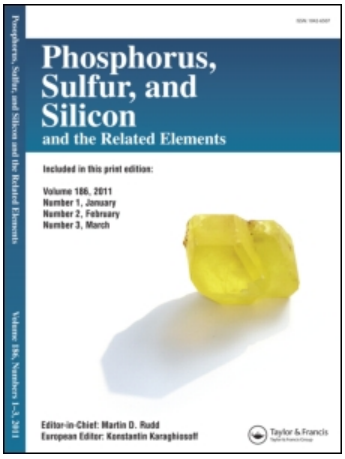

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Synthesis of Bis(7-Methyl-2- or 6-Purinyl) Disulfides

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Substituted 7-methyl-2- or 6-purinethiones were obtained in series of reactions by nucleophilic substitution with oxygen, chloro, and sulfur nucleophiles. Oxidation of the sulfur atom at position 6 or 2 in purinethiones to corresponding disulfides depended on the conditions of the reaction and oxidizing agent.

Keywords 7-Methyl-2 or 6-purinethiones; bis(7-methyl-2- or 6-purinyl) disulfides; oxidation reaction

INTRODUCTION

The purine ring system is a key structural element of substrates and ligands of many biosynthetic, regulatory, and signal transduction proteins including cellular kinases, G proteins and polymerases.[1] 6-Mercaptopurine and 6-thioguanine are considered among the most effective drugs used in cancer chemotherapy for the treatment of a number of types of leukemia, non-Hodgkin's lymphoma and other neoplastic conditions.[2–5] Azathioprine is an immunosuppressive agent, which is widely used in clinical treatment of autoimmune disorders as well as in organ and tissue transplantation.[6,7] The sulfur containing purines are metabolically activated by hepatic cytochrome P-450 systems to reactive metabolites, and the oxidation reactions play an important role in their metabolism. The biological activity of mercaptopurines has been found to be related to its ease of oxidation to disulfides, sulfenic, and sulfinic acids, resulting from reaction of thiol radicals with molecular oxygen.[1,3] The reactive metabolites of mercaptopurines are capable of binding to microsomal proteins largely through formation of mixed disulfide with protein thiols.[5,8] Protein disulfide isomerase (PDI) is a

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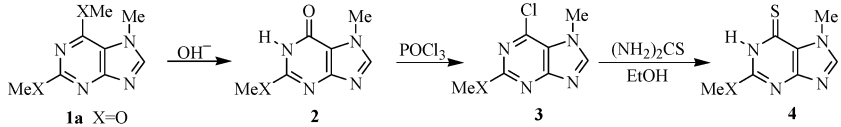
multifunctional protein catalyzing the formation, reduction and isomerization of disulfide bonds, and their ability to bind to polypeptide chains. Formation of the methyltransferases-DNA complexes via a disulfide covalent bond can repair a variety of premutagenic lesions arising from exposure of DNA to alkylating agents.[10] Some mixed disulfide derivatives of purinethiones (mercaptopurine, thioguanine) and their nucleosides have activity in experimental tumor systems (Leukemia L-1210, Sarcoma – 180).[5,11–13]

RESULTS AND DISCUSSION

In order to find more effective substances, a series of symmetrical bis(7-methyl-2- or 6-purinyl) disulfides were prepared by the oxidation of the corresponding purinethiones.

6-Thiopurines **4** containing methoxy and methylthio groups in position 2 were prepared in three steps from 2,6-dimethoxy- or 2,6-dimethylthio-7-methylpurines **1** by nucleophilic substitution at position 6 (Scheme 1).

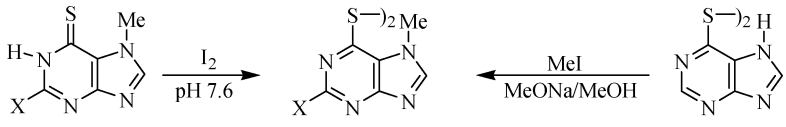


1a X=O
1b X=S

2 **3** **4**

SCHEME 1

Oxidation of 2-substituted 6-purinethiones **4** with iodine in phosphate buffer, pH 7.6, according to Doerr's procedure,[11] leads to 6,6′-dipurinyl disulfides **5** (Scheme 2).



4a X=OMe
4b X=SMe
4c X=Cl

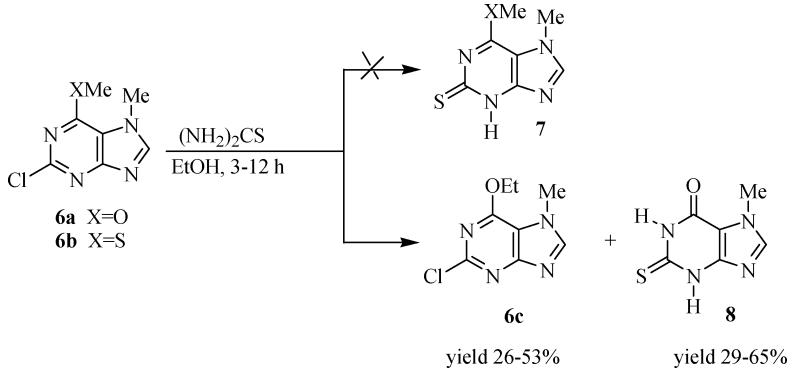
5a X=OMe 80%
5b X=SMe 75%
5c X=Cl 96%
5d X=H 68%

5e

SCHEME 2

Symmetrical 7,7′-dimethyl-6,6′-dipurinyl disulfide **5d** was obtained by the N-methylation reaction of 6,6′-dipurinyl disulfide **5e**. The lower reactivity of position 2 in the purine ring, observed in the reaction of 2-chloro-7-methyl-6-substituted purines **6** with thiourea, did not provide the expected 6-substituted 2-purinethiones **7**, but led to two products:

2-chroro-6-ethoxy-7-methylpurine **6c** and 7-methyl-2-thioxanthine **8**. Yields of both compounds depended on the reaction time (Scheme 3). Prolongated time (from 3 h to 12 h) discriminated in favor of formation of **6c** from 53% to 26% (see Experimental).

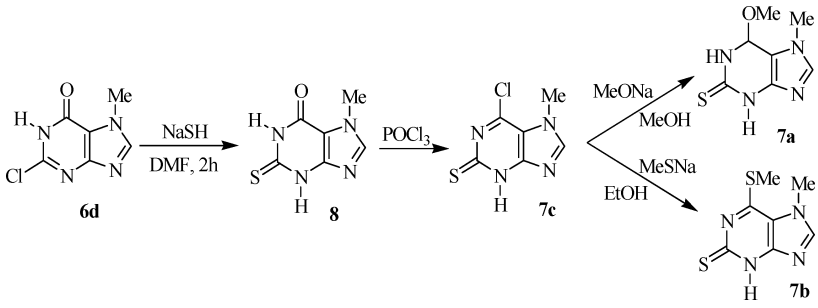


SCHEME 3

The formation of **6c** and **8** was a result of the high reactivity of position 6 in 2-chloro-6-methoxy- or 6-methylthio-7-methylpurines (**6a**, **6b**) to oxygen nucleophilic agents, observed previously in other purine derivatives.[14–16] This reaction probably proceeds through substitution with ethoxide anion generated from solvent followed by 0-6-dealkylation.

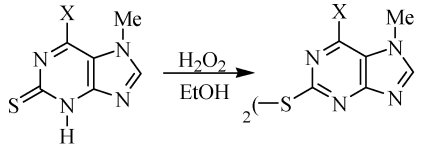
On the other hand, the chlorine atom in position 2 smoothly underwent nucleophilic substitution in the reaction of 7-methyl-2-chloroxanthine **6d** with sodium hydrosulfide in dimethylformamide.

Treatment of 7-methyl-2-thioxanthine **8** with phosphorus oxychloride gave the respective 6-chloro derivative **7c**, which underwent nucleophilic displacement of the halogen atom by the methoxide and methanethiolate anions resulting in 7-methyl-6-substituted-2-purinethiones **7a** and **7b** (Scheme 4).



SCHEME 4

Failure of the oxidation of 6-substituted 2-purinethiones **7** under the same conditions as the 6-isomers **4**, was unexpected. Oxidation of compounds **7**, however, with hydrogen peroxide in 70% ethanol led to the respective disulfides **9** in 73–80% yield (Scheme 5).



7a X=OMe **9a** X=OMe 73%
7b X=SMe **9b** X=SMe 72%
7c X=Cl **9c** X=Cl 80%

SCHEME 5

All disulfides were identified by their physical and spectroscopic properties. Complete oxidation of purinethiones **4a–c** and **7a–c** was assessed by TLC analysis. Whereas 6,6′-dipurinyl disulfides **5a–c** were isolated as insoluble solids from the alkaline buffer solution at the end of the reaction, 2,2′-dipurinyl disulfides **9a–c** were isolated after evaporation of the solvent. TLC analysis (silica gel, chloroform-methanol 9:1) showed that disulfides **5** and **9** were more mobile than the starting purinethiones **4** and **7** by $\Delta R_f = 0.17–0.22$. Analysis of ^{1}H NMR spectra of disulfides **5** and **9** revealed a characteristic downfield shift of the H-8 proton signal by $\Delta\delta = 0.26–0.39$ ppm and $\Delta\delta = 0.27–0.33$ ppm, respectively, in comparison with purinethiones **4** and **7**. A lack of an acidic NH proton signal which was found at $\delta = 13.48–14.54$ ppm and $\delta = 11.02–12.18$ ppm in purinethiones **4** and **7**, as well. Mass spectra revealed easy cleavage of the S-S linkage. In model disulfide **5e**, the base peak was $[M/2 + 1]^+$ and molecular peak (M^+) was not observed. In disulfides **5** and **9**, molecular peaks (M^+) possess an intensity of 12.3–18.5% and 15.2–21.2% in comparison with the base peak of $[M\ 1/2 + 1]^+$.

From above results, it appears that oxidation of the sulfur atom at position 6 in 6-purinethiones **4** to the corresponding disulfides proceeded easier than at position 2 in 2-purinethiones **7** and depended on the oxidizing agent.

Although 2,6-dithio-7-methylpurine was obtained from the 2,6-dichloro analog by reaction with thiourea in ethanol in about 95% yield,[17] the 2-monochloro derivatives **6** did not react under the same conditions. We report the synthesis of 13 new 2- and 6-thiopurines such as purinethiones, methylthiopurines, and dipurinyl disulfides.

EXPERIMENTAL

Melting points were determined on a Boetius melting point apparatus and are uncorrected. The ^{1}H NMR spectra were recorded on a Varian Unity-Inova-300 spectrometer at 300 MHz in deuteriochloroform and dimethyl sulphoxide-d_6 with tetramethylsilane as the internal standard. Electron impact mass spectra (EI MS) were run on a LKB 9000S at 70eV. Thin layer chromatography (TLC) was performed on silica gel 60_{254}F plates (Merck) using a solution of chloroform-methanol (9:1) as the developing system. Chromatograms were visualized in UV light or by iodine vapor.

2-Methoxy- and 2-methylthio-7-methyl-6-oxo-1,6-dihydropurines **2** were prepared from symmetrical 2,6-dimethoxy- or 2,6-dimethylthio-7-methylpurines **1a**, **1b** with sodium hydroxide solution according to known procedures.[14,20]

Reactions of Xanthines 2a, 2b, and 8 with Phosphorus Oxychloride

Dry 2-methoxy-, 2-methylthio-7-methylhypoxanthines **2a**, **2b** or 7-methyl-2-thioxanthine **8** (10 mmol) were refluxed with 35 mL of phosphorus oxychloride for 4 h. The excess phosphorus oxychloride was removed under reduced pressure and the residue was added to 35 g of crushed ice. Reactions were then neutralized with conc. ammonia at 0–5°C up to pH ~7. The solid was filtered off or the mixture was extracted with chloroform (3 × 15 mL). The extracts were combined and dried over anhydrous sodium sulfate. The solvent was evaporated under vacuum, and the residue was recrystallized from ethanol or purified by column chromatography (silica gel 60, chloroform) to obtain:

1. **6-Chloro-2-methoxy-7-methylpurine 3a**, (yield 74%), m.p. 156-157°C, lit.[18] m.p. 156-158°C.
2. **6-Chloro-2-methylthio-7-methylpurine 3b**, (yield 88%), m.p. 176–177°C. ^{1}H NMR ($CDCl_3$)δ: 8.05 (s, 1H, H-8), 4.10 (s, 3H, N-CH_3), 2.65 (s, 3H, S-CH_3), EI MS (70 eV) m/z: 214 (M^+, 100). Anal. Calcd. for $C_7H_7ClN_4S$ (214.67): C, 39.17; H, 3.29; N, 26.10. Found: C, 39.50; H, 3.22; N, 25.91.
3. **6-Chloro-7-methyl-2-thioxanthine 7c**, (yield 79%), m.p. >300°C. ^{1}H NMR (DMSO-d_6)δ: 12.18 (s, 1H, N-H), 8.28 (s, 1H, H-8), 4.15 (s, 3H, N-CH_3), EI MS (70 eV) m/z: 200 (M^+, 100), TLC $R_f = 0.20$. Anal. Calcd. for $C_6H_5ClN_4S$ (200.64): C, 35.92; H, 2.51; N, 27.92. Found: C, 35.61; H, 2.65; N, 28.12.

Synthesis of 6-Purinethiones 4

6-Chloropurines **3a**,**3b** (5 mmol) were heated under reflux in 75 mL of absolute ethanol with 0.76 g (10 mmol) of thiourea for 1.5 h. The solvent was removed in vacuo, and the residue was dissolved in dilute sodium hydroxide. Product was precipitated with dilute hydrochloric acid, and the process was repeated twice to give pure 6-purinethiones **4a** and**4b** in 74% and 87% yields, respectively.

1. **2-Methoxy-7-methyl-6-purinethione 4a**, (yield 74%), m.p. 239–240°C. ^{1}H NMR (DMSO-d_6)δ: 13.48 (s, 1H, N-H), 8.26 (s, 1H, H-8), 4.13 (s, 3H, O-CH_3), 3.94 (s, 3H, N-CH_3), EI MS (70 eV) m/z: 196 (M^+, 100), TLC $R_f = 0.19$. Anal. Calcd. for $C_7H_8N_4OS$ (196.22): C, 42.85; H, 4.11; N, 28.55. Found: C, 42.67; H, 4.02; N, 28.82.
2. **2-Methylthio-7-methyl-6-purinethione 4b**, (yield 87%) m.p. 216–217°C. ^{1}H NMR (DMSO-d_6)δ: 13.81 (s, 1H, N-H), 8.32 (s, 1H, H-8), 4.13 (s, 3H, N-CH_3), 2.54 (s, 3H, S-CH_3), EI MS (70 eV) m/z: 212 (M^+, 100), TLC $R_f = 0.22$. Anal. Calcd. for $C_7H_8N_4S_2$ (212.28): C, 39.61; H, 3.80; N, 26.39. Found: C, 39.85; H, 3.69; N, 26.16.
3. **2-Chloro-7-methyl-6-purinethione 4c**, (yield 95%), m.p. >300°C, lit.[17] m.p. > 300°C was prepared by reaction of 2,6-dichloro-7-methylpurine with sodium sulfide ($Na_2S \times 9H_2O$) by a described method.[17] ^{1}H NMR (DMSO-d_6)δ: 14.54 (s, 1H, N-H), 8.38 (s, 1H, H-8), 4.16 (s, 3H, N-CH_3), TLC $R_f = 0.18$.

Synthesis of 2-Purinethiones 7

6-Chloro-7-methyl-2-thioxanthine **7c** (1 g, 5 mmol) was added to a solution of sodium (0.14 g, 6 mmol) in 50 mL of absolute methanol or sodium methanethiolate (0.52 g, 7.5 mmol) in 150 mL of absolute ethanol. The mixture was boiled for 3 h and an insoluble solid (up to 10% of the total amount of product) was separated by hot filtration from the reaction mixture. The filtrate was evaporated to dryness. The residue was dissolved in dilute sodium hydroxide and precipitated by neutralization with dilute hydrochloric acid to pH~5. The crude product was crystallized from ethanol to give compounds **7a** or **7b**.

1. **6-Methoxy-7-methyl-2-purinethione 7a**, (yield 79%), m.p. 246–248°C. ^{1}H NMR (DMSO-d_6)δ: 11.02 (s, 1H, N-H), 8.19 (s, 1H, H-8), 4.06 (s, 3H, O-CH_3), 3.95 (s, 3H, N-CH_3), EI MS (70eV) m/z: 196 (M^+, 100), TLC $R_f = 0.21$. Anal. Calcd. for $C_7H_8N_4OS$ (196.22): C, 42.85; H, 4.11; N, 28.55. Found: C, 42.76; H, 4.20; N, 28.79.

2. **6-Methylthio-7-methyl-2-purinethione 7b**, (yield 82%), m.p. 200–202°C. ^{1}H NMR (DMSO-d_6)δ: 11.42 (s, 1H, N-H), 8.21 (s, 1H, H-8), 4.12 (s, 3H, N-CH_3), 2.65 (s, 3H, S-CH_3), EI MS (70eV) m/z: 212 (M^+, 100), TLC $R_f = 0.23$. Anal. Calcd. for $C_7H_8N_4S_2$ (212.28): C, 39.61; H, 3.80; N, 26.39. Found: C, 39.47; H, 3.65; N, 26.61.

Reactions of Chloropurines 6a and 6b with Thiourea

2-Chloropurines **6a** and **6b** (5 mmol) were heated under reflux in 75 mL of absolute ethanol with 0.76 g (10 mmol) of thiourea for 3 or 12 h. The solvent was removed in vacuo, and the residue was extracted with chloroform (3 × 10 mL) to give 2-chloro-6-ethoxy-7-methylpurine **6c**.[19] The residue was dissolved in dilute sodium hydroxide solution and next was acidified with dilute hydrochloric acid to give 7-methyl-2-thioxanthine **8**.[17] Yields of both products depended on the reaction time.

TABLE I

Substrate	Reaction time [h]	Products (%)	
		6c	**8**
6a	3	51	30
6a	12	26	65
6b	3	53	29
6b	12	32	52

7-Methyl-2-thioxanthine 8, m.p. >300°C.

^{1}H NMR (DMSO-d_6)δ: 13.23 (s, 1H, N_1-H), 12.18 (s, 1H, N_3-H), 8.03 (s, 1H, H-8), 4.03 (s, 3H, N-CH_3), EI MS (70eV) m/z: 182 (M^+, 100).

Synthesis of 7-Methyl-2-Thioxanthine 8, (Yield 88%).

To a suspension of 2-chloro-7-methyl-6-oxo-1,6-dihydropurine **6d** (1.84 g, 10 mmol) in 200 mL of dimethylformamide (DMF), (0.99 g, 12 mmol) sodium hydrosulfide (NaSH × 1.5 H_2O) was added. The mixture was refluxed for 2 h, cooled to room temperature, and the DMF was evaporated in vacuo. The resulting solid was dissolved in 5% aqueous sodium hydroxide and product was precipitated by dilute hydrochloric acid. The compound was identical with the product described above.

Oxidation Reaction of 6- and 2-Purinethiones 4 and 7

A. 6-Purinetlhiones **4a–c** (1 mmol) were dissolved in 100 mL of warm phosphate buffer, pH 7.6, the solution was filtered and cooled to room

temperature. To the stirred solution, 1 mL (0,5 mmol) of aqueous 1N iodine solution (containing sodium iodide in the proportion of 2 parts of sodium iodide to 1 part iodine by weight) was added over a period of 10 min. The precipitate was filtered and washed with water and ethanol. The crude products were recrystallized from 85% ethanol or purified by column chromatography (silica gel 60, chloroform, ethanol) to give:

1. **Bis (7-methyl-2-methoxy-6-purinyl) disulfide 5a**, (yield 80%), m.p. 228–229°C. ^{1}H NMR ($CDCl_3$)δ: 8.52 (s, 2H, H-8), 4.17 (s, 6H, O-CH_3), 4.14 (s, 6H, N-CH_3), EI MS (70 eV) m/z: 390 (M^+, 15.7), 195 (1/2 M, 59.5), 196 (1/2 M + 1, 100), TLC $R_f = 0.36$. Anal. Calcd. for $C_{14}H_{14}N_8O_2S_2$ (390.43): C, 43.07; H, 3.61; N, 28.70. Found: C, 43.34; H, 3.43; N, 28.41.
2. **Bis (7-methyl-2-methylthio-6-purinyl) disulfide 5b**, (yield 75%), m.p. 205–206°C. ^{1}H NMR ($CDCl_3$)δ: 8.61 (s, 2H, H-8), 4.27 (s, 6H, N-CH_3), 2.56 (s, 6H, S-CH_3), EI MS (70 eV) m/z: 422 (M^+, 18.5), 211 (1/2 M, 76.7), 212 (1/2 M + 1, 100), TLC $R_f = 0.43$. Anal. Calcd. for $C_{14}H_{14}N_8S_4$ (422.55): C, 39.79; H, 3.34; N, 26.52. Found: C, 40.16; H, 3.20; N, 26.26.
3. **Bis (7-methyl-2-chloro-6-purinyl) disulfide 5c**, (yield 96%), m.p. 223–224°C. ^{1}H NMR ($CDCl_3$)δ: 8.77 (s, 2H, H-8), 4.24 (s, 6H, N-CH_3), EI MS (70 eV) m/z: 399 (M^+, 12.3), 199 (1/2 M, 79.3), 200 (1/2 M + 1, 100), TLC $R_f = 0.40$. Anal. Calcd. for $C_{12}H_8Cl_2N_8S_2$ (399.27): C, 36.10; H, 2.02; N, 28.06. Found: C, 35.72; H, 2.24; N, 27.77.

B. To a stirred suspension of 2-purinethiones **7a–c** in 10 mL of 70% ethanol, 0.5 mL of 10% hydrogen peroxide was added. The reaction ran with gradual solubilization of purine substrate **7a–c** up to full dissolution. After 10 min stirring at room temperature, the solution was evaporated to dryness. The residue was dissolved in chloroform and purified by column chromatography on silica gel (200–300 mesh) using chloroform as eluent to give:

1. **Bis (7-methyl-6-methoxy-2-purinyl) disulfide 9a** (yield 73%), m.p. 238–239°C. ^{1}H NMR ($CDCl_3$) δ: 8.46 (s, 2H, H-8), 4.10 (s, 6H, O-CH_3), 4.08 (s, 6H, N-CH_3), EI MS (70 eV) m/z: 390 (M+, 21.2), 195 (1/2 M^+, 62.8), 196 (1/2 M + 1, 100), TLC $R_f = 0.42$. Anal. Calcd. for $C_{14}H_{14}N_8O_2S_2$ (390.43): C, 43.07; H, 3.61; N, 28.70. Found: C, 42.83; H, 3.47; N, 28.45.
2. **Bis (7-methyl-6-methylthio-2-purinyl) disulfide 9b** (yield 72%), m.p. 209–210°C. ^{1}H NMR ($CDCl_3$) δ: 8.49 (s, 2H, H-8), 4.29 (s, 6H, N-CH_3), 2.68 (s, 6H, S-CH_3), EI MS (70 eV) m/z: 422 (M+, 19.7), 211 (1/2 M^+, 75.4), 212 (1/2 M + 1, 100), TLC $R_f = 0.38$. Anal. Calcd. for

$C_{14}H_{14}N_8S_4$ (422.55): C, 39.79; H, 3.34; N, 26.52. Found: C, 39.52; H, 3.16; N, 26.20.

3. Bis (7-methyl-6-chloro-2-purinyl) disulfide 9c (yield 80%), m.p. 232–233°C. ^{1}H NMR ($CDCl_3$) δ: 8.61 (s, 2H, H-8), 4.22 (s, 6H, N-CH_3), EI MS (70 eV) m/z: 399 (M^+, 15.2), 199 (1/2 M, 72.8), 200 (1/2 M^+ 1, 100), TLC $R_f = 0.37$. Anal. Calcd. for $C_{12}H_8Cl_2N_8S_2$ (399.27): C, 36.10; H, 2.02; N, 28.06. Found: C, 35.89; H, 2.14; N, 28.17.

Synthesis of Bis(7-Methyl-6-purinyl) Disulfide 5d (yield 68%), m.p. 219–220°C

To a stirred solution of 6,6′-dipurinyl disulfide **5e** (0.3g, 1 mmol) in a mixture of sodium methoxide (0.54 g, 1 mmol) and 40 mL dry methanol, at 20°C, methyl iodide (0.14 g, 1 mmol) was added. After 1 h, the resulting solid was collected by filtration and washed with water. The crude product was purified by column chromatography (silica gel 200–300 mesh, chloroform) to give disulfide **5d**.

^{1}H NMR ($CDCl_3$)δ: 8.68 (s, 2H, H-8), 8.33 (s, 2H, H-2), 3.74 (s, 6H, N-CH_3), EI MS (70 eV) m/z: 332 (M^+, 7.9), 166 (1/2 M, 82.5), 167 (1/2 M + 1, 100), TLC $R_f = 0.44$. Anal. Calcd. for $C_{12}H_{10}N_8S_2$ (330.38): C, 43.63; H, 3.05; N, 33.92. Found: C, 43.36; H, 3.27; N, 33.60.

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