Pyrimidine Derivatives. IX [1]. Synthesis of Bromo-substituted 5-Nitro-2,4(1*H*,3*H*)-pyrimidinedione Derivatives

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The following 5-nitro-2,4(1*H*,3*H*)-pyrimidinediones possessing bromo substituted side chains at the 1- and 6-positions were prepared by bromination of 3,6-dimethyl-1-(ω-hydroxyalkyl)-5-nitro-2,4(1*H*,3*H*)-pyrimidinediones **4a** and **4b** and its nitrates **2a** and **2b**. The three of mono-bromo derivatives are: 1-(ω-acetoxyalkyl and ω-hydroxyalkyl)-6-bromomethyl-3-methyl- **6a**, **6b**, **7a** and **7b** and 1-(ω-bromoalkyl)-3,6-dimethyl-2,4(1*H*,3*H*)-pyrimidinediones **8a** and **8b**. The one type dibromo derivatives are: 1-(ω-bromoalkyl)-6-bromomethyl-3-methyl-2,4(1*H*,3*H*)-pyrimidinediones **5a** and **5b**.

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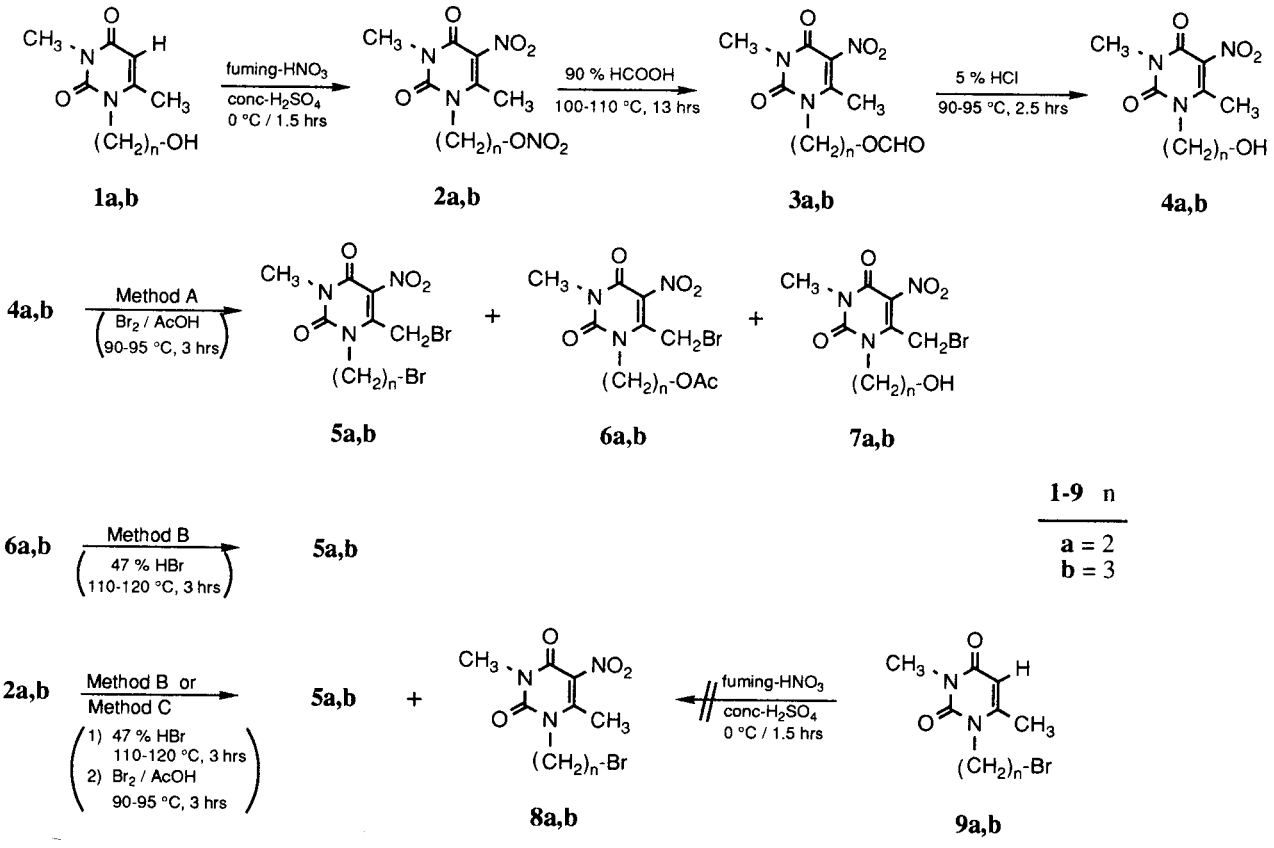
There has been considerable interest in the reactivity of 5-bromo-1-(ω-bromoalkyl)-6-bromomethyl-3-methyl-2,4-(1*H*,3*H*)-pyrimidinediones (these compounds are written as "tribromopyrimidines" in this report) with nucleophiles. Previously, we have described the preparation [2,3] of several bromopyrimidine derivatives possessing a bromo substituent at the 5-position and/or side chains at the 1- and/or 6-positions by various means, and the reaction [2,4] of the tribromopyrimidines with several nucleophiles. Thus, 5-bromo-1-(2-bromoethyl)-6-bromomethyl-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione was converted to some condensed heterocyclic compounds, for example pyrazino[4,3-*c*]- [4], [1,4]-thiazino[4,3-*c*]pyrimidines [4], and pyrimido-[6,1-*c*][1,4]-oxazines [1], by reaction with *iso*-butylamine, thioacetamide, and 2-nitropropane/sodium methoxide, respectively. Therefore, tribromopyrimidine has been found to be a useful intermediate for the preparation of condensed heterocyclic compounds possessing a pyrimidine ring.

For the purpose of comparing the reactivity of the tribromopyrimidines with that of the corresponding dibromo substituted- (side chains at the 1- and 6-positions) 5-nitropyrimidine, we prepared some dibromo substituted 5-nitropyrimidines **5**, **6**, **7**, and **8** and the results are described

Chart 1



herein.

Several procedures were considered for the preparation of the dibromo substituted 5-nitropyrimidinediones **5a** and **5b**. At first, we modified the preparation of tribromopyrimidine [2,3], which were accomplished by the bromination of the corresponding 1-(ω-hydroxyalkyl) derivatives with bromine in acetic acid.

The following procedure were considered for the preparation of 5-nitro-3,6-dimethyl-1-(ω-hydroxyalkyl)-2,4(1*H*,3*H*)-pyrimidinediones. The 3,6-dimethyl-1-(ω-hydroxyalkyl)-2,4(1*H*,3*H*)-pyrimidinediones **1a** and **1b** were treated with mixed acid [5] (prepared from fuming nitric acid and concentrated sulfuric acid) at 0° for 1.5 hours giving the nitro-esters **2a** and **2b** of 5-nitro-3,6-dimethyl-1-(ω-hydroxyalkyl)-2,4(1*H*,3*H*)-pyrimidinediones **4a** and **4b**. For the preparation of the corresponding hydroxyl compounds **4a** and **4b**, the nitro-esters were treated with diluted hydrochloric acid, however, complex reaction products were obtained and we could not isolate any pure products. The nitro-esters **2a** and **2b** were then reacted with 90% formic acid to give the corresponding formyloxy derivatives **3a** and **3b**. These compounds were easily hydrolyzed to the objective hydroxy compounds **4a** and **4b** with 5% hydrochloric acid.

Table I

Bromination of Some Pyrimidine Derivatives

Entry No.	Starting Materials	Methods [a]	Products (%) [b] 5	6	7	8
1	**4a**	A	44	43		
2	**4b**	A	10	66	8	
3	**6b**	B	90			
4	**2b**	B	36			6
5	**2a**	C	73			
6	**2b**	C	86			

[a] A, Reacted with bromine-acetic acid; B, reacted with 47% hydrobromic acid; C, reacted with 47% hydrobromic acid followed by bromine-acetic acid. [b] Isolated yields are shown.

Some bromination methods were examined as follows and the results are summarized in Table I. The obtained hydroxy compound **4a** was treated with bromine in acetic acid, and the objective dibromo substituted 5-nitro compound **5a** and 1-(2-acetoxyethyl) compound **6a** were isolated in nearly the same yields by column chromatography (entry 1). Especially, in the case of compound **4b**, which possesses three carbon atoms on the side chain at the 1-position, the acetoxypropyl compound **6b** was isolated as the major product and **5b** was obtained in a maximum 10% yield (entry 2). As previously mentioned, since the objective compounds **5a** and **5b** could not be obtained in satisfactory yields, we examined some methods using other starting materials as follows. The acetoxyl compound **6b** was converted to compound **5b** in excellent yield by reaction with 47% hydrobromic acid (entry 3). Treatment of **2b** with 47% hydrobromic acid afforded the monobromo-compound **8b** and compound **5b** in fair yield (entry 4). Generally, the methyl group at the 6-position could not be brominated by reaction with hydrobromic acid. In this case the hydrobromide would be oxidized to bromine by the generated nitrous and/or nitric acid and then the 6-methyl group was brominated by bromine under acidic conditions.

Therefore, compound **2b** was treated with 47% hydrobromic acid followed by bromine-acetic acid. The objective dibromo compound **5b** was obtained as the sole product in excellent yield (entry 6). Similarly, compound **2a** was converted to **5a** in excellent yield (entry 5). In order to find another route for the preparation of compound **5a** and **5b**, the nitration of 1-(ω-bromoalkyl) compounds **9a** and **9b** [3] were examined by mixed acid, however, several products were observed using thin layer chromatography (tlc) and no pure compounds were isolated. Therefore, we abandoned this route.

EXPERIMENTAL

General.

Melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. The ir spectra were taken in potassium bromide pellets with a JASCO IR-810 spectrophotometer. The uv spectra were measured in ethanol solution on a Hitachi 323 spectrophotometer. The nmr spectra were taken in deuteriochloroform solution on a Hitachi R-600 (60 MHz for ^{1}H), a JEOL JNM FX-90Q (90 MHz for ^{1}H, 22.5 MHz for ^{13}C), and a JEOL JNM GX-400 (400 MHz for ^{1}H, 100 MHz for ^{13}C) Fourier-transform spectrometer. Chemical shifts are reported in ppm (δ) relative to tetramethylsilane as an internal standard. Mass spectra (ms) were obtained by the electron impact (EI) ionization method on a JEOL JMS-DX-303 equipped with a JMA-DA-5000 data processor.

2-[1-(3,6-Dimethyl-5-nitro-2,4-dioxo-1,2,3,4-tetrahydro)pyrimidinyl]ethyl Nitrate (**2a**).

Fuming nitric acid (10 ml) was added dropwise to concentrated sulfuric acid (10 ml) with stirring and ice cooling. After the addition the mixture was allowed to stir for 20 minutes. Compound **1a** (7.37 g, 40 mmoles) was added to the mixed acid in the same manner and the mixture was allowed to stand while cooled with ice for an additional 1.5 hours. The reaction mixture was poured on crushed ice and the separated yellowish crystalline mass was collected. The mass was washed with 5% sodium hydrogen carbonate and recrystallized from methanol to give 9.61 g (88%) of pale yellow cubes, mp 142-143°; ir: 1720, 1675 (C=O), 1520, 1350, 1280 (O-NO_2 and C-NO_2) cm^{-1}; uv: λ max nm (log ε) 272 (3.899), 350 (2.829); ^{1}H-nmr: (90 MHz) δ 2.43 (3H, s, C(6)-CH_3), 3.40 (3H, s, N-CH_3), 4.32 (2H, t, J = 4.6 Hz, C(2')-H_2), 4.76 (2H, t, J = 4.6 Hz, C(1')-H_2); ms: m/z 274 (M^+).

Anal. Calcd. for $C_8H_{10}N_4O_7$: C, 35.04; H, 3.68; N, 20.44. Found: C, 35.01; H, 3.58; N, 20.34.

3-[1-(3,6-Dimethyl-5-nitro-2,4-dioxo-1,2,3,4-tetrahydro)pyrimidinyl]propyl nitrate (**2b**).

Compound **1b** (7.92 g, 40 mmoles) was treated as previously mentioned, yield 78%, pale yellow needles (methanol), mp 95-96°; ir: 1720, 1670 (C=O), 1520, 1365, 1275 (O-NO_2 and C-NO_2) cm^{-1}; uv: λ max nm (log ε) 275 (3.924), 350 (2.990); ^{1}H-nmr: (90 MHz) δ 2.16 (2H, m, C(2')-H_2), 2.42 (3H, s, C(6)-CH_3), 3.37 (3H, s, N-CH_3), 4.07 (2H, t, J = 6.2 Hz, C(3')-H_2), 4.58 (2H, t, J = 5.9 Hz, C(1')-H_2); ms: m/z 288 (M^+).

Anal. Calcd. for $C_9H_{12}N_4O_7$: C, 37.51; H, 4.20; N, 19.44. Found: C, 37.41; H, 4.07; N, 19.58.

3,6-Dimethyl-1-(2-formyloxyethyl)-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione (**3a**).

A solution of **2a** (1.4 g, 5.1 mmoles) in 90% formic acid (20 ml) was heated at 100-110° for 13 hours. After removal of the excess solvent *in vacuo*, the residue was dissolved in chloroform. The solution was washed with 5% sodium hydrogen carbonate, dried over magnesium sulfate, and filtered. The filtrate was concentrated to dryness, the residue was crystallized from methanol to give 1.02 g (80%) of pale yellow prisms, mp 153-154°; ir: 1720, 1640 (C=O), 1535, 1360 (C-NO_2) cm^{-1}; uv: λ max nm (log ε) 274 (3.931), 347 (2.976); ^{1}H-nmr: (90 MHz) δ 2.45 (3H, s, C(6)-CH_3), 3.39 (3H, s, N-CH_3), 4.23 (2H, t, J = 5.5 Hz, C(2')-H_2), 4.46 (2H, t, J = 5.5 Hz, C(1')-H_2), 8.07 (1H, br s, O-CHO); ms: m/z 257 (M^+).

Anal. Calcd. for $C_9H_{11}N_3O_6$: C, 42.03; H, 4.31; N, 16.34. Found: C, 41.91; H, 4.23; N, 16.33.

3,6-Dimethyl-1-(3-formyloxypropyl)-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione (**3b**).

Compound **2b** (1.44 g, 5.0 mmoles) was treated as previously mentioned, yield 80%, pale yellow needles (*n*-hexane and benzene), mp 68-70°; ir: 1710, 1660 (C=O), 1520, 1365 (C-NO_2) cm^{-1}; uv: λ max nm (log ε) 271 (3.929); ^{1}H-nmr: (90 MHz) δ 2.10 (2H, m, C(2')-H_2), 2.42 (3H, s, C(6)-CH_3), 3.38 (3H, s, N-CH_3), 4.06 (2H, dd, J = 5.5, 7.5 Hz, C(1')-H_2), 4.28 (2H, dt, J = 0.7, 6.0 Hz, C(3')-H_2), 8.08 (1H, t, J = 0.7 Hz, O-CHO); ms: m/z 271 (M^+).

Anal. Calcd. for $C_{10}H_{13}N_3O_6$: C, 44.28; H, 4.83; N, 15.49. Found: C, 44.14; H, 4.68; N, 15.50.

3,6-Dimethyl-1-(2-hydroxyethyl)-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione (**4a**).

A solution of **3a** (5.0 g, 19.4 mmoles) in 5% hydrochloric acid (100 ml) was heated at 90-95° for 2.5 hours. After removal of the solvent *in vacuo*, the residue was dissolved in chloroform. The solution was washed with 5% sodium hydrogen carbonate, dried over magnesium sulfate, and filtered. The filtrate was concentrated to dryness, the residue was crystallized from methanol to give 3.85 g (87%) of yellow cubes, mp 118-119°; ir: 3460 (OH), 1715, 1643 (C=O), 1525, 1355 (C-NO_2) cm^{-1}; uv: λ max nm (log ε) 274 (3.918), 350 (2.972); ^{1}H-nmr: (90 MHz) δ 2.38 (1H, t, J = 5.0 Hz, O-H), 2.55 (3H, s, C(6)-CH_3), 3.37 (3H, s, N-CH_3), 3.94 (2H, td, J = 3.9, 5.0 Hz, C(2')-H_2), 4.10 (2H, t, J = 3.9 Hz, C(1')-H_2); ms: m/z 229 (M^+).

Anal. Calcd. for $C_8H_{11}N_3O_5$: C, 41.92; H, 4.84; N, 18.33. Found: C, 42.07; H, 4.81; N, 18.16.

3,6-Dimethyl-1-(2-hydroxypropyl)-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione (**4b**).

Compound **3b** (5.42 g, 20.0 mmoles) was treated as previously mentioned, yield 78%, yellow cubes (ethyl acetate), mp 105-107°; ir: 3510, 3350-3200 (OH), 1710, 1640 (C=O), 1530, 1365 (C-NO_2) cm^{-1}; uv: λ max nm (log ε) 275 (3.927), 346 (3.002); ^{1}H-nmr: (90 MHz) δ 1.93 (2H, m, C(2')-H_2), 2.29 (1H, br t, O-H), 2.46 (3H, s, C(6)-CH_3), 3.39 (3H, s, N-CH_3), 3.67 (2H, m, C(3')-H_2), 4.12 (2H, t, J = 6.9 Hz, C(1')-H_2); ms: m/z 243 (M^+).

Anal. Calcd. for $C_9H_{13}N_3O_5$: C, 44.44; H, 5.39; N, 17.28. Found: C, 44.48; H, 5.21; N, 17.29.

General Procedure for Reaction of **4** with Bromine-Acetic Acid (Method A).

To a solution of **4a** or **4b** (20.0 mmoles) in acetic acid (40 ml), bromine (4.5 equivalents) was added dropwise with stirring. The mixture was heated at 90-95° for 3 hours. After removal of the solvent *in vacuo*, water (50 ml) was added and the mixture was alkalized with sodium hydrogen carbonate powdered. The mixture was extracted with chloroform (3 times). The combined extract was dried over magnesium sulfate, and filtered. The filtrate was concentrated to small volume and this was chromatographed on a silica gel column eluting with chloroform. The resulting fractions were treated as the usual manner (Table I).

General Procedure for Reaction of **6** or **2** with 47% Hydrobromic Acid (Method B).

A solution of **6b** or **2b** (20.0 mmoles) in 47% hydrobromic acid (40 ml) was heated at 120-130° for 3 hours. After removal of the solvent *in vacuo*, the residue was dissolved in chloroform (50 ml) and this was alkalized with an aqueous sodium hydrogen carbonate solution. The organic layer was separated and the aqueous layer was extracted with chloroform (3 times). The combined extract was dried over magnesium sulfate and filtered. The filtrate was concentrated to dryness and the resulting crystalline mass was recrystallized from methanol (**6b** → **5b**). In the case of **2b**, the filtrate was concentrated to small volume and this was chromatographed on a silica gel column eluting with chloroform. The resulting fractions were treated in the usual manner (Table I).

General Procedure for the Reaction of **2** with 47% Hydrobromic Acid Followed by Bromine-Acetic Acid (Method C).

A solution of **2** (5.76 g, 20.0 mmoles) in 47% hydrobromic acid (50 ml) was heated at 120-130° for 3 hours. After removal of the solvent *in vacuo*, the residue was dissolved in acetic acid (100 ml) and bromine (10 ml, *ca.* 9 equivalents) was added dropwise. The mixture was treated as mentioned above in method A. The filtrate was concentrated to dryness and the resulting crystalline mass was recrystallized from methanol (Table I).

1-(2-Bromoethyl)-6-bromomethyl-3-methyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione (**5a**).

The yield is reported in Table I, yellow needles (methanol), mp 125-127°; ir: 1720, 1670 (C=O), 1530, 1350 (C-NO_2) cm^{-1}; uv: λ max nm (log ε) 289 (3.850); ^{1}H-nmr: (90 MHz) δ 3.49 (3H, s, N-CH_3), 3.77 (2H, t, J = 5.8 Hz, C(2')-H_2), 4.49 (2H, t, J = 5.8 Hz, C(1')-H_2), 4.45 (2H, s, C(6)-CH_2); ms: m/z 373 (M^+ for 2 x ^{81}Br), 371 (M^+ for ^{81}Br + ^{79}Br), 369 (M^+ for 2 x ^{79}Br).

Anal. Calcd. for $C_8H_9Br_2N_3O_4$: C, 25.90; H, 2.45; Br, 43.08; N, 11.33. Found: C, 25.78; H, 2.42; Br, 42.67; N, 11.12.

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

The yield is reported in Table I, pale yellow (ethyl acetate and ether), mp 78-79°; ir: 1743, 1720, 1665 (C=O), 1520, 1350 (C-NO_2) cm^{-1}; uv: λ max nm (log ε) 289 (3.862); ^{1}H-nmr: (90 MHz) δ 2.08 (3H, s, CO-CH_3), 3.41 (3H, s, N-CH_3), 4.35 (4H, m, C(1')-H_2 and C(2')-H_2), 4.42 (2H, s, C(6)-CH_2); ms: m/z 335 (M^+ for ^{81}Br), 333 (M^+ for ^{79}Br).

Anal. Calcd. for $C_{10}H_{12}BrN_3O_6$: C, 34.30; H, 3.45; Br, 22.82; N, 12.00. Found: C, 34.27; H, 3.32; Br, 22.95; N, 12.08.

1-(2-Bromoethyl)-3,6-dimethyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione (**8a**).

The yield is reported in Table I, pale yellow (methanol), mp 120-122°; ir: 1710, 1660 (C=O), 1530, 1355 (C-NO_2) cm^{-1}; uv: λ max nm (log ε) 268 (3.9398); ^{1}H-nmr: (90 MHz) δ 2.48 (3H, s, C(6)-H_3), 3.39 (3H, s, N-CH_3), 3.68 (2H, dd, J = 5.7, 6.4 Hz, C(2')-H_2), 4.30 (2H, dd, J = 5.7, 6.4 Hz, C(1')-H_2); ms: m/z 293 (M^+ for ^{81}Br), 291 (M^+ for ^{79}Br).

Anal. Calcd. for $C_8H_{10}BrN_3O_4$: C, 32.89; H, 3.45; Br, 27.36; N, 14.39. Found: C, 32.94; H, 3.29; Br, 27.90; N, 14.36.

6-Bromomethyl-1-(3-bromopropyl)-3-methyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione (**5b**).

The yield is reported in Table I, yellow cubes (methanol), mp 77-79°; ir: 1725, 1663 (C=O), 1535, 1360 (C-NO_2) cm^{-1}; uv: λ max nm (log ε) 291 (3.919); ^{1}H-nmr: (90 MHz) δ 2.37 (2H, m, C(2')-H_2), 3.40 (3H, s, N-CH_3), 3.51 (2H, t, J = 5.9 Hz, C(3')-H_2), 4.19 (2H, t, J = 5.9 Hz, C(1')-H_2), 4.35 (2H, s, C(6)-CH_2); ms: m/z 386 (M^+ for 2 x ^{81}Br), 384 (M^+ for ^{81}Br + ^{79}Br), 382 (M^+ for 2 x ^{79}Br).

Anal. Calcd. for $C_9H_{11}Br_2N_3O_4$: C, 28.07; H, 2.88; Br, 41.51; N, 10.91. Found: C, 28.07; H, 2.87; Br, 41.98; N, 10.73.

1-(3-Acetoxypropyl)-6-bromomethyl-3-methyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione (**6b**).

The yield is reported in Table I, yellow cubes (methanol), mp 98-99°; ir: 1740, 1725, 1675 (C=O), 1520, 1480, 1365 (C-NO_2 and O-NO_2) cm^{-1}; uv: λ max nm (log ε) 291 (3.916); ^{1}H-nmr: (90 MHz) δ 2.09 (3H, s, CO-CH_3), 1.9-2.4 (2H, m, C(2')-H_2), 3.41 (3H, s, N-CH_3), 4.0-4.3 (4H, m, C(3')-H_2, C(1')-H_2), 4.30 (2H, s, C(6)-CH_2); ms: m/z 365 (M^+ for ^{81}Br), 363 (M^+ for ^{79}Br).

Anal. Calcd. for $C_{11}H_{14}BrN_3O_6$: C, 36.28; H, 3.87; Br, 21.94; N, 11.52. Found: C, 36.44; H, 3.75; Br, 21.88; N, 11.61.

6-Bromomethyl-1-(3-hydroxypropyl)-3-methyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione (**7b**).

The yield is reported in Table I, pale yellow viscous oil. This compound was converted to **6b** by reaction with acetic anhydride and it was identified with the authentic sample of **6b**; ir (neat): 1700, 1660 (C=O), 1530, 1350 (C-NO_2) cm^{-1}; ^{1}H-nmr: (90 MHz) δ 2.0 (2H, m, C(2')-H_2), 3.1 (1H, br s, OH), 3.38 (3H, s, N-CH_3), 3.69 (2H, t, J = 5.5 Hz, C(3')-H_2), 4.21 (2H, t, J = 6.5 Hz, C(1')-H_2), 4.48 (2H, s, C(6)-CH_2); ms: m/z 323 (M^+ for ^{81}Br), 321 (M^+ for ^{79}Br); ms: (high-resolution) Calcd. for $C_9H_{12}{}^{79}BrN_3O_5$: 320.9960. Found: 320.9951.

1-(3-Bromopropyl)-3,6-dimethyl-5-nitro-2,4(1*H*,3*H*)-pyrimidinedione (**8b**).

To a solution of **4b** (0.73 g, 3.0 mmoles) in chloroform (20 ml), phosphorus tribromide (3 ml) was added dropwise and the mixture was refluxed for 4 hours. Some ice-water was added to the reaction mixture and alkalized with sodium hydrogen carbonate powder. The organic layer was separated and the aqueous layer was extracted with chloroform (3 times). The combined extract was dried over magnesium sulfate and filtered. The filtrate was concentrated to dryness and the oily residue was purified by passing through a short silica gel column. The resulting substance was crystallized from ethyl acetate to give 0.66 g (72%) of pale yellow needles, mp 91-92°, yield in Table I (by reaction with 47% hydrobromic acid); ir: 1720, 1660 (C=O), 1520, 1360 (C-NO_2 and O-NO_2) cm^{-1}; uv: λ max nm (log ε) 271 (3.921); ^{1}H-nmr: (90 MHz) δ 2.25 (2H, m, C(2')-CH_2), 2.45 (3H, m, C(6)-H_3), 3.38 (3H, s, N-CH_3), 3.50 (2H, t, J = 6.0 Hz, C(3')-H_2), 4.11 (2H, dd, J = 3.1, 7.5 Hz, C(1')-CH_2); ms: m/z 307 (M^+ for ^{81}Br), 305 (M^+ for ^{79}Br).

Anal. Calcd. for $C_9H_{12}BrN_3O_4$: C, 35.31; H, 3.95; Br, 26.10; N, 13.73. Found: C, 35.44; H, 3.98; Br, 25.98; N, 13.63.

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