

Toshio Kinoshita*, Shirou Odawara, Keiko Fukumura and Sunao Furukawa

Faculty of Pharmaceutical Sciences, Nagasaki University,
1-14 Bunkyo-machi, Nagasaki 852, Japan

Received April 10, 1985

Several 3,3'-(1,6-hexanediyl)bis[6-methyl-2,4(1*H*,3*H*)-pyrimidinedione] derivatives (**4a**, **4b**, and **4c**) were synthesized from 1,6-(hexanediyl)bis[6-methyl-2*H*-1,3-oxazine-2,4(3*H*)-dione] (**3**). Compound **4c** was converted to **6**, which reacted with thiourea giving thiuronium salt **7**. 3,3'-(1,6-Hexanediyl)bis[1-(2-mercaptoethyl)-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione] (**9**) was obtained by the hydrolysis of **7**, and then **9** was oxidized to 12,22-dimethyl-3,4-dithia[6.6](1.3)-1,2,3,4-tetrahydro-2,4-dioxypyrimidinophane (**10**).

J. Heterocyclic Chem., **22**, 1573 (1985).

Generally, thiol groups have good affinity to 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 hexanediyl bis-pyrimidine system possessing thiol and 2,4-pyrimidinedione moiety as potential formation of metal complex among metal, thiol and carbonyl groups.

In this paper, we would like to report the synthesis of dithiol compound **9** and its oxidizing compound **10** (dithiaprimidinophane). A spot test of **9** with heavy metal ions were carried out, then precipitation was deposited. Probably, the precipitation is complex of the metal and **9**, but the structure is uncertain. Further work is in progress on the structural study of the complex and analytical application of **9**.

The starting material, 3,3'-(1,6-hexanediyl)bis[6-methyl-

Chart 1

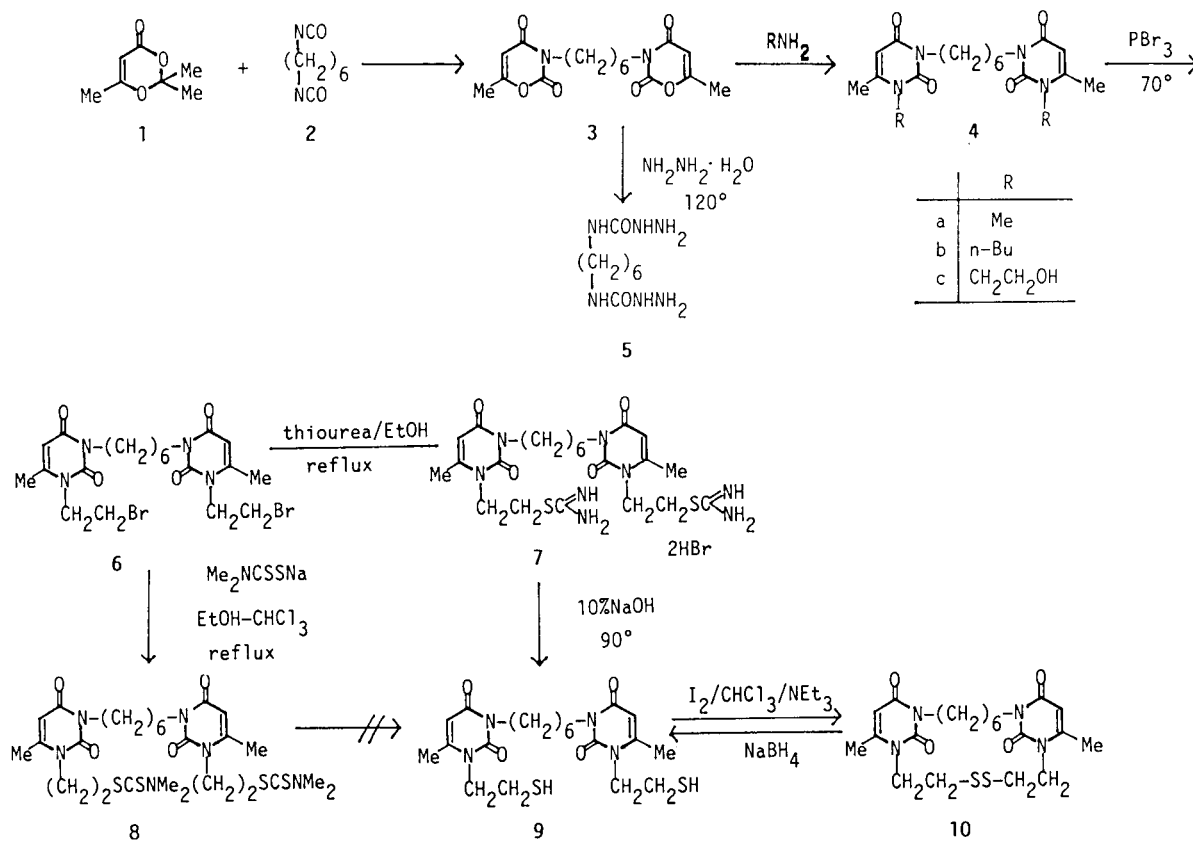


Table I
¹H-NMR Spectra of **3**, **4**, **6**, **8**, **9**, and **10** in Deuteriochloroform (60 MHz)

Compound No.	ring	N1-CH ₂	R-CH ₂	N3-CH ₂	C-CH ₃	CH ₂ × 4	Other
3	5.72, 2H, d, J = 1			3.85, 4H, t, J = 8	2.18, 6H, d, J = 1	1.8-1.2, 8H, m	
4a	5.60, 2H, s			3.94, 4H, t, J = 6.6	2.22, 6H, s	1.9-1.1, 8H, m	3.40, 6H, s, N1-CH ₃
4b	5.52, 2H, s	4.2-3.5, 8H, m			2.20, 6H, s	1.8-1.2, 16H, m	0.95, 6H, t, J = 6, CH ₂ CH ₃
4c	5.59, 2H, s		4.0-3.5, 12H (4H × 3), m		2.30, 6H, s	1.7-1.2, 8H, m	4.91, 2H, t, J = 6, OH
6 [a]	5.59, 2H, q, J = 0.88	4.17, 4H, t, J = 7.0	3.62, 4H, t, J = 7.0	3.89, 4H, t, J = 7.5	2.30, 6H, d, J = 0.88	1.7-1.2, 8H, m	
8 [a]	5.55, 2H, q, J = 0.88		4.2-3.8, 8H, m and 3.7-3.4, 4H, m (4H × 3)		2.38, 6H, d, J = 0.88	1.7-1.2, 8H, m	3.56, 3.39, 3H × 2 s, N-CH ₂
9	5.57, 2H, q, J = 0.9		4.2-3.7, 8H, m and 3.2-2.6, 4H, m, (4H × 3)		2.28, 6H, d, J = 0.9	1.8-1.2, 8H, m	
10 [a]	5.57, 2H, q, J = 0.88	4.15, 4H, dd, J = 6.8, J = 7.9	3.09, 4H, dd, J = 6.8 J = 7.9	3.92, 4H, t, J = 7.0	2.25, 6H, d, J = 0.88	1.7-1.2, 8H, m	

[a] Recorded on a JEOL Model JNM FX-90Q spectrometer.

2*H*-1,3-oxazine-2,4(3*H*)-dione] (**3**), was prepared by the reaction of 2,2,6-trimethyl-1,3-dioxine (**1**) with hexamethylene diisocyanate (**2**) in 51% yield, modified Jager and Wenzelburger's method [2]. In order to examine the reactivity of compound **3** it was treated with various amines. Corresponding pyrimidine derivatives (**4a**, **4b**, and **4c**) were obtained by the reaction with methylamine, *n*-butylamine, and ethanolamine in 17, 30, 47% yields, respectively. However, starting material was recovered by the treatment of iso-, sec-, *t*-butylamine, aniline, and phenylhydrazine. When **3** was heated with hydrazine hydrate, ring opening compound **5** was obtained, this compound was confirmed by an elemental analysis and spectral data. Similar alkali degradation have been reported by Takemoto *et al.* in case of uracil derivatives [3]. From above results, polymethylene bis-oxazinone is less reactive than monoxazine derivatives [4].

Bromination of 3,3'-(1,6-hexanedyl)bis[1-(2-hydroxyethyl)-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione] (**4c**) was carried out with phosphorous tribromide giving bromo-compound **6** in 83% yield. However 47% hydrobromic acid was used as brominating reagent, the yield of **6** only 25%. This bromo compound was treated with thiourea in ethanolic solution in general method for the preparation of thiuronium bromide (**7**), followed by hydrolysis to 3,3'-(1,6-hexanedyl)bis[1-(2-mercaptoethyl)-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione] (**9**) in a nitrogen atmosphere. For the preparation of **9** by another route, **6** reacted with sodium *N,N*-dimethyldithiocarbamate to give **8**, subsequently hydroly-

sis was attempted, however **8** was not hydrolyzed to **9** with various concentration of sodium hydroxide aqueous solution and hydrazine hydrate according to Kulka [5].

There are many methods for the oxidation of thiol to disulfide group [6] in this case iodine was used as an oxidizer and triethylamine was added to preserve basic medium of the solution [7]. In order to prevent intermolecular reaction, **9** was oxidized using high dilution conditions (3.25 mmoles). The resultant mixture was purified by silicagel column chromatography, 35% of 12,22-dimethyl-3,4-dithia[6.6](1.3)1,2,3,4-tetrahydro-2,4-dioxypyrimidinophane (**10**) was obtained. The structure of **10** was confirmed by an elemental analysis, ¹H and ¹³C nuclear magnetic resonance spectra (Table I), and mass spectrometry which showed molecular ion peak at *m/z* 452 [8]. Compound **10** was treated with DBPM [9] no fluorescence was observed, however, fluoresced by addition of sodium borohydride to this mixture. This observation indicates that compound **10** is disulfide and **9** is dithiol and these compounds are interconvertible.

EXPERIMENTAL

Melting points reported are uncorrected. Infrared spectra were recorded on a JASCO Model IRA-2 spectrophotometer. Ultraviolet spectra were recorded in ethanol on a Hitachi Model 323 spectrophotometer. The nmr spectra were obtained on a Hitachi Model R-600 (60 MHz, ¹H) and a JEOL Model JNM FX-90Q (90 MHz for ¹H and 22.5 MHz for ¹³C) spectrometer. Chemical shifts are reported in ppm (δ) relative to tetramethylsilane as internal standard. Mass spectra were recorded on JEOL Model JMS-01-SG and JMS-DX-303 spectrometer.

3,3'-(1,6-Hexanediy)bis[6-methyl-2*H*-1,3-oxazine-2,4(3*H*)-dione] (**3**).

A mixture of 2,2,6-trimethyl-1,3-dioxin-4-one (**1**) (19.4 g, 136 mmoles) and hexamethylene diisocyanate (**2**) (10.0 g, 60 mmoles) was heated at 160° for 1 hour. The resulting crystalline mass was recrystallized from chloroform-ethanol giving 10.3 g (51%) of colorless needles, mp 154-155°; ir (potassium bromide): 1760, 1710 (shoulder), 1687, 1655 (C=O) cm⁻¹; uv (ethanol): λ max (log ε), 231 (4.59), 276 (3.64).

Anal. Calcd. for C₁₆H₂₀N₂O₆: C, 57.14; H, 6.00; N, 8.33. Found: C, 57.20; H, 6.19; N, 8.18.

3,3'-(1,6-Hexanediy)bis[1,6-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione] (**4a**).

Methylamine (40% aqueous solution, 2.79 ml, 36 mmoles) was added to a solution of **3** (2.02 g, 6 mmoles) in 40 ml of chloroform by dropwise then the mixture was refluxed for 8 hours. After evaporation of solvent, the residue was purified by silicagel column chromatography. The resultant powder was recrystallized from ethyl acetate giving 0.37 g (17%) of colorless powder, mp 140-142°; ir (potassium bromide): 1688, 1653 (C=O) cm⁻¹; uv (ethanol): λ max (log ε), 268 (4.26); ms: 362 (M⁺).

Anal. Calcd. for C₁₈H₂₆N₄O₄: C, 59.65; H, 7.23; N, 15.46. Found: C, 59.61; H, 7.36; N, 15.37.

3,3'-(1,6-Hexanediy)bis[1-*n*-butyl-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione] (**4b**).

A mixture of **3** (1.0 g, 3 mmoles) and *n*-butylamine (3.8 g, 50 mmoles) was heated at 100° for 5.5 hours. The separated crystals were collected and recrystallized from ethyl acetate giving 0.4 g (30%) of colorless needles, mp 157-158°; ir (potassium bromide): 1688, 1656, 1644 (C=O) cm⁻¹; uv (ethanol): λ max (log ε), 269 (4.30).

Anal. Calcd. for C₂₄H₃₈N₄O₄: C, 64.55; H, 8.58; N, 12.55. Found: C, 64.41; H, 8.72; N, 12.41.

3,3'-(1,6-Hexanediy)bis[1-(2-hydroxyethyl)-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione] (**4c**).

A mixture of **3** (6.0 g, 18 mmoles) and ethanolamine (4.0 g, 66 mmoles) was heated at 130° for 3 hours. The reaction mixture was suspended in water, insoluble crystalline mass was collected and recrystallized from chloroform-methanol giving 3.6 g (47%) of pale yellow needles, mp 207-208°; ir (potassium bromide): 3400 (OH), 1647 (broad) (C=O) cm⁻¹; uv (ethanol) λ max (log ε), 268 (4.42).

Anal. Calcd. for C₂₂H₃₀N₄O₆: C, 56.86; H, 7.16; N, 13.26. Found: C, 56.61; H, 7.38; N, 13.33.

1,6-Hexanediy-bis(4-semicarbazide) (**5**).

A mixture of **3** (0.5 g, 1.5 mmoles) and hydrazine hydrate (0.3 g, 6 mmoles) was heated at 120° for 3 hours. The reaction mixture was diluted with water and the mixture was concentrated *in vacuo* to dryness. The residue was recrystallized from methanol giving 0.16 g (46%) of colorless needles, mp 162-164°; ¹H nmr (DMSO-*d*₆): δ 6.81 (2H, s, CONHNH₂, deuterium oxide exchangeable), 6.26 (2H, t, J = 6, CH₂NHCO, deuterium oxide exchangeable), 4.01 (4H, s, CONHNH₂, deuterium oxide exchangeable), 3.02 (4H, q, J = 6, NHCH₂), 1.28 (8H, broad singlet, CH₂ × 4); ms: 232 (M⁺, 16), 201 (M-31, 60), 143 (M-89, 86), 32 (100).

Anal. Calcd. for C₈H₂₀N₆O₂: C, 41.37; H, 8.67; N, 36.18. Found: C, 41.48; H, 8.66; N, 35.82.

3,3'-(1,6-Hexanediy)bis[1-(2-bromoethyl)-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione] (**6**).

a) A solution of **4c** (0.85 g, 2.0 mmoles) and 47% hydrobromic acid (10 ml) was heated at 150° for 8.5 hours. After reaction, excess hydrobromic acid was removed *in vacuo*, the residue was diluted with water, crystals were separated, the mixture was neutralized with 5% aqueous sodium bicarbonate. The separated crystals were collected and recrystallized from acetone 0.3 g (25%) of colorless prisms, mp 211-212°; ir (potassium bromide): 1683, 1645 (C=O) cm⁻¹; uv (ethanol): λ max (log ε), 266 (4.25); ¹³C-nmr (deuteriochloroform): δ 161.9 (s), 151.8 (s), 150.6 (s), 102.3 (d), 46.3 (t), 41.2 (t), 28.2 (t), 27.4 (t), 26.6 (t), 20.3 (q); ms: 550 (6), 548 (11.5), 546 (5.5) (M⁺).

Anal. Calcd. for C₂₀H₂₈Br₂N₄O₄·½H₂O: C, 43.38; H, 5.22; N, 10.12.

Found: C, 43.26; H, 5.24; N, 9.88.

b) Phosphorus tribromide (10 ml, 105 mmoles) was added dropwise to **4c** (3.0 g, 7.1 mmoles) with ice cooling. The mixture was heated at 70° for 4 hours. After removal of excess phosphorus tribromide, some ice was added to the residue, the mixture was extracted with chloroform. The extract was washed with 5% aqueous sodium bicarbonate, dried over anhydrous sodium sulfate, and evaporated *in vacuo*. The residue was recrystallized from chloroform-ethanol giving 3.22 g (83%) of **6**, mp 211-212°.

3,3'-(1,6-Hexanediy)bis[1-(2-carbamimidoylthioethyl)-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione] (**7**).

A solution of thiourea (1.5 g, 19.8 mmoles) in 30 ml of ethanol was added to a solution of **6** (3.0 g, 5.4 mmoles) in 20 ml of chloroform. The mixture was refluxed for 6.5 hours, the separated crystals were collected and recrystallized from methanol giving 2.1 g (56%) of colorless powder, mp 259-262° dec; ir (potassium bromide): 3000 (broad NH₂), 1635 (C=O) cm⁻¹; ms: 479 (M-2HBr-59, 1.5), 454 (M-2HBr-C₂H₄N₄, 18), 425 (M-2HBr-C₂H₆N₄, 79).

Anal. Calcd. for C₂₂H₃₄N₈O₄S₂·2HBr: C, 37.72; H, 5.18; N, 16.00; S, 9.15. Found: C, 37.54; H, 5.34; N, 15.75; S, 8.93.

3,3'-(1,6-Hexanediy)bis[1-(2-*N,N*-dimethylaminothiocarbonylthioethyl)-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione] (**8**).

A solution of sodium *N,N*-dimethyldithiocarbamate (0.8 g, 5.6 mmoles) in 20 ml of ethanol was added to a solution of **6** (1.0 g, 1.8 mmoles) in 20 ml of chloroform. The mixture was refluxed for 11 hours. The separated crystals were collected and washed with water then extracted with chloroform. The extract was dried over anhydrous sodium sulfate. After removal of the solvent, the resulting residue was recrystallized from a mixture of chloroform and ethanol giving 0.71 g (61%) of colorless needles, mp 252-255°; ir (potassium bromide): 1682, 1650 (C=O) cm⁻¹; uv (ethanol): λ max (log ε), 272 (4.56); ms: 540 (M-88, 75), 509 (540-31, 50), 508 (540-32, 100), 421 (509-88, 21), 420 (508-88, 15), 88 (Me₂NCS₂, 93).

Anal. Calcd. for C₂₆H₄₀N₆O₄S₂·H₂O: C, 48.27; H, 6.54; N, 12.99; S, 19.82. Found: C, 48.47; H, 6.35; N, 12.74; S, 19.71.

3,3'-(1,6-Hexanediy)bis[1-(2-mercaptoethyl)-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione] (**9**).

A mixture of **7** (2.1 g, 3 mmoles), 0.6 g of sodium hydroxide in 60 ml of water was heated at 90° for 5 hours under a nitrogen atmosphere. The reaction mixture was acidified with acetic acid, the separated crystals were collected and recrystallized from chloroform-methanol giving 1.1 g (80%) of colorless powder, mp 200-204°; ir (potassium bromide): 1675 (shoulder), 1640 (C=O) cm⁻¹; uv (ethanol): λ max (log ε), 268 (4.30); ms: 454 (M⁺, 12), 420 (M-H₂S, 5).

Anal. Calcd. for C₂₀H₃₀N₄O₄S₂·½H₂O: C, 51.82; H, 6.74; N, 12.09; S, 13.83. Found: C, 52.14; H, 6.79; N, 11.94; S, 13.82.

12,22-Dimethyl-3,4-dithia[6.6](1.3)1,2,3,4-tetrahydropyrimidinophane (**10**).

A solution of iodine (0.18 g, 0.71 mmoles) in 20 ml of ethanol was added dropwise to a solution of **9** (0.3 g, 0.65 mmole), triethylamine (0.2 g, 2.0 mmoles), potassium iodide (as catalyst) in 200 ml of chloroform-ethanol (1:1, mixture) with stirring at room temperature. The mixture was stirred at room temperature overnight. The reaction mixture was concentrated to dryness *in vacuo* and diluted with water, then extracted with chloroform. The extract was washed with sodium thiosulfate aqueous solution and water then dried over anhydrous sodium sulfate. The solvent was evaporated to dryness *in vacuo* and the residue was purified by a silicagel column chromatography. The resulting crystals were recrystallized from chloroform-ethanol giving 0.1 g (35%) of colorless powder, mp 230-232°; ir (potassium bromide): 1675 (shoulder), 1645 (C=O) cm⁻¹; uv (ethanol): λ max (log ε), 268 (4.31); ¹³C-nmr (deuteriochloroform): δ 162.1 (s), 151.7 (s), 150.2 (s), 102.1 (d), 43.6 (t), 40.5 (t), 35.1 (t), 26.1 (t), 24.9 (t), 19.9 (q); ms: 452 (M⁺, 42).

Anal. Calcd. for C₂₀H₂₈N₄O₄S₂: C, 53.07; H, 6.23; N, 12.37; S, 14.16. Found: C, 52.81; H, 6.39; N, 12.12; S, 13.98.

Acknowledgement.

The authors are indebted to Mrs. H. Mazume for the elemental analyses, and to Mrsrs. K. Inada, N. Yamaguchi and M. Ohwatari for the measurements of nmr, ms, ir and uv spectra, respectively.

REFERENCES AND NOTES

- [1] A. L. Fluharty, "The Chemistry of the Thiol Group", Part 2, S. Patai, ed, John Wiley and Sons, London, 1974, p 589.
- [2] G. Jager and J. Wenzelberger, *Ann. Chem.*, 1689 (1976).
- [3] F. Yoshizaki, Y. Kondo and T. Takemoto, *Heterocycles*, **3**, 827 (1975).
- [4] S. Ahmed, R. Lofthouse and G. Shaw, *J. Chem. Soc.*, 1969 (1976).
- [5] M. Kulka, *Can. J. Chem.*, **34**, 1093 (1956).
- [6] G. Capotti and G. Modena, "The Chemistry of the Thiol Group", Part 2, S. Patai, ed, John Wiley and Sons, London, 1974, p 785.
- [7] M. H. Goodrow and W. K. Musker, *Synthesis*, 457 (1981).
- [8] The ms was obtained by electron impact ionization method.
- [9] DBPM: *N*-[4-[2-(6-dimethylamino)benzofuranyl]phenyl]maleimide: K. Nakashima, H. Akimoto, K. Nishida, S. Nakatsuji and S. Akiyama, *Talanta*, **32**, 167 (1985).