Addition of Methanesulfenyl Chloride and Sulfur Chloride to 1,4-Dimethyl-3,6-dimethylene-2,5-piperazinedione and Substitution of the Adducts

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Addition of methanesulfenyl chloride or sulfur chloride to 3,6-dimethylene-(**1a**) and 3,6-dibenzylidene-1,4-dimethyl-2,5-piperazinediones (**1b**) gave the Markownikoff products. The addition of methanesulfenyl chloride to **1a** proceeded stepwise within 1 hr, and gave a mixture of (*Z,Z*)-, (*Z,E*)-, and (*E,E*)-isomers of the corresponding 3,6-bis(methylthiomethylene) derivative, accompanied by gradual elimination of hydrogen chloride. 3,6-Dichloro groups of the adduct were substituted with water, ethanethiol and ethanol to give the corresponding hydroxy, ethylthio, and ethoxy derivatives, respectively. A similar substitution with ethanedithiol and hydrogen sulfide followed by aeration gave 7,9-dimethyl-1,6-bis(methylthiomethyl)-8,10-dioxo-2,5-dithia-7,9-diazabicyclo[4,2,2]-decane and the corresponding 3,6-epitetrathio derivative, respectively. The same mode of reaction of sulfur chloride with **1a** and **1b** gave a few 1,6-disubstituted-7,9-dimethyl-8,10-dioxo-3,4-dithia-7,9-diazabicyclo[4,2,2]-decanes. Mass fragmentations of new compounds were also described.

It was found that bromination of 1,3,4,6-tetramethyl-2,5-piperazinedione with bromine was accompanied by elimination of hydrogen bromide and re-addition of bromine gave the corresponding 3,6-dibromo-3,6-bis-(bromomethyl) derivative, and that tetrabromide was successfully substituted with water or methanol to give the corresponding 3,6-disubstituted derivatives, while that substituted with sulfur-containing nucleophiles gave only 1,4-dimethyl-3,6-dimethylene-2,5-piperazinedione (**1a**) and sulfur.[1] The latter elimination seems to proceed through the formation of the spiro-thiiranium ion of the substitued compounds, in participation with the bromine atom of bromomethyl groups. In order to extend the synthetic pathway of 3,6-epidithio-2,5-piperazinediones by substitution of 3,6-dihalogeno groups with mercapto groups and the subsequent oxidative disulfide-ring formation,[2] addition of methanesulfenyl chloride to **1a** was examined. Schmidt and Csizmadia[3] reported that the relative amount of Markownikoff and anti-Markownikoff adducts formed in the addition of 4-chlorobenzenesulfenyl chloride to *cis*- and *trans*-1-phenylpropene are strongly dependent upon the solvent and reaction temperature. Concurrent anti-Markownikoff addition of sulfur chloride to two olefinic functions of **1a** and 3,6-dibenzylidene-1,4-dimethyl-2,5-piperazinedione (**1b**)[4] was also examined with the expectation that it would give directly the 3,6-epidithio derivative. In both additions, only Markownikoff adduct was formed.

Results and Discussion

NMR analysis of the addition of methanesulfenyl chloride[5] to **1a** in chloroform (Fig. 1) showed that the first (b) and second (c) additions proceed stepwise during 10 min and 1 hr, respectively, followed by gradual elimination of hydrogen chloride (d) when the reaction mixture was kept at room temperature for a week. The elimination was accelerated by refluxing the reaction mixture for several hours to give the corresponding 3,6-bis(methylthiomethylene) derivative (**2**) in a good yield. This indicates that the addition occurs in the Markownikoff mode, and the adduct

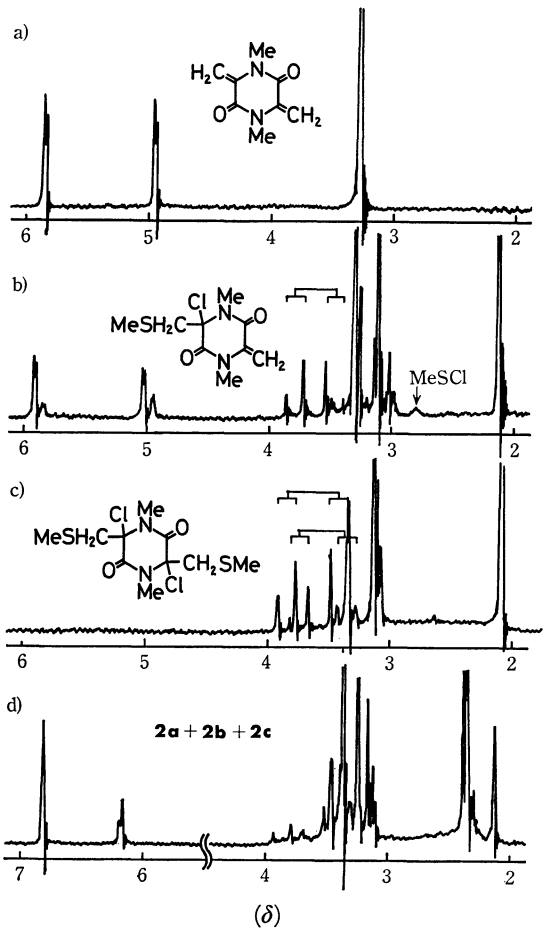

Fig. 1. A progressive change of the NMR spectrum in the addition of methanesulfenyl chloride to **1a** at room temperature.
a) before the reaction; b) after 10 min; c) after 1 hr; d) after 1 week

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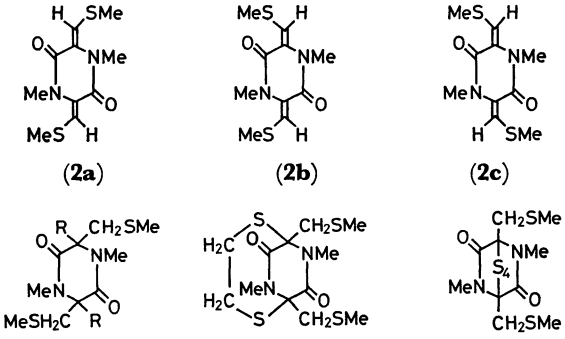
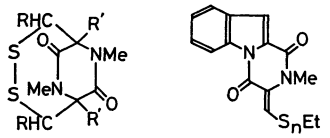
does not turn into the spiro-thiiranium ion, as was observed previously.[1] Separation of **2** on tlc gave the possible three isomers in the ratio 4(**2a**): 3(**2b**): 1(**2c**). From the chemical shifts of vinyl protons (Table 1), their configurations were assigned to (*Z,Z*), (*Z,E*), and (*E,E*), respectively, the vinyl proton in *Z*-configuration being deshielded about 0.55 ppm by the neighboring carbonyl group.[6] It is worth noting that irradiation of (*E,E*)-isomer in chloroform with high-pressure mercury light for 20 hr gave a mixture of **2a**, **2b**, and **2c** in the ratio 1: 2: 1.



(**2a**) (**2b**) (**2c**)

(**3a**) R=OH
(**3b**) R=SEt
(**3c**) R=OEt

(**4**) (**5**)



(**6a**) R=H, R′=OH
(**6b**) R=Ph, R′=OH
(**6c**) R=H, R′=OAc

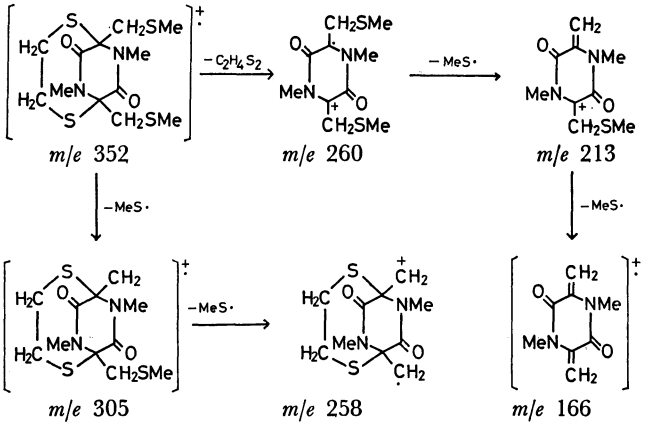
(**7a**) *n*=2
(**7b**) *n*=3

Table 1. Proton chemical shifts (δ) of geometrical isomers of **2**

Compound	Olefinic Protons	NMe	SMe
2a	6.81	3.36	2.43
2b	6.80; 6.15	3.45; 3.22	2.41; 2.34
2c	6.15	3.23	2.34

Since the Markownikoff adduct was fairly stable, though it could not be isolated in a pure state, substitution of its 3,6-dichloro groups was attempted. Treatment of the adduct, obtained by evaporating the reaction mixture, with dioxane–water at room temperature overnight gave 3,6-dihydroxy-1,4-dimethyl-3,6-bis(methylthiomethyl)-2,5-piperazinedione (**3a**) in 42% yield. 3,6-Bis(ethylthio) (**3b**) and 3,6-diethoxy (**3c**) derivatives were obtained similarly by treatment with excess ethanethiol and ethanol in chloroform, respectively. A similar substitution with ethanedithiol in a dilute solution gave the bicyclic compound; 7,9-dimethyl-1,6-bis(methylthiomethyl)-8,10-dioxo-2,5-dithia-7,9-diazabicyclo[4,2,2]decane (**4**) in 18% yield. However, treatment of the adduct with sodium thioacetate or sodium tetrasulfide induced the elimination reaction to give **2** as the predominant product, even at lower temperatures with less than stoichiometric amount of nucleophiles, while that with hydrogen sulfide gave the corresponding epitetrathio derivative (**5**). In the latter case, another product which seemed to be the corresponding dimercapto derivative was detected on tlc. However, the compound polymerized easily to give an intractable sirup, compound **5** being isolated in 34% yield by aeration of the reaction mixture in a large amount of chloroform. Hydrogenation of **5** with sodium borohydride again gave the unstable dimercapto derivative, though it could not be isolated in a pure state.

Though the steric configuration of **3** could not be determined, the NMR spectra indicated that **3b** is composed of a *ca.* 1: 3 mixture of *cis* and *trans* isomers, and the others only of one isomer. In general, mass spectra of these new compounds show intense fragment peaks of $(M-SCH_3)^+$ and $(M-CH_2SCH_3)^+$; for example, the base peak of **3a** at *m/e* 233 $(M-CH_2SCH_3)^+$ strongly supports the structure. In the case of **5**, the parent peak could not be observed, but the first fragmentation stage $M^{\ddagger}\rightarrow(M-4S)^{\ddagger}$ was deduced from a metastable ion peak, *m/e* 174.5. In the fragmentation pattern of **4** (Fig. 2) deduced from metastable ion peaks (*m/e* 221, 192, 186, 174.5, and 129.5), the *m/e* 260 $(M-C_2H_4S_2)^{\ddagger}$ peak shows the structure unambiguously.



m/e 352 *m/e* 260 *m/e* 213

m/e 305 *m/e* 258 *m/e* 166

Fig. 2. The major fragmentation pathways of **4**.

NMR analysis of the addition reaction of sulfur chloride to **1a** gave similar information to that for methanesulfenyl chloride. However, isolation of the adduct was very difficult in high concentration of reactants, since its bifunctionality causes polymerization due to the intermolecular addition reaction. Examination of the effect of concentration on the relative amount of polymeric and monomeric adducts (Fig. 3) indicates that 0.0125 M solution was the best for the formation of the monomeric adduct, which was isolated as 1,6-dihydroxy-7,9-dimethyl-8,10-dioxo-3,4-dithia-7,9-diazabicyclo[4,2,2]decane (**6a**) by treatment of the reaction mixture with water. In the mass fragmentation pattern of **6a** (Fig. 4; metastable ion peaks, *m/e* 143.3, 136, 120.5, and 115.5), the peak at *m/e* 218 $(M-CH_2S)^{\ddagger}$ proves its characteristic structure. Formation of **6a** also indicates that the addition proceeded in the Markownikoff mode. Addition of sulfur chloride to **1b** proceeds very slowly in dioxane in the presence of zinc chloride, and does not proceed in tetrahydrofuran or chloroform. Consequently, the addition in dioxane

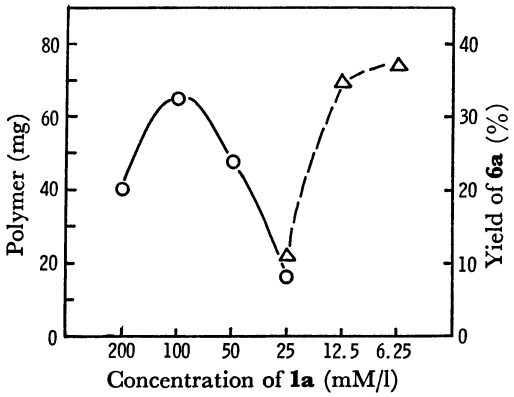


Fig. 3. The effect of concentration on the products in the addition of equimolar amount of sulfur chloride to 100 mg of **1a**.
○—○: Polymer, △—△: **6a**

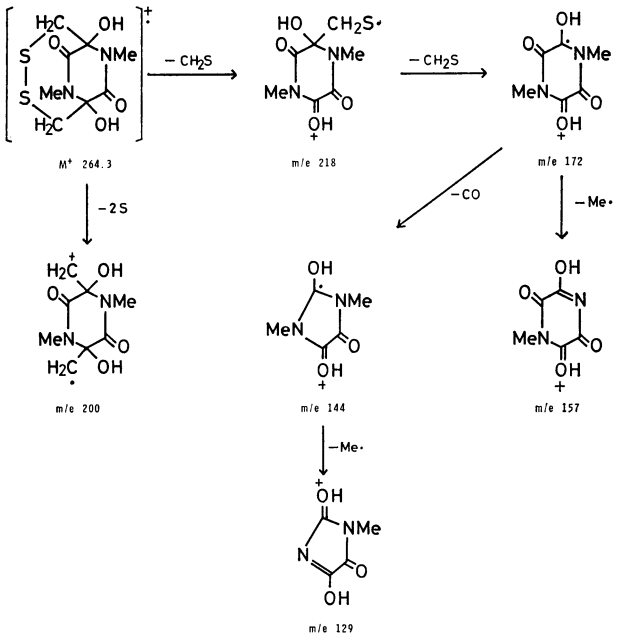


Fig. 4. The major fragmentation pathways of **6a**.

was easily subjected to side-reactions such as elimination, polymerization, and disproportionation of sulfur, making the yield of monomeric adduct (**6b**) very low. Acetylation of **6a** with acetic anhydride in pyridine gave the corresponding diacetate (**6c**).

Addition of sulfur chloride to 1,2,3,4-tetrahydro-2-methyl-3-methylene-1,4-dioxopyrazino[1,2-*a*]indole[7] gave only intractable products. However, the prevention of side-reactions by fixation of the terminal chlorodithio group of the corresponding adduct with ethanethiol gave 3-ethyldithiomethylene (**7a**) and 3-ethyltrithiomethylene derivative (**7b**) in 11% and 13% yield, respectivly.

Experimental

All the melting points are uncorrected. The solutions were evaporated under reduced pressure at a bath temperature not exceeding 60 °C. The infrared spectra were measured in KBr disks, and the NMR spectra were obtained at 100 MHz with a JNM-100H spectrometer in deuteriochloroform unless otherwise stated, using TMS as an internal reference. The mass spectra were obtained on a GEOL JNS-01S mass spectrometer, using a direct inlet and an ionization energy of 70 eV. Chemical shifts and coupling constants were recorded in δ and Hz units, respectively, and frequencies in cm^{-1}.

1,4-Dimethyl-3,6-bis(methylthiomethylene)-2,5-piperazinedione (2a, 2b, and 2c). To a solution of 1,4-dimethyl-3,6-dimethylene-2,5-piperazinedione (0.2 g, 1.2 mmol) in chloroform (20 ml) was added dropwise methanesulfenyl chloride (0.6 g, 7.2 mmol), and the resulting solution was evaporated, after being left to stand for 1 hr at room temperature. A solution of the residual sirup in chloroform (20 ml) was refluxed for 8 hr, and evaporated to give crystals (0.17 g, 56%) from ether, which were separated into three isomers (R_f= a; 0.38, b; 0.25, c; 0.2) on a preparative tlc, using benzene–ethyl acetate (5: 1) as the developing solvent. **4a**: mp 138—139 °C; yield, 0.08 g (26%), **4b**: mp 172—174 °C; yield, 0.06 g (19%), **4c**: mp 275 °C (sublime); yield, 0.02 g (6.4%).

Found: **4a**: C, 46.69; H, 5.51; N, 10.86; S, 24.58%. **4b**: C, 46.67; H, 5.46; N, 10.72; S, 24.61%. **4c**: C, 46.37; H, 5.25; N, 10.71; S, 24.72%. Calcd for $C_{12}H_{22}N_2O_2S_2$: C, 46.49; H, 5.46; N, 10.84; S, 24.82%.

These compounds show the characteristic olefinic double bond absorption at *ca.* 1570 cm^{-1}.

3,6-Dihydroxy-1,4-dimethyl-3,6-bis(methylthiomethyl)-2,5-piperazinedione (3a). Methanesulfenyl chloride (0.6 g, 7.2 mmol) was added to a solution of 1,4-dimethyl-3,6-dimethylene-2,5-piperazinedione (0.2 g, 1.2 mmol) in dry chloroform (10 ml). The mixture was allowed to stand at room temperature for 1 hr, and then evaporated to give a sirup. A solution of the sirup in dioxane–water was left to stand at room temperature overnight and evaporated to give amorphous solid (200 mg) which was recrystallized from acetone. Yield, 180 mg (42%). Mp 193—195 °C, IR: 3260 (OH), 1625 (amide); NMR (DMSO): 6.80 (OH), 3.13 and 2.95 (SCH_2; ABq, J=13.8), 2.78 (NMe), 1.92 (SMe).

Found: C, 40.99; H, 5.69; N, 9.46%. Calcd for $C_{10}H_{18}N_2O_4S_2$: C, 40.79; H, 6.16; N, 9.51%.

3,6-Bis(ethylthio)-1,4-dimethyl-3,6-bis(methylthiomethyl)-2,5-piperazinedione (3b). Excess ethanethiol (20 ml) was added to a solution of the same addition product in chloroform as for **3a** and the mixture was evaporated, after being left to stand overnight at room temperature. The sirup obtained was purified on a preparative tlc, using benzene–ethyl acetate (5: 1) as the developing solvent. The portion of R_f=0.75 (0.2 g, 43%) was collected, and recrystallized from petroleum ether. Mp 72—73 °C; IR: 1640 (amide); NMR of the main isomer in the mixture of 3: 1: 3.65 and 3.09 (CH_2S; ABq, J=15), 3.07 (NMe), 2.17 (SMe), 2.65—3.00 (CH_2S; q), 1.20 (CH_3; t, J=7.5).

Found: C, 43.64; H, 6.45; N, 7.18; S, 33.55%. Calcd for $C_{14}H_{26}N_2O_2S_4$: C, 43.97; H, 6.85; N, 7.33; S, 33.48%.

3,6-Diethoxy-1,4-dimethyl-3,6-bis(methylthiomethyl)-2,5-piperazinedione (3c). Ethanol (20 ml) was added to a solution of the same addition product in chloroform (40 ml) as for **3b**, and the resulting solution was left to stand at room temperature overnight. Evaporation of the reaction mixture gave a sirup which was purified on a preparative tlc, using benzene–ethyl acetate (10: 1) as the developing solvent. The portion of R_f=0.42 was recrystallized from ether. Mp 135—136 °C, yield, 100 mg (23%); IR: 1645 (amide), 1045 (C–O–C). NMR: 3.60 (OCH_2; q), 3.35 and 3.05 (CH_2S; ABq, J=14), 2.98 (NMe), 2.07 (SMe), 1.19 (CH_3; t, J=7.5).

Found: C, 47.99; H, 7.49; N, 8.05; S, 18.21%. Calcd for $C_{14}H_{26}N_2O_4S_2$: C, 47.99; H, 7.48; N, 8.00; S, 18.27%.

7,9-Dimethyl-1,6-bis(methylthiomethyl)-8,10-dioxo-2,5-dithia-7,9-diazabicyclo[4,2,2]decane (4). Ethanedithiol (113 mg, 1.2

mmol) was added to a solution of the same addition product in dioxane (30 ml) as for **3c**, and the resulting solution was then evaporated, after being left to stand overnight at room temperature. The residual sirup was purified on a preparative tlc, using benzene–ethyl acetate (5: 1) as the developing solvent (R_f=0.35) to give crystals which were recrystallized from methanol. Mp 170—171 °C, yield, 80 mg (18%), IR: 1650 (amide); NMR: 3.63 and 2.99 (CH_2; ABq, J=14), 3.14 (NMe), 2.14 (SMe), 1.55 (SCH_2CH_2S; s).

Found: C, 40.92; H, 5.87; N, 7.89; S, 36.41%. Calcd for $C_{12}H_{20}N_2O_2S_4$: C, 40.92; H, 5.72; N, 7.95; S, 36.38%.

1,4-Dimethyl-3,6-bis(methylthiomethyl)-3,6-epitetrathio-2,5-piperazinedione (5). To a solution of excess hydrogen sulfide in chloroform (30 ml) was added a solution of the same addition product in chloroform (20 ml) as for **4**, and the resulting solution was left to stand at room temperature overnight, and then evaporated. The solution of the residual sirup in chloroform (300 ml) was oxidized by airing for 1 day and evaporated. The residue was purified on a preparative tlc using benzene–ethyl acetate (5: 1) as the developing soluent (R_f= 0.7), to give crystals (160 mg, 34%) which were recrystallized from methanol. Mp 183—184 °C; IR: 1650 (amide); NMR: 3.63 and 3.13 (CH_2; ABq, J=14), 3.08 (NMe), 2.18 (SMe).

Found: C, 30.75; H, 4.05; N, 7.25; S, 49.39%. Calcd for $C_{10}H_{16}N_2O_2S_6$: C, 30.91; H, 4.15; N, 7.21; S, 49.50%.

1,6-Dihydroxy-7,9-dimethyl-8,10-dioxo-3,4-dithia-7,9-diazabicyclo[4,2,2]decane (6a). To a solution of **1a** (100 mg, 0.6 mmol) in dry dioxane (48 ml) was added sulfur chloride (80 mg, 0.59 mmol) and a catalytic amount of zinc chloride, and the mixture was allowed to stand at room temperature for 1 day. After addition of water (10 ml) to the solution, the mixed solution was evaporated and the residue was treated with acetone (100 ml). Insoluble materials were filtered off, and the filtrate was treated with active carbon and concentrated to 5 ml volume to give crystals (55 mg, 35%). Recrystallization from acetone gave white needles. Mp *ca.* 260 °C (sublime). IR: 3325 (OH), 1650 (amide). NMR (DMSO): 3.18 and 3.46 (CH_2; ABq, J=14), 2.82 (NMe).

Found: C, 36.08; H, 4.50; N, 10.96; S, 24.45%. Calcd for $C_8H_{12}N_2O_4S_2$: C, 36.35; H, 4.58; N, 10.60; S, 24.26%.

1,6-Dihydroxy-7,9-dimethyl-2,5-diphenyl-8,10-dioxo-3,4-dithia-7,9-diazabicyclo[4,2,2]decane (6b). A solution of 3,6-dibenzylidene-1,4-dimethyl-2,5-piperazinedione (630 mg, 1.9 mmol), sulfur chloride (370 mg, 2.7 mmol) and a small amount of zinc chloride in dioxane (20 ml) was allowed to stand for 48 hr at room temperature. The reaction mixture was extracted with chloroform (100 ml), and the extract was washed twice with water (100 ml), and evaporated to give a white powder which was recrystallized from chloroform to give white crystals (20 mg, 2.5%). Mp 229 °C (decomp.). IR: 3350 (OH), 1640 (amide).

Found: C, 75.72; H, 4.60; N, 6.37; S, 15.61%. Calcd for $C_{20}H_{20}N_2O_4S_2$: C, 57.67; H, 4.84; N, 6.73; S, 15.40%.

1,6-Diacetoxy-7,9-dimethyl-8,10-dioxo-3,4-dithia-7,9-diazabicyclo-[4,2,2]decane (6c). A solution of **6a** (50 mg, 0.19 mmol) in pyridine (10 ml) and acetic anhydride (5 ml) was allowed to stand at room temperature for 3 hr, evaporated, and the residue was treated with chloroform–ethanol to give white crystals (34 mg, 52%) which were recrystallized from chloroform–ethanol. Mp 268—271 °C. IR: 1760 (OAc), 1670 (amide). NMR: 3.85 and 3.15 (CH_2; ABq, J=15), 2.88 (NMe), 2.13 (OAc).

Found: C, 41.78; H, 4.61; N, 8.12%. Calcd. for $C_{12}H_{16}N_2O_6S_2$: C, 41.37; H, 4.63; N, 8.04%.

3-Ethyldithiomethylene- (7a) and 3-Ethyltrithiomethylene-1,2,3,4-tetrahydro-2-methyl-1,4-dioxopyrazino[1,2-a]-indole (7b). A solution of 1,2,3,4-tetrahydro-2-methyl-3-methylene-1,4-dioxopyrazino[1,2-*a*]indole (0.4 g, 1.8 mmol), sulfur chloride (2.0 g, 15 mmol) and a small amount of zinc chloride in dioxane (16 ml) was allowed to stand for 20 min. A solution of ethanethiol (4.4 g, 71 mmol) in chloroform (100 ml) was added to the reaction mixture which was left to stand for 20 min. The solution was washed with water, evaporated, and the residue was fractionated on a C-200 silicic acid column, using benzene and benzene–ethyl acetate (6: 1) as an effluent. The latter fraction was evaporated, and then the residue was again fractionated on a C-200 silicic acid column, being eluted with benzene–ethyl acetate (20: 1) to give **7b** (80 mg, 13%) and **7a** (60 mg, 11%). They were recrystallized from chloroform–ligroin to give orange and yellow needles, respectively Mp **7a**; 136 °C, **7b**; 148 °C. IR: **7a**; 1660 (amide), **7b**; 1650 (amide). NMR: **7a**; 1.40 and 2.94 (SEt; J=7.5), 3.43 (NCH_3), 7.0 (=CHSS), 8.51 (H_6: $J_{6,7}$=7.5), **7b**; 1.42 and 2.97 (SC_2H_5; J=7.5), 3.43 (NCH_3), 7.07 (=CHSSS), 8.41 (H_6; $J_{6,7}$=7.5).

7a: Found: C, 56.38; H, 4.20; N, 8.60%. Calcd for $C_{15}H_{14}N_2O_2S_2$: C, 56.58; H, 4.43; N, 8.80%.

7b: Found: C, 51.47; H, 3.74; N, 7.76%. Calcd for $C_{15}H_{14}N_2O_2S_3$: C, 51.40; H, 4.03; N, 7.99%.

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