Pyrimidine Derivatives. VI [1]. Synthesis of Mono-, Di-, Tri-, and Tetrabromo-Substituted Pyrimidine Derivatives

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Received May 15, 1991

The following bromo-2,4(1*H*,3*H*)-pyrimidinediones possessing a bromo substituent at the 5-position and side chains at the 1- and 6-positions were prepared. The three types of mono-bromo derivatives are: 1-(bromoalkyl)-3,6-dimethyl- **3a-d**, 5-bromo-3,6-dimethyl-1-(hydroxyalkyl)- **4a-d**, and 1-(acetoxyalkyl)-5-bromo-3,6-dimethyl-2,4(1*H*,3*H*)-pyrimidinediones **11a-d**. The three types of dibromo derivatives are: 5-bromo-1-(bromoalkyl)-3,6-dimethyl- **5a-d**, 1-(acetoxyalkyl)-5-bromo-6-bromomethyl- **8a**, **8c**, and **8d**, and 5-bromo-6-bromomethyl 1-(hydroxyalkyl)-2,4(1*H*,3*H*)-pyrimidinediones **9a**, **9c**, and **9d**. Likewise one group of tribromo and one group of tetrabromo derivatives are: 5-bromo-1-(bromoalkyl)-6-bromomethyl-**7a-d** and 5-bromo-1-(bromoalkyl)-6-dibromomethyl-2,4(1*H*,3*H*)-pyrimidinediones **6a-d**.

J. Heterocyclic Chem., **28**, 1901 (1991).

A number of papers have appeared on the reactions of 5-bromouracil derivatives with nucleophiles to give 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 amines to give 6-aminomethyl-2,4(1*H*,3*H*)-pyrimidinedione and the 5-debrominated Schiff's base.

Previously, we described [1] the bromination of 1-(2-hydroxyethyl and 2-hydroxypropyl)-3,6-dimethyl-2,4(1*H*,-3*H*)-pyrimidinediones **2a** and **2b** with bromine in acetic acid to give 5-bromo-1-(2-bromoalkyl)-6-bromomethyl-2,4-(1*H*,3*H*)-pyrimidinediones **7a** and **7b** as major products and the reactions of **7a** and **7b** with several nucleophiles.

There has been considerable interest in the reactivity of bromopyrimidine derivatives with nucleophiles. Therefore, we prepared several bromopyrimidine derivatives possessing a bromo substituent at the 5-position and side chains at the 1- and 6-positions by various means, and the results are reported herein.

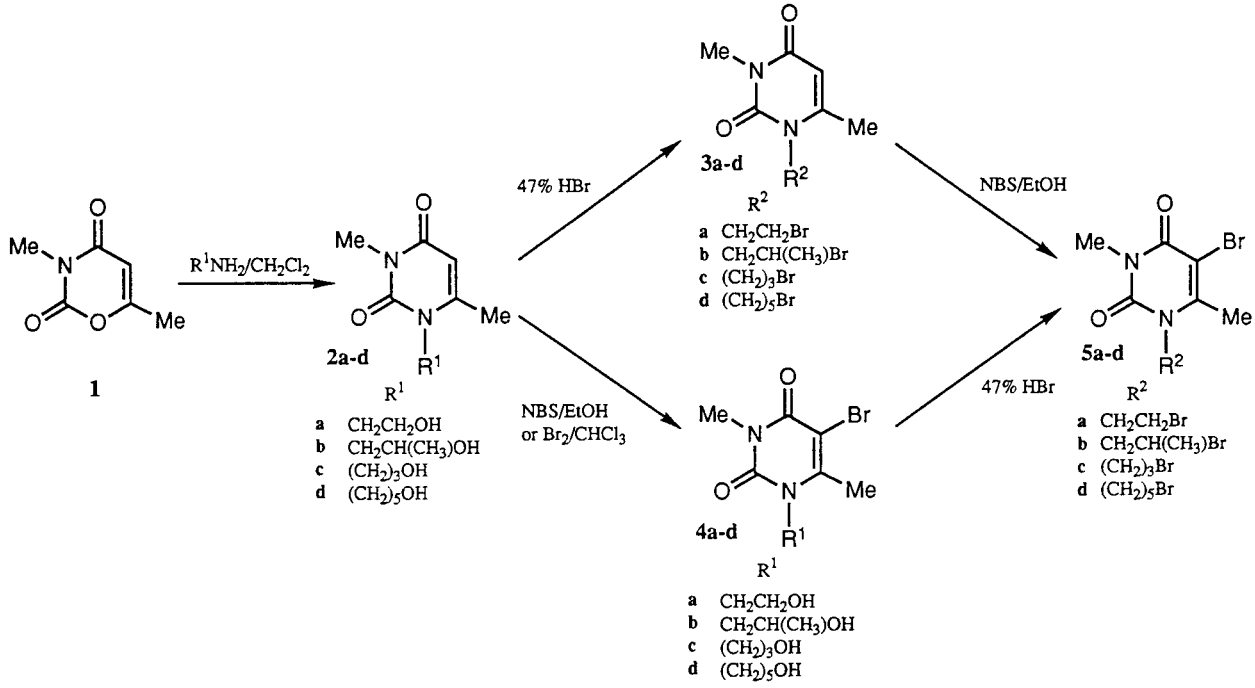

Chart 1

The starting materials **2a-d**, 3,6-dimethyl-1-(hydroxyalkyl)-2,4(1*H*,3*H*)-pyrimidinediones, were prepared in a manner similar to that described in a previous paper [1]. Thus 1,3-oxazinedione (**1**) was treated with the corresponding aminoalcohols.

The 1-hydroxyalkyl compounds **2a-d** were converted to 1-bromoalkyl compounds **3a-d** by treatment with 47% hydrobromic acid in a general method.

For the preparation of the 6-bromomethyl derivatives, 3,6-dimethylpyrimidines **2a-d** were treated with *N*-bromosuccinimide (NBS) in the presence of benzoyl peroxide. However, we could not obtain the desired 6-bromomethyl compounds, instead we preferentially obtained the 5-bromo compounds **4a-d**. Also compounds **4a-d** were obtained by reaction with bromine in chloroform.

One dibromo compound series **5a-d** was obtained by the following two methods: a) by reaction of 1-bromoalkyl pyrimidines **3a-d** with *N*-bromosuccinimide; b) by reaction of 5-bromo-1-(hydroxyalkyl)-pyrimidines **4a-d** with 47% hydrobromic acid.

Table I

Reactions [a] of Compound 2c with Bromine-Acetic Acid (Water)

Entry No.	Concentration of Acetic Acid %	ml	Products [b] (%) 6	7	8	9	4
1	100	40	28	51	2		
2	100 [c]	40	4	76	3		
3 [d]	100 [c]	40	24	69			
4	95	40		39	13	23	
5	50	40					47
6	20	40					71

[a] Compounds 2c (5.0 g. 25.2 mmoles) reacted with bromine (3.8 ml, 75.7 mmoles) at 90-95° for 2 hours except entry 3. [b] Isolated yields are shown. [c] Contained five drops of water. [d] Reaction was carried out at 100-105° for 2 hours.

We have described [1] that bromination of the 6-methyl groups of **2a** and **2b** was accomplished by treatment with bromine in acetic acid (either glacial or aqueous) and thus we prepared the tetrabromo **6a**, tribromo **7a** and **7b**,

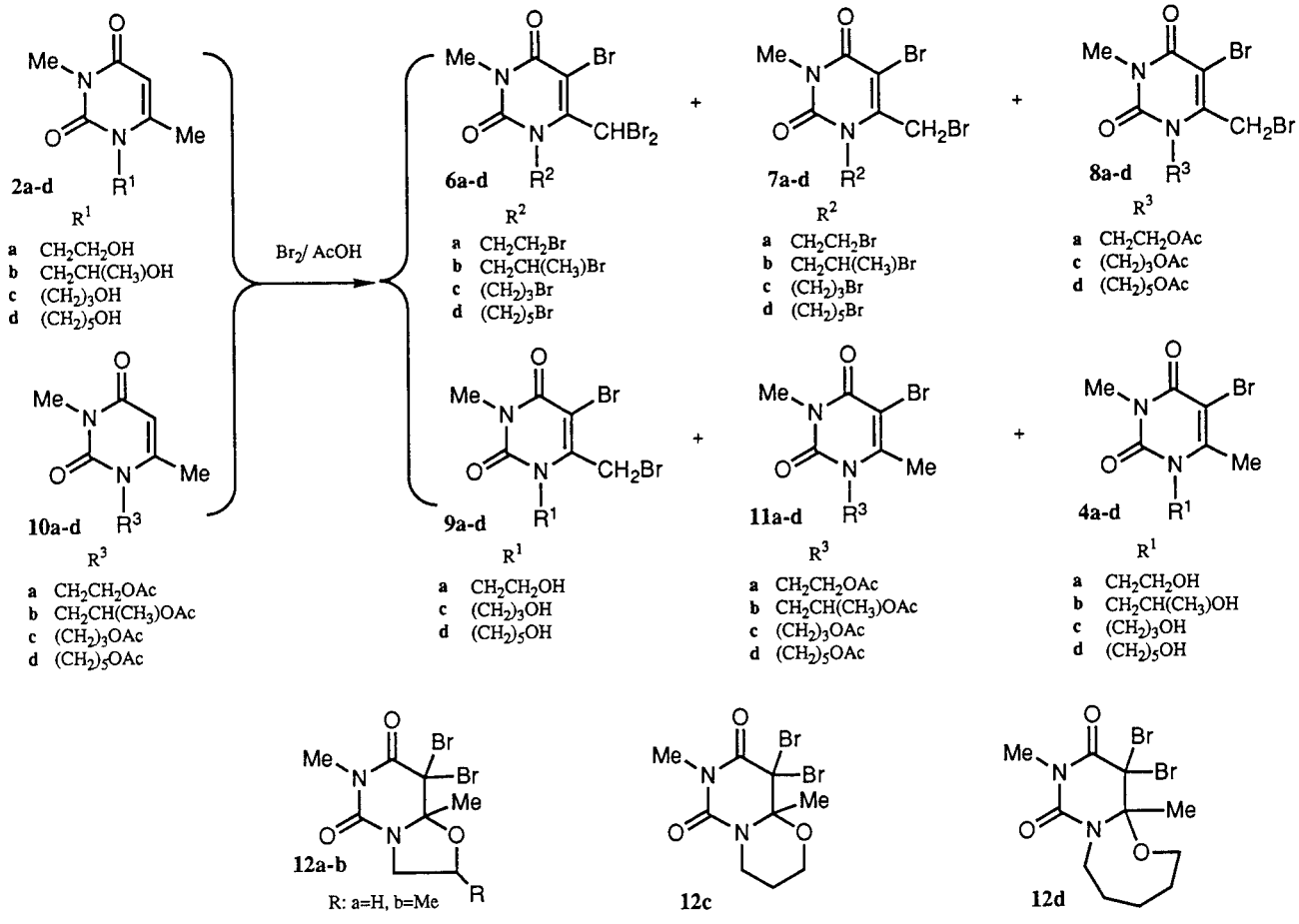

Chart 2

Table II

Reactions [a] of Compound 4a-d with Bromine-Acetic Acid (Water)

Entry No.	Compound Number	Concentration of Acetic Acid %	ml	Products [b] (%) 6	7	8/9	5	4/11	12
1	10a	100	7	3	70		3		
2	10b	100	7		48		16	23	
3	10c	100	7	6	63	2			
4	10d	100	7	17	56	6			
5	10a	95	7		34	20	17	9	
6	10b	95	7		39		16	3	7
7	10c	95	7		32	44			
8	10d	95	7		26	63			
9	10a	50	14			23		26	38
10	10b	50	14					29	53
11	10c	50	14			10		59	
12	10d	50	14			14		53	

[a] Compounds 10a-d (4.0 mmoles) reacted with bromine (12.0 mmoles) at 90-95° for 2 hours. [b] Isolated yields are shown.

Table III

Physical and Analytica Data for Pyrimidine Derivatives

Compound No.	R^1	R^5	R^6	Yield (%)	Mp (°C) Solvent	Formula	Analysis Calcd. (Found) C	H	N	Br
2c	$(CH_2)_3OH$	H	CH_3	65	94-96 Acetone	$C_9H_{14}N_2O_3$	54.53 (54.69	7.12 7.22	14.13 13.99)	
2d	$(CH_2)_5OH$)	H	CH_3	62	104-105 AcOEt	$C_{11}H_{18}N_2O_3$	58.39 (58.34	8.02 8.04	12.38 12.26)	
3a	$(CH_2)_2Br$	H	CH_3	94	96-97 Ether	$C_8H_{11}BrN_2O_2$	38.89 (38.69	4.49 4.54	11.34 11.32	32.34 32.55)
3b	CH_2CHBr | CH_3	H	CH_3	70	98-99 AcOEt	$C_9H_{13}BrN_2O_2$	41.40 (41.41	5.02 4.92	10.73 10.84	30.60 30.49)
3c	$(CH_2)_3Br$	H	CH_3	91	104-105 AcOEt	$C_9H_{13}BrN_2O_2$	41.40 (41.42	5.02 4.96	10.73 10.63	30.60 30.17)
3d	$(CH_2)_5Br$	H	CH_3	68	69-70 *n*-Hexane	$C_{11}H_{17}BrN_2O_2$	45.69 (45.88	5.93 5.81	9.69 9.79	27.63 27.59)
4a	$(CH_2)_2OH$	Br	CH_3	63	147-148 AcOEt	$C_8H_{11}BrN_2O_3$	36.52 (36.58	4.21 4.13	10.65 10.63	30.37 30.29)
4b	CH_2CHOH | CH_3	Br	CH_3	85	140-141 AcOEt	$C_9H_{13}BrN_2O_3$	39.01 (39.03	4.73 4.59	10.11 10.21	28.84 28.59)
4c	$(CH_2)_3OH$	Br	CH_3	78	145-146 AcOEt	$C_9H_{13}BrN_2O_3$	39.01 (38.98	4.73 4.68	10.11 10.21	28.84 28.98)
4d	$(CH_2)_5OH$	Br	CH_3	73	76-78 AcOEt	$C_{11}H_{17}BrN_2O_3$	43.29 (43.23	5.61 5.47	9.18 9.08	26.18 26.02)
5a	$(CH_2)_2Br$	Br	CH_3	77	198-200 $CHCl_3$-AcOEt	$C_8H_{10}Br_2N_2O_2$	29.48 (29.36	3.09 3.05	8.59 8.67	49.02 48.88)
5b	CH_2CHBr | CH_3	Br	CH_3	68	107-108 AcOEt	$C_9H_{12}Br_2N_2O_2$	31.79 (32.04	3.56 3.66	8.24 8.31	47.00 46.93)
5c	$(CH_2)_3Br$	Br	CH_3	63	116-117 AcOEt	$C_9H_{12}Br_2N_2O_2$	31.79 (31.86	3.56 3.40	8.24 8.19	47.00 46.97)
5d	$(CH_2)_5Br$	Br	CH_3	62	103-104 AcOEt	$C_{11}H_{16}Br_2N_2O_2$	35.90 (36.17	4.38 4.29	7.61 7.71	43.42 43.09)

Table IV

Proton Nuclear Magnetic Resonance Spectral Data for Pyrimidine Derivatives

Compound No.	δ (ppm, deuteriochloroform), J (Hz)						
			R^1		$N\text{-}CH_3$	R^5	R^6
	$-NCH_2-$	-CHnY	$-CH_2-/CH_3$	$OH/OCOCH_3$			
2c	4.02 t J = 6.8	3.65 t J = 5.7	1.89 q J = 5.7, 6.8	3.33 s	3.32 s	5.62 s	2.32 s
2d	3.83 t J = 7.6	3.65 t J = 6.0	1.38-1.78 m	2.29 s	3.31 s	5.60 s	2.26 s
3a	4.19 t J = 6.5	3.64 t J = 6.5	–	–	3.33 s	5.63 q J = 0.9	2.32 d J = 0.9
3b	3.90 dd J = 9.0, 14.5 4.13 dd J = 4.6, 14.5	4.6 m	1.76 (CH_3) d, J = 6.6	–	3.32 s	5.62 q J = 0.9	2.35 d J = 0.9
3c	4.00 dd J = 5.5, 7.3	3.47 t J = 6.2	2.1-22 m	–	3.32 s	5.61 q J = 0.9	2.29 d J = 0.9
3d	3.73 dd J = 6.5, 9.0	3.43 t J = 6.4	1.4-2.0 m	–	3.32 s	5.60 q J = 0.9	2.25 d J = 0.9
4a	3.8-4.4 m		–	3.6 bs	3.34 s	–	2.63 s
4b	3.75 dd J = 9.2, 14.1 4.08 dd J = 2.4, 14.1	4.6 m	1.30 (CH_3) d, J = 6.2	3.47 d J = 4.8	3.35 s	–	2.64 s
4c	4.13 t J = 6.7	3.62 dd J = 4.6, 5.5	1.70-2.04 m	2.70 t J = 4.6	3.41 s	–	2.58 s
4d	3.92 m	3.68 m	1.2-1.8 m	3.3 bs	3.40 s	–	2.54 s
5a	4.31 t J = 6.6	3.61 t J = 6.6	–	–	3.41 s	–	2.62 s
5b	4.03 dd J = 9.0, 14.5 4.26 dd J = 4.8, 14.5	4.6 m	1.76 (CH_3) d, J = 6.6	–	3.41 s	–	2.65 s
5c	4.11 t J = 5.7	3.48 t J = 5.9	2.0-2.4 m	–	3.40 s	–	2.59 s
5d	3.92 dd J = 6.5, 8.6	3.43 t J = 6.4	1.4-2.04 m	–	3.40 s	–	2.54 s

dibromo **8a** derivatives and bicyclic compounds **12a** and **12b**. For the preparation of 6-bromomethyl derivatives, 3,6-dimethyl-1-(3-hydroxypropyl)-2,4(1*H*,3*H*)-pyrimidinedione **2c** was treated with bromine in acetic acid (either glacial or aqueous) and the results are shown in Table I.

When the reaction was carried out in acetic acid at 90-95°, **6c** (28%), **7c** (51%), and a small amount of **8c** were obtained (entry 1). A small amount of water (5 drops) was added to the reaction solvent and the reaction was carried out in the same way as described above. The resulting product could be purified by just recrystallization and compound **7c** was isolated in good yield (76%) (entry 2). At an elevated reaction temperature (100-105°), the yield of **7c** was slightly decreased (69%) and **6a** was increased (24%) (entry 3). The reaction was carried out in 95% acetic acid, yielding three products **7c**, **8c**, and **9c** (entry 4). When 50% acetic acid was used as the solvent, **4c** was obtained as the sole product (entry 5). Compound **4c** was prepared exclusively in 20% acetic acid (entry 6). As mentioned above, the yield of **4c** increased with increased dilution of the solvent. However, under any reaction conditions mentioned above, a bicyclic compound such as **12c** could not be obtained.

Similar treatment of compound **2d** with bromine in acetic acid gave 5-bromo-6-bromomethyl-1-(5-bromopentyl)- **7d** (74%) and 5-bromo-6-bromomethyl-1-(5-hydroxypentyl)-2,4(1*H*,3*H*)-pyrimidinedione **9d** (11%). Also in this case, no bicyclic compound **12d** was obtained under any reaction conditions.

In order to find a convenient method of preparation of 5-bromo-6-bromomethyl derivatives **8** and/or **9**, 3,6-dimethyl-1-(acetoxyalkyl)-2,4(1*H*,3*H*)-pyrimidinediones **10a-d** was treated at 90-95° for 2 hours with bromine in acetic acid (glacial or aqueous) and the results are summarized in Table II. The reactions were carried out in acetic acid, and the major products were **7a-d** in all cases (entries 1-4). A distinct difference was observed between two carbon atoms or more on the side chain at the

Table V
Physical and Analytical Data for Pyrimidine Derivatives

Compound No.	R^1	R^5	R^6	Mp (°C) Solvent	Formula	Analysis Calcd. (Found) C	H	N	Br
6b	CH_2CHBr | CH_3	Br	$CHBr_2$	paste	$C_9H_{10}Br_4N_2O_2$	hrms was satisfactory, see experimental			
6c	$(CH_2)_3Br$	Br	$CHBr_2$	135-136 Acetone	$C_9H_{10}Br_4N_2O_2$	21.71 (21.93	2.02 2.00	5.63 5.63	64.20 63.84)
6d	$(CH_2)_5Br$	Br	$CHBr_2$	paste	$C_{11}H_{14}Br_4N_2O_2$	hrms was satisfactory, see experimental			
7c	$(CH_2)_3Br$	Br	CH_2Br	104-105 MeOH	$C_9H_{11}Br_3N_2O_2$	25.80 (25.70	2.65 2.71	6.69 6.65	57.22 57.18)
7d	$(CH_2)_5Br$	Br	CH_2Br	94-95 AcOEt	$C_{11}H_{15}Br_3N_2O_2$	29.56 (29.86	3.38 3.36	6.27 6.18	53.63 53.41)
8c	$(CH_2)_3OAc$	Br	CH_2Br	96-97 MeOH	$C_{11}H_{14}Br_2N_2O_4$	33.19 (33.25	3.55 3.52	7.04 6.91	40.15 39.93)
8d	$(CH_2)_5OAc$	Br	CH_2Br	81-82 Ether	$C_{13}H_{18}Br_2N_2O_4$	36.64 (36.76	4.26 4.10	6.57 6.58	37.50 37.24)
9a	$(CH_2)_2OH$	Br	CH_2Br	161-162 Acetone	$C_8H_{10}Br_2N_2O_3$	28.10 (28.35	2.95 3.06	8.19 8.01	46.73 46.42)
9c	$(CH_2)_3OH$	Br	CH_2Br	93-95 Acetone	$C_9H_{12}Br_2N_2O_3$	30.36 (30.63	3.40 3.40	7.86 7.96	44.89 44.50)
9d	$(CH_2)_5OH$	Br	CH_2Br	82-83 AcOEt	$C_{11}H_{16}Br_2N_2O_3$	34.40 (34.45	4.20 4.10	7.29 7.27	41.61 41.19)
10a	$(CH_2)_2OAc$	H	CH_3	113-114 Acetone	$C_{10}H_{14}N_2O_4$	53.09 (53.22	6.24 6.27	12.38 12.52)	
10b	CH_2CHOAc | CH_3	H	CH_3	88-89 Ether	$C_{11}H_{16}N_2O_4$	54.99 (55.00	6.71 6.66	11.66 11.68)	
10c	$(CH_2)_3OAc$	H	CH_3	89-90 AcOEt	$C_{11}H_{16}N_2O_4$	54.99 (54.86	6.71 6.62	11.66 11.61)	
10d	$(CH_2)_5OAc$	H	CH_3	59-60 Ether	$C_{13}H_{20}N_2O_4$	58.19 (58.24	7.51 7.43	10.44 10.43)	
11a	$(CH_2)_2OAc$	Br	CH_3	130-131 AcOEt	$C_{10}H_{13}BrN_2O_4$	39.36 (39.46	4.29 4.08	9.18 9.31	26.17 26.39)
11b	CH_2CHOAc | CH_3	Br	CH_3	112-113 AcOEt	$C_{11}H_{15}BrN_2O_4$	41.40 (41.42	4.74 4.58	8.78 8.77	25.04 24.98)
11c	$(CH_2)_3OAc$	Br	CH_3	60-61 Ether	$C_{11}H_{15}BrN_2O_4$	41.40 (41.56	4.74 4.61	8.78 8.99	25.04 25.31)
11d	$(CH_2)_5OAc$	Br	CH_3	71-73 AcOEt	$C_{13}H_{19}BrN_2O_4$	44.97 (45.12	5.52 5.36	8.07 7.96	23.01 22.86)

1-position in the case of the reaction in 95% and 50% acetic acid. Thus compounds **7a** and **7b** were the major products in the case of two carbon atoms (entries 5 and 6) and compounds **8c** and/or **9c** and **8d** and/or **9d** were the major products with more than two carbon atoms (entries 7 and 8). In the reaction with 50% acetic acid, cyclic compounds **12a** and **12b** were the major products (entries 9 and 10) as in a similar reaction with **2a** and **2b** and 5-bromo compounds **4c**, **4d**, **11c**, **11d** were the major products (entries 11 and 12).

The tribromopyrimidines **7a-d** could be also obtained by the following three methods: (a) brimination of **5a-d** with bromine in acetic acid; (b) reaction of **8a-d** with hydrobromic acid; and (c) reaction of **9a-d** with hydrobromic acid. The treatment of compounds **7a-d** with bromine-acetic acid resulted in tetrabromopyrimidines **6a-d**. However, these were incomplete reactions and the starting materials were recovered in the case of **7b** and **7d**.

Conclusion.

Two types of monobromo- **3a-d**, **4a-d** and four types of dibromopyrimidinediones **5a-d**, **8a-d**, **9a-d**, **12a-d** were obtained. In addition tribromo- **7a-d** and tetrabromopyrimidinediones **6a-d** were prepared. However, some of

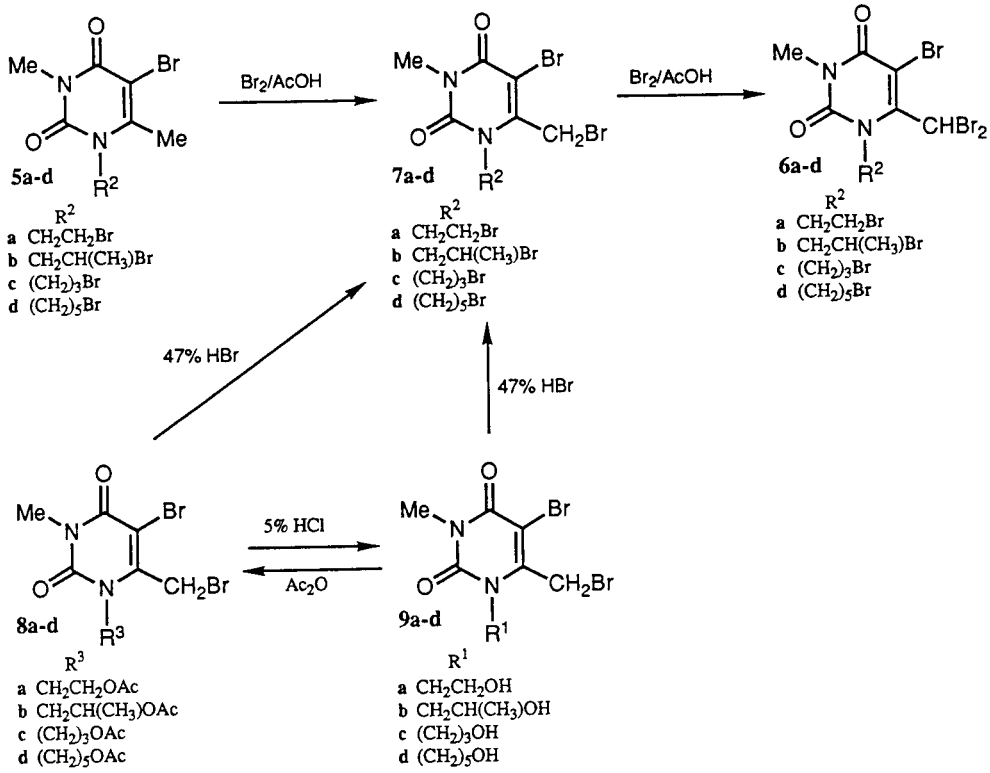

Chart 3

Table VI

Proton Nuclear Magnetic Resonance Spectral Data for Pyimidine Derivatives

Compound No.	δ (ppm, deuteriochloroform), J (Hz) $-NCH_2-$	$-CHnY$	R^1 $-CH_2-/CH_3$	$OH/OCOCH_3$	$N-CH_3$	R^5	R^6
6b	4.4 m	5.1 m	1.80 d J = 6.6	–	3.43 s	–	7.41 s
6c	4.47 m	3.55 t J = 6.4	2.5 m	–	3.43 s	–	7.49 s
6d	4.33 t J = 6.5	3.45t J = 6.2	1.3-2.0 m	–	3.42 s	–	7.48 s
7c	4.21 m	3.50 t J 6.1	2.3 m	–	3.41 s	–	4.59 s
7d	4.05 dd J = 6.4, 8.8	3.44 t J = 6.4	1.4-2.1 m	–	3.41 s	–	4.51 s
8c	4.0-4.4 m		2.10 m	2.05 s ($COCH_3$)	3.37 s	–	4.54 s
8d	4.0-4.2 m		1.2-2.0 m	2.05 s ($COCH_3$)	3.41 s	–	4.50 s
9a	4.26 t J = 5.5	3.96 q J = 0.9	–	2.71 bt J = 5.5	3.39 s	–	4.96 s
9c	4.22 t J = 6.6	3.68 t J = 5.5	1.98 m	2.4 bs	3.42 s	–	4.64 s
9d	4.03 t J = 6.5	3.68 t J = 5.5	1.2-2.0 m		3.41 s	–	4.51 s

10a	4.1-4.3 m		–	2.06 s ($COCH_3$)	3.32 s	5.61 s	2.28 s
10b	3.71 dd J = 8.8, 14.5 4.10 dd J = 3.7, 14.5	5.26 m	1.30 d J = 6.4	1.99 s ($COCH_3$)	3.31 s	5.57 q J = 0.9	2.28 d J = 0.9
10c	4.15 t J = 6.0	3.94 t J = 5.7	2.04 m	2.06 s ($COCH_3$)	3.32 s	5.61 q J = 0.9	2.26 d J = 0.9
10d	4.09 t J = 5.8	3.83 t J = 5.6	1.6 m	2.04 s ($COCH_3$)	3.32 s	5.58 q J = 0.9	2.24 d J = 0.9
11a	4.2-4.4 m			2.07 s ($COCH_3$)	3.40 s	–	2.59 s
11b	3.89 dd J = 8.8, 14.7 4.16 dd J = 3.7, 14.7	5.3 m	1.31 d J = 6.4	1.99 s ($COCH_3$)	3.39 s	–	2.58 s
11c	4.0-4.2 m			2.06 s ($COCH_3$)	3.40 s	–	2.56 s
11d	4.09 t J = 6.2	3.94 t J = 6.6	1.6 m	2.05 s ($COCH_3$)	3.40 s	–	2.54 s

bromo derivatives, 6-bromomethyl-3-methyl-1-(hydroxyalkyl and bromoalkyl)pyrimidinediones, could not be obtained.

EXPERIMENTAL

Melting points were determined on a Yanagimoto micro-melting point apparatus and are uncorrected. The ir spectra were recorded with a JASCO IR-810 spectrophotometer. The uv spectra were recorded on a HITACHI 323 spectrophotometer. The nmr spectra were recorded on a HITACHI R-600 (60 MHz for ^1H), a JEOL FX-90Q (90 MHz for ^1H, 22.5 MHz for ^{13}C), and a JEOL GX-400 (400 MHz for ^1H, 100 MHz for ^{13}C) Fourier-transform spectrometer. 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.

[I] General Procedure for 3,6-Dimethyl-1-(hydroxyalkyl)-2,4(1*H*,3*H*)-pyrimidinedione (**2**).

Aminoalcohol (100 mmoles) was added to a solution of 1,3-oxazine **1** (60 mmoles) in dichloromethane (20 ml) with stirring at room temperature or with ice cooling. The mixture was stirred for 1 hour at room temperature. The solvent was removed and the residue was heated on a boiling water bath for 3 hours. The reaction mixture was acidified with 10% hydrochloric acid and extracted with chloroform (3 times). The combined extract was dried over magnesium sulfate and the solvent was removed. The residue was crystallized from a suitable solvent.

Compounds **2a** [5] and **2b** [1] have been previously reported and were obtained.

Compound **2c** [7] had ir (potassium bromide): ν 1700, 1698, 1680, 1640 (C=O), 3300, 3250 (OH) cm^{-1}; uv (ethanol): λ max nm (log ϵ) 270 (4.080).

Compound **2d** had ir (potassium bromide): ν 1703, 1685, 1657 (C=O), 3470, 2940 (OH) cm^{-1}; uv (ethanol): λ max nm (log ϵ) 268 (4.047).

[II] General Procedure for 1-(Bromoalkyl)-3,6-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (**3**).

(a) A mixture of **2** (10.0 mmoles) and 47% hydrobromic acid (15 ml) was heated at 130-140° for 3 hours. The reaction mixture was concentrated to dryness under reduced pressure. The residue was neutralized with 5% sodium hydrogen carbonate and the mixture was extracted with chloroform (3 times). After drying over magnesium sulfate, the solvent was removed and the resulting mass was crystallized from a suitable solvent.

(b) Phosphorus tribromide (3 ml) was added to a solution of **2** (3.0 mmoles) in chloroform (20 ml) with stirring at room temperature. The mixture was refluxed for 4 hours. After removal of the solvent, the residue was quenched with water, and the mixture was extracted with chloroform (3 times). The combined extract was washed with 5% sodium hydrogen carbonate and dried over magnesium sulfate. The solvent was removed and the residue was crystallized from a suitable solvent.

Compound **3a** [7] had ir (potassium bromide): ν 1695, 1663 (C=O) cm^{-1}; uv (ethanol): λ max nm (log ϵ) 265 (3.952); ^{13}C-nmr (deuteriochloroform): δ 20.24 (C-Me), 27.71 (N-Me), 28.28 ($-CH_2Br$), 46.24 ($N-CH_2$), 101.86 (C_5), 150.84 (C_6), 151.95 (C_2), 162.00 (C_4).

Compound **3b** had ir (potassium bromide): ν 1700, 1670 (C=O) cm^{-1}; uv (ethanol): λ max nm (log ϵ) 265 (4.046).

Compound **3c** had ir (potassium bromide): ν 1690, 1655 (C=O) cm^{-1}; uv (ethanol): λ max nm (log ϵ) 212 (3.880), 266 (4.030).

Compound **3d** had ir (potassium bromide): ν 1690, 1668 (C=O) cm^{-1}; uv (ethanol): λ max nm (log ϵ) 214 (3.795), 268 (4.010).

[III] General Procedure for 5-Bromo-3,6-dimethyl-1-(hydroxyalkyl)-2,4(1*H*,3*H*)-pyrimidinedione (**4**).

(a) A mixture of *N*-bromosuccinimide (NBS) (5.0 mmoles) in ethanol (30 ml) was added to a solution of **2** (4.0 mmoles) in ethanol (20 ml) with stirring, and the mixture was allowed stand at room temperature for 2 hours. After removal of the solvent under reduced pressure, the residue was washed with ether and crystallized from a suitable solvent.

(b) A solution of bromine (12.0 mmoles) in chloroform (15 ml)

was added dropwise with stirring to a solution of **2** (10 mmoles) in chloroform (30 ml). The mixture was stirred at room temperature for 2 hours. The reaction mixture was washed with 5% sodium hydrogen carbonate. After drying over magnesium sulfate, the solvent was removed. The resulting crystalline mass was recrystallized from a suitable solvent.

Compound **4a** [6] had ir (potassium bromide): ν 1683 (C=O), 3420 (OH) cm^{-1}; uv (ethanol): λ max nm (log ϵ) 283 (4.006).

Compound **4b** had ir (potassium bromide): ν 1700, 1640 (C=O), 3470 (OH) cm^{-1}; uv (ethanol): λ max nm (log ϵ) 212 (3.945), 283 (3.998).

Compound **4c** had ir (potassium bromide): ν 1698, 1640 (C=O), 3500 (OH) cm^{-1}; uv (ethanol): λ max nm (log ϵ) 213 (4.213), 283 (4.279).

Compound **4d** had ir (potassium bromide): ν 1685, 1636 (C=O), 3490 (OH) cm^{-1}; uv (ethanol): λ max nm (log ϵ) 283 (4.435).

[IV] General Procedure for 5-Bromo-1-(bromoalkyl)-3,6-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (**5**).

(a) Preparation from **3**. A mixture of **3** (5.0 mmoles) and *N*-bromosuccinimide (6.0 mmoles) was stirred at room temperature for 1.5 hours. The reaction mixture was treated in a manner similar to that described in the experimental [III] (a).

(b) Preparation from **4**. A mixture of **4** (10.0 mmoles) and 47% hydrobromic acid (15 ml) was heated at 130-140° for 3 hours. The reaction mixture was treated in a manner similar to that described in the experimental [II] (a).

Compound **5a** ir had (potassium bromide): ν 1692, 1640 (C=O) cm^{-1}; uv (ethanol): λ max nm (log ϵ) 212 (3.929), 280 (4.004).

Compound **5b** had ir (potassium bromide): ν 1700, 1660 (C=O) cm^{-1}; uv (ethanol): λ max nm (log ϵ) 212 (3.929), 281 (4.000).

Compound **5c** had ir (potassium bromide): ν 1700, 1650 (C=O) cm^{-1}; uv (ethanol): λ max nm (log ϵ) 215 (3.849), 283 (3.975); ms: m/z 342 (M^++4, 51), 340 (M^++2, 100) 338 (M^+, 54).

Compound **5d** had ir (potassium bromide): ν 1700, 1658 (C=O) cm^{-1}; uv (ethanol): λ max nm (log ϵ) 212 (3.867), 284 (3.983); ms: m/z 370 (M^++4, 34), 368 (M^++2, 62), 366 (M^+, 37).

[V] General Procedure for 5-Bromo-1-(bromoalkyl)-6-dibromomethyl-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione (**6**).

(a) Preparation from **2**. Reaction conditions are described in the experimental [VI] (a) and **6** was obtained by separation by column chromatography.

(b) Preparation from **7**. A solution of **7** (3.0 mmoles) and bromine (7.0 mmoles) in acetic acid (25 ml) was heated at 100-110° for 2 hours. The resulting mixture was treated in a manner similar to that described in the experimental [VI] (a) and **6a** [1] was obtained.

Compound **6b** was obtained in 10% yield by method (b) and the starting material was recovered in 70% yield; ir (potassium bromide): ν 1713, 1662 (C=O) cm^{-1}; uv (ethanol): λ max nm (log ϵ) 302 (3.887); hrms: Calcd. for $C_9H_{10}Br_4N_2O_2$: 493.7476 (Br = 79); Found: 493.4788. Compound **6c** was obtained in 61% yield by method (b); ir (potassium bromide): ν 1705, 1660 (C=O) cm^{-1}; uv (ethanol): λ max nm (log ϵ) 304 (4.062); ms: m/z 502 (M^++8, 4), 500 (M^++6, 12), 498 (M^++4, 22), 496 (M^++2, 15), 494 (M^+, 4).

Compound **6d** was obtained in 12% yield by method (b) and the starting material was recovered in 63% yield; ir (potassium bromide): ν 1703, 1660 (C=O) cm^{-1}; uv (ethanol): λ max nm (log ϵ) 303 (3.895); hrms: Calcd. for $C_{11}H_{14}Br_4N_2O_2$: 521.7790 (Br = 79); Found: 521.7803.

[VI] General Procedure for 5-Bromo-1-(bromoalkyl)-6-bromomethyl-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione (**7**).

(a) Preparation from **2**. A solution of **2** (25.0 mmoles) and bromine (75.0 mmoles) in acetic acid (40 ml) was heated at 90-95° for 2 hours. After removal of the excess bromine and acetic acid under reduced pressure, the residue was neutralized with 5% sodium hydrogen carbonate. The solution was extracted with chloroform (3 times). The combined extract was washed with 15% sodium thiosulfate, dried over magnesium sulfate, and the solvent was removed. The crystalline or oily residue was chromatographed on silica gel, eluting with chloroform to give the pure product.

(b) Preparation from **5**. This was done in a manner similar to that described in the above procedure except for the amount of bromine (1.2 equivalents).

(c) Preparation from **8** or **9**. A mixture of **8** or **9** in 47% hydrobromic acid was treated in a manner similar to that described in the experimental [II] (a) and **7a** and **7b** [1] were obtained.

Compound **7c** was obtained in 71% yield by method (a); ir (potassium bromide): ν 1714, 1644 (C=O) cm^{-1}; uv (ethanol): λ max nm (log ϵ) 302 (4.087); ^{13}C-nmr: δ 26.30 (N-Me), 29.61 (-CH_2-), 29.75 (-CH_2Br), 31.89 (-CH_2Br), 45.62 (N-CH_2), 101.07 (C_5), 146.88 (C_6), 150.16 (C_2), 158.50 (C_4); ms: m/z 422 (M^++6, 6), 420 (M^++4, 16), 418 (M^++2, 16), 416 (M^+, 6).

Compound **7d** was obtained in 74% yield by method (a); ir (potassium bromide): ν 1698, 1641 (C=O) cm^{-1}; uv (ethanol): λ max nm (log ϵ) 212 (3.957), 303 (3.970); ms: (FAB) m/z 451 (M^++7), 449 (M^++5), 447 (M^++3), 445 (M^++1).

[VII] General Procedure for 1-(Acetoxyalkyl)-5-bromo-6-bromomethyl-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione (**8**).

(a) Preparation from **2**. Reaction conditions were those described in experimental [VI] (a) and **8** was obtained upon separation by column chromatography.

(b) Preparation from **9**. A mixture of **9** in acetic anhydride was treated in a manner similar to that described in the experimental [IX].

Compound **8a** [1] was obtained.

Compound **8c** was obtained in 3% yield by method (a); ir (potassium bromide): ν 1702, 1660 (C=O) cm^{-1}; uv (ethanol): λ max nm (log ϵ) 211 (3.996), 302 (3.962).

Compound **8d** was obtained in 75% yield by method (b); ir (potassium bromide): ν 1720, 1703, 1665 (C=O) cm^{-1}; uv (ethanol): λ max nm (log ϵ) 212 (3.982), 301 (3.935).

[VIII] General Procedure for 5-Bromo-6-bromomethyl-1-(hydroxyalkyl)-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione (**9**).

(a) Preparation from **2**. Reaction conditions were those described in the experimental [VI] (a) and **9** was obtained upon separation by column chromatography.

(b) Preparation from **8**. A mixture of **8** (1.0 mmoles) in 5% hydrochloric acid (10 ml) and methanol (10 ml) was heated in a boiling water bath for 1 hour. After removal of the excess solvent, the residue was extracted with chloroform (3 times). The combined extract was washed with 5% sodium hydrogen carbonate and dried over magnesium sulfate. The solvent was removed and the crystalline residue was recrystallized from a suitable solvent to give **9**.

Compound **9a** was obtained in 77% yield by method (b); ir (potassium bromide): ν 1705, 1635 (C=O), 3400 (OH) cm^{-1}; uv (ethanol): λ max nm (log ϵ) 212 (4.034), 300 (3.985); ms: m/z 344

(M^++4, 5), 342 (M^++2, 10), 340 (M^+, 5).

Compound **9c** was obtained in 22% yield by method (b); ir (potassium bromide): ν 1700, 1648 (C=O), 3500 (OH) cm^{-1}; uv (ethanol): λ max nm (log ϵ) 212 (3.968), 303 (3.948); ms: m/z 358 (M^++4, 7), 356 (M^++2, 13), 354 (M^+, 7).

Compound **9d** was obtained in 11% yield by method (a); ir (potassium bromide): ν 1695, 1641 (C=O), 3520 (OH) cm^{-1}; uv (ethanol): λ max nm (log ϵ) 212 (3.973), 303 (3.965); ms: (FAB) m/z 387 (M^++5), 385 (M^++3), 383 (M^++1).

[IX] General Procedure for 1-(Acetoxyalkyl)-3,6-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (**10**).

A mixture of **2** (10 g) and acetic anhydride (50 ml) was refluxed for 1 hour. After removal of the excess acetic anhydride under reduced pressure, the residue was quenched with ethanol and evaporated to dryness. The resulting mass was recrystallized from a suitable solvent to give **10**.

Compound **10a** was obtained in 85% yield; ir (potassium bromide): ν 1738, 1690, 1660 (C=O) cm^{-1}; uv (ethanol): λ max nm (log ϵ), 264 (3.987).

Compound **10b** was obtained in 96% yield; ir (potassium bromide): ν 1740, 1705, 1670 (C=O) cm^{-1}; uv (ethanol): λ max nm (log ϵ), 263 (3.998).

Compound **10c** was obtained in 83% yield; ir (potassium bromide): ν 1725, 1700, 1660 (C=O) cm^{-1}; uv (ethanol): λ max nm (log ϵ) 267 (4.031).

Compound **10d** was obtained in 85% yield; ir (potassium bromide): ν 1720, 1700, 1670 (C=O) cm^{-1}; uv (ethanol): λ max nm (log ϵ), 266 (4.015).

[X] General Procedure for 1-(Acetoxyalkyl)-5-bromo-3,6-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (**11**).

A mixture of *N*-bromosuccinimide (NBS) (5.0 mmoles) in ethanol (30 ml) was added to a solution of **10** (4.0 mmoles) in ethanol (20 ml) with stirring, and the mixture was allowed stand at room temperature for 1.5 hours. After removal of the solvent under reduced pressure, the residue was dissolved in water and extracted with chloroform (3 times). The combined solvent was dried over magnesium sulfate and the solvent was removed. The crystalline residue was recrystallized from a suitable solvent to give **11**.

Compound **11a** was obtained in 88% yield; ir (potassium bromide): ν 1733, 1700, 1660 (C=O) cm^{-1}; uv (ethanol): λ max nm (log ϵ) 210 (4.005), 279 (3.966).

Compound **11b** was obtained in 93% yield; ir (potassium bromide): ν 1735, 1700, 1670 (C=O) cm^{-1}; uv (ethanol): λ max nm (log ϵ) 210 (4.058), 279 (4.028).

Compound **11c** was obtained in 94% yield; ir (potassium bromide): ν 1735, 1702, 1658 (C=O) cm^{-1}; uv (ethanol): λ max nm (log ϵ) 210 (4.039), 281 (4.021).

Compound **11d** was obtained in 95% yield; ir (potassium bromide): ν 1728, 1700, 1662 (C=O) cm^{-1}; uv (ethanol): λ max nm (log ϵ) 211 (3.942), 281 (3.966).

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