Synthesis and Substitution of 1,3,4,6-Tetra-substituted-3,6-dihalogeno-2,5-piperazinediones

Juji YOSHIMURA, Yuichi SUGIYAMA, and Hiroshi NAKAMURA

Laboratory of Chemistry for Natural Products, Faculty of Science, Tokyo Institute of Technology, Meguro-ku, Tokyo 152

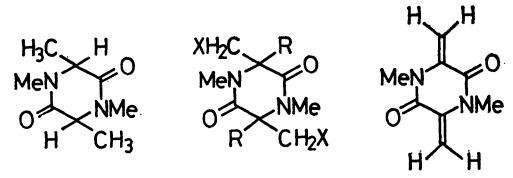
(Received April 25, 1973)

Addition of chlorine to 3,6-dimethylene- (**3**) and 3,6-dibenzylidene-1,4-dimethyl-2,5-piperazinediones gave isomers of the corresponding tetrachloride, and substitution of 1,3,4,6-tetramethyl-2,5-piperazinedione with bromine also gave tetrabromide (**2**) of the same type *via* successive elimination and addition reactions. Treatment of **2** with water and with methanolic sodium acetate gave the corresponding 3,6-dihydroxy and dimethoxy derivatives, respectively, while treatment with sodium iodide, sodium sulfide, sodium thiocyanate, or sodium thioacetate gave only **3** and sulfur in a good yield. Similar results were obtained in the case of octahydro-5*H*,10*H*-dipyrrolo[1,2-*a*: 1′,2′-*d*]pyrazine-5,10-dione. However, bromination of 6,13-dioxo-6a,7,13a,14-tetrahydro-6*H*,13*H*-pyrazino[1,2-*a*: 4,5-*a*′]diindole gave rise only to aromatization. Configurations of the isomers obtained and the reaction processes were discussed.

3,6-Epidithio-2,5-piperazinedione skeleton is a unique partial structure of a class of antibiotics such as gliotoxin,[1] sporidesmin,[2] and others.[3,4] A few homologues were synthesized by substitution of the halogeno group of 3,6-dihalogeno-2,5-piperazinediones, having no alkyl substituents at 3- and 6-positions, with the mercapto group followed by intramolecular disulfide-ring formation.[5–7] In order to clarify the limitation of this synthetic route, synthesis and reactivity of 3,6-dihalogeno-2,5-piperazinediones were examined.

Results and Discussion

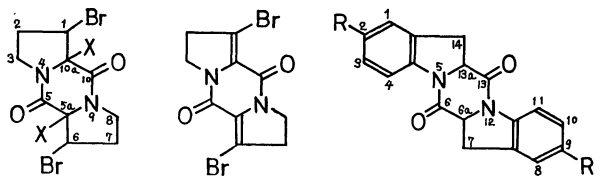
Bromination of *meso* or *racemic* 1,3,4,6-tetramethyl-2,5-piperazinedione (**1a** and **1b**) in benzene, newly obtained by condensation of two moles of *N*-methylalanine,[8] gave one isomeric 3,6-dibromo-3,6-bis(bromomethyl)-1,4-dimethyl-2,5-piperazinedione (**2**) and HBr_3 adduct of **1** which gave **1** in water with liberation of bromine. Treatment of **2** with sodium iodide gave 3,6-dimethylene-1,4-dimethyl-2,5-piperazinedione (**3**) in a good yield, which was reversely converted into **2** by addition of bromine. Bromo functions at 3- and 6-positions in **2** were selectively converted into hydroxy (**4**) or methoxy (**5**) groups in aqueous ethanol or methanolic sodium acetate, whereas attempted substitution with acetylthio, methylthio, mercapto, or cyanothio groups gave only **3** and sulfur. Similarly, substitution of octahydro-5*H*,10*H*-dipyrrolo[1,2-*a*: 1′,2′-*d*]pyrazine-5,10-dione[9] with bromine in benzene gave 1,5a,6,10a-tetrabromo-octahydro-5*H*,10*H*-dipyrrolo[1,2-*a*: 1′,2′-*d*]-pyrazine-5,10-dione (**6**) and HBr_3 adduct of the starting material. Treatment of **6** with methanol or sodium acetate in acetic acid gave 1,6-dibromo-5a,10a-dimethoxy-octahydro-5*H*,10*H*-dipyrrolo[1,2-*a*: 1′,2′-*d*]-pyrazine-5,10-dione (**7**) and 1,6-dibromo-2,3,7,8-tetrahydro-5*H*,10*H*-dipyrrolo[1,2-*a*: 1′,2′-*d*]pyrazine-5,10-dione (**8**), respectively. However, treatment of **6** with potassium iodide gave a mixture of **8** and its mono and di-debrominated compounds. Furthermore, bromination of 6,13-dioxo-6a,7,13a,14-tetrahydro-6*H*,13*H*-pyrazino[1,2-*a*: 4,5-*a*′]diindole (**9**) in methanol, obtained from two moles of ethyl 2-indoline-carboxylate,[10] deposited selectively the corresponding 2,9-dibromo derivative (**10**) in 79% yield, the position of their bromo groups being determined from the splitting of magnetically equivalent H_4 and H_{11} (δ 7.96, J=8.5 Hz) appearing in the lowest magnetic field in the NMR spectrum and characteristic absorptions (825—835 cm^{-1}) in the IR spectrum. Further bromination of **10** in chloroform gave exclusively 2,9-dibromo-6,13-dioxo-6*H*,13*H*-pyrazino[1,2-*a*: 4,5-*a*′]diindole (**11**).



(**1**) a:
b:

(**2**) X=R=Br
(**4**) X=Br, R=OH
(**5**) X=Br, R=OMe

(**3**)

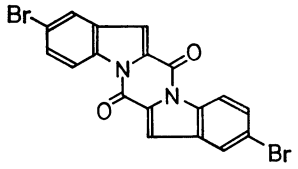


(**6**) X=Br
(**7**) X=OMe

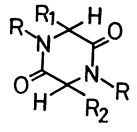
(**8**)

(**9**) R=H
(**10**) R=Br

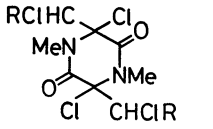
1) M. R. Bell, J. R. Johnson, B. S. Wildi, and R. B. Woodward, *J. Amer. Chem. Soc.*, **80**, 1001 (1958).
2) S. Safe and A. Taylor, *J. Chem. Soc., C*, **1970**, 432.
3) R. Nagarajan, L. L. Huckstep, D. H. Lively, D. C. DeLong, M. M. Marsh, and N. Neuss, *J. Amer. Chem. Soc.*, **90**, 2980 (1968).
4) D. Hauser, H. P. Weber, and H. P. Sigg, *Helv. Chim. Acta*, **53**, 1061 (1970); F. A. Anet and J. M. Muchowski, *Chem. Ind.*, **1963**, 81.
5) P. W. Trown, *Biochem. Biophys. Res. Commun.*, **33**, 402 (1968).
6) H. Poisel and U. Schmidt, *Chem. Ber.*, **104**, 1714 (1971).
7) S. G. Svokos and R. B. Angier., Ger. 2029305 (1971).
8) P. J. Fodor, V. E. Price, and J. P. Greenstein, *J. Biol. Chem.*, **180**, 193 (1949).
9) J. Kapthammer and A. Matthes, *Z. Physiol.*, **223**, 43 (1934).
10) E. J. Corey, R. J. McCaully, and H. S. Sachdey, *J. Amer. Chem. Soc.*, **92**, 2476 (1970).



(11)



(14) R=CH_3, R_1=R_2=SCH_3
(15) R=H, R_1=R_2=CH_3
(16) R=H, R_1=CH_3, R_2=$CH_2CH(CH_3)_2$



(12a—d) R=C_6H_5
(13) R=H

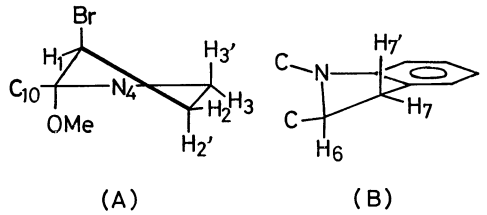
On the other hand, simple halogenation of 3,6-dibenzylidene-1,4-dimethyl-2,5-piperazinedione[11] or **3** with sulfur dichloride in the presence of zinc chloride or chlorine gave 3,6-bis(α-chlorobenzyl)- (**12**) and 3,6-bis(chloromethyl)-3,6-dichloro-1,4-dimethyl-2,5-piperazinedione (**13**), respectively. Although each compound from **2** to **10** consisted of only one isomer, four isomers (**12a—d**) among the theoretically possible four *racemic* and two *meso* forms were separated by fractional crystallization in the former case, but, not the approximate 1 to 1 mixture of *racemic* and *meso* isomers in the latter.

Table 1. Proton chemical shifts in isomeric 2,5-piperazinediones

Compounds	Chemical shift (δ) of main protons			
	N–Me or N–H	C–Me	C–H	S–Me
14 *meso*	2.06	—	4.86	3.10
racemic	2.38	—	4.60	3.09
15 *meso*	7.72	1.22	4.00	—
(D, D)	7.92	1.25	3.98	—
16 *meso*	7.83	1.21	4.13	—
(L, L)	7.93	1.27	4.07	—
1b *meso*	2.94	1.52	3.95	—
1a *racemic*	2.94	1.49	3.89	—
12a	1.53, 2.65	—	5.83, 6.47	—
b	3.29	—	5.61	—
c	2.35, 3.58	—	5.67, 5.82	—
d	3.39	—	5.74	—

Meso and *racemic* 3,6-disubstituted-2,5-piperazinediones were deduced by X-ray analysis[12] to have planar and skewed boat conformations, respectively. They do not seem to be distinguishable by NMR technique, but a comparison of NMR data of both isomers of 1,4-dimethyl-3,6-bis(methylthio)- (**14**),[6] 3,6-dimethyl- (**15**),[13] and 6-methyl-3-isobutyl-2,5-piperazinedione (**16**)[13] indicates that the chemical shift fo 3,6-hydrogens of *meso* form is usually greater (in δ) than that of the *racemic* or optically active form (Table 1). This was utilized to deduce the configuration of **1a** and **1b**, though such similarity is not observed in the C-methyl groups.

11) M. O. Forster and W. B. Saville, *J. Chem. Soc.*, **121**, 816 (1922).
12) E. Sletten, *J. Amer. Chem. Soc.*, **92**, 172 (1970).
13) A. Chemizard and S. David, *Bull. Soc. Chim. Fr.*, **1966**, 184.



(A) (B)

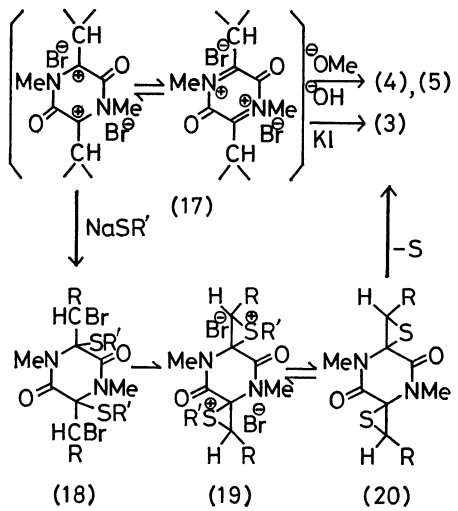
Fig. 1. Conformation of the five-membered rings in **6** and **7** (A), and in **9** and **10** (B).

NMR data of **12a—d** indicate that they are certainly isomers to each other, although their configurations could not be determined.

On the other hand, coupling constants of protons in the five-membered ring of **7** and **9** ascertained by simulation indicated that they exist in twist and flattened envelope conformation, as shown in Fig. 1(A) and (B), respectively. Conformation (A) suggests that **7** is the *meso* isomer with planar 2,5-piperazinedione skeleton. The five-membered ring in *N*-acyl-indoline derivatives exists in a planar conformation,[14] but conformation (B) in **9** might be attributed to the condensed planar benzene ring.

The fact that tetrabromides (**2** and **6**) were obtained by simple substitution with bromine and that the former was also produced by addition reaction indicates that the substitution of 3,6-dialkyl-2,5-piperazinediones with bromine is usually followed by elimination of hydrogen bromide and re-addition of bromine, even though bromine was used in a smaller amount than stoichiometric. Exceptional formation of the elimination product **11** from **10** would be attributed to the resonance stabilization of the indole moiety. In all successful syntheses of 3,6-epidithio-2,5-piperazinediones *via* the corresponding 3,6-dibromo derivatives,[5-7] the bromides included only 3,6-substituents having no hydrogen at α-position such as the phenyl group. Easy elimination of hydrogen bromide would be due to the polarized structure of 3,6-dibromo derivatives (**17**) stabilized by mesomeric resonance of immonium and carbonium ions[6] (Fig. 2).

The fact that attempted substitution of **2** with sulfur-containing nucleophiles gave sulfur and **3** would be



(18) (19) (20)

Fig. 2. Possible passways in substitution of **2**.

due to the character of sulfur atom and the presence of the vicinal bromine atom. Compounds (**18**) once substituted would easily shift to the spiro-type thiiranium ions (**19**). It is well-known that the sulfonium halides frequently decompose to thioether and other products depending on the conditions,[14] especially smoothly in alcohols,[15] and that ethylenesulfides having aromatic substituents such as diphenylene-dichloroethylenesulfide turned to the corresponding olefin and sulfur, even under cooling.[16] Thus, it could be concluded that **19** was smoothly transformed into **3** through the corresponding spiro-sulfide (**20**) with liberation of sulfur (Fig. 2).

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 discs with a Hitachi EPI-G2 spectrometer. The NMR spectra were obtained at 100 MHz with a JNM-4H-100 spectrometer in deuteriochloroform unless otherwise stated, using TMS as an internal reference. Chemical shifts and coupling constants were recorded in δ and Hz units, and frequencies in cm^{-1}.

*1,3,4,6-Tetramethyl-2,5-piperazinedione (**1a** and **1b**).* A suspension of *N*-methylalanine (10 g, 59 mmol) in ethyleneglycol (10 g) was heated at 180—190 °C for 6 hr on an oil bath, poured into water (100 ml) and extracted with three portions of chloroform (100 ml). The combined extracts were dried over sodium sulfate and evaporated to give a sirup, which was fractionated on a silica gel column (WAKO-GEL C-200) by elution with chloroform–ligroin (3:1) to give **1a** (2.2 g, 44%) and **1b** (1.2 g, 24%) which were recrystallized from ether. Mp **1a**: 121—123 °C, **1b**: 135—136 °C. IR: **1a**: 1640 (NC=O), **1b**: 1630 (NC=O).

Found: C, 56.47; H, 8.24; N, 15.93%. Calcd for $C_8H_{14}N_2O_2$: C, 56.45; H, 8.29; N, 16.46%.

*3,6-Dibromo-3,6-bis(bromomethyl)-1,4-dimethyl-2,5-piperazinedione (**2**).* Bromine (0.7 ml, 13.3 mmol) was added to a solution of **1a** (1 g, 5.9 mmol) in dried benzene (50 ml) and kept at room temperature for 24 hr to give a yellow precipitate, which was filtered and washed with dried benzene. The precipitate was deduced to be a HBr_3 adduct of **1a** from analytical data (Found: C, 23.38; H, 3.80; N, 6.87; Br, 57.81%. Calcd for $C_8H_{15}N_2O_2Br_3$: C, 23.38; H, 3.68; N, 6.82; Br, 58.34%) and from the fact that treatment of the adduct with saturated sodium bicarbonate and sodium sulfite followed by extraction with chloroform gave **1a** in 66% recovery. Evaporation of the filtrate from the adduct gave a white precipitate of **2** (500 mg, 18%) which was washed with ethanol and recrystallized from chloroform. Mp 185—188 °C (decomp.); NMR: 3.22 ($N-CH_3$), 4.03 and 4.74 (CH_2: ABq, J=11.0). IR: 1700 (C=O).

Found: C, 19.97; H, 2.15; N, 5.80; Br, 65.62%. Calcd for $C_8H_{10}N_2O_2Br_4$: C, 19.78; H, 2.07; N, 5.77; Br, 65.77%.

*1,4-Dimethyl-3,6-dimethylene-2,5-piperazinedione (**3**).* A suspension of **2** (1 g, 2.1 mmol) and sodium iodide (2 g, 13 mmol) in ethanol (20 ml) was stirred at room temperature for 1 day and then evaporated. The residue was treated with chloroform (50 ml) and aqueous sulfite. The chloroform layer was washed with water and evaporated to give white needles which were recrystallized from ethanol. Yield, 320 mg (90%). Mp 230 °C (decomp.). NMR: 3.31 (N–Me), 4.98 and 5.87 (CH_2; ABq, J_{gem}=2.0). IR: 1600 (C=C), 1670 (NC=O).

Found: C, 58.23; H, 6.08; N, 17.09%. Calcd for $C_8H_{10}N_2O_2$: C, 57.82; H, 6.07; N, 16.86%.

*3,6-Bis(bromomethyl)-3,6-dihydroxy-1,4-dimethyl-2,5-piperazinedione (**4**).* A suspension of **2** (1 g, 2.1 mmol) in 50 ml of 50% ethanol was stirred at 70 °C for 2 days and then evaporated. The residue was triturated and recrystallized from methanol to give white crystals. Yield, 230 mg (35%); Mp 230 °C (decomp.); NMR (CF_3COOH): 3.15 (N–Me), 3.68 and 3.88 (CH_2; ABq, J_{gem}=11.5). IR: 1640 (NC=O), 3260 (OH).

Found: C, 26.61; H, 3.30; N, 7.68; Br, 43.95%. Calcd for $C_8H_{12}N_2O_4Br_2$: C, 26.68; H, 3.36; N, 7.78; Br, 44.40%.

*3,6-Bis(bromomethyl)-3,6-dimethoxy-1,4-dimethyl-2,5-piperazinedione (**5**).* A suspension of **2** (1 g, 2.1 mmol) and sodium acetate (1 g, 12 mmol) in methanol (50 ml) was stirred at room temperature for 10 hr and then evaporated. The residue was extracted with chloroform. Evaporation of the extracts gave crystals (700 mg, 86%) which were recrystallized from chloroform–ligroin. Mp 165 °C (decomp.); NMR: 3.00 (OMe), 3.20 (NMe), 3.52 and 4.10 (CH_2: ABq, J_{gem}=11.3). IR: 1670 (NC=O).

Found: C, 31.40; 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%.

*1,5a,6,10a-Tetrabromo-octahydro-5H,10H-dipyrrolo[1,2-a: 1',2'-d]pyrazine-5,10-dione (**6**).* Bromine (0.7 ml, 13.3 mmol) was added to a dried benzene (50 ml) solution of L-proline anhydride (1 g, 5.1 mmol) and allowed to stand at room temperature for 1 day. Yellow precipitates which appeared were treated with saturated sodium bicarbonate and sodium sulfite to give insoluble white powder. A second crop was obtained from the first filtrate by evaporation and washing the residue with ethanol (5 ml). Total yield, 500 mg (19%). Unchanged starting material (700 mg) was recovered from the aqueous filtrate by extraction with chloroform (100 ml). Mp 183—185 °C (decomp.); IR: 1690 (NC=O).

Found: C, 23.18; H, 1.94; N, 5.29%. Calcd for $C_{10}H_{10}N_2O_2Br_4$: C, 23.56; H, 1.98; N, 5.49%.

*1,6-Dibromo-5a,10a-dimethoxy-octahydro-5H,10H-dipyrrolo[1,2-a: 1',2'-d]pyrazine-5,10-dione (**7**).* A solution of **6** (400 mg, 0.78 mmol) and sodium acetate (400 mg, 4.9 mmol) in methanol (50 ml) was refluxed for 8 hr, evaporated, and the residue was extracted with chloroform (50 ml). Evaporation of extracts gave a sirup which was crystallized from ethanol. Yield, 115 mg (36%); mp 267—268 °C; NMR: 2.28 (H_2 and H_7; oct), 2.71 ($H_{2'}$ and $H_{7'}$; nine peaks, $J_{2,2'}=J_{7,7'}=14.4$), 3.35 (OMe; s), 3.61 (H_3 and H_8; oct, $J_{2,3}=J_{7,8}=1.7$, $J_{2',3}=J_{7',8}=9.6$), 4.03 ($H_{3'}$ and $H_{8'}$; oct, $J_{2,3'}=J_{7,8'}=8.0$, $J_{2',3'}=J_{7',8'}=10.0$, $J_{3,3'}=J_{8,8'}=12.5$), 4.62 (H_1 and H_6; d, $J_{1,2'}=J_{6,7'}=4.6$). IR: 1660 (NC=O).

Found: C, 34.97; H, 3.79; N, 7.01; Br, 39.31%. Calcd for $C_{12}H_{16}N_2O_4Br_2$: C, 34.97; H, 3.91; N, 6.79; Br, 38.79%.

*1,6-Dibromo-2,3,7,8-tetrahydro-5H,10H-dipyrrolo[1,2-a: 1',2'-d]pyrazine-5,10-dione (**8**).* A solution of **6** (1 g, 2.1 mmol) and anhydrous sodium acetate (1 g, 12 mmol) in acetic acid (20 ml) was heated at 100 °C for 5 hr with stirring, evaporated, and the resulting residue was extracted with several portions of chloroform (50 ml). The extracts were mixed with ethanol

14) H. J. Emeleus and H. G. Heal, *J. Chem. Soc.*, **1946**, 1126; F. Krollpfeiffer and H. Hartmann, *Chem. Ber.*, **83**, 90 (1950); F. Krollpfeiffer, K. L. Schneider, and A. Wissner, *Ann. Chem.*, **566**, 139 (1950).

15) J. L. Gleave, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.*, **1935**, 236; E. D. Hughes, C. K. Ingold, and G. A. Maw, *ibid.*, **1948**, 2072; H. Böhme and P. Heller, *Chem. Ber.*, **36**, 443, 785 (1953).

16) H. Staudinger and J. Siegwart, *Helv. Chim. Acta*, **3**, 833, 840 (1920).

(10 ml), and concentrated to 5 ml, from which yellow powder was precipitated on standing in a refrigerator. It was recrystallized from ethanol. Yield, 100 mg (27%). It decomposes gradually over 150 °C. NMR: 3.03 and 3.99 (CH_2-CH_2; each t, J=9.0). IR: 1650 (NC=O).

Found: C, 34.00; H, 2.19; N, 8.05; Br, 46.36%. Calcd for $C_{10}H_8N_2O_2Br_2$: C, 34.51; H, 2.32; N, 8.05; Br, 45.92%.

*6,13-Dioxo-6a,7,13a,14-tetrahydro-6*H,*13*H-*pyrazino*[*1,2*-a: *4,5*-a′]*diindole* (**9**). A suspension of ethyl 2-indolinecarboxylate[10] (10 g, 52 mmol) and sodium ethoxide (900 mg, 13 mmol) in dried benzene (70 ml) was refluxed for 24 hr, washed three times with water, and evaporated to give crystals which were recrystallized from benzene–ligroin. Yield, 6.13 g (81%). Mp 263—265 °C. MNR: 3.42 ($H_{7'}$ and $H_{14'}$; q), 3.78 (H_7 and H_{14}; q, $J_{7',7}=J_{14,14'}=17.1$), 4.95 (H_{6a} and H_{13a}; q, $J_{7',6a}=J_{14,13a}=11.0$, $J_{7,6a}=J_{14',13a}=9.2$). IR: 1670 (NC=O).

Found: C, 74.19; H, 4.97; N, 9.70%. Calcd for $C_{18}H_{14}N_2O_2$: C, 74.47; H, 4.86; N, 9.65%.

*2,9-Dibromo-6,13-dioxo-6a,7,13a,14-tetrahydro-6*H,*13*H-*pyrazino*[*1,2*-a: *4,5*-a′]*diindole* (**10**). A suspension of **9** (90 mg, 0.31 mmol) and bromine (1.0 g, 19.5 mmol) in methanol (80 ml) was stirred for 1 hr to give a white powder (120 mg, 79%) which was recrystallized from chloroform–ligroin. Mp 309 °C. NMR: 7.40 (H_1; s), 7.37 (H_3; d), 8.40 (H_4; d, $J_{3,4}=8.5$). Other proton signals are almost the same as for **9**. IR: 1670, 1700 (NC=O).

Found: C, 48.07; H, 2.56; N, 6.26%. Calcd for $C_{18}H_{12}N_2O_2Br_2$: C, 48.24; H, 2.89; N, 6.25%.

*2,9-Dibromo-6,13-dioxo-6*H,*13*H-*pyrazino*[*1,2*-a: *4,5*-a′]*diindole* (**11**). Excess bromine was added to a solution of **10** (300 mg, 1.3 mmol) in chloroform (60 ml) and allowed to stand at room temperature for 1 day to give yellow precipitates (260 mg, 87%). These were recrystallized from a large amount of chloroform to give fine yellow needles. Mp 359 °C (sublime). IR: 1687 (C=O).

Found: C, 48.28; H, 1.56; N, 6.23%. Calcd for $C_{18}H_8N_2O_2Br_2$: C, 48.68; H, 1.82; N, 6.31%.

*3,6-Dichloro-3,6-bis(*α*-chlorobenzyl)-1,4-dimethyl-2,5-piperazinedione* (**12a—d**). A solution of 3,6-dibenzylidene-1,4-dimethyl-2,5-piperazinedione (12 g, 38 mmol), sulfur dichloride (40 ml) and a catalytic amount of zinc chloride in dioxane (40 ml) was allowed to stand at room temperature for 2 days, and then poured into a mixed solution of saturated sodium sulfite and chloroform. The chloroform layer was evaporated, and the residual powder was recrystallized from chloroform–ligroin to give fine crystals (**12**). **12a** (3.46 g, 20%), **12b** and **12c** (6.45 g, 37%) were separated by fractional crystallization from chloroform–ligroin. Mp **12a**; 227 °C (decomp.), **12b**; 203—205 °C (decomp.), **12c**; 186 °C. IR: **12a**; 1675, **12b**; 1670, **12c**; 1680 (NC=O).

Found: **12a**; C, 52.15; H, 3.65; N, 5.95%. **12b**; C, 52.35; H, 3.77; N, 5.77%. **12c**; C, 52.30; H, 3.93; N, 6.09%. Calcd for $C_{20}H_{18}N_2O_2Cl_4$: C, 52.20; H, 3.94; N, 6.08%.

The other isomer (**12d**) was obtained as follows. A solution of 3,6-dibenzylidene-1,4-dimethyl-2,5-piperazinedione (5.0 g, 16 mmol) in sulfur dichloride (50 ml) containing chlorine was treated as above. The white powder (2.1 g) obtained was fractionally recrystallized from chloroform–ligroin to give **12d** (0.6 g, 8%) and **12b** (1.02 g, 14%). Mp **12d**; 183 °C. IR: 1682 (NC=O).

Found: C, 51.94; H, 3.76; N, 6.09%. Calcd for $C_{20}H_{18}N_2O_2Cl_4$: C, 52.20; H, 3.94; N, 6.08%.

3,6-Dichloro-3,6-bis(chloromethyl)-2,5-piperazinedione (**13**). A solution of **3** (100 mg, 0.92 mmol) in chloroform (10 ml) saturated with chlorine was left to stand for 30 min, and then evaporated to give a crude product (175 mg), which was recrystallized from chloroform to give white crystals. Yield, 110 mg (39%). Mp 150—200 °C.

Found: C, 31.63; H, 3.43; N, 9.07%. Calcd for $C_8H_{10}N_2O_2Cl_4$: C, 31.20; H, 3.27; N, 9.10%.

NMR spectrum of this compound showed the two methylene and *N*-methyl signals with intensity ratio of nearly 1 to 1, indicating a mixture of *meso* and *racemic* isomers.

The authors are indebted to the members of the Laboratory of Organic Analysis for the microanalysis and to Mr. H. Matsumoto for NMR measurements.