Studies on 1-(Thiosulfinylaminothio)piperidines

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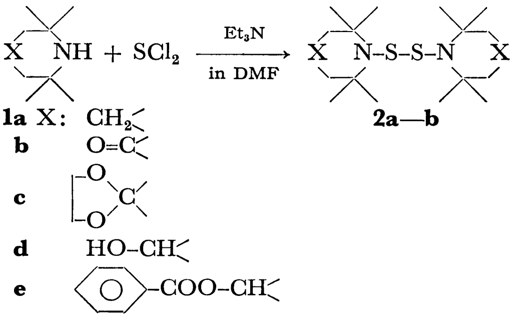
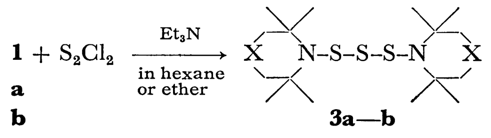
Hindered piperidine derivatives with a new functional group(–S–N=S=S), 2,2,6,6-tetramethyl-1-(thiosulfinylaminothio)piperidines (**4**) were obtained from the corresponding piperidines **1**, sulfur monochloride and ammonia. These compounds were also prepared from bis(2,2,6,6-tetramethylpiperidino) disulfides or bis(2,2,6,6-tetramethylpiperidino) trisulfides under similar reaction conditions. In much lower yields, unhindered 1-(thiosulfinylaminothio)piperidines (**8**) were also obtained. The photochemical and thermal stabilities of **4** and **8** were nearly the same. Reaction pathways were disucssed.

Recently the reaction of hindered amines such as 2,2,6,6-tetramethylpiperidine (**1b**) with sulfur chlorides has been studied by Bennett *et al.*[1] who found that sulfur dichloride (SCl_2) curiously gave bis(2,2,6,6-tetramethylpiperidino) disulfide (**2b**) in the presence of triethylamine and *N,N*-dimethylformamide (DMF) (Eq. 1), and that sulfur monochloride (S_2Cl_2) gave bis(2,2,6,6-tetramethylpiperidino) trisulfide (**3b**) in



2a—b (Eq. 1)



3a—b (Eq. 2)

hexane or ether (Eq. 2). The disulfides **2** have been shown by us to be effective stabilizing reagents for polyurethane.[2] While trying to find an improved means of synthesizing **2**, it was found that in the presence of

$$\mathbf{1} + S_2Cl_2 \longrightarrow \mathbf{2} \qquad \text{(Eq. 3)}$$

DMF and an excess amount of **1**, S_2Cl_2 normally gives the disulfides **2** in excellent yields (Eq. 3).[2] During this research, we further found that piperidine derivatives with a new functional group (–S–N=S=S), 2,2,6,6-tetramethyl-1-(thiosulfinylaminothio)piperidines (**4**) are obtained when equimolar amounts of **1** and S_2Cl_2 are allowed to react and the resulting mixture is quenched with aqueous ammonia. In this paper, we wish to report the preparation and properties of **4** as well as possible reaction pathways for formation of **4**.

Results and Discussion

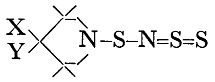
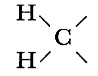
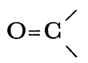
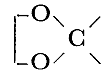
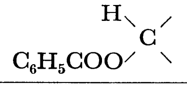
Compounds **4** was prepared not only from **1** but also from the disulfide **2** or the trisulfide **3**, under similar reaction conditions.

*Preparation of 2,2,6,6-Tetramethyl-1-(thiosulfinylaminothio)piperidines (**4a—d**) from 2,2,6,6-Tetramethylpiperidines (**1a—d**).* The reaction mixture of **1** with S_2Cl_2 was pale yellow. When the mixture was treated with 10% aqueous ammonia, the color turned to deep red immediately. The red mixture contained the trisulfide **3** (major product) accompanied by a small amount of the disulfide **2** (Eq. 4). However pure **2** and **3** are colorless.

$$\mathbf{1} \xrightarrow[\text{ii) aq NH}_3]{\text{i) S}_2\text{Cl}_2} \text{red subst. } \mathbf{4} + \mathbf{3}\text{(maj.)} + \mathbf{2}\text{(min.)} \qquad \text{(Eq. 4)}$$

A comparative experiment showed that similar treatment of the reaction mixture (from **1b**) with a 10% aqueous solution of potassium hydrogencarbonate instead of aqueous ammonia gave a colorless mixture containing **3b** (major product) and **2b** (minor product) (Eq. 5). Thus it became apparent that ammonia is

Table 1. Properties of compounds **4a—d**

No.	 X Y N-S-N=S=S	Mp/°C	Vis. spectrum λ_{max}/nm(log ε)	R_f-SiO_2 (Solvent)
4a		(red oil)	413 in E	0.75 (B/H:1)
4b		116.5—118 (red prisms)	409(4.11) in H 411(4.11) in E	0.13(B)
4c		98—99 (red prisms)	412(4.14) in H 414(4.14) in E	0.50(B)
4d		99—100 (red prisms)	411(4.15) in H 413(4.15) in E	0.62(B)

H: hexane, E: EtOH, B: benzene.

$$\mathbf{1b} \xrightarrow[\text{ii) ap KHCO}_3]{\text{i) S}_2\text{Cl}_2} \mathbf{3b}(\text{maj.}) + \mathbf{2b}(\text{min.}) \qquad (\text{Eq. 5})$$

the cause of the coloration. In order to clarify the cause of the coloration, the red substances were isolated and their structures were determined. Chromatographic separation of the mixture gave small amounts (Y=6—14 %) of red oils or prisms (**4a**—**d**) whose physical properties are given in Table 1. Typical structure determination was carried out as follows. **4c** has the formula, $C_{11}H_{20}N_2O_2S_3$, based on the satisfactory elemental analysis and molecular weight determination (308), as shown both by VPO method and mass spectrum. Since the NMR spectrum showed three singlets at δ 1.45 (12H), 1.92 (4H), and 3.97 (4H), the "$C_{11}H_{20}NO_2$" part of **4c** ("$C_{11}H_{20}NO_2$"+NS_3) was characterized as both the piperidine part with four methyl groups and the ethylene acetal part ($CDCl_3$). However, the "NS_3" part of **4c** ($C_{11}H_{20}NO_2$+"NS_3") could not be characterized by spectroscopic analysis. Thus the whole structure determination was carried out by X-ray crystallographic analysis.[3a] Phases were assignable by the symbolic addition procedure, and structure factors were refined by the block-diagonal least-squares technique to a final R-factor of 6.7%. Consequently, **4c** was determined as 7,7,9,9-tetramethyl-1-(thiosulfinylaminothio)-1,4-dioxa-8-azaspiro[4.5]-decane (**4c**), containing the new thiosulfinylaminothio group, –S–N=S=S (Fig. 1). Structures **4a**, **4b**, and **4d** were analogously assigned on the basis of visible, mass, NMR spectra and/or elemental analyses. The new compounds **4a**—**d** indicated fungicidal activity,[3b] besides offering UV protecting in polyolefins, like polypropylene.

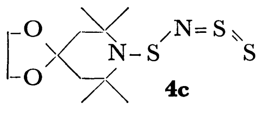


Fig. 1.

Preparation of 4 from Bis(2,2,6,6-tetramethylpiperidino) disulfide (2) or Bis(2,2,6,6-tetramethylpiperidino) trisulfide (3). First, we wanted to see whether 1-(thiosulfinylaminothio)piperidine (**4**) was the secondary product given by an interaction of ammonia with the disulfide **2** and/or trisulfide **3**. This is because, as shown in Eqs. 4 and 5, treatment of the reaction mixture with 10% aqueous ammonia gave **4**, **3**, and **2**; whereas treatment of the same mixture with 10% aqueous $KHCO_3$ gave **3** and **2** without **4**.

The desired examination was carried out as follows. Treatment of pure, freshly prepared **2a** or **3a** with 10% aqueous ammonia caused no reaction under reaction conditions similar to those used in Eq. 4. However, in the presence of equimolar amounts of S_2Cl_2 relative to **2a** or **3a**, similar treatment with ammonia gave the expected **4a** (Eq. 6) in a yield of 35.2 or 32.7%, respectively, higher than that of 8.6% from **1a**. The yields were based on the assumption that 1 mol of the starting **1**, **2**, or **3** gives 1 mol of **4**. Thus **2** and/or **3** may be the precursor of **4**. The relatively low yield of **4** from **1** is reasonably explained by assuming that **1** consumes sulfur monochloride to give **2** and/or **3**.

$$\begin{aligned} &\mathbf{2a} \xrightarrow[\text{ii) aq NH}_3]{\text{i) S}_2\text{Cl}_2} \mathbf{4a} \\ &\mathbf{3a} \xrightarrow[\text{ii) aq NH}_3]{\text{i) S}_2\text{Cl}_2} \mathbf{4a} \end{aligned} \qquad (\text{Eq. 6})$$

Although the reaction of secondary amines with sulfur monochloride has been shown in many papers to give bis(disubstituted amino) polysulfides,[4] no compounds having the –S–N=S=S group have yet been reported. For primary amines, on the contrary, the analogous function, the thiosulfinylamino group (–N=S=S) was recently reported by Barton *et al.*[5] and Inagaki *et al.*[6] Aromatic primany amines having an electron-donating group at the *p*-position, or bulky groups at the 2 and 6-positions, *e.g.* *p*-dimethylaminoaniline or 2,4-di-*t*-butyl-6-methylaniline, react with sulfur monochloride to give the corresponding *N*-thiosulfinylaniline **5** or **6**, as shown in Fig. 2, which was relatively stable. Interestingly, substituted aniline with less bulky groups at the 2 and 6 positions, such as 2,4,6-trimethylaniline, gives the corresponding *N*-thiosulfinylaniline in a low yield. They explained the stability of *N*-thiosulfinylaniline in term of the steric effect.[6]

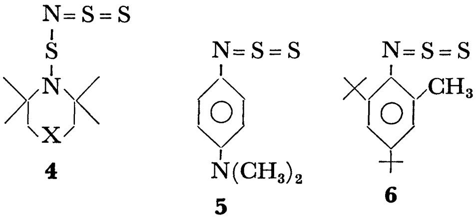
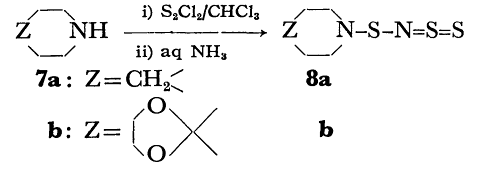
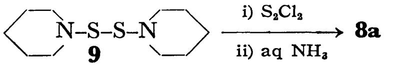


Fig. 2.

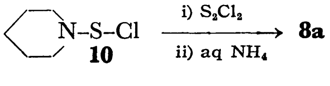
Formation of Non-Hindered 1-(Thiosulfinylaminothio)-piperidines (8). In order to investigate whether the contribution of the steric effect by the tetramethyl group is necessary for the formation of 1-(thiosulfinylaminothio)piperidines (**8**), piperidines unsubstituted at the 2 and 6-positions (**7a** and **7b**) were examined. **7a** and **7b** similarly gave the corresponding 1-thiosulfinylaminothio derivatives **8a** and **8b** (Eq. 7), respectively, in much lower yield (*ca.* 0.4%),[7] under the same reaction conditions as described in Eq. 4. The isolated **8a** was characterized by its high resolution mass spectrum exhibiting an M$^+$ peak at m/e 193.9986, which consisted with the calculated value for $C_5H_{10}N_2S_3$ (194.0006), and by its visible spectrum (410 nm in ethanol). Additionally, the compound **8a** was also prepared in 2.8% yield[7] from the corresponding disulfide **9** (Eq. 8)



(Eq. 7)



(Eq. 8)



(Eq. 9)

in a manner similar to that shown in Eq. 6.

As will be discussed later, 1-sulfenylpiperidine chloride (**10**)[8] may be one of the precursors of **8a** (Eq. 9). In order to examine this assumption, freshly prepared **10** was treated by a method similar to that described in Eq. 6. Expectedly **10** also gave **8a** (Eq. 9) in 1.2% yield.[7]

Thus it was found that **8a** was obtained from **7a**, **9**, or **10**. However the yield of **8a** is much lower than that of **4a**. The difference may depend upon that of the stability of **4a** and **8a**. In order to check this explanation, we tried following experiments.

The Photo- and Thermal Behavior of Hindered (4) and Nonhindered (8) 1-(Thiosulfinylaminothio)piperidines.

The photochemical behavior of sterically hindered 1-(thiosulfinylaminothio)piperidines (**4**) and unhindered 1-(thiosulfinylaminothio)piperidines (**8**) under natural diffused light at room temperature was studied. Relative fading rates of both **4** and **8** were compared at a concentration of 5—10$\times$10^{-5} M in hexane or ethanol for a period of 1 h, measuring the decrease in visible absorption at 410 nm (Table 2). Blank experiments on **4** and **8** in the dark at room temperature showed no detectable change in hexane and ethanol. Table 2 shows that the photochemical behavior of **4** and **8** are nearly the same, and therefore, their photochemical behavior does not depend on the bulk of the substituents at the 2 and 6 positions.

Table 2. Photochemical behavior of 1-(thiosulfinylaminothio)-piperidines, **4** and **8**

Compound	% Loss during 1 h[a],[b]	Solvent[c]
4a	5	H and E
4b	5	H and E
4c	7	H and E
4d	7	H and E
8a	5	H and E

a) On allowing to stand under natural diffused light. b) By measuring the decrease at 410 nm. c) H: hexane; E: ethanol.

Thermal behavior of **4** and **8** was similarly studied. Refluxing a 5—10$\times$10^{-5} M solution of **4** or **8** in chloroform for 3 h showed no detectable change in visible absorption.

Accordingly the much lower yield of **8** than **4** could not be explained in terms of the product stability. Thus the difference in the yield of **4** or **8** seems to depend on other causes, *e.g.*, properties of an uncertain intermediate to be discussed later.

Possible Reaction Pathways. Equation 2, along with as described in Eqs. 4, 5, and footnote 9 shows that piperidines, **1** or **7**, react with sulfur monochloride to give the corresponding disulfides, **2** or **9**, and the trisulfide **3**. The resulting **2**, **3**, or **9** may further react with sulfur monochloride at the first stage (Fig. 3) to give the corresponding 1-sulfenyl chloride **10** or **12**, since sulfur monochloride has been known to polarize to $Cl^{\delta-}$......$^{\delta+}S_2Cl$.[4] Additionally, a presumed compound, **11** simultaneously prepared from **2**, **3**, or **9** may also give **10** or **12**. Equations 6 and 8 show that the di- and trisulfides **2**, **9**, and **3** actually give the corresponding 1-(thiosulfinylaminothio)piperidines **4** and **8**. Further Eq. 9 also shows that the sulfenyl chloride **10** actually gives **8**.

Thus it can be explained that the new 1-(thiosulfinylaminothio)piperidines **4** or **8** are prepared *via* the corresponding disulfides **2** or **9** and/or the trisulfides **3** and, subsequently, such sulfenyl chloride as **10**. Tentatively it is assumable that **4** and **8** may be prepared *via* the postulated intermediates **13** and **14** derived from the sulfenyl chloride **12** or **10** (Fig. 3) although the intermediary presence of **13** and **14** are unconfirmed. From this assumption, the much lower yield of **8** (R=H), described above, may be explained by the decrease of stability of the intermediate **13** or **14** (R=H).

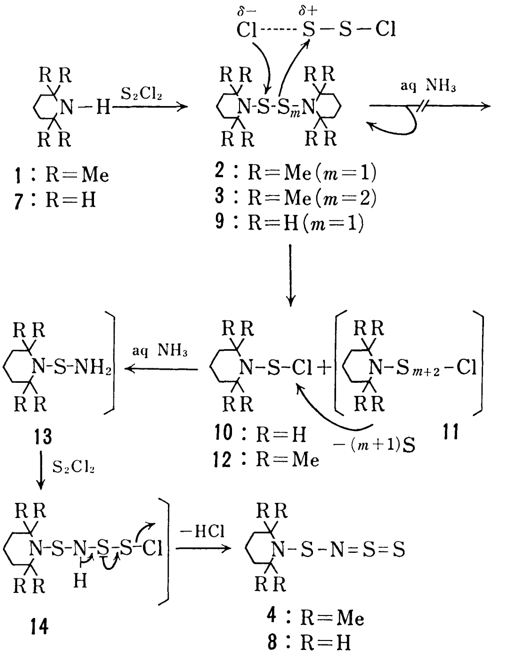


Fig. 3.

Experimental

Mps were not corrected.

NMR spectra were obtained using a Varian A-60 NMR spectrometer, using TMS as an internal standard.

Mass spectra were obtained using a JEOL-JMS-OISG mass spectrometer with an ionizing energy of 75 eV.

Thin-layer chromatography (TLC) was performed on TLC-plates Silica Gel F_{254} (0.25 mm) (Merk).

Bis(2,2,6,6-tetramethylpiperidino) Disulfide (2a) (X: CH_2<). Into a solution of 48 g (0.34 mol) of 2,2,6,6-tetramethylpiperidine (**1a**) (X: CH_2<) in 120 ml of DMF and 350 ml of hexane was added dropwise a solution of 4.58 g (0.034 mol) of sulfur monochloride in 40 ml of hexane with stirring at −20—−25 °C for 30 min. After the addition was completed, the internal temperature was gradually raised to room temperature over a period of 30 min. The reaction mixture was then poured into ice and extracted with benzene. The benzene layer was washed with a 3% aqueous solution of hydrochloric acid and three times with water and dried over sodium sulfate. Evaporation of the benzene under diminished pressure gave 11.2 g of the crude product **2a** which was recrystallized from methanol to give 9.4 g of an analytically pure colorless compound (needles), mp 83—84 °C, [lit,[1] mp 84—85 °C]. The combined yield of crystalline product (80.2%) and of the residue in solution (as determined by NMR using anisol as an internal standard) was 88.8% based on the starting sulfur monochloride. Found: C, 62.49; H, 10.71; N, 7.97; S, 18.60%. Calcd for $C_{18}H_{36}N_2S_2$: C, 62.73; H, 10.52; N, 8.12; S, 18.60%.

*Bis(4-oxo-2,2,6,6-tetramethylpiperidino) Disulfide (**2b**) (X: O=C<)* was prepared by our improved method described in Refs. 2a and 2c.

*Bis trisulfides **3a** and **3b*** were prepared by the method of Bennett *et al.*[1]

Isolation of 1-(Thiosulfinylaminothio)piperidines (4) and Detection of Bis(2,2,6,6-tetramethylpiperidino) Disulfides (2) and Bis(2,2,6,6-tetramethylpiperidino) Trisulfides (3). (Eq. 4)

*4-Oxo-2,2,6,6-tetramethyl-1-(thiosulfinylaminothio)piperidine (**4b**):* Into a solution of 31 g (0.2 mol) of **1b** in 500 ml of toluene was added dropwise a solution of 27 g (0.2 mol) of sulfur monochloride in 80 ml of hexane with stirring at 10—15 °C over a period of about 2 h. After the addition was completed, the reaction mixture was poured into 300 g of ice and 200 g of 35% aqueous ammonia. The organic phase was then separated, washed with water and dried over magnesium sulfate. Evaporation of the solvent under diminished pressure gave a red solid, which was chromatographed on 1.5 kg of Silica Gel 60 (Merck, 70—230 mesh) with benzene to give red crude crystals in 14% yield. Recrystallization of the crude crystals from hexane gave analytically pure red prisms, mp 116.5—118 °C. NMR (CCl_4) δ 1.47 (S, 12H), 2.60 (S, 4H). MS *m/e* 264 (M^+). Found: C, 40.52; H, 6.00; N, 10.61; S, 36.04%. Calcd for $C_9H_{16}N_2OS_3$: C, 40.87; H, 6.09; N, 10.59; S, 36.73%.

*The trisulfide **3b** and a trace amount of the disulfide **2b*** were detected in the reaction mixture by TLC and NMR-analysis.

*4-Benzoyloxy-2,2,6,6-tetramethyl-1-(thiosulfinylaminothio)-piperidine, (**4d**).* Into a solution of 4.8 g (0.0184 mol) of 4-benzoyl-2,2,6,6-tetramethylpiperidine **1d** in 20 ml of chloroform was added dropwise a solution of 2.5 g (0.0185 mol) of sulfur monochloride in 10 ml of chloroform with stirring at 10—15 °C over a period of 20 min. After the addition was completed, the reaction mixture was poured into 30 g of ice and 20 g of 35% aqueous ammonia. Then the chloroform was separated, washed with water, and dried over magnesium sulfate. Evaporation of the chloroform under diminished pressure gave a red solid, which was chromatographed on 150 g of Silica Gel 60 (Merck, 70—230 mesh) with a mixture of benzene and hexane (1:1) to give red crude crystals in 6% yield. Recrystallization of the crude crystals from hexane gave analytically pure red prisms, mp 99—100 °C. NMR ($CDCl_3$) δ 1.46 (S, 6H), 1.54 (S, 6H), 1.75 (br. d, 2H), 2.27 (dd, 2H, $J=12$ and 4.5 Hz), 5.58 (tt, $J=12$ and 4.5 Hz), 7.3—8.3 (m, 5H). MS *m/e* 370 (M^+). Found: C, 51.53; H, 5.91; N, 7.68; S, 26.21%. Calcd for $C_{16}H_{22}N_2O_2S_3$: C, 51.86; H, 5.98; N, 7.55; S, 25.95%.

*1-(Thiosulfinylaminothio)piperidines, **4a**, **4c**, **8a**, and **8b**,* were prepared from the corresponding amines by a method similar to that described for **4b** and **4d**. **4a** ($Y=8.6\%$) was identified visible, NMR, and mass spectra. NMR ($CDCl_3$) δ 1.40 (S, 12H), 1.5—1.8 (m, 6H). MS *m/e* 250 (M^+). Data of **4c** ($Y=7\%$) were given in the text. Found: C, 42.83; H, 6.31; N, 9.00; S, 31.46%. Calcd for $C_{11}H_{20}N_2O_2S_3$: C, 42.82; H, 6.53; N, 9.08; S, 31.18%. Unhindered **8a** and **8b**, separated by column chromatography, were identified by visible, mass, and/or high resolution mass spectra. Data of **8a** was given in the text. R_f-value (SiO_2-TLC/hexane) was 0.25. **8b**: The mass spectrum (*m/e* 252, M^+) was consistent with the theoretical value. λ_{max} (in EtOH): 410 nm.

Experiment A (Eq. 5). The reaction mixture, which was obtained during the preparation of **4b**, was poured into ice and 10% aqueous potassium hydrogencarbonate instead of ammonia. In the resulting organic phase, **3b** and a trace amount of **2b** were observed by TLC and NMR analysis.

Experiment B (Eqs. 6, 8, and 9). Under the same reaction conditions as used in Eq. 4, an equimolar mixture of **2a**, **2b**, **3a**, **9**, or **10** and sulfur monochloride were treated with aqueous ammonia. The results were shown in the text.

7b was prepared from the corresponding 1-methylpiperidine by the modified method of Fischer *et al.*[12]

9 was prepared by the method of Dogadkin *et al.*[10]

10 was prepared by the method of Weiss *et al.*[8]

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7) Yields were measured by visible absorption (410 nm), and were based on the assumptions that equimolar **4a** and **8a** should show the same ε-value and that 1 mol of the starting **7**, **9**, and **10** should give 1 mol of **8a**.

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9) Piperidine **7a** has been known to react with sulfur monochloride giving the corresponding disulfide **9**.[10]

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