A New Synthesis of 3,6-Dialkyl-1,4-dimethyl-3,6-epithio- and -3,6-epidithio-2,5-piperazinediones

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A new route for synthesis of 3,6-dialkyl-1,4-dimethyl-3,6-epithio- (**8**) and -3,6-epidithio-2,5-piperazinediones (**9**) *via* the corresponding bromo derivatives was described. Bromination of 3,6-dialkyl-1,4-dimethyl-2,5-piperazinedione with *N*-bromosuccinimide gave 3,3α,6,6α-tetrabromo (**2**) and 3,6-dibromo (**3**) derivatives, depending upon the straight chain (methyl, ethyl, propyl, butyl) or α-branched (isopropyl, *sec*-butyl) alkyl groups, respectively. After tentative substitution of 3,6-bromine atoms of **2** with methanol, 3α,6α-bromine atoms were reduced to give the corresponding 3,6-dialkyl-3,6-dimethoxy derivatives (**5**). Substitution of **3** or **5** with hydrogen sulfide in the absence or presence of zinc chloride, and successive oxidation with potassium triiodide gave **8** and **9** at the same time. Discussions were made on the structure of isomers and on the reaction mechanisms.

3,6-Epidithio-2,5-piperazinedione skeleton is the unique partial structure of a class of antibiotics such as gliotoxin,[1] sporidesmin,[2] and others.[3,4] The simplest compound has been first synthesized through substitution of 3,6-dibromo-1,4-dimethyl-2,5-piperazinedione with sodium thioacetate or sodium tetrasulfide,[5] and the method was successfully applied only for 3,6-diphenyl derivative.[6] A few derivatives were synthesized through condensation of sulfur or sulfur chloride with the corresponding 3,6-dicarbanions obtained by treatment of parent 2,5-piperazinediones with sodium hydride[7] or sodium amide.[8] Recently, Kishi *et al.* synthesized dehydrogliotoxin and sporidesmin A by alkylation of similar carbanions of 3,6-dimercapto-2,5-piperazinediones whose mercapto groups were protected as thioacetal of anisaldehyde.[9] We have tried to extend the first method to 3,6-dialkyl derivatives. However, bromination of 1,3,4,6-tetramethyl-2,5-piperazinedione gave the 3,3α,6,6α-tetrabromo derivative, and substitution of its 3,6-bromine atoms with sulfur-containing nucleophiles gave only 3,6-dimethylene derivative and sulfur, in participation with 3α,6α-bromine atoms.[10] To exclude the participation, reductive removal of the 3α,6α-bromine atoms prior to the introduction of mercapto groups gave successful results. Thus, it was communicated that substitution of 3,6-bromine atoms of the tetrabromide with methanol, reduction of 3α,6α-bromine atoms, substitution of 3,6-methoxy groups with mercapto groups in the presence of zinc chloride,[11] and oxidation gave the corresponding 3,6-epithio and 3,6-epidithio derivatives.[12]

In this paper, this new synthesis is described in detail, together with discussions on the structure of related compounds and on reaction mechanism of the final step.

Results and Discussion

3,6-Dialkyl-1,4-dimethyl-2,5-piperazinediones and their bromination with N-*bromosuccinimide.* *N*-Methylation of 3,6-dialkyl-2,5-piperazinediones obtained by thermal dehydration of α-amino acids[13] with methyl iodide and sodium hydride, instead of silver oxide as a neutralizing reagent,[14] gave a *cis* and *trans* mixture of the corresponding 1,4-dimethyl derivatives (**1**) in over 80% yields. The ratios of isomers were determined by glc, and pure isomers were isolated by fractional crystallization from ether or ether–petroleum ether. As standards, *cis* isomers of **1a**, **1e** and **1f** were synthesized by *N*-methylation of optically active 3,6-dialkyl-2,5-piperazinediones with methyl iodide and silver oxide, and the glc data of the latter one and *cis*-**1g** were supported with that of Manger.[15] For examination of the relationship between the configuration and properties of isomers, physical constants of **1** were summarized in Table 1, in which an isomer having a shorter retention time was arranged at first.

Among the above four examples, **1a** showed an exceptional relationship between the configuration and retention time. However, the chemical shift of 3,6-hydrogens in *trans* isomer showed commonly larger δ value than that of *cis* isomer, as was pointed out for several derivatives in a previous paper.[10] Thus, the common observation was applied for the deduction of the configuration of isomers of **1b–d**. It was shown by X-ray analysis that *cis* and *trans* 3,6-disubstituted-2,5-piperazinedione have a skewed boat and a planar conformation, respectively.[16] If these conformations are maintained to some extent in a solution state, 3,6-hydrogens in *trans* isomer are sterically closer to the plane of vicinal carbonyl groups than those in *cis* isomer, and consequently show a more larger δ value.

The *cis* and *trans* mixture of **1** was used for the next bromination, because the 2,5-piperazinedione ring has a strong tendency to make carbonium cations in substitutions at 3,6-positions. Treatment of **1a** in carbon tetrachloride with four equimolar amount of *N*-bromosuccinimide (NBS) in the presence of 2,2′-azobisisobutyronitrile as an initiator gave the 3,3α,6,6α-tetrabromide (**2a**) in a much better yield (80%) than that with bromine (less than 20%).[10] When two equimolar amount of NBS was used, the corresponding 3,3α-dibromo derivative was produced, which was ascertained as 3-bromomethyl-3-methoxy derivative (**2a′**) by treatment with methanol. This fact indicates that the bromination at 3,6-positions takes place stepwise, and it is followed by elimination of hydrogen bromide addition of bromine produced from hydrogen bromide and NBS to give **2a**. Such successive reactions; *i.e.*,

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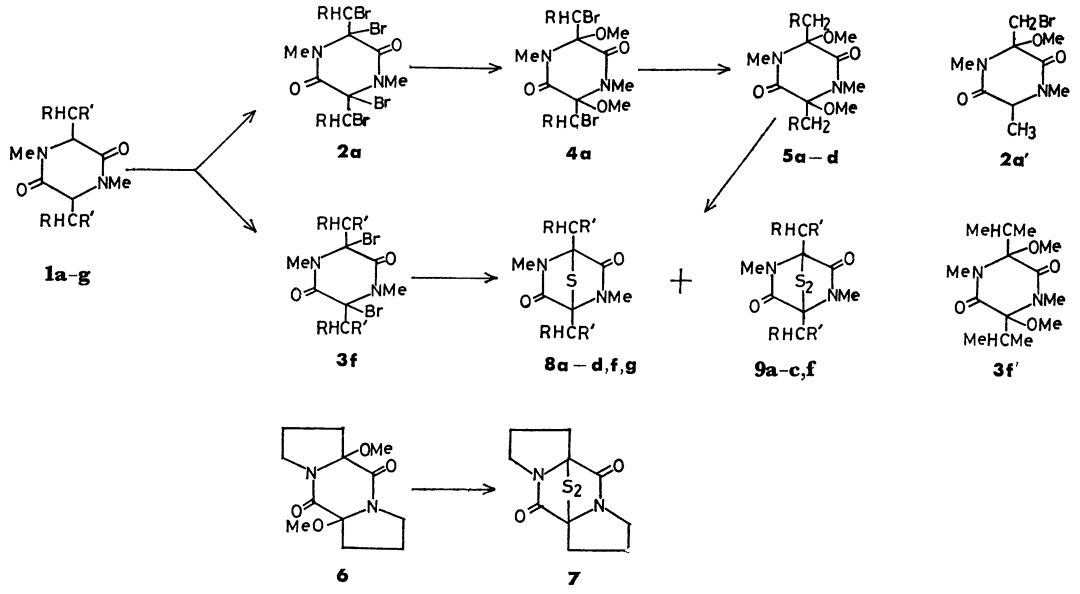
Table 1. Physical properties of 3,6-dialkyl-1,4-dimethyl-2,5-piperazinediones (**1**)

Compound		Yield[a] (%)	Mp (°C)	glc[b] Ratio	glc[b] Time	IR (cm^{-1}) amide	NMR (δ) NMe	NMR (δ) $H_{3,6}$	Molecular formula	Anals. (Calcd)[c] C%	H%	N%
a	*cis*	40	122—123	1	3.15	1640	2.94	3.89	$C_8H_{14}N_2O_2$	56.47	8.24	16.03
	trans	19	135—136	0.56	3.5	1630	2.94	3.95		(56.45	8.29	16.46)
b	*trans*[d]	52	126—127	1	3.5	1640	2.94	4.03	$C_{10}H_{18}N_2O_2$	60.72	9.13	14.07
	cis	13	73—74.5	0.5	4.4	1650	2.96	3.82		(60.58	9.15	14.13)
c	*trans*	49	105—106	1	7.75	1640	2.96	3.98	$C_{12}H_{22}N_2O_2$	63.78	9.88	12.46
	cis	20	83—85	0.86	9.5	1650	2.94	3.81		(63.68	9.80	12.38)
d	*trans*	52	131—133	1	10.9	1640	2.92	4.02	$C_{14}H_{26}N_2O_2$	66.55	10.25	11.15
	cis	2	49—50	0.75	13.0	1640	2.97	3.83		(66.10	10.30	11.01)
e	*trans*	48	96—97	1	10.0	1640	2.94	4.00	$C_{14}H_{26}N_2O_2$	66.07	10.46	10.95
	cis	22	114—116	0.85	10.9	1645	2.93	3.80		(66.10	10.30	11.01)
f	*trans*	25	151—153	1	5.5	1640	2.93	3.83	$C_{12}H_{22}N_2O_2$	63.69	9.65	12.35
	cis	36	133—134	1.4	7.3	1650	3.02	3.47		(63.68	9.80	12.38)
g	*trans*	44	122—124	1	10.0	1640	2.89	3.86[e] 3.91	$C_{14}H_{26}N_2O_2$	66.37	10.26	11.04
	cis	—	—	0.54	13.3	—	—	—		(66.10	10.30	11.01)

a) Actually separated yield. b) Silicone SE-52 on Chromosorb G-AW; 200 °C; N_2 flow rate, 60 ml/min; retention time in min. c) Analytical values before the fractional crystallization. d) Configurations in parentheses were deduced from NMR data. e) The appearance of two kinds of 3,6-proton signals also indicates the trans configuration. Such a magnetic environmental difference should be caused by the asymmetric 3,6-dialkyl groups only into *trans* **1g** derived from L-isoleucine, but not into *cis* **1g**.



a: R=R'=H **b**: R=Me, R'=H **c**: R=Et, R'=H **d**: R=*n*-Pr, R'=H
e: R=*iso*-Pr, R'=H **f**: R=R'=Me **g**: R=Et, R'=Me

Fig. 1. The synthetic routes to **8** and **9**.

bromination, elimination and addition, were also observed in the bromination with bromine.[10]

In a similar way, **1b–d** having linear alkyl groups gave homologous 3,3α,6,6α-tetrabromides, whereas **1f** having α-branched alkyl groups gave the corresponding 3,6-dibromide (**3f**), which was proved by conversion into 3,6-diisopropyl-3,6-dimethoxy-1,4-dimethyl-2,5-piperazinedione (**3f'**) by treatment with methanol. This fact will be attributed to the steric hindrance to be arose in the corresponding elimination product.[17] Although **2b–d** and **3g** were not isolated, the above relation between the structure of 3,6-alkyl groups and the bromination product was confirmed by their conversions to be mentioned in the next item.

Conversion of Bromo Derivatives into 3,6-Epithio- and 3,6-Epidithio-2,5-Piperazinediones. To avoid the participation of 3α,6α-bromine atoms of **2** to the substitution of 3,6-bromine atoms with hydrogen sulfide,[10] the former were removed by hydrogenation after tentative conversion of the latter into methoxy groups, and then the methoxy groups were substituted with mercapto groups. Treatment of **2a** with methanol gave the 3,6-dimethoxy derivative (**4a**) in 86% yield, and hydrogenation of **4a** with tri-*n*-butyltin hydride

TABLE 2. 3,6-DIALKYL-1,4-DIMETHYL-3,6-EPITHIO- AND -3,6-EPIDITHIO-2,5-PIPERAZINEDIONES (**8** AND **9**)

Compd.	Yield[a] (%)	Mp. (°C)	Molecular formula	Anals. (Calcd) C%	H%	N%	S%	NMR (δ) NMe	IR (cm^{-1}) amide[b]
8a	72	63—65	$C_8H_{12}N_2O_2S$	47.82 (47.98)	6.00 (6.04)	13.91 (13.99)	15.99 (16.01)	2.81	1700
9a	18	145—146	$C_8H_{12}N_2O_2S_2$	41.67 (41.36)	5.28 (5.21)	12.45 (12.06)	27.40 (27.60)	3.05	1680
8b	20	76—78	$C_{10}H_{16}N_2O_2S$	52.78 (52.61)	7.01 (7.06)	12.02 (12.27)	14.02 (14.04)	2.77	1700
9b	56	110—111	$C_{10}H_{16}N_2O_2S_2$	46.25 (46.13)	6.27 (6.19)	10.50 (10.76)	24.60 (24.63)	3.05	1680
8c	27	96—98	$C_{12}H_{20}N_2O_2S$	56.48 (56.22)	8.01 (7.86)	10.68 (10.93)	12.26 (12.51)	2.76	1700
9c	17	sirup	$C_{12}H_{20}N_2O_2S_2$	50.22 (49.97)	6.99 (6.99)	9.72 (9.71)	22.18 (22.23)	3.05	1670
8d[c]	69	sirup	$C_{14}H_{24}N_2O_2S$	58.92 (59.12)	8.25 (8.51)	10.03 (9.85)	11.10 (11.27)	2.77	1710
8f	88	146—147	$C_{12}H_{20}N_2O_2S$	56.06 (56.22)	7.91 (7.86)	10.69 (10.93)	12.41 (12.51)	2.72	1700
9f	2	109—110	$C_{12}H_{20}N_2O_2S_2$	50.21 (49.97)	6.84 (6.99)	9.72 (9.71)	22.20 (22.23)	3.06	1680
8f	43	146—147	$C_{12}H_{20}N_2O_2S$	56.01 (56.22)	7.93 (7.86)	10.70 (10.93)	12.30 (12.51)	2.72	1700
9f	2.3	109—110	$C_{12}H_{20}N_2O_2S_2$	50.12 (49.97)	6.90 (6.99)	9.70 (9.71)	22.15 (22.23)	3.06	1680
8g[c]	19	89—90	$C_{14}H_{24}N_2O_2S$	59.18 (59.12)	8.62 (8.51)	9.87 (9.85)	11.38 (11.27)	2.70	1700

a) The first five runs (a—f) indicate yields from **6**, and the last two (f, g) from **1** *via* **3**. b) It is characteristic that the amide absorptions of **8** and **9** appeared broad and sharp, respectively. c) The corresponding **9** could not be obtained.

gave 1,3,4,6-tetramethyl-3,6-dimethoxy-2,5-piperazinedione (**5a**) quantitatively. In the case of **1b–d**, **5b–d** were synthesized by the successive reactions without isolation of **2b–d** and **4b–d**, because they include too many isomers and **2b–d** are unstable. The compound **5e** could not be separated in a pure state by the similar reactions of **1e**. By the same hydrogenation as above, 5a,10a-dimethoxyoctahydro-5*H*,10*H*-dipyrrolo-[1,2-*a* : 1′,2′-*d*]pyrazine-5,10-dione (**6**) was quantitatively obtained from the corresponding 1,6-dibromo-5a,10a-dimethoxy derivative.[10]

The most of **5**, **3f′** and **4a** were separated into two isomers, but, their configurations could not be determined. It seems likely that the configuration of 2,5-piperazinediones having two substituents at both 3,6-positions should be determined by X-ray analysis at the present stage.

For preparation of epidithio derivatives, **6** was treated with hydrogen sulfide in the presence of zinc chloride and then oxidized with potassium triiodide, according to the method of Schmidt *et al.*[11] which was applied to the corresponding 5a, 10a-dihydroxy derivative, to give desired epidithio derivative (**7**) in 78% yield. However, application of the same procedure to **5** gave a mixture of 3,6-epithio (**8**) and 3,6-epidithio-(**9**) derivatives. Moreover, the simple substitution of **3** with hydrogen sulfide and successive oxidation gave again a mixture of **8** and **9**. These mixtures were separated by preparative tlc, and physical constants of pure compounds were summarized in Table 2.

The remarkable difference in the reaction products from **6** and **3** or **5** will be attributed to the rigid planar conformation of **6**, which is caused by fused pyrrolidine rings. The ratios of **8** to **9** were not so much changed by the configuration of **5** (*cis* or *trans*) and also by reaction conditions (temperature and molar ratio of reagents). An attempted reaction of **3f′** with thioacetic acid in the presence of zinc chloride gave directly **8f** as a main product. Similar results were obtained in the conversion of **3f** into **8f** and **9f**. These facts indicate that the both conversions of **3** and **5** into **8** and **9** proceed by the S_N1 mechanism. The first substitution of **3** or **5** with thiol anion and the

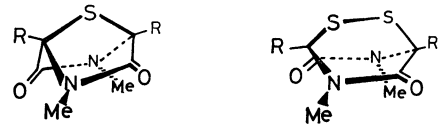


Fig. 3. The conformation of **8** and **9**.

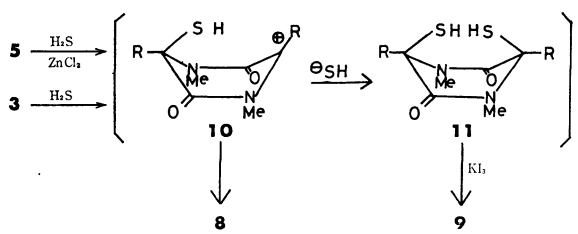


Fig. 2. The mechanism of the formation of **8** and **9**.

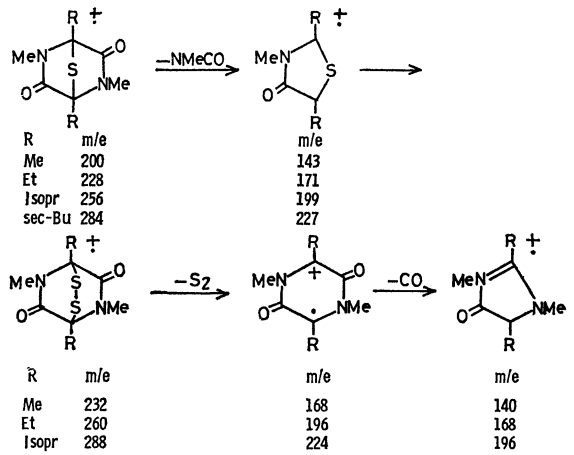


Fig. 4. The characteristic fragmentation of **8** and **9**.

formation of the second carbonium ion will give the key-intermediate (**10**), in which the intramolecular nucleophilic attack of sulfur atom to the carbonium ion affords **8**. While, an intermolecular attack of a thiol anion to **10** gives the corresponding dithiol (**11**), which is oxidized to **9** by potassium triiodide.

On the other hand, NMe proton signal of **8** in NMR spectra appeared generally in higher magnetic field than that of **9**. This fact indicates that the more strained conformation of **8** than **9** draws NMe groups into the diamagnetic field of the carbonyl group in the opposite side of the molecule sterically closer than that of **9**. The characteristic IR absorption of amido groups also clearly distinguishes **8** and **9** (Table 2). Moreover, mass fragmentations of **8** and **9** showed the most intense peaks of *m/e* (M–NMeCO) and *m/e* (M–2S), respectively, as the characteristic peaks.

Experimental

All 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 discs with a Hitachi EPI-G2 spectrometer. The NMR spectra were obtained at 100 MHz with a JEOL JNM-100H spectrometer in deuteriochloroform, using TMS as an internal reference. Specific rotations were measured in a 0.5-dm tube with a Carl Zeiss LEP-Al polarimeter. The mass spectra were obtained on a JEOL JNS-OLS 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, and IR frequencies in cm^{-1}.

*3,6-Dialkyl-1,4-dimethyl-2,5-piperazinediones (**1a–g**).* To a suspension of 3,6-dialkyl-2,5-piperazinedione (0.11 mol) in dried DMF (200 ml) was added sodium hydride (10.5 g, 50% in oil, 0.22 mol) portionwise during 30 min under a violent stirring. After the evolution of hydrogen gas subsided, methyl iodide (0.25 mol) was added dropwise to the solution with stirring under ice-cooling, and the reaction mixture was kept at room temperature for 30 min, and then evaporated. The residue in water (200 ml) was extracted with carbon tetrachloride (2×100 ml), and the chloroform layer was dried over sodium sulfate, and evaporated to give **1** quantitatively, which were fractionally recrystallized from ether (**1a-b**) or ether-petroleum ether (**1c–g**) (Table 1).

*Optically Active 3,6-Dialkyl-1,4-dimethyl-2,5-piperazine-diones (**1a, 1e** and **1f**).* Optically active 3,6-dimethyl-, 3,6-diisobutyl- and 3,6-diisopropyl-2,5-piperazinediones were methylated in DMF (*ca* 100 part) with methyl iodide (60 equivalent) and silver oxide (20 part), according to the reported method,[14] to give *N*-methyl derivatives in 2%, 10% and 50% yields, respectively. The low yield of **1a** will be attributed to the insolubility of the starting material, but the reaction does not proceeded in HMPA. These compounds gave correct analytical values, and spectral (IR and NMR) and glc data were consistent with those of *cis* isomers in Table 1.

1a: mp 120 °C, $[\alpha]_D^{23}$ +56.99° (*c* 0.55, $CHCl_3$); **1e**: mp 110 °C, $[\alpha]_D^{23}$ +48.81° (*c* 1.0, $CHCl_3$): **1f**: mp 104—105 °C, $[\alpha]_D^{23}$ −33.31° (*c* 1.0, $CHCl_3$).

*3,6-Dibromo-3,6-bis(bromomethyl)-1,4-dimethyl-2,5-piperazinedione (**2a**).* A solution of **1a** (1 g, 5.9 mmol), NBS (4 g, 24 mmol) and 2,2′-azobisisobutyronitrile (10 mg) in carbon tetrachloride was refluxed until NBS has dissolved, and succinimide deposited was filtered and washed with chloroform (50 ml). The filtrate and washings were evaporated to give white powder, which was triturated with a small amount of ethanol and filtered. Yield, 2.4 g (82%), mp 186—188 °C (lit, [10] 185—188 °C, 18%).

*3-Bromomethyl-3-methoxy-1,4,6-trimethyl-2,5-piperazinedione (**2a′**).* A solution of **1a** (300 mg, 1.765 mmol), NBS (628 mg, 3.53 mmol) and 2,2′-azobisisobutyronitrile (10 mg) in carbon tetrachloride (50 ml) was refluxed for 20 min, and succinimide deposited was filtered and washed with chloroform (20 ml). The filtrate and washings were evaporated, and then a solution of the residue and sodium acetate (1 g, 12.2 mmol) in methanol (50 ml) was refluxed for 2 hr, evaporated, and the residue was extracted with chloroform. The extract was washed with water, dried, and evaporated to give a mixture of **1a**, **2a** and **2a′**, which were separated on a preparative tlc. **2a** and **2a′** were obtained in 24% (165 mg) and 22% (110 mg) yield, respectively. **2a′**: mp 88 °C, IR: 1660 (amide), NMR: 1.59 (CMe; d, J_{vic}=6.5), 2.90 and 3.04 (NMe), 4.01 and 3.53 (CH_2Br; ABq, J_{gem}=10.8).

Found: C, 38.61; H, 5.28; N, 10.01; Br, 28.90%. Calcd for $C_9H_{15}N_2O_3Br$: C, 38.72; H, 5.42; N, 10.03; Br, 28.62%.

*3,6-Diisopropyl-1,4-dimethyl-3,6-dimethoxy-2,5-piperazinedione (**3f′**).* A solution of **1f** (0.5 g, 2.2 mmol), NBS (800 mg, 4.5 mmol) in carbon tetrachloride (30 ml) was treated as above to give a sirupy **3f**, which was then treated with methanol and sodium acetate in a similar manner using benzene as extracting solvent. The sirupy product was crystallized and recrystallized from petroleum ether to give a mixture of isomers (270 mg, 43%) which was separated on a silica gel column using benzene – ethyl acetate (20 : 1) as an eluent.

A: mp 113—115 °C, IR: 1660 (amide), NMR: 0.79 and 1.14 (CMe; d, J_{vic}=7.0), 2.33 (CH; sep), 2.94 (NMe), 3.09 (OMe).

B: mp 193—194 °C, IR: 1660 (amide), NMR: 0.88 and 1.08 (CMe; d, J_{vic}=7.0), 2.27 (CH; sep), 2.87 (NMe), 3.17 (OMe).

Found (A): C, 58.47; H, 9.35; N, 9.67%. (B): C, 58.50; H, 9.31; N, 9.66%. Calcd for $C_{14}H_{26}N_2O_4$: C, 58.72; H, 9.15; N, 9.78%.

*3,6-Bis(bromomethyl)-1,4-dimethyl-3,6-dimethoxy-2,5-piperazinedione (**4a**).* A solution of **2a** (1 g, 2.1 mmol) and sodium acetate (1 g, 12 mmol) in methanol (50 ml) was stirred at room temperature for 10 hr, evaporated, and the residue was extracted with chloroform. The extract was washed with water three times, dried, and evaporated to give crystals (700 mg, 86%) which were recrystallized from chloroform–ligroin. Analytical values of the crystals were consistent with theoreticals, but which were fractionally crystallized into two isomers. A: mp 160 °C (decomp.), IR: 1670 (amide), NMR: 3.01 (OMe), 3.35 (OMe), 3.54 and 4.12 (CH_2Br; ABq, J_{gem}=11.0). B: mp 198—200 °C (sublime), IR: 1670 (amide), NMR: 308 (NMe), 3.28 (OMe), 3.60 and 4.18 (CH_2Br; ABq, J_{gem}=11.3).

Found: C, 31.30; H, 3.91; N, 7.16%. Calcd for $C_{10}H_{16}N_2O_4Br_2$: C, 30.95; H, 4.16; N, 7.22%.

*3,6-Dimethoxy-1,3,4,6-tetramethyl-2,5-piperazinedione (**5a**).* A solution of **4a** (300 mg, 0.77 mmol), tri-*n*-butyltin hydride (465 mg, 1.6 mmol) and 2,2′-azobisisobutyronitrile (5 mg) in toluene (50 ml) was heated at 70 °C for 1 hr under nitrogen atmosphere, and evaporated to give a half-crystalline mass which was triturated with ligroin and filtered. The crystals (180 mg, quantitative) obtained were recrystallized from ether. Analytical values of the crystals were consistent with theoreticals, but which were separated into two isomers by a preparative tlc. A: mp 130 °C (sublime), IR: 1670

(amide), NMR: 1.58 (CMe), 2.98 (NMe), 3.12 (OMe). B: 201—202 °C, IR: 1670 (amide), NMR: 1.69 (CMe), 2.98 (NMe), 3.07 (OMe).

Found: C, 51.70; H, 7.88; N, 12.08%. Calcd for $C_{10}H_{18}N_2O_4$: C, 52.16; H, 7.88; N, 12.17%.

*3,6-Dialkyl-1,4-dimethyl-3,6-dimethoxy-2,5-piperazinedione (**5b–d**).* The compounds **1b–d** (500 mg) were brominated with NBS (4 equivalent) and then methylated, in the same manner as **2a** and **4a**, to give sirupy products (**4b**: 850 mg, **4c**: 830 mg, **4d**: 930 mg, respectively). These sirups were reduced with tri-*n*-butyltin hydride (2.1 equivalent) in the same manner as above to give products (**5b**: 470 mg, 72%, **5c**: 210 mg, 34%, **5d**: 280 mg, 47%, respectively), which were separated into two isomers on a silicagel column using benzene-ethyl acetate (15 : 1) as an eluent.

5b: mp 165—167 °C, IR: 1660 (amide), NMR: 0.83 (CMe; t, J_{vic}=7.2), 1.82 and 2.29 (CH_2; each sex, J_{gem}= 14.5), 2.95 (NMe), 3.16 (OMe).

Found: C, 55.84; H, 8.48; N, 10.97%. Calcd for $C_{12}H_{22}N_2O_4$: C, 55.78; H, 8.58; N, 10.85%.

5c: A: mp 82—83 °C, IR: 1665 (amide), B: mp 110 °C, IR: 1660 (amide). NMR: 0.91 (CMe; t, J_{vic}= 6.5), 0.7—2.45 (CH_2: broad m), 2.94 (NMe), 3.14 (OMe).

Found (A): C, 59.02; H, 8.84; N, 10.01%. (B): C, 59.00; H, 8.90; N, 9.98%. Calcd for $C_{14}H_{26}N_2O_4$: C, 58.72; H, 9.15; N, 9.78%.

5d: A: mp 85—86 °C, IR: 1655 (amide), B: sirup, IR: 1670 (amide). NMR: 0.7–2.5 (CMe and CH_2; broad m), 2.94 (NMe), 3.16 (OMe).

Found (A): C, 60.82; H, 9.46; N, 8.84%. (B): C, 60.65; H, 9.29; H, 8.54%. Calcd for $C_{16}H_{30}N_2O_4$: C, 61.12; H, 9.62; N, 8.91%.

Isomers of **5c** and **5d** could notbe distinguished by NMR spectra.

*5a,10a-Dimethoxyoctahydro-5H,10H-dipyrrolo[1,2-a : 1′,2′-d]-pyradine-5,10-dione (**6**).* 1,6-Dibromo-5a,10a-dimethoxy-octahydro-5*H*,10*H*- dipyrrolo[1,2-*a*: 1′2′-*d*]pyridine- 5,10-dione[10] (300 mg, 0.73 mmol) was hydrogenated with tri-*n*-butyltin hydride in the same manner as **5a** to give crystals (185 mg, 99%) which were recrystallized from petroleum ether. Mp 185 °C. IR: 1660 (amide).

Found: C, 56.32; H, 7.11; N, 11.00%. Calcd for $C_{12}H_{18}N_2O_4$: C, 56.68; H, 7.14; N, 11.02%.

*Tetrahydro-6H,10H-5a,10a-epidithio-1H,5H-dipyrrolo[1,2-a : 1′,2′-d]pyradine-5,10-dione (**7**).* To a suspension of **6** (100 mg, 39.3 mmol) in chloroform (30 ml, saturated with hydrogen sulfide) was added zinc chloride (10 mg) and passed dried hydrogen sulfide for 3 hr, and then evaporated. The residue was extracted with chloroform, and the extract was washed with water and shaked with potassium triiodide solution until the chloroform layer colored with iodine. The colored solution was washed successively with sodium thiosulfate and water, dried, and then evaporated to give crystals which were recrystallized from ether. Yield, 78.5 mg (78%), mp 135—136 °C (lit,[11] 135—136 °C), IR: 1680 (amide).

Found: C, 46.55; H, 4.56; N, 10.98%. Calcd for $C_{10}H_{12}N_2O_2S_2$: C, 46.88; H, 4.72; N, 10.93%.

*General Procedure for Preparation of 3,6-Dialkyl-1,4-dimethyl-3,6-epithio- (**8**) and -3,6-epidithio-2,5-piperazinedione (**9**).* i) From 3,6-dialkyl-3,6-dimethoxy derivatives (**8a–d,f** and **9a–d,f**). Compounds **5a–d** and **3f′** were treated in a similar manner as above to give crude products, which were purified and separated into **8** and **9** on a silica gel column (WAKOGEL C–200) using benzene-ethyl acetate (20 : 1) as an eluent.

ii) From **1f,g** *via* the corresponding 3,6-dialkyl-3,6-dibromide (**8f,g** and **9f,g**). Compounds **1f** and **1g** were brominated with NBS (2 equivalent) in the same manner as described in **3f′**. Hydrogen sulfide was passed into a solution of the resulting dibromide in chloroform for 3 hr in the absence of zinc chloride, and the reaction mixture was treated as above to give **8f,g** and **9f,g**.

The yields and their physical constants were summarized in Table 2.

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