Notes

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Synthesis of 5,5′-Methylenebispyrimidine Derivatives and 3,4-Dithia[6.1](1.5)pyrimidinophane

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Convenient syntheses of 3,6-dimethyl-1,3-oxazine-2,4(3*H*)-dione (**3**) and 5,5′-methylenebis[1-(2-hydroxyethyl)-3,6-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione] (**5**) are described. Compound **3** was prepared by the reaction of *N*-methylurethane with diketene, followed by alkali treatment, and **5** was obtained by treatment of 1-(2-hydroxyethyl)-3,6-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (**4**) with paraformaldehyde and hydrochloric acid in quantitative yield. Bromination of **5** was carried out with 47% hydrobromic acid to give 5,5′-methylenebis[1-(2-bromoethyl)-3,6-dimethyl-2,4-(1*H*,3*H*)-pyrimidinedione] (**6**). The reaction of **6** with thiourea afforded **7** and subsequent treatment of **7** with sodium hydroxide gave 5,5′-methylenebis[1-(2-mercaptoethyl)-3,6-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione] (**9**). Compound **9** was oxidized to 8,11,15,18-tetramethyl-3,4-dithia[6.1](1.5)-1,2,3,4-tetrahydro-2,4-dioxopyrimidinophane (**10**) with iodine under conditions of high dilution.

Keywords——methylenebispyrimidine; dithiapyrimidinophane; 1,3-oxazine-2,4-dione; ring transformation; diketene; *N*-methylurethane; *N*-acetoacetyl-*N*-methylurethane

Generally, thiol groups have high affinity for heavy metals. For example, polythiol ligands have come to be thought of as relatively selective for cadmium.[1] Actually, a number of metal ions including mercury, zinc, lead, copper and iron bind quite well at such thiol groups.[1]

We were interested in preparing examples of the methylenebispyrimidine system possessing thiol and 2,4-pyrimidinedione moieties as potential complexing agents for metals.

We have already described[2] the synthesis of 3,3′-(1,6-hexanediyl)bis[1-(2-mercaptoethyl)-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione] and 12,22-dimethyl-3,4-dithia[6.6](1.3)-1,2,3,4-tetrahydro-2,4-dioxopyrimidinedione. In this paper, we would like to report the synthesis of 5,5′-methylenebispyrimidinedione (**5**) and 3,4-dithiapyrimidinophane (**10**), the latter being connected at the 1 and 5 positions of two pyrimidine rings through 3,4-dithiahexamethylene and methylene chains, respectively.

Warrener and Cain have reported[3] that the reaction of *N*-methylurethane (**1**) with diketene in acetic acid afforded *N*-acetoacetyl-*N*-methylurethane (**2**) as an oily product, but cyclization to 3,6-dimethyl-1,3-oxazine-2,4(3*H*)-dione (**3**) did not occur on treatment with sulfuric acid. We found that **2** was converted to **3** by treatment with 5% sodium hydrogen carbonate at room temperature. This synthetic method is better than other methods[4] in that the reagents are readily available and economical, and the procedures are easy. Moreover, the overall yield from diketene is almost the same[4a] or better than [4b,c] those of other methods.

The reactivity of **2** was examined with various bases and acids, and the results are summarized in Table I. In the case of alkaline treatment, cyclization and/or decarboxylation reactions were observed. The yield of the cyclization product (**3**) decreased with increasing basicity, whereas the yield of decarboxylation product (**11**) increased. When **2** was treated with triethylamine, no reaction occurred and the starting material was recovered, though **2**

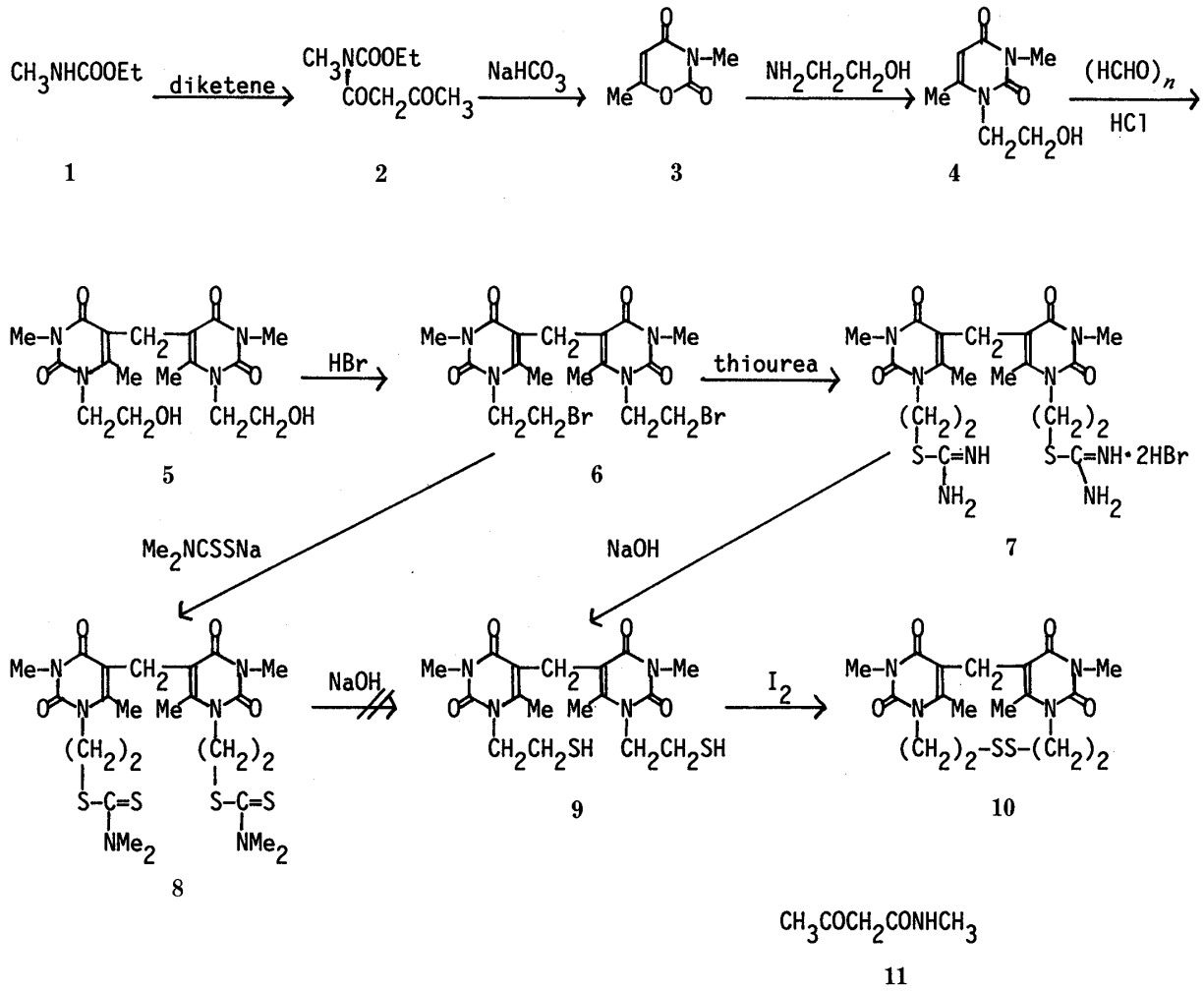

Chart 1

TABLE I. The Treatment of **2** with Bases and Acids

2 g (mmol)	Reagent		Reaction Time (h)	Reaction Temp. (°C)	Reaction products (g)	Ratio of products by NMR[a] **1** (%)	**2** (%)	**3** (%)	**11** (%)	Isolation of **3** g (%)
2.0 (10.7)	5% $NaHCO_3$	8 ml	1	22	1.56	—	10	90	—	1.10 (73.0)
2.0 (10.7)	10% Na_2CO_3	10 ml	1	22	1.15	8	—	79	13	0.85 (56.3)
2.0 (10.7)	5% NaOH	10 ml	1	22	0.88 (oil)	16	—	14	70	
2.0 (10.7)	10% NaOH	10 ml	1	22	0.30 (oil)	37	—	—	63	
1.0 (5.4)	Et_3N	1 ml	1	22	1.0 (oil)	—	100	—	—	
1.0 (5.4)	Et_3N H_2O	1 ml 1 ml	1	22	0.6	—	—	>95	—	0.53 (70.3)
5.0 (26.7)	Ac_2O	10 ml	4	160	3.08	—	100	—	—	
2.0 (10.7)	10% HCl	3 ml	2	22	1.80	—	95	—	—	

a) The ratios were determined by comparing the methyl signals of N-CH_3, $COCH_3$, and CH_2CH_3 as circumstances required.

was converted to **3** in almost the same yield as with 5% sodium hydrogen bicarbonate by the reaction with triethylamine–water. It seems that addition of water accelerates the enolization of the acetoacetyl moiety. On the other hand, hydrolyzed products **1** and **11** were obtained, with no cyclized product **3**, by reaction with 10% sodium hydroxide.

The treatment of **2** with acetic anhydride or 10% hydrochloric acid according to Shaw *et al.*[5] resulted in quantitative recovery of the starting material. Compound **3** was converted to 1-(2-hydroxyethyl)-3,6-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (**4**)[6] in 66.3% yield by reaction with ethanolamine. Direct conversion of **2** to **4** was attempted, but the yield was only 33.4%.

For the preparation of 5,5′-methylenebis[1-(2-hydroxyethyl)-3,6-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione] (**5**), **4** was treated with paraformaldehyde according to Pfleiderer *et al.*,[7] but no reaction occurred and the starting material was recovered almost quantitatively. Then we attempted this reaction in acidic medium using 5% hydrochloric acid, **5** was obtained in almost quantitative yield in a short reaction time.[8] In general, the reaction of pyrimidine derivatives with paraformaldehyde[9] afforded 5-hydroxymethyl derivatives as major products, and methylenebispyrimidines were obtained as by-products. Bromination of **5** was achieved with 47% hydrobromic acid to give 5,5′-methylenebis[1-(2-bromoethyl)-3,6-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione] (**6**) in excellent yield.

Compound **6** was converted to **7** by reaction with thiourea in ethanol solution, and alkaline hydrolysis of **7** afforded 5,5′-methylenebis[3,6-dimethyl-1-(2-mercaptoethyl)-2,4-(1*H*,3*H*)-pyrimidinedione] (**9**). Compound **9** was oxidized to 8,11,15,18-tetramethyl-3,4-dithia[6.1](1.5)-1,2,3,4-tetrahydro-2,4-dioxopyrimidinophane (**10**) with iodine under conditions of high dilution using triethylamine as a base.[10] The structure of **10** was confirmed by the elemental analysis and spectral data.

In order to obtain **9** by another route, **6** reacted with sodium *N*,*N*-dimethyldithiocarbamate in ethanolic solution and the resultant **8** was treated with sodium hydroxide under various conditions according to Kulka,[11] however, **9** could not be obtained.

When **10** was treated with DBPM,[12] no fluorescence was observed, but the addition of sodium borohydride to this mixture caused fluorescence to appear. This observation indicates that compound **10** is a disulfide and **9** is a dithiol, and that they are mutually interconvertible.

Experimental

Melting points reported here are uncorrected. Infrared (IR) spectra were recorded on a JASCO IRA-2 spectrophotometer. Ultraviolet (UV) spectra were recorded in ethanol on a Hitachi 323 spectrophotometer. The nuclear magnetic resonance (NMR) spectra were obtained on Hitachi R-600 (60 MHz, ^{1}H) and JEOL JNM FX-90Q (90 MHz for ^{1}H and 22.5 MHz for ^{13}C) spectrometers. Chemical shifts are reported in ppm (δ) relative to tetramethylsilane as an internal standard. Mass spectra (MS) were recorded on JEOL JMS-01-SG and JMS-DX-303 spectrometers.

3,6-Dimethyl-1,3-oxazine-2,4(3*H*)-dione (3)——A solution of *N*-methylurethane (**1**) (51.5 g, 0.5 mol), and diketene (42 g, 0.5 mol) in 150 ml of acetic acid was heated at 90—95 °C. After 1 h, further diketene (42 g, 0.5 mol) was added to this mixture and heating was continued for 3 h. The reaction mixture was concentrated *in vacuo*. The residue was neutralized with 5% aq. $NaHCO_3$ and extracted with $CHCl_3$. The extract was dried over $MgSO_4$ and the solvent was evaporated off. The oily residue was distilled under reduced pressure, giving 76.3 g (81.7%) of **2** as a colorless liquid, $bp_{0.3}$ 93—94 °C (lit.,[4] $bp_{0.35}$ 96 °C). IR (neat): 1730, 1700 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.24 (2H, q, CH_2CH_3), 4.02 (2H, s, CH_2), 3.22 (3H, s, NCH_3), 2.25 (3H, s, $COCH_3$), 1.32 (3H, t, CH_2CH_3). MS *m/z*: 187 (M^+), 145 ($M-C_2H_2O$), 103 ($M-C_4H_4O_2$), 85 ($COCH_2COCH_3$), 43 ($COCH_3$).

A mixture of **2** (2.0 g, 10.7 mmol) and 8 ml of 5% aq. $NaHCO_3$ was stirred at 22 °C for 1 h. After 30 min, white crystals separated, then the mixture was extracted with $CHCl_3$, dried over $MgSO_4$ and concentrated to dryness. The residue was recrystallized from acetone giving 1.1 g (73.0%) of **3** as colorless prisms, mp 105—106 °C (lit.[4] 108—109 °C). IR (KBr): 1752, 1680 (br) (C=O) cm^{-1}. UV $\lambda_{max}^{ethanol}$ nm (log ε): 232 (3.88).

1-(2-Hydroxyethyl)-3,6-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (4)[6]——a) A mixture of **3** (78.7 g, 0.56 mol) and ethanolamine (36.7 g, 0.6 mol) was heated at 95 °C for 1.5 h. The solidified reaction mixture was recrystallized from $CHCl_3$, giving 67.3 g (66.3%) of colorless prisms, mp 136—137 °C. IR (KBr): 3410 (OH), 1680, 1653 (C=O) cm^{-1}.

TABLE II. ^{1}H-NMR Data for Compounds **3**—**10** (90 MHz in $CDCl_3$, J=Hz)

Compd. No.	Ring	N(1)–CH_2	R–CH_2	N–CH_3	C–CH_3	CH_2	Other
3	5.77, 1H, q, J=0.88			3.32, 3H, s	2.20, 3H, d, J=0.88		
4	5.57, 1H, q, J=0.88	4.1—3.8, 4H, m, br		3.30, 3H, s	2.32, 3H, d, J=0.88		2.4, 1H, br, OH
5[a]		3.92, 4H, t, J=5	3.63, 4H, m	3.19, 6H, s	2.37, 6H, s	3.55, 2H, s	4.90, 1H, t, J=5, OH
6		4.27, 4H, t, J=6.9	3.57, 4H, t, J=6.9	3.29, 6H, s	2.57, 6H, s	3.53, 2H, s	
7[b]		4.32, 4H, dd, J=6.2, J=5.3	3.47, 4H, dd, J=6.2, J=5.3	3.28, 6H, s	2.51, 6H, s	3.65, 2H, s	
8		4.17, 4H, dd, J=6.2, J=4.8	3.53, 4H, dd, J=6.2, J=4.8	3.31, 6H, s	2.62, 6H, s	3.57, 2H, s	3.57 and 3.40, 12H, s, NCH_3
9		4.05, 4H, dd, J=7.3, J=5.8	2.79, 4H, m	3.29, 6H, s	2.56, 6H, s	3.51, 2H, s	1.48, 2H, t, J=9.2, SH
10[c]		3.8—2.6, 8H, m		3.47, 6H, s	2.22, 6H, s	3.35, 2H, s	

a) Recorded on a Hitachi R-600 (60 MHz) spectrometer in DMSO-d_6 solution. *b*) D_2O solution (sodium 3-(trimethylsilyl)propanesulfonate as an internal standard). *c*) Pyridine-d_6 solution.

UV $\lambda_{max}^{ethanol}$ nm (log ε): 268 (4.02). ^{13}C-NMR ($CDCl_3$) δ: 162.70 (s, C=O(2)), 152.73 (s, C=O(4)), 152.51 (s, C(6)), 101.15 (d, C(5)), 60.36 (t, OCH_2), 47.52 (t, NCH_2), 27.79 (q, NCH_3), 20.59 (q, CCH_3).

b) A mixture of **2** (1 g, 5.4 mmol), ethanolamine (0.6 g, 9.8 mmol) and 5 ml of EtOH was refluxed for 2.5 h. The reaction mixture was concentrated *in vacuo*, and the residue was duiluted with water. The solution was acidified with 10% HCl and extracted with $CHCl_3$. The extract was dried over $MgSO_4$ and evaporated to dryness (0.6 g). The residue was recrystallized from $CHCl_3$, giving 0.3 g (33.4%) of colorless prisms, mp 136—137 °C.

5,5′-Methylenebis[(2-hydroxyethyl)-3,6-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione][8] **(5)**——A mixture of **4** (15 g, 81.5 mmol) and paraformaldehyde (4.95 g, 163 mmol) in 0.5 N hydrochloric acid (50 ml) was heated at 140 °C for 2 h. The separated crystalline mass was collected and recrystallized from water, giving 15.0 g (97.5%) of colorless needles, mp 280 °C. *Anal.* Calcd for $C_{17}H_{24}N_4O_6$: C, 53.68; H, 6.36; N, 14.72. Found: C, 53.39; H, 6.40; N, 14.96. IR (KBr): 3300 (OH), 1688 (C=O) cm^{-1}. UV $\lambda_{max}^{ethanol}$ nm (log ε): 278 (4.30).

5,5′-Methylenebis[1-(2-bromoethyl)-3,6-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione] (6)——A mixture of **5** (0.7 g, 1.8 mmol) and 47% HBr (7 ml) was heated at 160 °C for 6 h. The reaction mixture was concentrated *in vacuo* and the residue was diluted with water. The mixture was concentrated *in vacuo*. The residue was extracted with $CHCl_3$, dried over Na_2SO_4 and concentrated to dryness. The residue was recrystallized from $CHCl_3$ giving 0.75 g (82.3%) of colorless needles, mp 240—242 °C. *Anal.* Calcd for $C_{17}H_{22}Br_2N_4O_4$: C, 40.34; H, 4.38; Br, 31.57; N, 11.07. Found: C, 40.65; H, 4.42; Br, 31.46; N, 11.24. IR (KBr): 1683, 1640 (br) (C=O) cm^{-1}. UV $\lambda_{max}^{ethanol}$ nm (log ε): 295 (4.27). ^{13}C-NMR ($CDCl_3$) δ: 162.81 (s, C=O(2)), 151.38 (s, C=O(4)), 148.83 (s, C(6)), 109.39 (s, C(5)), 46.54 (t, CH_2Br), 28.07 (q, NCH_3), 27.85 (t, NCH_2), 25.19 (t, CCH_2), 17.28 (q, CCH_3).

5,5′-Methylenebis[1-(2-carbamimidoylthioethyl)-3,6-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione] (7)——A mixture of **6** (2.0 g, 4.0 mmol) and thiourea (1.2 g, 8 mmol) in 20 ml of a mixture of $CHCl_3$–EtOH (1 : 1.5) was refluxed for 3 h. The separated crystals were collected and recrystallized from MeOH, giving 1.9 g (72.0%) of colorless powder, mp 287—289 °C. *Anal.* Calcd for $C_{19}H_{28}N_8O_4S_2 \cdot 2HBr$: C, 34.66; H, 4.59; N, 17.02; S, 9.74. Found: C, 34.54; H, 4.52; N, 16.73; S, 9.44. IR (KBr): 3380 (br), 3160 (br) (NH^+), 1678, 1625 (br) (C=O) cm^{-1}. UV $\lambda_{max}^{ethanol}$ nm (log ε): 275 (4.29). MS m/z: 412 ($M-2HBr-C_2H_4N_4$).

5,5′-Methylenebis[3,6-dimethyl-1-(*N*,*N*-dimethylaminothiocarbonylthioethyl)-2,4(1*H*,3*H*)-pyrimidinedione] (8)——A solution of sodium *N*,*N*-dimethyldithiocarbamate (1.8 g, 12 mmol) in 20 ml of MeOH was added to a solution of **6** (3.0 g, 6 mmol) in 15 ml of $CHCl_3$. The mixture was refluxed for 2 h and then evaporated to dryness. Water was added to the residue and the whole was extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and evaporated to dryness. The residue was recrystallized from a mixture of $CHCl_3$–EtOH, giving 3.35 g (95%) of colorless powder, mp 273—274 °C. *Anal.* Calcd for $C_{23}H_{34}N_6O_4S_4$: C, 47.08; H, 5.84; N, 14.32; S, 21.85. Found: C, 46.81; H, 5.89; N, 14.14; S, 21.64. IR (KBr): 1685, 1623 (br) (C=O) cm^{-1}. UV $\lambda_{max}^{ethanol}$ nm (log ε): 252 (4.36), 277 (4.61).

5,5′-Methylenebis[1-(2-mercaptoethyl)-3,6-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione] (9)——A mixture of **7** (4.0 g,

6.1 mmol) and NaOH (1.6 g, 40.0 mmol) in 120 ml of water was heated at 95 °C for 3 h under a nitrogen atmosphere. After cooling, the mixture was acidified with acetic acid and extracted with $CHCl_3$. The extract was dried over $MgSO_4$ and evaporated to dryness. The residue was purified by silica gel column chromatography, then recrystallized from $CHCl_3$–EtOH, giving 1.2 g (48.0%) of colorless powder, mp 226—228 °C. *Anal.* Calcd for $C_{17}H_{24}N_4O_4S_2 \cdot 1/4H_2O$: C, 48.96; H, 5.92; N, 13.44; S, 15.38. Found: C, 48.87; H, 5.87; N, 13.14; S, 15.55. IR (KBr): 1682, 1628 (br) (C=O) cm^{-1}. UV $\lambda_{max}^{ethanol}$ nm (log ε): 276 (4.16). ^{13}C-NMR ($CDCl_3$) δ: 162.86 (s, C=O(2)), 151.49 (s, C=O(4)), 148.99 (s, C(6)), 109.12 (s, C(5)), 48.33 (t, CH_2SH), 28.09 (q, NCH_3), 25.19 (t, NCH_2), 22.54 (t, CH_2), 17.23 (q, CCH_3). MS *m/z*: 412 (M^+).

8,11,15,18-Tetramethyl-3,4-dithia[6.1](1.5)1,2,3,4-tetrahydro-2,4-dioxopyrimidinophane (10)——A solution of iodine (0.25 g, 0.97 mmol) in $CHCl_3$ (20 ml) was added dropwise to a solution of **9** (0.4 g, 0.97 mmol) and triethylamine (0.2 g, 2.0 mmol) in $CHCl_3$ (500 ml) at room temperature, and the mixture was allowed to stand at the same temperature overnight, then concentrated to dryness *in vacuo*. The residue was acidified with 10% HCl and extracted with $CHCl_3$. The extract was dried over $MgSO_4$ and concentrated to dryness. The residue was recrystallized from MeCN, giving 0.32 g (80.5%) of colorless powder, mp 330—332 °C. *Anal.* Calcd for $C_{17}H_{22}N_4O_4S_2$: C, 49.74; H, 5.40; N, 13.65; S, 15.62. Found: C, 49.47; H, 5.35; N, 13.37; S, 15.49. MS *m/z*: 410 (M^+).

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