Pyrimidine Derivatives. VII [1]. Nucleophilic Reactions of 5-Bromo-1-(bromoalkyl)-6-bromomethyl-2,4(1*H*,3*H*)-pyrimidinediones

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Received November 19, 1991

The reactions of 1-(bromoalkyl)-5-bromo-6-bromomethyl-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione (**1**) with several nucleophiles were examined as follows: by reaction with sodium methoxide, 6-(bismethoxy)methyl-5-debrominated derivatives **2**, **3**, and **4** were prepared; the corresponding di-substituted compounds (side chains in 1- and 6-positions) **5**, **6**, **7**, and **9** were obtained by treatment with silver nitrate, silver acetate, potassium thiocyanate, and potassium thioacetate; the reaction with thioacetamide and *iso*-butylamine gave bicyclic compounds [1,4]thiazino[4,3-*c*]- **11**, pyrazino[1,2-*c*]- **12**, and [1,4]diazepino[1,2-*c*]pyrimidinedione **13**, respectively; pyrrolidine, morpholine, and sodium azide afforded the corresponding 6-substituted compounds **14**, **15**, and **16**.

J. Heterocyclic Chem., **29**, 741 (1992).

A number of papers have reported the reactions of 5-bromouracil derivatives with nucleophiles producing the corresponding 5-substituted uracils [2] and 5-debrominated 6-substituted uracils [3]. Moreover, Hirota *et al.* [4] have found that 5-bromo-6-bromomethyl-1,3-dimethyl-2,4(1*H*,-3*H*)-pyrimidinedione reacts with amine to give 6-aminomethyl-2,4(1*H*,3*H*)-pyrimidinedione and the 5-debrominated Schiff's base.

Previously, we described the preparation of 5-bromo-1-(2-bromoethyl [5], 2-bromopropyl [5], 3-bromopropyl [1], and 5-bromopentyl [1])-6-bromomethyl-2,4(1*H*,3*H*)-pyrimidinediones **1a**, **1b**, **1c**, and **1d** (these compounds are written "tribromo pyrimidine" as a general name herein) by the bromination of the corresponding 1-(hydroxyalkyl)-3,6-dimethyl-2,4(1*H*,3*H*)-pyrimidinediones with bromine in acetic acid and the reactions of **1a** and **1b** with several nucleophiles [5].

There has been considerable interest in the reactivity of the tribromo pyrimidine derivatives possessing a bromo substituent at the 5-position and on the side chains at the 1- and 6-positions with nucleophiles. We now report the nucleophilic reactions for the tribromopyrimidine derivatives.

Reactions with Oxygen Nucleophiles.

As described in a previous paper [5], compound **1a** was treated with 3 equivalents of sodium methoxide to give a mixture of **2a** (5.7%), **3a** (1.6%), and **4a** (12%). For all of these reaction products, two methoxyl groups were introduced into the side chain at the 6-positions and the bromine atom at the 5-position was removed. A plausible reaction mechanism had been discussed [5]. However, the bromine atom on the side chain in the 1-position showed a characteristic reaction. Thus, the following reactions were

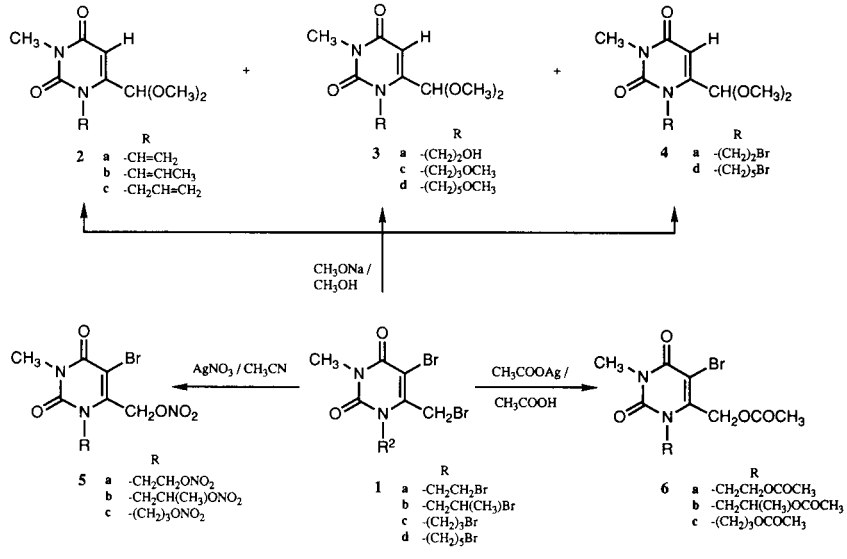

Chart 1

observed: elimination of hydrogen bromide, **2a**, substitution of the methoxyl group, **3a**, and no reaction for the bromine atom, **4a**.

In order to examine the position effect of bromine at the 1-position of the side chain, additional reactions were performed on **1b**, **1c**, and **1d** with sodium methoxide. Compound **1b**, possessing a methyl group as an electron donor on the same position to the bromine, gave the *trans*-form olefin compound **2b** by elimination of hydrogen bromide in high yield as the sole product. However, compound **1c** was converted to the olefin **2c** in 18% and substituted compound **3c** in 65%. In this case, the substitution reaction was preferable to elimination. It might be considered that the greater the separation from the nitrogen atom of the pyrimidine ring, the weaker the acidity of the hydrogen atom at the 2-position in the *N*-substituted side chain. For compound **1d**, the bromine atom is separated farther from the nitrogen atom of the pyrimidine ring than in compound **1c**, therefore, it did not afford an elimination product, but a substituted **3d** and non substituted compound **4d** in fair yields.

For the preparation of disubstituted oxygen derivatives, silver nitrate and silver acetate were examined. Therefore, those regents would be expected to have sufficient nucleophilicity toward the bromine atoms and lower basicity than sodium methoxide. Two bromine atoms, on the side chains at the 1- and 6-positions, were substituted by nitroxyl and acetoxyl anions to give the corresponding dinitrate and diacetoxyl compounds **5a**, **5b**, **5c**, **6a**, **6b**, and **6c** in excellent yields, respectively. Noda and Seebach [6] have described that the allylic bromide moiety of 5-bromo-6-(bromomethyl)-2-(*tert*-butyl)-2*H*,4*H*-1,3-dioxin-4-one was converted to a formyl group, and they observed the formation of a nitrate by the nmr spectra, however, they could not isolate the nitrate compound.

Reactions with Sulfur Nucleophiles.

Compounds **1** reacted with 2.2 equivalents of potassium thiocyanate to give the corresponding disubstituted compounds **7a**, **7b**, and **7c** in fair to excellent yields. In some cases, the monosubstituted product **8** was obtained as a by-product. Similarly, by treatment of compounds **1** with 2.2 equivalents of potassium thioacetate, the disubstituted compounds **9a**, **9b**, and **9c** were produced in fair yields, however, in case of **1c** the mono-substituted compound **10** was obtained as a by-product.

When compound **1a** was treated with thioacetamide, two products **11a-1** and **11a-2** were obtained. The structure of those compounds were established to be [1,4]thiazino[1,2-*c*]pyrimidine by elemental analysis and spectral data. Similar reactions of **1b** with thioacetamide gave the corresponding bicyclic compound **11b**. However, we could not isolate the bicyclic compound by reaction of **1c** with thioacetamide, expected to be [1,4]thiazepino[4,3-*c*]pyrimidine.

Reaction with Nitrogen Nucleophiles.

In a previous paper [5], we reported that compound **1a** and **1b** were treated with sodium succinimide to give the corresponding 6-succinimidylmethyl derivatives. We describe herein the reaction of **1** with a primary amine and some secondary amines. Thus, reactions of **1a-c** with *iso*-butylamine gave the corresponding bicyclic compounds,

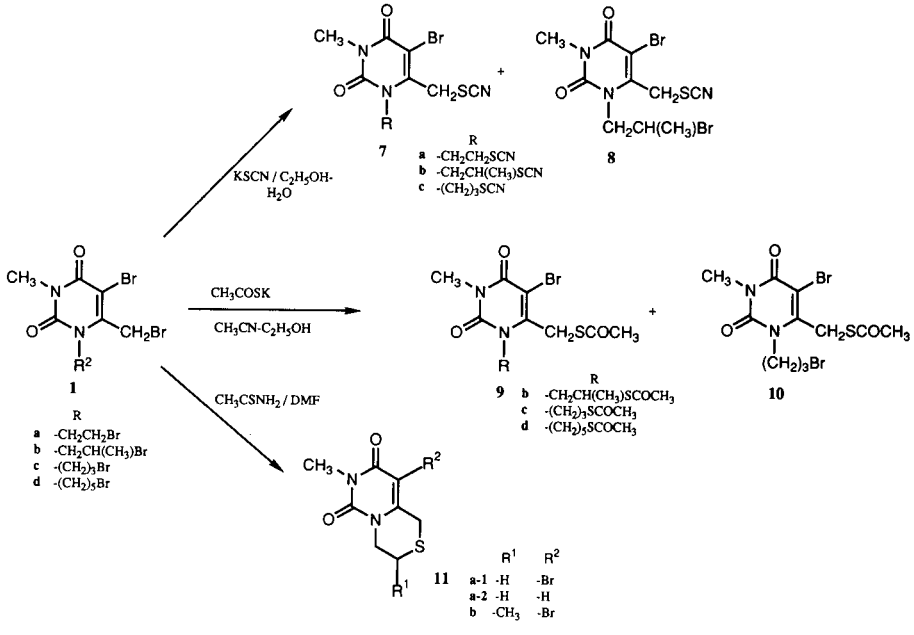

Chart 2

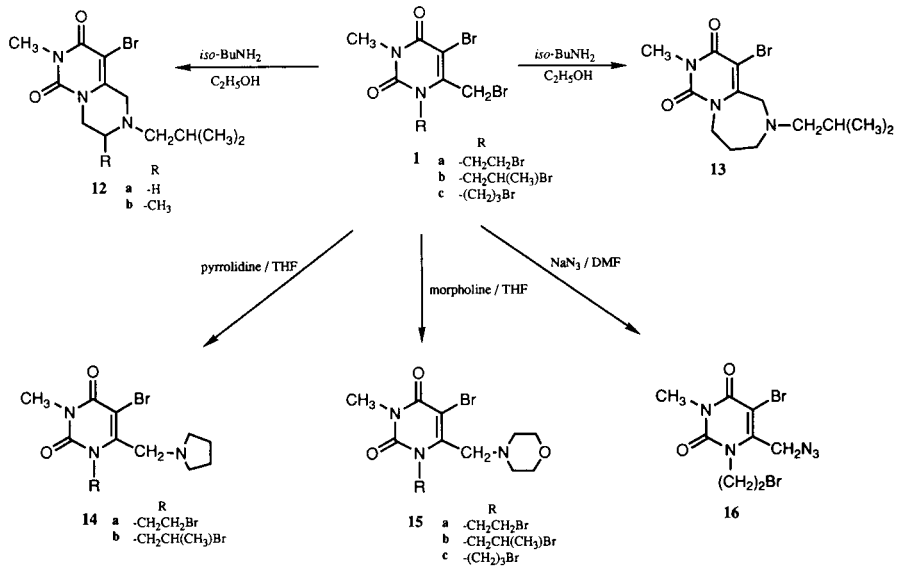

Chart 3

pyrazino[1,2-*c*]pyrimidines **12a** and **12b** and [1,4]diazepino[2,1-*c*]pyrimidine **13**. The structures of these compounds were established by elemental analysis and spectral data.

When **1** was treated with 2.2 equivalents of the secondary amines, pyrrolidine and morpholine, only 6-substituted compounds **14a**, **14b**, **15a**, **15b**, and **15c** were obtained. Similarly, the reaction of **1a** with sodium azide afforded a 6-substituted compound **16**.

EXPERIMENTAL

Melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. Spectral data were recorded on the following instruments: ir, JASCO IR-810 spectrophotometer, with all samples compressed into potassium bromide pellets; uv, HITACHI 323 spectrophotometer, were obtained in ethanol; nmr, HITACHI R-600 (60 MHz for ^{1}H), JEOL FX-90Q (90 MHz for ^{1}H, 22.5 MHz for ^{13}C), and JEOL GX-400 (400 MHz for ^{1}H, 100 MHz for ^{13}C) Fourier-transform spectrometer, were obtained in deuteriochloroform, unless indicated otherwise. Chemical shifts are reported in ppm (δ) relative to tetramethylsilane as internal standard. Mass spectra were obtained on a JEOL JMS-DX-303 and a JEOL JMA-DA-5000 data processor.

General Procedure for Reactions of Compounds **1** with Sodium Methoxide.

A solution of sodium methoxide in methanol (prepared from 0.35 g (15 mmoles) of sodium and 7 ml of methanol) was added to a solution of compound **1** (5.0 mmoles) in methanol (13 ml). The mixture was stirred at room temperature for 2 hours. After removal of the solvent at room temperature *in vacuo*, small amount of water was added to the residue and it was extracted with chloroform (3 times). The combined extracts were dried over magnesium sulfate and the solvent was removed to give an oil. The product was purified by silica gel column chromatography, eluting with chloroform.

6-(Bismethoxy)methyl-3-methyl-1-(1-propenyl)-2,4(1*H*,3*H*)-pyrimidinedione (**2b**).

This compound had bp 170°/2 mm Hg (Kugelrohr, colorless oil), 76%; ir: ν 1713 and 1650 (C=O) cm^{-1}; uv: λ max nm (log ϵ) 270 (3.669); ^{1}H-nmr: (90 MHz) δ 1.88 (3H, dd, J = 0.9, 5.9 Hz, CH-C*H*$_3$), 3.33 (3H, s, N-CH$_3$), 3.34 (6H, s, 2 x O-CH$_3$), 5.09 (1H, s, C(6)-CH), 5.89 (1H, dq, J = 5.9, 13.8 Hz, CH=C*H*CH$_3$), 6.05 (1H, s, C(5)-H), 6.09 (1H, tq, J = 0.9, 13.8 Hz, CH$_3$C*H*=CH); ms: (EI) m/z (relative intensities) 240 (M$^+$, 35), 225 (M-15, 25), 210 (M-30, 16), 75 ((CH$_3$O)$_2$CH, 100).

Anal. Calcd. for $C_{11}H_{16}N_2O_4$: C, 54.99; H, 6.71; N, 11.66. Found: C, 54.83; H, 6.76; N, 11.64.

6-(Bismethoxy)methyl-3-methyl-1-(2-propenyl)-2,4(1*H*,3*H*)-pyrimidinedione (**2c**) and 6-(Bismethoxy)methyl-3-methyl-1-(3-methoxypropyl)-2,4(1*H*,3*H*)-pyrimidinedione (**3b**).

Compound **2c** was obtained from the former fractions of chromatography as a pale yellow viscous oil, 18%; ir: ν 1710 (C=O) cm^{-1}; uv: λ max nm (log ϵ) 270 (3.961); ^{1}H-nmr: (90 MHz) δ 3.35 (9H, s, 2 x O-CH$_3$ and N-CH$_3$), 4.60 (2H, dt, J = 1.5, 5.1 Hz, N-CH$_2$), 5.08 (1H, s, C(6)-CH), 5.09 (1H, dt, J = 1.5, 16.8 Hz, one of CH=C*H*$_2$), 5.21 (1H, dt, J = 1.5, 10.6 Hz, one of CH=C*H*$_2$), 5.80 (1H, ddt, J = 5.1, 10.6, 16.8 Hz, CH$_2$-C*H*=CH$_2$), 6.04 (1H, s, C(5)-H); ms: (EI) m/z (relative intensities) 240 (M$^+$, 35), 225 (M-15, 25), 210 (M-30, 16), 75 ((CH$_3$O)$_2$CH, 100); ms: (HR) high resolution-mass spectrometry Calcd. for $C_{11}H_{16}N_2O_4$: 240.1110. Found: 240.1123.

Compound **3b** was obtained from the later fractions of chromatography and had mp 59-60° (petroleum ether, colorless needles), 65%; ir: ν 1700, 1668 (C=O) cm^{-1}; uv: λ max nm (log ϵ) 270 (3.995); ^{1}H-nmr: (400 MHz) δ 1.94 (2H, m), 3.33 (3H, s, N-CH$_3$), 3.34 (3H, s, O-CH$_3$), 3.39 (6H, s, 2 x OCH$_3$), 3.42 (2H, t, J = 5.9 Hz, CH$_3$O-C*H*$_2$), 4.01 (2H, t, J = 7.6 Hz, N-CH$_2$), 5.17 (1H, s, C(6)-CH), 6.01 (1H, s, C(5)-H); ^{13}C-nmr: (100 MHz, C-H COSY) δ

27.87 ($N-CH_3$), 28.72 (CH_2), 42.70 ($N-CH_2$), 53.87 (2 x $O-CH_3$), 58.54 ($O-CH_3$), 69.75 (CH_3O-CH_2), 98.94 (C(6)-$CH(OCH_3)_2$), 101.04 (C(5)), 148.60 ((C(6)), 152.37 (C(2)), 162.61 (C(4)); ms: (EI) m/z 272 (M^+), 241 ($M-CH_3O$), 225 (241-CH_4), 197 [$M-CH(O-CH_3)_2$], 75 [$CH(OCH_3)_2$].

Anal. Calcd. for $C_{12}H_{20}N_2O_5$: C, 52.93; H, 7.40; N, 10.28. Found: C, 52.91; H, 7.28; N, 10.23.

6-(Bismethoxy)methyl-1-(5-methoxypentyl)-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione (**3d**) and 6-(Bismethoxy)methyl-1-(5-bromopentyl)-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione (**4d**).

Compound **3d** was obtained from the later fractions of chromatography as colorless oil in 55% yield; ir: ν 1705 and 1665 (C=O) cm^{-1}; uv: λ max nm (log ϵ) 271 (3.984); ^{1}H-nmr: (60 MHz) δ 1.53 (6H, m, 3 x CH_2), 3.32 (6H, s, $O-CH_3$ and $N-CH_3$), 3.41 (6H, s, 2 x $O-CH_3$), 3.93 (4H, m, 2 x CH_2), 5.12 (1H, s, C(6)-CH), 5.95 (1H, s, C(5)-H); ms: (EI) m/z (relative intensities) 300 (M^+, 8), 285 (M-15, 11), 225 ($M-CH(OCH_3)_2$, 32), 75 ($(CH_3O)_2CH$, 100); ms: (HR) Calcd. for $C_{14}H_{24}N_2O_5$: 300.1685. Found: 300.1668.

Anal. Calcd. for $C_{14}H_{24}N_2O_5$: C, 55.95; H, 8.05; N, 9.33. Found: C, 55.76; H, 7.94; N, 9.25.

Compound **4d** was obtained from the former fractions of chromatography and had mp 57-58° (ether, colorless needles), 35% yield; ir: ν 1705 and 1660 (C=O) cm^{-1}; uv: λ max nm (log ϵ) 271 (3.920); ^{1}H-nmr: (60 MHz) δ 1.72 (6H, m, 3 x CH_2), 3.32 (3H, s, $N-CH_3$), 3.41 (6H, s, 2 x $O-CH_3$), 4.00 (4H, m, 2 x CH_2), 5.07 (1H, s, C(6)-CH), 5.95 (1H, s, C(5)-H); ms: (EI) m/z (relative intensities) 350 and 348 (M^+, 17 and 17), 320 and 318 (M-30, 31 and 33), 275 and 273 ($M-(CH_3O)_2CH$, 26 and 27), 75 ($(CH_3O)_2CH$, 100); ms: (HR) Calcd. for $C_{13}H_{21}Br-N_2O_4$: 348.0685 (for ^{79}Br). Found: 348.0679.

Anal. Calcd. for $C_{13}H_{21}BrN_2O_4$: C, 44.71; H, 6.06; Br, 22.88; N, 8.02. Found: C, 44.76; H, 5.95; Br, 22.67; N, 8.07.

General Procedure for Reactions of Compounds **1** with Silver Nitrate.

A solution of silver nitrite (26 mmoles) in acetonitrile (30 ml) was added to a solution of **1** (13 mmoles) in acetonitrile (70 ml) was heated at 90-95° for 2 hours. The resulting crystalline mass was filtered and the filtrate was washed with brine. Separated white mass was filtered off and the filtrate was dried over magnesium sulfate. After removal of the solvent *in vacuo*, the oily residue was crystallized from a suitable solvent.

Dinitrate of 5-Bromo-6-hydroxymethyl-1-(2-hydroxyethyl)-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione (**5a**).

This compound had mp 74-75° (benzene, colorless needles), 95%; ir: ν 1703 and 1660 (C=O), 1640 and 1280 (ONO_2) cm^{-1}; uv: λ max nm (log ϵ) 288 (3.627); ^{1}H-nmr: (60 MHz) δ 3.41 (3H, s, $N-CH_3$), 4.33 (2H, t, J = 5.5 Hz, $N-CH_2$), 4.77 (2H, t, J = 5.5 Hz, NO_2O-CH_2), 5.77 (2H, s, C(6)-CH_2-ONO_2); ms: (EI) m/z 370 and 368 (M^+).

Anal. Calcd. for $C_8H_9BrN_4O_8$: C, 26.03; H, 2.46; N, 15.18. Found: C, 26.17; H, 2.42; N, 15.15.

Dinitrate of 5-Bromo-6-hydroxymethyl-1-(2-hydroxypropyl)-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione (**5b**).

This compound has mp 143-144° (ethyl acetate, colorless powder), 63%; ir: ν 1713 and 1670 (C=O), 1633, 1280 and 1275 (ONO_2) cm^{-1}; uv: λ max nm (log ϵ) 288 (3.965); ^{1}H-nmr: (90 MHz) δ 1.41 (3H, d, J = 6.4 Hz, $CH-CH_3$), 3.43 (3H, s, $N-CH_3$), 3.85 (1H, dd, J = 9.4, 15.6 Hz, one of $N-CH_2$), 4.37 (1H, dd, J = 2.6, 15.6 Hz, one of $N-CH_2$), 5.43 (1H, m, $NCH_2CH(CH_3)-ONO_2$), 5.52 and 6.02 (each 1H, d, J = 13.3 Hz, C(6)-CH_2-ONO_2); ms: (EI) m/z 384 and 382 (M^+).

Anal. Calcd. for $C_9H_{11}BrN_4O_8$: C, 28.22; H, 2.89; Br, 20.86; N, 14.63. Found: C, 28.49; H, 2.97; Br, 21.11; N, 14.67.

Dinitrate of 5-Bromo-6-hydroxymethyl-1-(3-hydroxypropyl)-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione (**5c**).

This compound had mp 90-91° (benzene, white powder), 94%; ir: ν 1710 and 1660 (C=O), 1630, 1358, and 1285 (ONO_2) cm^{-1}; uv: λ max nm (log ϵ) 205 (4.110), 287 (3.953); ^{1}H-nmr: (60 MHz) δ 2.18 (2H, m, CH_2), 3.39 (3H, s, $N-CH_3$), 4.07 (2H, t, J = 6.5 Hz, $O-CH_2$), 4.58 (2H, t, J = 6.0 Hz, $N-CH_2$), 5.72 (2H, s, C(6)-CH_2-ONO_2); ms: (EI) m/z 384 and 382 (M^+).

Anal. Calcd. for $C_9H_{11}BrN_4O_8$: C, 28.22; H, 2.89; Br, 20.86; N, 14.63. Found: C, 28.45; H, 2.87; Br, 20.75; N, 14.52.

General Procedure for Reactions of Compounds **1** with Silver Acetate.

Silver acetate (5.5 mmoles) was added to a solution of **1** (2.5 mmoles) in acetic acid (20 ml). The mixture was heated under refluxing for 4 hours with stirring. The separated crystalline mass was filtered off and the filtrate was concentrated under reduced pressure. The residue was dissolved in chloroform and the insoluble material was filtered off. After removal of the solvent, the residue was crystallized from a suitable solvent.

1-(2-Acetoxyethyl)-6-acetoxymethyl-5-bromo-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione (**6a**).

This compound had mp 84-85° (ethyl acetate, white powder), 94%; ir: ν 1745, 1703, and 1655 (C=O) cm^{-1}; uv: λ max nm (log ϵ) 208 (3.951), 283 (3.954); ^{1}H-nmr: (90 MHz) δ 2.07 and 2.16 (each 3H, s, $COCH_3$), 3.42 (3H, s, $N-CH_3$), 4.1-4.4 (4H, m, $N-CH_2CH_2-O$), 5.35 (2H, s, C(6)-$CH_2-OCOCH_3$).

Anal. Calcd. for $C_{12}H_{15}BrN_2O_6$: C, 39.69; H, 4.16; N, 7.71. Found: C, 39.71; H, 4.08; N, 7.75.

6-Acetoxymethyl-1-(2-acetoxypropyl)-5-bromo-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione (**6b**).

This compound had mp 91-92° (benzene, colorless prisms), 92%; ir: ν 1740, 1712, and 1640 (C=O) cm^{-1}; uv: λ max nm (log ϵ) 212 (3.960), 288 (3.980); ^{1}H-nmr: (90 MHz) δ 1.31 (3H, d, J = 6.4 Hz, $CH-CH_3$), 1.99 and 2.16 (each 3H, s, $COCH_3$), 3.41 (3H, s, $N-CH_3$), 3.99 (1H, dd, J = 9.2, 14.9 Hz, one of $N-CH_2$), 4.22 (1H, dd, J = 3.3, 14.9 Hz, one of $N-CH_2$), 5.22 (1H, m, $NCH_2-CH(CH_3)-OCOCH_3$), 5.29 and 5.45 (each 1H, d, J = 13.4 Hz, C(6)-$CH_2-OCOCH_3$); ms: (EI) m/z 378 and 376 (M^+).

Anal. Calcd. for $C_{13}H_{17}BrN_2O_6$: C, 41.40; H, 4.54; Br, 21.18; N, 7.43. Found: C, 41.34; H, 4.39; Br, 21.42; N, 7.50.

6-Acetoxymethyl-1-(3-acetoxypropyl)-5-bromo-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione (**6c**).

This compound had mp 105-106° (ethyl acetate, colorless prisms), 74%; ir: ν 1742, 1702, and 1665 (C=O) cm^{-1}; uv: λ max nm (log ϵ) 212 (3.984), 289 (3.983); ^{1}H-nmr: (90 MHz) δ 2.0-2.1 (2H, m, CH_2), 2.04 and 2.17 (each 3H, s, $CO-CH_3$), 3.42 (3H, s, $N-CH_3$), 4.00 (2H, t, J = 5.7 Hz, $N-CH_2$ or $O-CH_2$), 4.15 (2H, t, J = 5.7 Hz, $O-CH_2$ or $N-CH_2$), 5.27 (2H, s, C(6)-CH_2); ms: (EI) m/z 378 and 376 (M^+).

Anal. Calcd. for $C_{13}H_{17}BrN_2O_6$: C, 41.40; H, 4.54; Br, 21.18; N, 7.43. Found: C, 41.36; H, 4.37; Br, 21.20; N, 7.49.

General Procedure for Reactions of Compounds **1** with Potassium Thiocyanate.

Method A.

A mixture of **1** (5.0 mmoles) and potassium thiocyanate (11.0 mmoles, 2.2 equivalents) in a mixture of ethanol and water (30 ml and 10 ml) was heated at 90-95° for 2 hours. After removal of excess solvent, the residue was extracted with chloroform (3 times) and the combined extracts were dried over magnesium sulfate. The solvent was removed and the residue was purified on a silica gel column chromatograph, eluting with chloroform. After removal of the solvent, the residue was crystallized from a suitable solvent.

Method B.

In this method 1.1 equivalents of potassium thiocyanate was used. The resulting oil was chromatographed on a silica gel column, eluting with chloroform.

5-Bromo-3-methyl-1-(2-thiocyanatoethyl)-6-thiocyanatomethyl-2,4(1*H*,3*H*)-pyrimidinedione (**7a**).

This compound had mp 164-166° (ethyl acetate-acetone, colorless cubes), 64% (method A), 23% (method B); ir: ν 2150 (S-CN), 1698 and 1662 (C=O) cm^{-1}; uv: λ max nm (log ϵ) 295 (4.000); ^{1}H-nmr: (90 MHz) δ 3.38 (2H, t, J = 6.6 Hz, S-CH_2), 3.44 (3H, s, N-CH_3), 4.39 (2H, t, J = 6.6 Hz, N-CH_2), 4.50 (2H, s, C(6)-CH_2-SCN).

Anal. Calcd. for $C_{10}H_9BrN_4O_2S_2$: C, 33.25; H, 2.51; Br, 22.12; N, 15.51; S, 17.75. Found: C, 33.37; H, 2.58; Br, 21.88; N, 15.56; S, 17.83.

5-Bromo-3-methyl-6-thiocyanatomethyl-1-(2-thiocyanatopropyl)-2,4(1*H*,3*H*)-pyrimidinedione (**7b**) and 5-Bromo-1-(2-bromopropyl)-3-methyl-6-thiocyanatomethyl-2,4(1*H*,3*H*)-pyrimidinedione (**8**).

Compound **7b** was obtained from the later fractions of chromatography and had mp 137-138° (ethyl acetate, colorless cubes), yield 59% (method A), 6.5% (method B); ir: ν 2150 (S-CN), 1697 and 1660, (C=O) cm^{-1}; uv: λ max nm (log ϵ) 210 (3.983), 295 (3.939); ^{1}H-nmr: (90 MHz) δ 1.61 (3H, d, J = 6.6 Hz, CH-C*H*$_3$), 3.43 (3H, s, N-CH_3), 3.95 (1H, m, one of N-CH_2), 4.01 (1H, d, J = 8.0, one of N-CH_2), 4.36 (1H, m, NCH_2-C*H*-CH_3), 4.42 and 4.64 (2H, each d, J = 14.3 Hz, C(6)-C*H*$_2$-SCN).

Anal. Calcd. for $C_{11}H_{11}BrN_4O_2S_2$: C, 35.21; H, 2.95; Br, 21.29; N, 14.93; S, 17.09. Found: C, 35.38; H, 3.00; Br, 21.15; N, 14.86; S, 16.96.

Compound **8** was obtained from the former fractions of chromatography and had mp 125-126° (ethyl acetate, colorless prisms), 18%; ir: ν 2150 (S-CN), 1706 and 1650 (C=O) cm^{-1}; uv: λ max nm (log ϵ) 210 (3.982), 296 (3.920); ^{1}H-nmr: (90 MHz) δ 1.82 (3H, d, J = 6.6 Hz, CH-C*H*$_3$), 3.44 (3H, s, N-CH_3), 3.98 (1H, dd, J = 10.5, 15.8 Hz, one of N-CH_2), 4.44 (1H, m, one of N-CH_2), 4.58 and 4.69 (2H, each d, J = 14.3 Hz, C(6)-CH_2-SCN), 4.60 (1H, m, NCH_2-C*H*-CH_3).

Anal. Calcd. for $C_{10}H_{11}Br_2N_3O_2S$: C, 30.25; H, 2.79; Br, 40.25; N, 10.58; S, 8.08. Found: C, 30.35; H, 2.76; Br, 40.02; N, 10.58; S, 8.28.

5-Bromo-3-methyl-6-thiocyanatomethyl-1-(3-thiocyanatopropyl)-2,4(1*H*,3*H*)-pyrimidinedione (**7c**).

This compound had mp 135-136° (acetone, colorless plates), 65% (method A), 37% (method B); ir: ν 2150 (S-CN), 1701 and 1650 (C=O) cm^{-1}; uv: λ max nm (log ϵ) 210 (4.007), 297 (3.952); ^{1}H-nmr: (90 MHz) δ 2.25 (2H, m, NCH_2-C*H*$_2$-CH_2S), 3.08 (2H, t, J = 7.5 Hz, CH_2-SCN), 3.43 (3H, s, N-CH_3), 4.23 (2H, m, N-CH_2), 4.43 (2H, s, C(6)-CH_2-SCN).

Anal. Calcd. for $C_{11}H_{11}BrN_4O_2S_2$: C, 35.21; H, 2.95; Br, 21.29; N, 14.93; S, 17.09. Found: C, 35.32; H, 2.96; Br, 21.55; N, 14.83; S, 17.03.

General Procedure for Reactions of **1** with Potassium Thioacetate.

A solution of **1** (12.0 mmoles) in acetonitrile (70 ml) was added to a solution of potassium thioacetate (30.0 mmoles, 2.5 equivalents) in ethanol (40 ml), the mixture was refluxed for 4 hours. After evaporation of the solvent *in vacuo*, water (small amount) was added to the residue and the mixture was extracted with chloroform (3 times). The combined organic layer was dried over magnesium sulfate and the solvent was removed. The residue was purified by recrystallization or chromatography.

6-Acetylthiomethyl-1-(2-acetylthiopropyl)-5-bromo-3-methyl-2,4-(1*H*,3*H*)-pyrimidinedione (**9b**).

This compound has mp 99-100° (ether, pale yellow needles), 34%; ir: ν 1703 and 1670 (C=O) cm^{-1}; uv: λ max nm (log ϵ) 220 (4.504), 292 (4.385); ^{1}H-nmr: (90 MHz) δ 1.36 (3H, d, J = 6.6 Hz, CH_3), 2.27 and 2.42 (each 3H, s, CO-CH_3), 3.42 (3H, s, N-CH_3), 3.8-4.3 (3H, m, N-C*H*$_2$C*H*(CH_3)-SCOCH_3), 4.48 (2H, s, C(6)-CH_2-SCOCH_3); ms: (EI) m/z 410 and 408 (M^+).

Anal. Calcd. for $C_{13}H_{17}BrN_2O_4S_2$: C, 38.15; H, 4.19; N, 6.84; S, 15.67. Found: C, 38.25; H, 4.05; N, 6.82; S, 15.88.

6-Acetylthiomethyl-1-(3-acetylthiopropyl)-5-bromo-3-methyl-2,4-(1*H*,3*H*)-pyrimidinedione (**9c**) and 6-Acetylthiomethyl-5-bromo-1-(3-bromopropyl)-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione (**10**).

Compound **9c** had mp 86-87° (ethyl acetate, colorless cubes), 37%; ir: ν 1695 and 1655 (C=O) cm^{-1}; uv: λ max nm (log ϵ) 223 (4.440), 292 (4.320); ^{1}H-nmr: (90 MHz) δ 1.8-2.2 (2H, m, CH_2-C*H*$_2$-CH_2), 2.35 and 2.45 (each 3H, s, CO-CH_3), 2.93 (2H, t, J = 7.0 Hz, S-CH_2), 3.39 (3H, s, N-CH_3), 3.99 (2H, dd, J = 6.6, 7.8 Hz, N-CH_2), 4.31 (2H, s, C(6)-C*H*$_2$-SCOCH_3).

Anal. Calcd. for $C_{13}H_{17}BrN_2O_4S_2$: C, 38.15; H, 4.19; Br, 19.52; N, 6.84; S, 15.68. Found: C, 38.21; H, 4.13; Br, 19.44; N, 6.84; S, 15.58.

Compound **10** was obtained from the mother liquor of the above resulting. The residue was purified by silica gel (Wako C-300) column chromatography using 2.5-8% of acetonitrile-chloroform mixture (graduation) as eluent. The former fractions were combined and resultant was recrystallized from acetone to give colorless cubes (14%), mp 103-104°; ir: ν 1697 and 1650 (C=O) cm^{-1}; uv: λ max nm (log ϵ) 217 (4.073), 291 (4.036); ^{1}H-nmr: (60 MHz) δ 2.2 (2H, m, CH_2-C*H*$_2$-CH_2), 2.40 (3H, s, $COCH_3$), 3.37 (3H, s, N-CH_3), 3.46 (2H, t, J = 6.5 Hz, Br-CH_2), 4.05 (2H, m, N-CH_2), 4.32 (2H, s, C(6)-C*H*$_2$-SCOCH_3).

Anal. Calcd. for $C_{11}H_{14}Br_2N_2O_3S$: C, 31.90; H, 3.41; Br, 38.59; N, 6.76. Found: C, 31.99; H, 3.35; Br, 38.41; N, 6.65.

6-Acetylthiomethyl-1-(5-acetylthiopentyl)-5-bromo-3-methyl-2,4-(1*H*,3*H*)-pyrimidinedione (**9d**).

This compound had mp 99-100° (ethyl acetate, colorless needles), 68%; ir: ν 1702, 1692, and 1645 (C=O) cm^{-1}; uv: λ max nm (log ϵ) 225 (4.039), 293 (4.024); ^{1}H-nmr: (90 MHz) δ 1.2-1.8 (6H, m,

3 x CH_2), 2.33 and 2.44 (each 3H, s, CO-CH_3), 2.89 (2H, t, J = 6.6, Hz,S-CH_2), 3.40 (3H, s, N-CH_3), 3.77 (2H, t, J = 6.6 Hz, N-CH_2), 4.32 (2H, s, C(6)-CH_2-SCOCH_3).

Anal. Calcd. for $C_{15}H_{21}BrN_2O_4S_2$: C, 41.19; H, 4.84; N, 6.41; S, 14.66. Found: C, 40.96; H, 4.74; N, 6.37; S, 14.54.

General Procedure for Reactions of **1** with Thioacetamide.

A solution of **1** (5.0 mmoles) and thioacetamide (6.0 mmoles) in dimethylformamide (20 ml) was heated at 80-90° for 3 hours. After removal of the solvent *in vacuo*, some water was added to the residue and the mixture was extracted with ethyl acetate (3 times). The combined extract was dried over magnesium sulfate and the solvent was removed. The residue was purified by column chromatography, eluting with chloroform (acetonitrile graduation).

9-Bromo-3,4-dihydro-6,8-dioxo-7-methyl[1,4]thiazino[4,3-*c*]pyrimidine (**11a-1**) and 3,4-Dihydro-6,8-dioxo-7-methyl[1,4]thiazino[4,3-*c*]pyrimidine (**11a-2**).

Compound **11a-1** was obtained from the former fractions of chromatography and had mp 134-137° (ethyl acetate, pale yellow prisms), 84%; ir: ν 1700 and 1652 (C=O) cm^{-1}; uv: λ max nm (log ϵ) 213 (3.972), 287 (4.027); ^{1}H-nmr: (90 MHz) δ 3.02 (2H, t, J = 6.1 Hz, C(3)-H_2), 3.42 (3H, s, N-CH_3), 3.89 (2H, s, C(1)-H_2), 4.34 (2H, t, J = 6.1 Hz, C(4)-H_2).

Anal. Calcd. for $C_8H_9BrN_2O_2S$: C, 34.67; H, 3.27; Br, 28.83; N, 10.11; S, 11.57. Found: C, 34.62; H, 3.25; Br, 28.84; N, 9.93; S, 11.58.

Compound **11a-2** was obtained from the later fractions and had mp 191-192° (ethyl acetate, colorless needles), 7.5%; ir: ν 1700 and 1659 (C=O) cm^{-1}; uv: λ max nm (log ϵ) 207 (3.925), 268 (4.028); ^{1}H-nmr: (90 MHz) δ 3.08 (2H, dd, J = 5.7, 6.4 Hz, C(3)-H_2), 3.35 (3H, s, N-CH_3), 3.51 (2H, s, C(1)-H_2), 4.28 (2H, dd, J = 5.7, 6.4 Hz, C(4)-H_2), 5.67 (1H, s, C(9)-H).

Anal. Calcd. for $C_8H_{10}N_2O_2S$: C, 48.48; H, 5.09; N, 14.14. Found: C, 48.46; H, 5.05; N, 13.98.

9-Bromo-3,7-dimethyl-6,8-dioxo-3,4-dihydro[1,4]thiazino[4,3-*c*]-pyrimidine (**11b**).

This compound had mp 159-160° (ethyl acetate, colorless prisms), 29.2% and also obtained by reaction with mercaptoacetic acid in 2.4% yield; ir: ν 1700 and 1650 (C=O) cm^{-1}; uv: λ max nm (log ϵ) 213 (3.937), 287 (4.014); ^{1}H-nmr: (90 MHz) δ 1.36 (3H, d, J = 6.4 Hz, C(3)-CH_3), 3.2-3.6 (1H, m, C(3)-H), 3.43 (3H, s, N-CH_3), 3.80 (1H, dd, J = 8.1, 13.8 Hz, one of C(4)-H_2), 3.90 (2H, s, C(1)-H_2), 4.49 (1H, dd, J = 4.0, 13.8 Hz, one of C(4)-H_2); ms: (EI) m/z 292 and 290 (M^+).

Anal. Calcd. for $C_9H_{11}BrN_2O_2S$: C, 37.13; H, 3.81; Br, 27.44; N, 9.62; S, 11.01. Found: C, 48.46; H, 5.05; Br, 27.03; N, 9.67; S, 11.03.

General Procedure for Reactions of **1** with *iso*-Butylamine.

A mixture of **1** (2.4 mmoles) and *iso*-butylamine (6.0 mmoles, 2.5 equivalents) in ethanol (15 ml) was refluxed for 3 hours. After removal of the solvent, the residue was treated with 10% hydrochloric acid and the mixture was extracted with chloroform (5 times) and the combined extract was dried over magnesium sulfate then the solvent was removed. The residue was purified by silica gel column chromatography, eluting with chloroform.

9-Bromo-6,8-dioxo-7-methyl-2-(2-methylpropyl)-1,2,3,4-tetrahydropyrazino[1,2-*c*]pyrimidine (**12a**).

This compound had mp 97-99° (ether, yellow plates), 66.0%; ir: ν 1700 and 1650 (C=O) cm^{-1}; uv: λ max nm (log ϵ) 287 (4.014); ^{1}H-nmr: (90 MHz) δ 0.94 (6H, d, J = 6.4 Hz, 2 x C(3')-H_3), 1.9 (1H, m, C(2')-H), 2.28 (2H, d, J = 6.8 Hz, C(1')-H_2), 2.73 (2H, t, J = 5.7 Hz, C(3)-H_2), 3.41 (3H, s, N-CH_3), 3.58 (2H, s, C(1)-H_2), 3.86 (2H, t, J = 5.7 Hz, C(4)-H_2).

Anal. Calcd. for $C_{12}H_{18}BrN_3O_2$: C, 45.58; H, 5.74; Br, 25.20; N, 13.29. Found: C, 45.77; H, 5.63; Br, 25.23; N, 13.09.

9-Bromo-3,7-dimethyl-6,8-dioxo-2-(2-methylpropyl)-1,2,3,4-tetrahydropyrazino[1,2-*c*]pyrimidine (**12b**).

This compound had mp 122-123° (ethyl acetate, pale yellow needles), 38%; ir: ν 1708, 1695, and 1650 (C=O) cm^{-1}; uv: λ max nm (log ϵ) 210 (3.596), 283 (3.978); ^{1}H-nmr: (90 MHz) δ 0.91 and 0.95 (each 3H, d, J = 6.4 Hz, 2 x C(3')-H_3), 1.13 (3H, d, J = 6.4 Hz, C(3)-CH_3), 1.8 (1H, m, C(2')-H), 2.3 (2H, m, C(4)-H), 3.0 (1H, m, C(3)-H), 3.42 (3H, s, N-CH_3), 3.5-4.0 (4H, m, C(1)-H_2 and C(4)-H_2). This compound might be a mixture of sterioisomers.

Anal. Calcd. for $C_{13}H_{20}BrN_3O_2$: C, 47.28; H, 6.11; Br, 24.20; N, 12.72. Found: C, 47.07; H, 6.02; Br, 24.19; N, 12.69.

10-Bromo-8-methyl-2-(2-methylpropyl)-7,9-dioxo[1,4]diazepino-[1,2-*c*]pyrimidine (**13**).

This compound had mp 96-97° (ether, colorless needles), 44%; ir: ν 1705 and 1660 (C=O) cm^{-1}; uv: λ max nm (log ϵ) 209 (3.990), 283 (3.942); ^{1}H-nmr: (90 MHz) δ 0.88 (6H, d, J = 6.4 Hz, 2 x C(3')-H_3), 1.84 (3H, m, C(2')-H and C(4)-H_2), 2.32 (2H, d, J = 7.5 Hz, C(1')-H_2), 2.91 (2H, dd, J = 5.3, 5.7 Hz, C(3)-H_2), 3.41 (3H, s, N-CH_3), 4.09 (2H, s, C(1)-H_2), 4.32 (2H, dd, J = 3.4, 4.6 Hz, C(5)-H_2).

Anal. Calcd. for $C_{13}H_{20}BrN_3O_2$: C, 47.28; H, 6.11; Br, 24.20; N, 12.72. Found: C, 47.15; H, 5.98; Br, 24.16; N, 12.76.

General Procedure for Reactions of Compounds **1** with Amines.

A mixture of **1** (2.0 mmoles) and amine (pyrrolidine, piperidine, morpholine, or sodium azide) (4.4 mmoles) in tetrahydrofuran (30 ml) was refluxed for 1 hour. The separated crystalline mass was collected and recrystallized from a suitable solvent.

5-Bromo-1-(2-bromoethyl)-3-methyl-6-pyrrolidinylmethyl-2,4-(1*H*,3*H*)-pyrimidinedione (**14a**).

This compound had mp >270° (methanol, colorless needles), 49%; ir: ν 1700 and 1640 (C=O) cm^{-1}; uv: λ max nm (log ϵ) 284 (3.954); ^{1}H-nmr: (90 MHz, DMSO-d_6) δ 2.17 (4H, m, CH_2CH_2 for pyrrolidine), 3.27 (3H, s, N-CH_3), 3.7 (4H, m, CH_2-N-CH_2 for pyrrolidine), 3.95 (2H, t, J = 9 Hz, Br-CH_2), 4.08 (2H, t, J = 9 Hz, N-CH_2), 4.75 (2H, s, C(6)-CH_2-N).

Anal. Calcd. for $C_{12}H_{17}Br_2N_3O_2$: C, 36.48; H, 4.34; Br, 40.45; N, 10.64. Found: C, 36.31; H, 4.27; Br, 40.71; N, 10.58.

5-Bromo-1-(2-bromopropyl)-3-methyl-6-pyrrolidinomethyl-2,4-(1*H*,3*H*)-pyrimidinedione (**14b**).

This compound had mp 223-227° (methanol-ethyl acetate, pale yellow needles), 45%; ir: ν 1698 and 1642 (C=O) cm^{-1}; uv: λ max nm (log ϵ) 284 (3.966); ^{1}H-nmr: (90 MHz, DMSO-d_6) δ 1.48 (3H, d, J = 6.6 Hz, CH-CH_3), 2.15 (4H, m, CH_2-CH_2, for pyrrolidine), 3.27 (3H, s, N-CH_3), 3.6-4.4 (7H, m, N-CH_2-CH-CH_3 and CH_2-N-CH_2 for pyrrolidine), 4.67 (2H, s, C(6)-CH_2-N).

Anal. Calcd. for $C_{13}H_{19}Br_2N_3O_2$: C, 38.16; H, 4.68; Br, 39.06; N, 10.27. Found: C, 38.44; H, 4.59; Br, 38.82; N, 10.28.

5-Bromo-1-(2-bromoethyl)-3-methyl-6-(4-morpholino)methyl-2,4-(1*H*,3*H*)-pyrimidinedione (**15a**).

This compound had mp 238-240° (methanol, colorless needles), 67%; ir: ν 1701, 1650 (C=O) cm^{-1}; uv: λ max nm (log ϵ) 284 (3.980); ^{1}H-nmr: (90 MHz, DMSO-d_6) δ 3.27 (3H, s, N-CH_3), 3.75 and 3.95 (8H, m, morpholine), 4.12 (4H, s, N-CH_2CH_2-Br), 4.92 (2H, s, C(6)-CH_2-N).

Anal. Calcd. for $C_{12}H_{17}Br_2N_3O_3$: C, 35.06; H, 4.17; Br, 38.88; N, 10.22. Found: C, 34.92; H, 4.08; Br, 39.08; N, 10.15.

5-Bromo-1-(2-bromopropyl)-3-methyl-6-(4-morpholino)methyl-2,4-(1*H*,3*H*)-pyrimidinedione (**15b**).

This compound had mp 204-205° (methanol, colorless needles), 51%; ir: ν 1700 and 1650 (C=O) cm^{-1}; uv: λ max nm (log ϵ) 284 (3.945); ^{1}H-nmr: (90 MHz, DMSO-d_6) δ 1.51 (3H, d, J = 6.8 Hz, CH-CH_3), 3.26 (3H, s, N-CH_3), 3.6-4.2 (10H, m, N-CH_2 and morpholine), 4.55 (1H, m, CH_3-C*H*Br), 4.89 (2H, s, C(6)-CH_2-N).

Anal. Calcd. for $C_{13}H_{19}Br_2N_3O_3$: C, 36.73; H, 4.51; Br, 37.59; N, 9.88. Found: C, 36.45; H, 4.38; Br, 37.44; N, 9.81.

5-Bromo-1-(3-bromopropyl)-3-methyl-6-(4-morpholino)methyl-2,4-(1*H*,3*H*)-pyrimidinedione (**15c**).

This compound had mp 201-203° (ethyl acetate, colorless powder), 43%; ir: ν 1700, 1650 (C=O) cm^{-1}; uv: λ max nm (log ϵ) 288 (4.005); ^{1}H-nmr: (90 MHz) δ 2.32 (2H, m, CH_2-CH_2-CH_2), 2.64 (4H, m, morpholine), 3.41 (3H, s, N-CH_3), 3.51 (2H, t, J = 5.8 Hz, Br-CH_2), 3.69 (4H, m, morpholine), 3.78 (2H, s, C(6)-CH_2-N), 4.28 (2H, m, N-CH_2).

Anal. Calcd. for $C_{13}H_{19}Br_2N_3O_3$: C, 36.73; H, 4.50; Br, 37.59; N, 9.88. Found: C, 36.95; H, 4.41; Br, 37.36; N, 9.81.

6-Azidomethyl-5-bromo-1-(2-bromoethyl)-3-methyl-2,4-(1*H*,3*H*)-pyrimidinedione (**16**).

This compound was obtained from the former fractions of chromatography and had mp 77-78° (ethanol, colorless cubes), 38%; ir: ν 2145, 2110, and 2060 (N_3), 1712 and 1660 (C=O) cm^{-1}; uv: λ max nm (log ϵ) 288 (3.931); ^{1}H-nmr: (60 MHz) δ 3.43 (3H, s, N-CH_3), 3.70 (2H, t, J = 6.0 Hz, Br-CH_2), 4.30 (2H, t, J = 6.0 Hz, N-CH_2), 4.78 (2H, s, C(6)-CH_2).

Anal. Calcd. for $C_6H_6Br_2N_5O_2$: C, 26.18; H, 2.47; Br, 43.55; N, 19.08. Found: C, 26.48; H, 2.50; Br, 43.27; N, 19.31.

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