Synthesis of Sulfur-Bridged Piperazinediones by Reaction of 3,6-Dibromo-1,4-dimethyl-2,5-piperazinedione with *Geminal* Dithiols

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The reaction of several *geminal* dithiols with 3,6-dibromo-1,4-dimethyl-2,5-piperazinedione gave in good yields piperazinedione derivatives substituted at the 3,6-position with a *geminal* dithiol-bridging group. These sulfur-bridged piperazinediones formally represent derivatives of the 2,4-dithia-6,8-diaza-7,9-dioxobicyclo[3.2.2]nonane ring system. Attempts to transform these sulfur-bridged piperazinediones to 3,6-epidithiopiperazinediones by removal of the bridging group common to the sulfur functionality were unsuccessful. Studies also are reported of addition of thioacetic acid to 3,6-dimethylene-2,5-piperazinedione to give 3,6-diacetylthio-3,6-dimethyl-2,5-piperazinedione. Conversion of the 3,6-diacetylthio derivative to the epithiopiperazinedione ring system yielded a mixture of epimono- and epidithiopiperazinediones.

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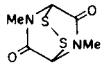
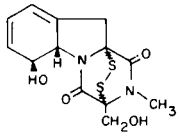
The 3,6-epidithio-2,5-piperazinedione ring system **1** is a common constituent of a class of antibiotics of which gliotoxin (2), sporidesmin and aranotin are representative members (1). The synthesis of major members of the epidithiopiperazinedione antibiotics has been accomplished by Kishi and co-workers (2). Syntheses of the parent epidithiopiperazinedione ring (3), as also structural derivatives (4), have been reported.



1



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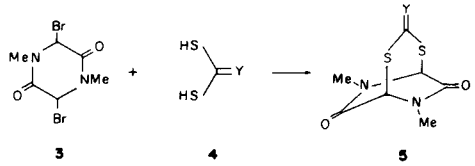
As an approach to the epidithiopiperazinedione ring, we have studied the reaction of 3,6-dibromo-1,4-dimethyl-2,5-piperazinedione (**3**) with geminal dithiols. Displacement of the 3,6-dibromo groups in **3** by sulfur nucleophiles is a well-known reaction (3). Reaction of known (5) geminal dithiols **4** with **3** (Scheme I) occurred in good yields to give piperazinedione derivatives **5** substituted at the 3,6-positions with sulfide functions that are interconnected by a carbon bridging group (Table I). The products formed represent derivatives of the 2,4-dithia-6,8-diaza-7,9-dioxobicyclo[3.2.2]nonane ring system substituted at the 3-position with either imino, methylene or *gem*-dialkyl groups.

Attempts to remove the bridging group between the two sulfur atoms of the piperazinediones **5** in order to effect oxidation to the epidithiopiperazinedione were unsuccessful in all cases. The methods used in these attempts were similar to procedures given in the literature for related transformations (6) upon analogous functional groups. The reactions that were carried out gave either recovered piperazinedione reactant or a complex mixture of products. Thus, treatment of **5a** to acid hydrolysis (6a) using 50% aqueous acetic acid, 50% aqueous trifluoroacetic acid or 48% hydrobromic acid led to recovered reactant. In the case of the ethylimine **5c**, hydrolysis with 50% aqueous trifluoroacetic acid gave the known (7) dithiocarbonate **5g**. Attempts to convert **5g** to the epidithiopiperazinedione system by treatment with sodium methoxide in methanol, followed by oxidation with iodine, gave a complex product mixture. Attempted hydrazone exchange (6b) by treatment of **5a** with acetylacetone in acetic acid did not occur and **5a** was recovered in good yield. Reaction of **5d** with zinc in aqueous sodium hydroxide (6c) gave a complex mixture. Treatment of **5c** or **5f** with sulfuryl chloride in methylene chloride containing wet silica (6d) resulted in isolation of a new product in low yield (8-22%). The ^{1}H nmr spectrum of this materal showed that the bridging alkyl groups had been removed; however, this material lacked sulfur and differed from the desired epidithiopiperazinedione **1** in terms of solubility, melting point and mass spectral data. The structure of this product has not been determined. Finally, attempted ketal exchange (6e) by treatment of **5e** with iodine in methanol-chloroform resulted in recovery of **5e** in good yield.

Scheme I

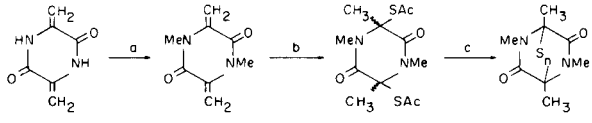


3 **4** **5**

4a, 5a, Y = NNHPh
b, Y = NPh
c, Y = NEt
d, Y = CHCOPh
e, Y = $(CH_2Ph)_2$
f, Y = Me and t-Bu
g, Y = O

The above studies involving use of *gem*-dithiols were prompted by earlier results obtained in the attempted conversion of 3,6-diacetylthiol-1,3,4,6-tetramethyl-2,5-piperazinedione (**8**) to the epidithiopiperazinedione (**9**). Compound **8** was prepared from the unsaturated piperazinedione **6** as given in Scheme II; **8** appeared to be a single compound, but of undefined stereochemistry. Conversion of **8** to the 3,6-epidithiopiperazinedione **9** led to a mixture of **9** and the epimonothio derivative **10**; similar results have been observed by Yoshimura (7) and Ottenheijm (8). The addition of hydrogen sulfide to **7** gave the epimonosulfide **10** in good yield. Likewise, a similar addition reaction of the *gem*-dithiol **4d** to **7** provided the sulfur-bridged piperazinedione **11** in 79% yield (Scheme III).

Scheme II



a) NaH, MeI, DMF, rt, 57%
b) AcSH, H^+, 86%
c) $NaBH_4$, MeOH, 57%

Scheme III

EXPERIMENTAL

Melting points were taken on a Thomas Hoover capillary melting point apparatus and are uncorrected. Solvents were removed under reduced pressure on a rotary evaporator. Acetonitrile and methylene chloride were stored over 3A molecular sieves and used directly. Proton magnetic resonance spectra were recorded on Varian XL-100-12 or Varian EM-360 spectrometers; the format of the data reported is chemical shift, multiplicity, integral intensity, proton assignment. Thin layer chromatography was performed on Quantum Industries silica gel 1" × 3" plates or on Brinkmann precoated silica gel plates with visualization by UV light or iodine vapors.

General Procedure for Reaction of 3,6-Dibromosarcosine Anhydride (**3**) with Geminal Dithiols **4**.

A solution of 3,6-dibromosarcosine anhydride (**3**) (3a) (2.0 to 20 mmoles) in acetonitrile was treated with an equimolar amount of the *gem*-dithiol derivative (**4**) at room temperature and the reaction mixture was stirred overnight. See reference 5 for preparation of the *gem*-dithiols used in this study. A solid often precipitated from the reaction solution after a short reaction period, though in some cases a suspension resulted from the beginning of the reaction. The reaction was worked up as described below for each product. The preparation of **5f** was carried out in dimethylformamide rather than acetonitrile as solvent. Yields of products obtained are given in Table I.

6,8-Dimethyl-2,4-dithia-6,8-diaza-7,9-dioxobicyclo[3.2.2]nonane-3-phenylhydrazone **5a**.

The reaction of **3** with **4a** was carried out as above. The reaction mixture was poured into water and the solid was collected by filtration, washed with water and ethanol and recrystallized from glacial acetic acid, mp 233-235°; ^{1}H nmr (trifluoroacetic acid): δ 3.30 (s, 6 H, *N*-methyls), 5.72 (s, 2 H, α-protons), 6.91-7.40 (m, 6 H, phenyl and NH).

Anal. Calcd. for $C_{13}H_{14}N_4S_2O_2$ (354.3): C, 48.30; H, 4.37; N, 17.46; S, 19.87. Found: C, 48.10; H, 4.59; N, 17.27; S, 19.87.

6,8-Dimethyl-2,4-dithia-6,8-diaza-7,9-dioxo-3-phenyliminobicyclo[3.2.2]nonane (**5b**).

Upon completion of the reaction, the major portion of the acetonitrile was removed in vacuum. The residue was dissolved in water and the aqueous solution was made alkaline with sodium bicarbonate. The solid that precipitated was collected by filtration, washed with water and air dried, mp 235.0-236.5° (chloroform-petroleum ether, bp 30-60°); ^{1}H nmr (trifluoroacetic acid): δ 3.29 and 3.36 (2 s, 6 H, non-equivalent *N*-methyls), 5.98 and 6.08 (2 s, 2 H, non-equivalent α-protons), 7.20-7.70 (m, 5 H, phenyl); ^{1}H nmr (DMSO-d_6): δ 3.07 (s, 6 H, *N*-methyls), 4.90 (s, 2 H, α-protons), 6.70-7.40 (m, 5 H, phenyl).

Anal. Calcd. for $C_{13}H_{13}N_3S_2O_2$ (307.3): C, 50.81; H, 4.23; N, 13.68; S, 20.84. Found: C, 50.60; H, 4.15; N, 13.41; S, 20.78.

6,8-Dimethyl-2,4-dithia-6,8-diaza-7,9-dioxo-3-ethyliminobicyclo[3.2.2]nonane (**5c**).

Upon completion of the reaction, the solid material present was filtered and washed with a small volume of acetonitrile. The solid was dissolved in water and the resulting solution was made alkaline with sodium bicarbonate. A solid was obtained, which was filtered, washed with water and dried, mp 190-193°. Recrystallization from dimethylformamide gave material melting at 200.5-201.0°; ^{1}H nmr (trifluoroacetic acid): δ 1.57 (t, 3 H, CH_2CH_3), 3.45 (s, 6 H, *N*-methyls), 3.93 (q, 2 H, CH_2CH_3), 6.08 and 6.25 (two s, 2 H, non-equivalent α-protons).

Anal. Calcd. for $C_9H_{13}N_3S_2O_2$ (259.30): C, 41.69; H, 5.01; N, 16.21; S, 24.71. Found: C, 41.42; H, 4.92; N, 16.06; S, 25.00.

6,8-Dimethyl-2,4-dithia-6,8-diaza-7,9-dioxo-3-phenacylidinebicyclo[3.2.2]nonane (**5d**).

At the end of the reaction period, the reaction mixture was poured into water and the solid that formed was filtered, washed with water and a small volume of alcohol and recrystallized from glacial acetic acid, mp 240-241°; ^{1}H nmr (trifluoroacetic acid): δ 3.45 (s, 6 H, *N*-methyls), 5.63 (s, 2 H α-protons), 7.60 (s, 1 H, vinyl), 7.7-8.1 (m, 5 H, phenyl).

Anal. Calcd. for $C_{15}H_{14}N_2S_2O_3$ (334.3): C, 53.89; H, 4.20; N, 8.38; S, 19.17. Found: C, 53.69; H, 4.38; N, 8.12; S, 19.23.

6,8-Dimethyl-2,4-dithia-6,8-diaza-7,9-dioxo-3,3-dibenzylbicyclo[3.2.2]nonane (**5e**).

The reaction of **3** with dithiol **4f** was slightly modified from the general procedure given above in that the reaction was performed at 0° in an ice bath for 5.75 hours, then at room temperature for 2 days. The reaction mixture was dissolved in chloroform, washed twice with water, and dried over magnesium sulfate. The solid obtained was recrystallized from acetone plus a small volume of methanol, mp 217-218°; ^{1}H nmr (chloroform): δ 2.95 (s, 6 H, *N*-methyl), 3.15 (s, 4 H, benzyl), 4.87 (s, 2 H, α-protons), 7.32 (s, 10 H, phenyl).

Anal. Calcd. for $C_{21}H_{22}N_2S_2O_2$ (398.5): C, 63.28; H, 5.56; N, 7.03; S, 16.09. Found: C, 63.09; H, 5.66; N, 7.09; S, 16.04.

3-*t*-Butyl-3,6,8-trimethyl-2,4-dithia-6,8-diaza-7,9-dioxobicyclo[3.2.2]nonane (**5f**).

The reaction of **3** with dithiol **4g** was carried out in dimethylformamide in place of acetonitrile. After a reaction period of 22 hours, an equal volume of methylene chloride was added and the resulting solution was washed with water and dried over magnesium sulfate. The solid product obtained was triturated with ethyl acetate and recrystallized from

methylene chloride-ethyl acetate to give material that had not begun to melt at 245°; ^{1}H nmr (chloroform): δ 1.18 (s, 9 H, *t*-butyl), 1.83 (s, 3 H, 3-methyl), 3.05 and 3.10 (two s, 6 H, non-equivalent *N*-methyls), 4.94 and 5.02 (two s, 2 H, α-protons).

Anal. Calcd. for $C_{12}H_{20}N_2S_2O_2$ (288.4): C, 49.97; H, 6.99; N, 9.71; S, 22.23. Found: C, 50.20; H, 7.07; N, 9.48; S, 22.06.

Attempted Coversion of Sulfur-bridged Piperazinedions to Epidithiopiperazinedione **1**.

(a) Attempted Hydrolysis of **5a**.

Compound **5a** (1-2 mmoles) was heated at reflux in the following acidic reagents: 50% aqueous acetic acid (6 hours), 50% aqueous trifluoroacetic acid (6 hours), 48% hydrobromic acid (3 hours). The solid, obtained by filtration of the cooled reaction solution or by removal of the solvent *in vacuo*, was washed with water and air dried. Comparison of the ^{1}H nmr spectra and mixture melting point with authentic **5a** established that reactant **5a** was recovered in good yield in each case.

(b) Hydrolysis of **5c** to the Dithiocarbonate **5g**.

A solution of the ethylimine **5c** (0.75 g, 2.9 mmoles) in 15 ml of 50% aqueous trifluoroacetic acid was heated at reflux for 6 hours. The solvent was removed *in vacuo* and the residue was suspended twice in water and the water was removed *in vacuo*. The solid residue was triturated with water, cooled in an ice bath, filtered and washed successively with small amounts of water and ethanol and air dried to yield **5g**, mp 220-222°, literature (7) mp 225° (aqueous acetic acid); yield 340 mg, 53%; ^{1}H nmr (DMSO-d_6): δ 3.12 (s, 6 H, *N*-methyls), 6.16 (s, 2 H, α-protons) (literature (7) δ 3.12 s, 6.16 s).

Attempted conversion of **5g** to **1** by treatment of 1.7 mmoles of **5g** with 3 mmoles of sodium methoxide in 25 ml of dry methanol at 25° for 20 minutes, followed by the addition of a slight excess of 5% iodine in methanol, gave a complex mixture of products from which **1** could not be isolated.

(c) Attempted Hydrazone Exchange.

A mixture of **5a** (0.32 g, 1 mmole) and acetylacetone (0.20 g, 2.0 mmoles) was heated at reflux for 7 hours in 5 ml of acetic acid. The solution was cooled to room temperature and the crystallized solid was collected by filtration, washed with water and air dried to give 0.30 g of recovered **5a**, mp 231-235°, mixture melting point not suppressed; ^{1}H nmr spectrum was superimposable with spectrum of **5a**.

(d) Reaction of **5d** with Zinc in Aqueous Alkali.

A suspension of **5d** (0.30 g, 1 mmole) in 5 ml of 1*N* sodium hydroxide containing 0.5 g of zinc powder was heated at reflux for 2 hours (6c). The solution was cooled to room temperature, the solid material was removed by filtration and the filtrate was acidified with dilute hydrochloric acid and extracted with chloroform. The organic extract was dried over magnesium sulfate and the solvent was removed *in vacuo* to give 0.20 g of an oil. Analysis of the oil by tlc showed 5 spots, while the ^{1}H nmr spectrum lacked peaks for the *N*-methyl protons.

(e) Reaction of **5f** with Sulfuryl Chloride-Silica.

A mixture of **5f** (1.45 g, 5.1 mmoles), 2 g of silica-gel (28-200 mesh) and 2 g of water in 40 ml of methylene chloride were stirred at room temperature. Sulfuryl chloride (1 ml, 12 mmoles) was added and the reaction mixture was heated at reflux for 1 hour. After cooling to room temperature, 40 ml of water were added and the mixture was made alkaline by addition of excess solid barium carbonate. The mixture was filtered through a fritted filter funnel. The phases were separated and the aqueous phase was washed with 25 ml of methylene chloride. The aqueous phase was evaporated *in vacuo* and the solid residue was triturated twice with hot isopropanol. The filtrate was evaporated *in vacuo* to about 25 ml, heated to boiling and solution was completed by addition of methanol. Upon cooling, white crystals formed and were collected by filtration, 0.12 g, mp 210-211.5°. Recrystallization from methanol gave material melting at 211.5-213°. Qualitative analysis revealed that the product did not contain sulfur; ^{1}H nmr (trifluoroacetic acid): δ 3.30 (s, 6 H), 5.59 and 5.68 (pair of singlets, 2 H); $M^{+\cdot}$ 216. From the data in hand, we were not able to assign a structure to this materail.

(f) Attempted Ketal Exchange with **5e**.

Compound **5e** (77 mg, 0.19 mmole) was heated at reflux in 2 ml of chloroform. Methanol (2 ml) was added, followed by the addition of 2 equivalents of iodine (99 mg, 0.39 mmole). The mixture was heated at reflux for 5 hours. After cooling to room temperature, 50 ml of methylene chloride was added and the resulting solution was washed once with aqueous soidum thiosulfate, once with saturated aqueous sodium bicarbonate, twice with water, and dried over magnesium sulfate. The tlc and ^{1}H nmr analysis showed this material to be recovered reactant.

1,4-Dimethyl-3,6-dimethylene-2,5-piperazinedione (**7**).

To a solution of 2.2 g (16 mmoles) of 3,6-dimethylene-2,5-piperazinedione (**6**), prepared from serine anhydride by the method of Augustin and Spangenberg (9), in 20 ml of dimethylformamide was added in portions 0.80 g (33 mmoles) of sodium hydride (from 1.6 g of a 50% dispersion in mineral oil) and the mixture was stirred until the evolution of gas subsided. Methyl iodide (4 ml) was added dropwise and the reaction mixture was stirred at room temperature for 2 hours. The mixture was poured onto crushed ice and the resulting solid was filtered, washed with water and air dried. Recrystallization from benzene gave product (1.54 g, 57%) melting at 230°, lit (9) 230° dec.

1,3,4,6-Tetramethyl-3,6-bis(acetylthio)-2,5-piperazinedione (**8**).

A suspension of 0.66 g (4 mmoles) of **7** in 6 ml of 4*N* hydrogen chloride in dioxane was treated with 6 ml of thioacetic acid. After stirring at room temperature for 30 minutes, a white solid began to form. The mixture was stirred at room temperature 2.5 hours, the solvent was removed *in vacuo* and the residue was triturated with diethyl ether, filtered and washed with ether. The product was recrystallized from carbon tetrachloride to give 1.1 g (86%) of product, mp 174-176°; ^{1}H nmr (deuteriochloroform): δ 2.08 (s, 6 H, methyls), 2.23 (s, 6 H, *S*-acetyls), 3.07 (s, 6 H, *N*-methyls).

Anal. Calcd. for $C_{12}H_{18}N_2S_2O_4$ (318.3): C, 45.28; H, 5.66; N, 8.80; S, 20.12. Found: C, 45.16; H, 5.75; N, 9.00; S, 20.27.

Conversion of bis-Acetylthiopiperazinedione **8** to Epidithio- and Epimonothiopiperazinediones **9** and **10**.

A solution of **8** (318 mg, 1.0 mmole) in 10 ml of methanol was treated with 200 mg of sodium borohydride added in portions over 10 minutes. The clear solution that resulted was stirred at room temperature for 1 hour. The solution was poured into water, a few drops of acetic acid were added and the solution was extracted with chloroform. The organic extract was dried over anhydrous sodium sulfate and the solvent removed *in vacuo* to yield 120 mg of an oil that slowly solidified, mp 64-77°. The ^{1}H nmr spectrum showed this material to be a mixture of the epidithio- and epimonothiopiperazinediones **9** and **10** in a ratio of 1:2 and representing a 19% yield of **9** and a 38% yield of **10**; ^{1}H nmr (chloroform) **9**: δ 2.01 (s, 6 H, *C*-methyls), 3.06 (literature (7) 3.05, s, 6 H, *N*-methyls); **10**: 1.81 (s, 6 H, *C*-methyls), 2.83 (literature (7) 2.81, s, 6 H, *N*-methyls).

Addition of Hydrogen Sulfide to **7** with Formation of Epimonothiopiperazinedione **10**.

Unsaturated piperazinedione **7** (166 mg, 1.0 mmole) in 5 ml of trifluoroacetic acid was treated with a slow stream of hydrogen sulfide for 5 minutes and the resulting solution was stoppered and allowed to stand at room temperature for 8 hours. Evaporation of the solvent *in vacuo* gave an oil (190 mg 95%) that was shown by ^{1}H nmr to be nearly pure epimonothio derivative **10**.

1,5,6,8-Tetramethyl-2,4-dithia-6,8-diaza-7,9-dioxo-3-phenacylidinebicyclo[3.2.2]nonane (**11**).

To a solution of the unsaturated piperazinedione **7** (166 mg, 1.0 mmole) in 1.0 ml of 4*N* hydrogen chloride in dioxane was added in one portion 196 mg (1.0 mmole) of the *gem*-dithiol **4d**. The mixture was stirred at room temperature for 6 hours. Removal of the solvent *in vacuo* gave a yellow oil that solidified upon standing. The solid was recrystallized from benzene-petroleum ether (bp 30-60°) to give 280 mg (79%) of product, mp 155-156°; ^{1}H nmr (chloroform): δ 1.87 and 1.92 (two s, 6 H, non-equivalent *C*-methyls), 3.08 (s, 6 H, *N*-methyl), 7.08 (s, 1 H, vinyl), 7.20-7.80 (m, 5 H, phenyl).

Anal. Calcd. for $C_{17}H_{18}N_2S_2O_3$ (362.4): C, 56.68; H, 5.00; N, 7.70; S, 17.68. Found: C, 56.58; H, 5.10; N, 7.50; S, 17.47.

Acknowledgements.

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Table 1

Preparation of

3-Substituted-2,4-dithia-6,8-diaza-7,9-dioxobicyclo[3.2.2]nonanes (**5**)

Compound	Y	Yield % (a)	Mp, °C	Solvent (b)
5a	NNHPh	62-88	233-235	Acetic Acid
5b	NPh	71-73	235-236.5	Chloroform-petroleum ether (c)
5c	NEt	52-71	200.5-201	DMF
5d	CHCOPh	75-79	240-241	Acetic Acid
5e	$(CH_2Ph)_2$	13-41	217-218	Acetone-methanol
5f	Me, *t*-Bu	44-51	>245	Dichloromethane-ethyl acetate

(a) Yields given are for isolated, crystallized product. Values given represent minimum and maximum yields obtained for each compound during the various preparations that were carried out. (b) Solvent of recrystallization. (c) Bp 30-60°.

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