dibromo-2,5-dimethylthiophene-1,1-dioxide with Piperidine. X-Ray Structure Determination of 3-Bromo-2-methyl-4-piperidino-5-piperidinomethyl-*cis*-4,5-dihydrothiophene-1,1-dioxide

Salo Gronowitz,[a] Grigorios Nikitidis,[a] Anders Hallberg[a] and Claes Stålhandske[b]

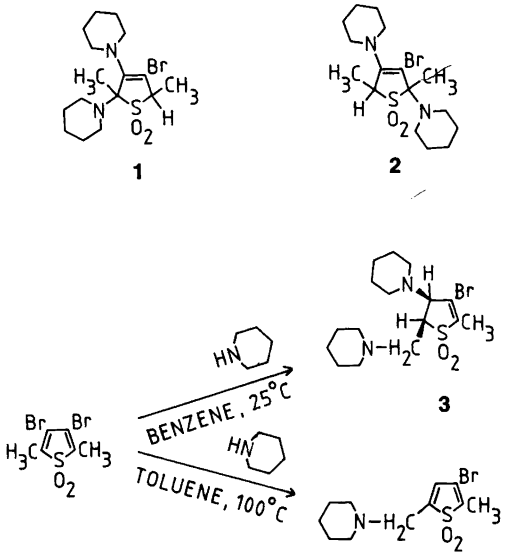
[a]Division of Organic Chemistry 1 and [b]Division of Inorganic Chemistry 2, Chemical Center, University of Lund, P.O. Box 124, S-221 00 Lund, Sweden

Gronowitz, S., Nikitidis, G., Hallberg, A. and Stålhandske, C., 1987. On the Reaction of 3,4-Dibromo-2,5-dimethylthiophene-1,1-dioxide with Piperidine. X-Ray Structure Determination of 3-Bromo-2-methyl-4-piperidino-5-piperidinomethyl-*cis*-4,5-dihydrothiophene-1,1-dioxide. – Acta Chem. Scand., Ser. B 41: 297–301.

The reaction of 3,4-dibromo-2,5-dimethylthiophene-1,1-dioxide with excess piperidine in benzene at room temperature leads to 3-bromo-2-methyl-4-piperidino-5-piperidinomethyl-*cis*-4,5-dihydrothiophene-1,1-dioxide (**3**). The structure was established by X-ray crystallography. Reaction with piperidine at 100 °C in toluene resulted in the formation of the unstable 3-bromo-2-methyl-5-piperidinomethylthiophene-1,1-dioxide (**4**) in high yield.

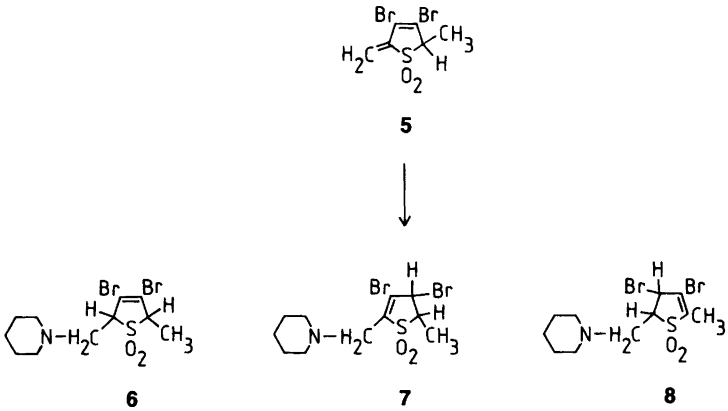
Thiophene-1,1-dioxides have recently attracted attention as useful precursors in organic synthesis.[1] We have studied the reaction of 2,5-dialkyl-substituted 3-bromothiophene-1,1-dioxides with various organolithium derivatives.[2,3] The dioxides were consumed in two competing ring-opening reactions: (a) via halogen-metal exchange, and (b) via organolithium attack on the 5-carbon. To our knowledge, reactions with other nucleophiles have been studied to only a very limited extent.

As a part of our research directed toward development of useful organic reactions based on the reactivity of 2,5-dialkylthiophene-1,1-dioxides we have reinvestigated the reaction of 3,4-dibromo-2,5-dimethylthiophene-1,1-dioxide with excess piperidine in benzene at room temperature. This reaction was reported to give a crystalline product assigned as either 2,5-dimethyl-2,3-dipiperidino-4-bromothiacyclopentene-3-1,1-dioxide (**1**) or 2,5-dimethyl-2,4-dipiperidino-3-bromothiacyclopentene-3-1,1-dioxide (**2**)[4] (Scheme 1).



Scheme 1.

The assignment was based on elemental analyses and on the non-reactivity of the bromine present in the molecule towards silver nitrate. We obtained a product with the same melting point as that given in the report. However, an analysis



5 **6** **7** **8**

Scheme 2.

of the ^{1}H NMR spectra, including decoupling experiments, revealed that this compound most probably was 3-bromo-2-methyl-4-piperidino-5-piperidinomethyl-*cis*-4,5-dihydrothiophene-1,1-dioxide (**3**) instead, and thus that a side-chain substitution had occurred. The 4,5-hydrogen coupling constant was found to be 8.2 Hz. According to a detailed analysis by Abraham *et al.*[5] of the ^{1}H NMR spectrum of 2,3-dihydrothiophene-1,1-dioxide, the *cis*-vicinal coupling of the CH_2–CH_2 group is 9.00 Hz and the *trans* coupling 4.20 Hz. In order to ascertain that the introduction of the piperidino and piperidinomethyl groups does not cause large changes in the geometry, and thus in the coupling constants in the 2,3-dihydrothiophene-1,1-dioxides, an X-ray crystallographic investigation of **3** was undertaken, which clearly proved the *cis* relationship between the piperidino and piperidinomethyl groups (see section on X-ray crystallography).

Performing the reaction at 100 °C in toluene resulted in formation of the dioxide **4** as an unstable compound in high yield.

The formation of **3** can be explained by assuming that a tautomer (**5**) of the starting material is involved as an intermediate and that its exomethylene group is attacked by piperidine (Scheme 2). Similar tautomers have been suggested to be involved in the reaction of 3,4-dimethylthiophene-1,1-dioxides with secondary amines.[6] Michael-type addition, followed by protonation of the allylic-type carbanion, would then lead primarily to **6** or **7**. Double bond isomerization via the α-carbanion of **6** could give **8**. The most straightforward formation of **3** would then be direct nucleophilic substitution of **8**. However, a more complex pathway, involving Michael addition to **7**, hydrogen bromide elimination and double bond isomerization to give **3**, cannot be excluded. Hydrogen bromide elimination from **8**, or piperidine elimination from **3** may account for the formation of **4**. Alternatively, **3** and **4** could have resulted from an initial Michael addition to 3,4-dibrono-2,5-dimethylthiophene-1,1-dioxide, followed by elimination of HBr, subsequent tautomerization and addition of piperidine.

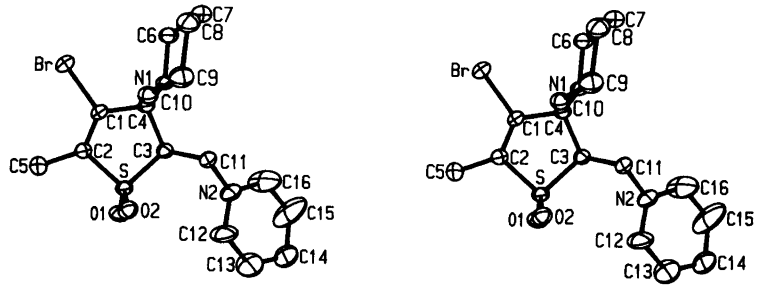


Fig. 1. Stereoscopic view of molecule **3**, with atomic numbering.

Table 1. Fractional atomic coordinates (with e.s.d.'s in parentheses) and equivalent isotropic thermal parameters of the form $U_{eq} = 1/3\ \Sigma i \Sigma j U_{ij} a_i a_j \mathbf{a}_i \mathbf{a}_j$ for 3-bromo-2-methyl-4-piperidino-5-piperidinomethyl-*cis*-4,5-dihydrothiophene-1,1-dioxide (**3**).

Atom	*x*	*y*	*z*	U_{eq}
Br	0.1716(1)	−0.3775(1)	1.0601(1)	0.0776(3)
S	−0.1571(2)	−0.0853(1)	0.8910(1)	0.0525(5)
O1	−0.2400(6)	0.0241(3)	0.9432(3)	0.070(1)
O2	−0.2742(6)	−0.1176(3)	0.8182(3)	0.066(1)
N1	0.3222(6)	−0.3020(3)	0.7925(3)	0.049(1)
N2	0.1440(10)	0.0472(5)	0.6763(5)	0.101(3)
C1	0.0759(8)	−0.2517(4)	0.9702(4)	0.052(2)
C2	−0.1268(8)	−0.1993(4)	0.9879(4)	0.054(2)
C3	0.1248(8)	−0.0956(4)	0.8317(4)	0.053(2)
C4	0.2373(7)	−0.2156(4)	0.8741(4)	0.050(2)
C5	−0.3187(10)	−0.2194(7)	1.0735(5)	0.082(3)
C6	0.5214(8)	−0.3792(5)	0.8041(5)	0.065(2)
C7	0.6261(9)	−0.4390(5)	0.6998(5)	0.076(2)
C8	0.4738(11)	−0.5052(5)	0.6645(5)	0.082(3)
C9	0.2610(10)	−0.4227(5)	0.6595(5)	0.077(3)
C10	0.1665(8)	−0.3642(4)	0.7650(4)	0.058(2)
C11	0.1820(10)	−0.0758(5)	0.7102(5)	0.071(2)
C12	−0.0551(13)	0.0966(8)	0.6633(10)	0.170(6)
C13	−0.0830(22)	0.2210(11)	0.6216(14)	0.263(9)
C14	0.0730(16)	0.2661(6)	0.5591(8)	0.126(4)
C15	0.2857(24)	0.2166(11)	0.5821(12)	0.207(8)
C16	0.3103(16)	0.0908(9)	0.6262(13)	0.196(8)

Table 2. Selected bond lengths (Å) and angles (°) in **3**. Standard deviations in parentheses.

Br–C1	1.890(5)	Br1–C1–C4	118.0(4)
C1–C2	1.316(7)	Br1–C1–C2	121.4(4)
C1–C4	1.509(7)	C4–C1–C2	120.6(4)
C2–C5	1.498(8)	C1–C2–S	109.2(4)
C2–S	1.758(5)	C1–C2–C5	131.7(5)
S–O1	1.438(4)	C2–S–C3	95.9(2)
S–O2	1.434(4)	O1–S–O2	117.2(2)
S–C3	1.794(5)	S–C3–C4	106.1(3)
C3–C11	1.527(8)	S–C3–C11	115.9(4)
C3–C4	1.566(7)	C3–C4–C1	105.3(4)
C4–N1	1.449(6)	C3–C4–N1	114.0(4)
N1–C6	1.458(6)	C4–N1–C6	115.3(4)
N1–C10	1.456(6)	C4–N1–C10	116.1(4)
C6–C7	1.514(9)	N1–C6–C7	109.6(5)
C7–C8	1.514(9)	C6–C7–C8	111.3(5)
C8–C9	1.536(9)	C7–C8–C9	110.0(5)
C9–C10	1.511(8)	C8–C9–C10	110.5(5)
		C9–C10–N1	109.9(4)
C11–N2	1.451(8)	C3–C11–N2	113.1(5)
N2–C12	1.351(11)	C11–N2–C12	118.8(6)
N2–C16	1.287(13)	C11–N2–C16	116.5(7)
C12–C13	1.493(16)	N2–C12–C13	116.8(8)
C13–C14	1.300(17)	C12–C13–C14	122.6(11)
C14–C15	1.474(18)	C13–C14–C15	112.8(10)
C15–C16	1.516(16)	C14–C15–C16	115.7(10)
		C15–C16–N2	120.5(10)

Further studies of the reactions of 2,5-dialkylthiophene-1,1-dioxides with amines under various conditions are in progress.

Molecular structure. The molecule with atomic numbering is shown in Fig. 1. Details of the structure determination are given in the Experimental section and atomic coordinates are listed in Table 1.

Distances and angles within the molecule are normal (Table 2), except in one piperidine group (N2, C12–C16). The atoms in this group have pronounced anisotropic vibrations (see Fig. 1) and the refined positions result in some short distances and large angles, as often found for disordered groups. The ordered piperidine group (N1, C6–C10) has a chair conformation. The five-membered ring is not planar and the maximum deviation from the least-squares plane through the atoms is 0.11 Å. Both the piperidine nitrogen, N1, and the methylene carbon, C11, are positioned on the same side of the plane, with deviations of 1.3 and 0.7 Å, respectively.

Experimental

Infrared spectra were recorded on a Perkin Elmer 298 spectrophotometer and were in accordance with the proposed structures. ^{1}H NMR spectra were recorded on a Varian XL-300 spectrometer. Quantitative gas chromatographic analyses were performed on a Perkin Elmer 900 gas chromatograph equipped with a 2.5 m column of 3 % OV 101 on Gaschrom. Q (100–120 mesh) and a flame ionisation detector.

Mass spectra were obtained with a Finnigan 4021 (Data System Incos 2100) gas chromatograph-mass spectrometer operating at 70 eV. Elemental microanalyses were performed by *Dornis und Kolbe, Mikroanalytisches Laboratorium,* Mülheim a.d. Ruhr, West Germany.

3-Bromo-2-methyl-4-piperidino-5-piperidinomethyl-cis-*4,5-dihydrothiophene-1,1-dioxide* (**3**). To a solution of 1.50 g (5 mmol) of 3,4-dibromo-2,5-dimethylthiophene-1,1-dioxide (**7**) in 15 ml of benzene is added 1.7 g (20 mmol) of piperidine. After 24 h the crystallized piperidinium bromide is removed by suction filtration. The filtrate is evaporated and the residue recrystallized three times from ethanol to give 0.80 g (41 %) of the title compound as colourless needles, m.p. 153–153.5 °C (lit.[4] 153–154.5 °C). ^{1}H NMR ($CDCl_3$): δ 4.03 (dq, 1H, 4-H, J = 8.2, 1.2 Hz), 3.52 (m, 1H, 5-H, J = 8.2, 6.8, 5.3 Hz), 3.00 (dd, 1H, 5-CH_2, J = 14.3, 5.3 Hz), 2.89 (dd, 1H, 5-CH_2, J = 14.3, 6.8 Hz), 2.07 (d, 3H, 2-CH_3, J = 1.2 Hz), 2.60–2.40 (m, 8H, piperidine), 1.60–1.30 (m, 12H, piperidine).

Irradiation at 4.03 ppm resulted in a singlet at 2.07 and a double doublet at 3.52 ppm. Irradiation at 3.52 ppm resulted in a quartet at 4.03 and two doublets at 3.00 and 2.89 ppm. Irradiation at 2.07 ppm gave a doublet at 4.03 ppm. Mass spectrum: *m/e* 390/392. Anal. $C_{16}H_{27}BrN_2O_2S$: C, H, N.

3-Bromo-2-methyl-5-piperidinomethylthiophene-1,1-dioxide (**4**). To a solution of 1.00 g (3.3 mmol) of 3,4-dibromo-2,5-dimethylthiophene-1,1-dioxide (**7**) in 50 ml of toluene is added 1.20 g (14 mmol) of piperidine at 100 °C. After exactly 10 minutes the reaction is stopped and the reaction mixture is extracted three times with 100 ml portions of 10 % aqueous NH_4Cl. After washing three times with water, the organic phase is dried over $MgSO_4$. Filtration, followed by evaporation of the solvent under nitrogen gave **4** in pure form as an oil in 84 % yield. The compound decomposes when heated. ^{1}H NMR ($CDCl_3$): δ 6.53 (tq, 4-H, J = 2.0, 1.5 Hz), 3.43 (dq, 2H, 5-CH_2, J = 2.0, 0.9 Hz), 2.08 (dt, 3H, 2-CH_3, J = 1.5, 0.9 Hz). Mass spectrum: *m/e* 305/307.

X-Ray structure analysis. A colourless crystal, elongated along *a,* with the dimensions 0.50×0.15×0.16 mm was used for the determination of the cell parameters and for collection of the intensity data. The analysis was carried out on a computer-controlled Enraf-Nonius CAD4 diffractometer using graphite-monochromated Mo$K\alpha$ radiation (λ = 0.71069 Å). The ω-2θ technique was employed with a maximum scan time of 120 s and a scan width of (0.80 + 0.50 tanθ)°. 3203 independent reflections with $\theta \leq 25°$ were measured and 1882 reflections with $I \geq 3\sigma(I)$ were considered as observed. The intensities of three test reflections showed an average linear decrease of 8 % during the data collection. The intensities were therefore corrected for this decrease and for Lp and absorption effects.

Crystal data. $C_{16}H_{27}BrN_2O_2S$, M.W. = 391.37; Space group P1; a = 6.4601((6), b = 11.591(2), c = 12.817(2) Å; α = 85.54(1), β = 76.96(1), γ = 79.56(1)°; Z = 2, V = 918.9(2) Å^3, D_x = 1.41 g cm^{-3}; μ(Mo$K\alpha$ = 23.3 cm^{-1}, t = 22 °C.

The structure was solved by direct methods (MULTAN 80)[8] and refined by full matrix least-squares, minimizing $\Sigma w(\Delta F)^2$, and allowing the non-hydrogen atoms to vibrate anisotropically. One of the piperidine groups (N2, C12–C16) showed pronounced anisotropic temperature factors, probably due to disorder, which could not, however, be resolved. The final refinement, which gave R = 0.040, included also the hydrogen atoms in the ordered part of the molecule with fixed positional parameters. The weights were given by $w^{-1} = [\sigma^2(F_o) + 0.0016F_o^2 + 0.5]$. The maximum shift/error was 0.02 and final Δρ excursions ≤0.38 e Å^3. The atomic scattering factors were taken from Ref. 9. A description of the computer programs used is given by Lundgren.[10] Lists of anisotropic temperature factors, hydrogen atom parameters and structure factors are available from one of the authors (C.S.) on request.

Acknowledgements. Grants from the Swedish National Science Research Council to S.G. and to A.H. are gratefully acknowledged.

References

1. Raasch, M. S. In: Gronowitz, S., Ed., *The Chemistry of Heterocyclic Compounds,* John Wiley and Sons, New York 1985, Vol. 44, Part I, p. 571.
2. Karlsson, J. O., Gronowitz, S. and Hallberg, A. *Chem. Scr. 20* (1982) 37.
3. Karlsson, J. O., Gronowitz, S. and Hallberg, A. *Acta Chem. Scand., Ser. B 36* (1982) 341.
4. Melles, J. L. *Recl. Trav. Chim. Pays-Bas 71* (1952) 869.
5. Abraham, R. J., Parry, K. and Thomas, W. A. *J. Chem. Soc. B* (1971) 446.
6. Wrobel, J. T. and Kabzinska, K. *Bull. Acad. Pol. 22* (1974) 129.
7. Melles, J. L. and Backer, H. J. *Recl. Trav. Chim. Pays-Bas 82* (1953) 314.
8. Main, P., Fiske, S. J., Hull, S. E., Lessinger, L., Germain, G., Declercq, J.-P. and Woolfson, M. M. *MULTAN 80: A System of Computer Programs for the Automatic Solution of Crystal Structures from X-Ray Diffraction Data.* Universities of York, England and Louvain, Belgium 1980.
9. *International Tables for X-Ray Crystallography,* Kynoch Press, Birmingham 1974, Vol. 4.
10. Lundgren, J.-O. *Crystallographic Computer Programs,* Report UUIC-B13-04-05, Institute of Chemistry, University of Uppsala, Uppsala 1982.

Received December 16, 1986.