X-ray Crystallographic and NMR Structural Studies of *trans*-2,3-Dichloro-5-ethyl-2,3-dihydrothieno[2 3-*b*]pyridine *syn*-1-Oxide Reactions of Thiophene Rings with Hypochlorite Reagents

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X-ray analysis of a crystalline product obtained by treatment of 5-ethylthieno[2,3-*b*]pyridine with excess acidified hypochlorite establishes its stereochemistry as *trans*-2,3-dichloro-5-ethyl-2,3-dihydrothieno-[2,3-*b*]pyridine *syn*-1-oxide (**5**), wherein the pyridine ring is planar and the dihydrothiophene ring is non-planar with a C2-S-C7a angle of 86.6°. The *trans* geometry is corroborated by a proton-proton coupling constant $J_{2,3}$ of 6.8 Hz. Comparison of ^1H and ^{13}C nmr data for **5** with analogous crystalline 2,3-dichloro-1-oxide addenda isolated in the isosteric benzo[*b*]thiophene and thieno[2,3-*b*]pyridine parent systems indicates that some proposed stereochemical assignments are questionable.

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The use of acidified aqueous hypochlorite solutions for *S*-oxidation and/or chlorination of thiophene compounds has been studied in a number of laboratories. Thus, thiophene itself is converted into *cis*-2,5-dichloro-2,5-dihydrothiophene 1-oxide (oxide stereochemistry undetermined) (**1**), plus chlorothiophenes by treatment with cold, concentrated hydrochloric acid and aqueous hypochlorite [1]. The acid is a necessary reagent since thiophene is inert toward sodium hypochlorite in basic solution [2]. Chemically, these results have been rationalized in terms of the equilibrium reaction for the reagent mixture.

$$HCl + HClO \rightleftharpoons Cl_2 + H_2O \text{ [3]}$$

When dilute hydrochloric acid solutions of benzo[*b*]-thiophene or its isosteric thieno[2,3-*b*]-, thieno[2,3-*c*]-, and thieno[3,2-*b*]pyridines were treated with aqueous sodium hypochlorite in the molar ratio of 1:2:2 (substrate:acid: hypochlorite) at room temperature, however, only low yields (13-37%) of sulfones **2** and **3a-3c**, respectively, were isolated [4,5]. Additionally, with thienopyridine **4a** as substrate, replacement of the hydrochloric acid by sulfuric acid in a molar ratio of 1:1:2 also gave **3a** (48% yield). Treatment of 5-ethylthieno[2,3-*b*]pyridine (**4b**) with excess acidified hypochlorite (molar ratio 1:2 sulfuric acid:4) in aqueous tetrahydrofuran at room temperature gave 2,3-dichloro-5-ethyl-2,3-dihydrothieno[2,3-*b*]pyridine 1-oxide (18% yield), mp 170-171° [3]. We now report the stereochemistry of this 171° product as *trans-syn* (as shown in structural formula **5**) by means of X-ray crystallography.

Meanwhile, Geneste and coworkers [6,7] reported the use of *t*-butyl hypochlorite in aqueous *tert*-butyl alcohol (95%) at 20° as an alternative to our procedure with benzo[*b*]thiophene as substrate. The added water was necessary in order to hydrolyze the *t*-butyl hypochlorite and produce hypochlorous acid *in situ*. The total mixed products were separated by chromatography, purified, and identified. In two particular

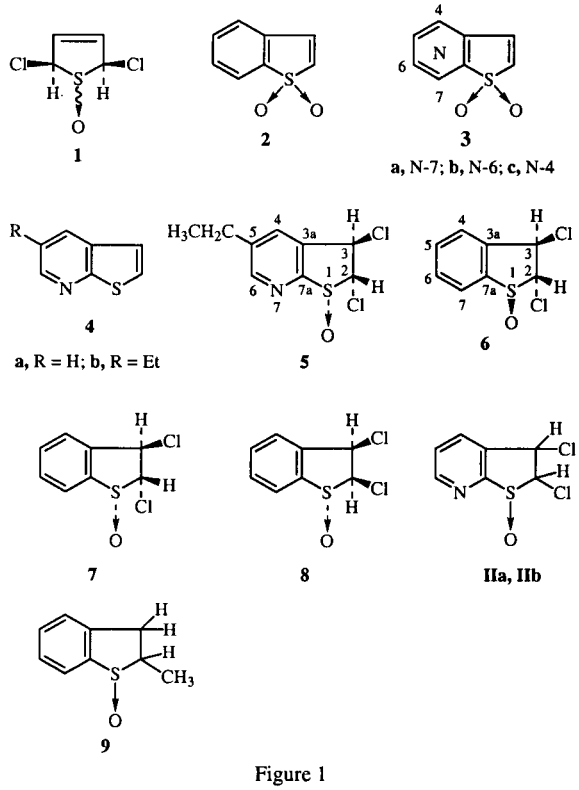

Figure 1

experiments using molar ratios of hypochlorite: benzothiophene of 1:1 and 2:1, respectively, combined product yields of 41% and 98% did not include observable sulfone **2** [7,8]. However, three isomeric 2,3-dichloro-2,3-dihydrobenzo[*b*]-thiophene 1-oxides, assigned stereochemistries of *trans-anti* **6**, *trans-syn* **7**, and *cis-anti* **8**, were isolated and characterized by ^1H and ^{13}C nmr spectra [9,10]. We, herewith, also compare nmr data for **5** and analogous products in the thieno-[2,3-*b*]pyridine series with those assigned to **6-8**.

X-ray crystallographic data for **5** are presented in Tables 1-4 and an Ortep view of it is shown in Figure 2. As indicated from Tables 3 and 4 the pyridine ring is planar (sum

Table 1

Crystallographic Data and Structural Refinement for **5**

Empirical formula	$C_9H_9Cl_2NOS$
Formula weight	250.14
Crystal appearance	colorless block
Crystal dimensions	0.25 x 0.36 x 0.36 mm
Crystal system	monoclinic
Space group	$P2_1/n$
Unit cell dimensions	a = 10.028 (1) Å
	b = 9.730 (2) Å
	c = 12.018 (2) Å
	α = 90°; β = 114.42 (1)°
Unit cell volume	1067.8 (6) Å^3
Z	4
Density (calculated)	1.556 g/cm^3
Linear absorption coefficient (μ)	7.62 cm^{-1}
F(000)	512
Diffractometer	Enraf-Nonius CAD-4
Radiation wavelength (λ)	Mo Kα, 0.71073 Å
Monochromator	graphite
Temperature	22° C
Maximum 2θ	50°
Index ranges	h, 0→ 11; k, 0 → 11; ℓ,-13 → 12
Scan mode	ω/2θ
Scan speed (on ω)	1.2-5.5° min^{-1}
Scan width	(1.10 + 0.35 tan θ)°
Standard reflections	3 for every 3600 s exposure
Independent reflections scanned	2003 (128 systematically absent)
R_{int} (on F^2 for o, k, $\pm\ell$)	0.059
Reflections in refinement (N)	1598 [I ≥ 1.5σ(I)]
Absorption correction	azimuthal scans
Relative correction factors	0.85-1.00
Secondary extinction parameter (g)	1.1 (2) x 10^{-6}
Number of parameters (V)	164
Function minimized	$\Sigma w(\|F_o\|-\|F_c\|)^2$
Weighting factor (w)	$1/\sigma^2(F)$
R(F), wR(F)	0.035, 0.042
S	2.24
Maximum Δ/σ, last cycle	0.014
Maximum, minimum in final diffraction map	0.37, -0.20e Å^{-3}
Algebraic relationships [18]	

Table 2

Bond Lengths in **5**, Å [a]

Atom	Atom	Distance	Atom	Atom	Distance
S	O	1.489 (2)	C3a	C4	1.385 (3)
S	C2	1.851 (3)	C4	C5	1.378 (4)
C2	C*l*2	1.767 (3)	C5	C6	1.384 (4)
C2	C3	1.507 (3)	N	C6	1.339 (4)
C3	C*l*1	1.793 (2)	N	C7a	1.327 (3)
C3	C3a	1.500 (3)	C5	C8	1.512 (4)
C3a	C7a	1.372 (3)	C8	C9	1.483 (5)
S	C7a	1.793 (3)			

[a] Standard deviations, shown in parentheses, refer to the least significant digits.

Table 3

Bond Angles in **5** [a,b]

Atom	Atom	Atom	Angle (°)	Atom	Atom	Atom	Angle (°)
O	S	C2	108.3 (1)	S	C7a	C3a	114.7 (2)
O	S	C7a	106.5 (1)	S	C7a	N	119.3 (2)
S	C2	C3	108.4 (2)	N	C7a	C3a	125.9 (2)
S	C2	C*l*2	109.5 (1)	C3a	C4	C5	118.4 (2)
C*l*2	C2	C3	113.3 (2)	C4	C5	C6	118.2 (3)
C2	C3	C3a	105.3 (2)	C4	C5	C8	121.6 (3)
C2	C3	C*l*1	110.4 (2)	C6	C5	C8	120.2 (3)
C*l*1	C3	C3a	112.3 (2)	N	C6	C5	125.0 (2)
C3	C3a	C7a	113.4 (2)	C6	N	C7a	114.5 (2)
C3	C3a	C4	128.5 (2)	C2	S	C7a	86.6 (1)
C4	C3a	C7a	118.0 (2)	C5	C8	C9	113.5 (3)

[a] Standard deviations, shown in parentheses, refer to the decimal part of the angle. [b] Sum of internal angles: 720.0 ±1.3° in the pyridine ring; 528.4 ±0.9° in the dihydrothiophene ring.

Table 4

Deviations (in Å) from the Least-squares Mean Plane in Each Ring [a]

For pyridine ring [b]		For dihydrothiophene ring [c]	
Ring atom	Deviation [d]	Ring atom	Deviation [d]
C3a	0.003 (2)	S	-0.014 (1)
C4	-0.002 (3)	C2	0.316 (3)
C5	-0.001 (3)	C3	-0.221 (3)
C6	0.004 (3)	C3a	-0.008 (2)
N	-0.001 (2)	C7a	0.145 (2)
C7a	-0.002 (2)		
Substituent Atom		Substituent Atom	
S	-0.117	O	-1.460
C3	-0.028	C*l*2	-0.392
C8	-0.024	C*l*1	0.637

[a] Dihedral angle between least-squares ring planes: 8.2°. [b] Mean deviation from planar ring: 0.002 Å. [c] Mean deviation from planar ring: 0.141 Å. [d] Standard deviations, shown in parentheses, refer to the least significant digits.

of internal angles = 720.0 ±1.3°; mean deviation from planarity = 0.002 Å) within experimental error, while the dihydrothiophene ring is non-planar (respective values 528.4 ± 0.9° and 0.141Å) and tilted from the plane of the pyridine ring. The C2-S-C7a angle of 86.6° is smaller than the C-S-C angles of 97.4° reported for dimethyl sulfoxide and diphenyl sulfoxide, but the S-O bond length (1.489 Å, Table 2) in **5** is intermediate between those of 1.53 and 1.47 Å in these other sulfoxides [11,12]. The C2-C*l*2 bond length is notably shorter (0.026 Å) than the C3-C*l*1 bond length, despite the expectation that the *syn* oxygen atom might repel electronically the vicinal chlorine atom.

Geneste and coworkers used a combination of proton coupling constants between H-2 and H-3, ^{13}C chemical shifts for C-2 and C-3, and other observations to assign the stereochemistry to compounds **6-8** [13]. Comparisons of pertinent ^1H nmr data are presented in Table 5 and ^{13}C nmr data, in Table 6. As based on the coupling constant $J_{2,3}$ for compounds **5-8** it seems appropriate to assign a value of 6-7 Hz to a *trans* configuration, as in **5-7**, and a value of *ca.* 4 Hz to a *cis* configuration as in **8**. Table 5 includes data on two isomeric 2,3-dichloro-2,3-dihydrothieno[2,3-*b*]pyridine

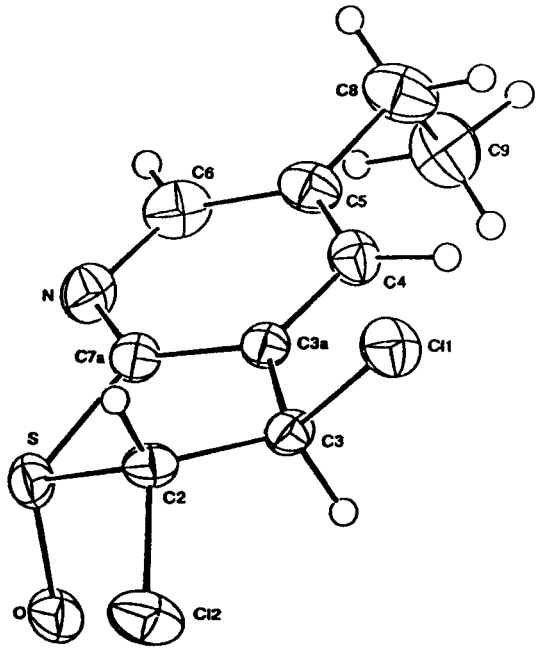

Figure 2. ORTEP Drawing of Compound **5**.

Table 5

Comparison of Chemical Shifts and Coupling Constants for ^{1}H NMR Spectra in Compounds **5-8**, **IIa**, and **IIb**

Compound Number	Solvent	Chemical Shift (δ) H-2 [a]	H-3 [a]	$J_{2,3}$ (Hz)	Comments
5	CD_3CN	5.41	5.87	6.8	this study, *trans-syn*
6 [b]	$CDCl_3$	5.22	5.43	6	*trans-anti* [c]
7 [d]	$CDCl_3$	5.15	5.80	6.5	*trans-syn* [c]
8 [e]	$CDCl_3$	5.36	6.23	4	*cis-anti* [c]
IIa [f]	CD_3CN	5.44	5.68	5.5	mp 165-166° [g]
IIa [f]	acetone-d_6	5.57	5.91	5.5	
IIb [f]	CD_3CN	5.47	5.93	6.5	mp 148.5-150.5° [g]
IIb [f]	acetone-d_6	5.70	6.05	7.0	

[a] Note that assignments of signals for H-2 and H-3 may be interchanged. [b] Shown as formula **5** in ref [7]. [c] Stereochemistry as proposed by Geneste et al (ref [7]). [d] Shown as formula **6** in ref [7]. [e] Shown as formula **7** in ref [7]. [f] Compound number as shown in ref [3]. [g] See text for a discussion of the stereochemistry of this compound. Also see footnote 13.

1-oxides, **IIa** and **IIb**, previously reported [3]. The intermediate value of 5.5 Hz for $J_{2,3}$ of **IIa**, however, leaves the question of *cis* or *trans* geometry in this compound uncertain. On the other hand, the close numerical values between **IIb** and **5** for the chemical shifts of H-2 and H-3 plus the coupling constant $J_{2,3}$ in the solvent trideuterioacetonitrile imply that **IIb** may have the *trans-syn* stereochemistry also, rather than the *cis-anti* geometry previously proposed [3].

It should be noted that for each compound in Table 5 the signal for H-3 is listed as downfield of that for H-2. This assignment is based on the observation of Geneste et al [7] that reactions of 2- and 3-deuteriobenzo[*b*]thiophenes with *t*-butyl hypochlorite give retention of the D atoms and establish the relative chemical shifts of H-3 and H-2, respectively. It is reasonably assumed that the D atoms do not migrate during the reaction. For comparison, Amann and Kresze [14] report a downfield shift of the signal for H-2 on going from the *syn* to the *anti* isomers of compound **9**. Albeit very small, this change is in the same direction as that reported for going from **7** to **6**. Unfortunately, Amann and Kresze did not report the effect on the H-3 signal for their change in isomers.

Table 6 compares ^{13}C nmr chemical shifts in **5-8**. It is clear that one cannot assign stereochemistry on the basis of the measured signals, though **6** can be distinguished from the other three by the shifts for C-2 and C-3. It appears, however, that one can calculate reasonable chemical shifts for the carbons of the benzene ring in **6-8** from an assumption of additivity of substituent effects. It is also apparent that additional X-ray crystallographic studies on some of the compounds **6-8**, **IIa**, and **IIb** may be needed in order to establish definitive stereochemical structures in these series.

Table 6

Comparison of Calculated and Measured ^{13}C NMR Chemical Shifts for Compounds **5-8**

Compound Number	Solvent	Chemical Shift (δ)								
		C-2	C-3	C-3a	C-4	C-5	C-6	C-7	C-7a	Comment
5	CD_3CN	78.6	64.2	136.5	136.1	146.4	154.0		160.0	*trans-syn* [a]
6	$CDCl_3$	83.3	61.9	139.2	131.4	133.4	126.9	127.1	142.7	*trans-anti* [b]
7	$CDCl_3$	78.6	64.1	139.9	131.0	133.7	126.9	127.4	141.5	*trans-syn* [b]
8	$CDCl_3$	78.9	64.2	140.1	131.1	133.9	127.1	127.7	141.8	*cis-anti* [b]
6-8 calcd	$CDCl_3$			132.8	129.9	131.1	129.6	123.7	146.4	[c]

[a] This study. [b] Stereochemistry as proposed by Geneste et al (ref [7]). [c] Stereochemically-independent calculated values from the table by D. E. Ewing *Org. Magn. Reson.*,**12**, 499 (1979), as based on the model compound of methyl 2-chloromethylphenyl sulfoxide and assuming additivity of effects of the substituents on the benzene ring. Substituent effects for the CH_2Cl group are taken as these: *ipso*, 9.3; *ortho*, 0.3; *meta*, 0.2; *para*, 0.0. Those for the SO group are taken as *ipso*, 17.6; *ortho*, -5.0; *meta*, 1.1; *para*, 2.4.

EXPERIMENTAL

trans-2,3-Dichloro-5-ethyl-2,3-dihydrothieno[2,3-*b*]pyridine *syn*-1-Oxide (**5**).

This compound was available in pure form from an earlier synthesis [3,15,16]; ^{1}H nmr (trideuterioacetonitrile): δ 1.28 (t, J_{Et} = 7.5 Hz, 3H, methyl group), 2.81 (q, 2H, methylene), 5.41 (d, $J_{2,3}$ = 6.8 Hz, 1H, H-2), 5.87 (d, 1H, H-3) [17], 7.91 (d, $J_{4,6}$ = 1.4 Hz, 1H, H-4), 8.63 (d, 1H, H-6); also see Table 5; ^{13}C nmr: see Table 6; X-ray analysis: see Tables 1-4 and Figure 2.

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[5] It should be noted that a high yield of sulfone **2** results from treatment of benzo[*b*]thiophene with hydrogen peroxide-acetic acid; see F. G. Bordwell, B. B. Lampert, and W. H. McKellin, *J. Am. Chem. Soc.,* **71**, 1702 (1949). However, treatment of thienopyridines with this reagent produces exclusively *N*-oxides rather than *S*-oxides; see L. H. Klemm, I. T. Barnish, and R. Zell, *J. Heterocyclic Chem.,* **7**, 81 (1970); see L. H. Klemm, S. B. Mathur, R. Zell, and R. E. Merrill, *J. Heterocyclic Chem.*, **8**, 931 (1971).

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[15] Compound **5** was designated as **XIX** in ref [3].

[16] The nmr spectra were obtained on a Varian INOVA 300 instrument.

[17] Note that assignments of signals to H-2 and H-3 may be interchanged.

[18] These are the same as given in L. H. Klemm, T. J. R. Weakley, R. D. Gilbertson, and Y.-H. Song, *J. Heterocyclic Chem.,* **35,** 1269 (1998).