Pyrimidine Derivatives. VIII.[1] One-Step Synthesis of 3,4-Dihydro-pyrimido[6,1-*c*][1,4]oxazine Derivatives by Reactions of 5-Bromo-1-(2-bromoethyl)-6-bromomethyl-2,4(1*H*,3*H*)-pyrimidinedione with Sodium Alkoxides and 2-Nitropropane

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The reaction of 5-bromo-1-(2-bromoethyl)-6-bromomethyl-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione (1) with the sodium alkoxide/2-nitropropane system and that of the dinitrate (2) of 5-bromo-1-(2-hydroxyethyl)-6-hydroxymethyl-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione with sodium alkoxide provide convenient routes to a wide range of 3,4-dihydro-pyrimido[6,1-*c*][1,4]oxazine derivatives (3) in excellent yields.

Keywords tribromo-pyrimidine; sodium alkoxide; 2-nitropropane; ring formation; pyrimido[6,1-*c*][1,4]oxazine; oxidation; pyridinium dichromate; 5-bromo-1-(2-bromoethyl)-6-bromomethyl-3-methyl-2,4(1*H*,3*H*)-pyrimidinedione

Only one report has been published concerning the synthesis of 3,4-dihydro-pyrimido[6,1-*c*][1,4]oxazine-triones, by Rambacher and Maeke,[2] and they observed anti-fungi and anti-filaria activity in some compounds. In the course of our work on the reaction of the 5-bromo-1-(ω-bromo-alkyl)-6-bromomethyl-3-methyl-2,4(1*H*,3*H*)-pyrimidinediones[1,3] (these compounds are described as "tribromo-pyrimidines" in this report) with nucleophiles, we found that 3,4-dihydro-pyrimido[6,1-*c*][1,4]oxazine derivatives (**3**) could be prepared by the reaction of a tribromo-pyrimidine[3] (**1**) with sodium alkoxide/2-nitropropane and by that of the dinitrate[4] (**2**) with sodium alkoxide, in excellent yields. We describe herein a new synthetic method and some reactions of the 3,4-dihydro-pyrimido[6,1-*c*][1,4]oxazine ring system.

As described in a previous paper,[4] tribromo-pyrimidines were treated with silver nitrate for the preparation of aldehydes according to Noda and Seebach.[5] However, the resulting products were only the dinitrates[4] of the corresponding dihydroxides. This time, we tried to convert the dinitrate (**2**) to an aldehyde according to Kornblum and Frazier.[6] However, we could not obtain the expected compound. A sodium methoxide and methanol system was then employed, and this yielded a pure material (**3a**) with a melting point of 163 °C. The structure was established as 9-bromo-3,4-dihydro-1-methoxy-7-methyl-1*H*-pyrimido-[6,1-*c*][1,4]oxazine-6,8(7*H*)-dione by elemental analysis and spectral examination. It was of interest that a methoxyl group was introduced at the 1-position of **3a** during the reaction.

We considered that compound **1** might be converted

TABLE I. Reactions[a] of **1** with Sodium Methoxide/2-Nitropropane

Entry No.	1 (eq)	NaOMe (eq)	Me_2CHNO_2 (eq)	Reaction products (%)[b]		
				3a	1	4
1	1.0	1.0	1.0	29	44	19
2	1.0	1.0	4.0	23	35	33
3	1.0	2.0	1.0	45	51	
4	1.0	2.0	1.2	51	42	
5	1.0	2.0	1.5	79	18	
6	1.0	2.0	1.7	82	14	
7	1.0	2.0	1.9	93	6	
8	1.0	2.0	2.0	93	4	
9	1.0	2.0	4.0	98		
10	1.0	4.0	4.0	99		

a) The reactions were carried out at room temperature for 3 h. *b*) The products ratio was determined by using an IATROSCAN MK-5.

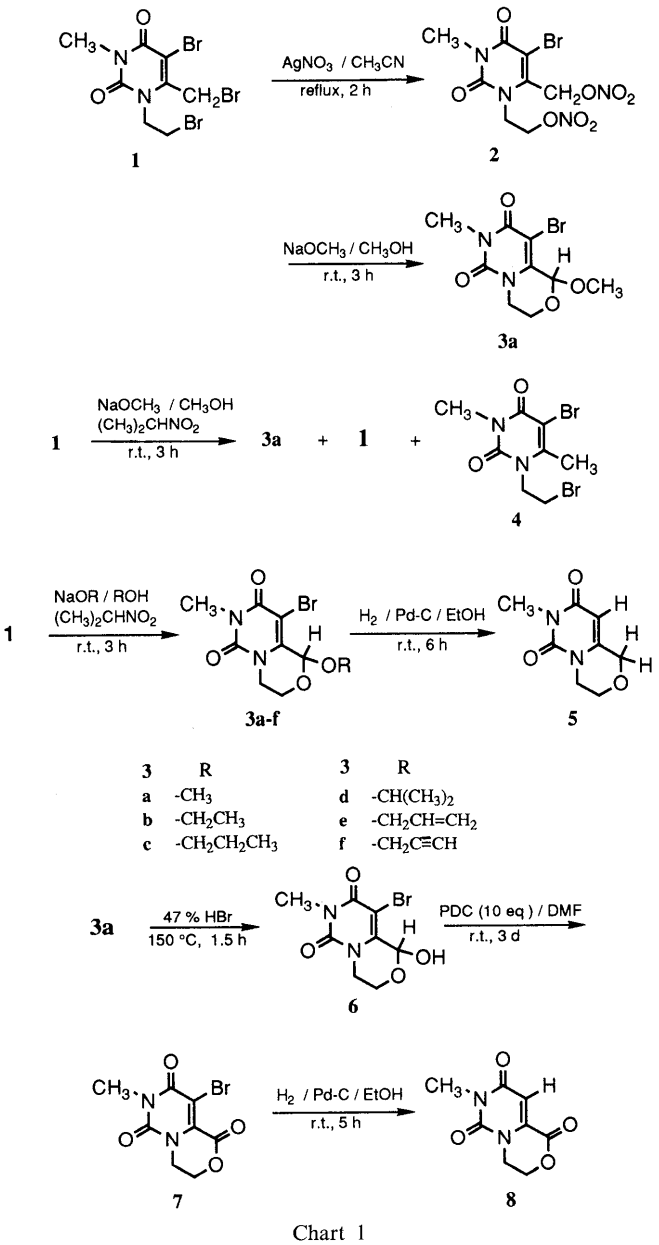

Chart 1

directly to the ring closure product (**3a**) by treatment with sodium alkoxide and 2-nitropropane.[7] Thus, the tribromo-pyrimidine (**1**) was treated with two equivalents of sodium methoxide and one equivalent of 2-nitopropane in methanol at room temperature (Table I, entry 3). The resulting crystalline mass was separated by column chromatography to give compound **3a** and the starting material. Since about 50% of the starting material was recovered, the reaction was examined using different molar ratios of reagents. The results are summarized in Table I. When one equivalent of sodium methoxide was used, the debrominated compound[4] (**4**) was identified in addition to **1** and **3a** (entries 1 and 2). The yield of **4** was somewhat increased as the molar ratio of 2-nitropropane increased. With increasing molar ratio of 2-nitropropane to that of sodium methoxide, the yield of compound **3a** increased (entries 3—8). It was evident that at least two equivalents of sodium methoxide and 2-nitropropane were necessary for one equivalent of **1** (entry 8). Compound **3a** was obtained in almost quantitative yield when four equivalents of sodium methoxide and 2-nitropropane were used (entry 10). Similarly, 3,4-dihydro-pyrimido[6,1-*c*][1,4]oxazines (**3b—f**) were obtained in excellent yields by the reaction of the corresponding sodium alkoxide and 2-nitropropane except in the case of isopropyl alcohol.

When compounds **3** were hydrogenated over palladium–charcoal, both bromine and alkoxyl groups were removed to give **5**. Compounds **3** were hydrolyzed to hydroxy compounds **6** by reaction with 47% hydrogen bromide and the reverse reaction occurred in alcohol containing a catalytic amount of mineral acid. Oxidation of **6** was very difficult, although several oxidant, *i.e.*, activated manganese(IV) oxide, potasssium permanganate, tetrabutylammonium permanganate,[8] tetrapropylammonium perruthenate and *N*-methyl morpholine *N*-oxide,[9] were examined. Unfortunately the desired compound (**7**) could not be isolated. A large amount (10 eq) of pyridinium dichromate (PDC)[10] and a prolonged reaction time were found to be effective for the oxidation of **6**, and the corresponding trione (**7**) was obtained in good yield. Debromination of **7** gave the corresponding trione (**8**) on hydrogenation over palladium–charcoal and this was identical with one of Rambacher's compounds.[2]

In conclusion, the reaction of the tribromo-pyrimidines (**1**) with the sodium alkoxide/2-nitropropane system provides a convenient way of preparing a wide range of 3,4-dihydro-pyrimido[6,1-*c*][1,4]oxazines (**3**).

Experimental

General Melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. IR spectra were recorded with a JASCO IR-810 spectrophotometer. UV spectra were recorded on a Hitachi 323 spectrophotometer. NMR spectra were recorded 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 JMN 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. Unless otherwise mentioned, organic extracts were dried with $MgSO_4$ and concentrated by using a rotary evaporator.

Reaction of Compound 2 with Sodium Methoxide; 9-Bromo-3,4-dihydro-1-methoxy-7-methyl-1*H*-pyrimido[6,1-*c*][1,4]oxazine-6,8(7*H*)-dione (3a) A mixture of sodium methoxide (prepared from sodium 0.14 g, 6 mmol and MeOH 5 ml) and **2** (1.11 g, 3 mmol) was stirred at room temperature for 3 h under a nitrogenn atmosphere. After removal of the solvent *in vacuo*, a small amount of water was added to the residue and the mixture was extracted with $CHCl_3$ (3 times). The resulting crystals were recrystallized from MeOH to give colorless needles of **3a** (0.64 g, 73%), mp 162—163 °C. *Anal.* Calcd for $C_9H_{11}BrN_2O_4$: C, 37.13; H, 3.81; Br, 27.45; N, 9.62. Found: C, 36.94; H, 3.71; Br, 27.36; N, 9.58. ^{13}C-NMR (100 MHz, $CDCl_3$, C–H COSY) δ: 29.21 (N–CH_3), 41.19 (C(4)), 56.29 (C(3) and O–CH_3), 95.06 (C(1)), 97.47 (C(9)), 143.91 (C(9a)), 150.60 (C(6)), 158.69 (C(8)).

Reactions of Compound 1 with Sodium Alkoxide and 2-Nitropropane; General Procedure for 1-Alkoxy-9-bromo-3,4-dihydro-7-methyl-1*H*-pyrimido[6,1-*c*][1,4]oxazine-6,8(7*H*)-diones (3) A mixture of sodium alkoxide and 2-nitropropane (prepared from sodium 20 mmol, the appropriate alcohol 20 ml, and 2-nitropropane 20 mmol) was added to a solution of compound **1** (5 mmol) in alcohol (40—50 ml). The mixture was stirred at room temperature for 3 h under a nitrogen atmosphere. After removal of the solvennt *in vacuo*, a small amount of water was added to the residue and the mixture was extracted with $CHCl_3$ (3 times). The product was purified by recrystallization from a suitable solvent.

9-Bromo-3,4-dihydro-1-ethoxy-7-methyl-1*H*-pyrimido[6,1-*c*][1,4]-oxazine-6,8(7*H*)-dione (**3b**): *Anal.* Calcd for $C_{10}H_{13}BrN_2O_4$: C, 39.36; H, 4.29; Br, 26.19; N, 9.18. Found: C, 39.38; H, 4.23; Br, 26.09; N, 9.22. ^{13}C-NMR (100 MHz, $CDCl_3$, C–H COSY) δ: 14.84 (C–$\underline{C}H_3$), 29.18 (N–CH_3), 41.16 (C(4)), 56.27 (C(3)), 64.97 (O$\underline{C}H_2CH_3$), 93.89 (C(1)), 97.23

TABLE II. Physical Data for Compounds **3**

Compd. No.	mp (°C)	Yield[a] (%)	IR (KBr) ν (cm^{-1})	UV λ_{max}^{EtOH} nm (log ε)	MS[b] (EI, 70 eV) *m/z*	
					M^+	$(M-OR)^+$
3a	162—163 Acetone	93	1708 (C=O) 1663 (C=O)	212 (3.887) 287 (3.927)	290	259
3b	116—117 Acetone	93	1703 (C=O) 1660 (C=O)	213 (3.939) 287 (3.960)	304	259
3c	76—77 AcOEt	92	1710 (C=O) 1665 (C=O)	213 (3.951) 287 (3.967)	318	259
3d	87—89 Ether	53	1715 (C=O) 1673 (C=O)	210 (3.968) 283 (3.960)	318	259
3e	109—111 AcOEt	80	1715 (C=O) 1670 (C=O)	209 (3.968) 283 (3.952)	316	259
3f	140—141 AcOEt	70	1710 (C=O) 1665 (C=O) 3245 (CH) 2120 (C≡C)	210 (3.946) 283 (3.956)	314	259

a) Yield refers to pure isolated compounds. *b*) Bromine refers to ^{79}Br.

TABLE III. ^{1}H-NMR Data[a] for Compounds **3**

Compd. No.	C(1)-OR	C(1)-H	O(2)-CH_2	N(5)-CH_2	N(7)-CH_3
3a[b]	OCH_3 3.57 (3H, s)	5.48 (1H, s)	3.64 (1H, m) 3.96 (1H, m)	4.00 (1H, m) 4.27 (1H, m)	3.42 (3H, s)
3b[b]	OCH_2 3.74 (1H, qd, J=7.0, 9.2) 3.94 (1H, qd, J=7.0, 9.2) CH_3 1.31 (3H, t, J=7.0)	5.59 (1H, s)	3.64 (1H, m) 3.98 (1H, m)	4.01 (1H, m) 4.33 (1H, m)	3.41 (3H, s)
3c	OCH_2 3.68 (2H, t, J=6.4) CH_2 1.68 (2H, m) CH_3 0.98 (3H, t, J=7.3)	5.57 (1H, s)	3.5—4.5 (4H, m)		3.41 (3H, s)
3d	OCH 3.6—4.2[c] (1H, m) CH_3 1.30 (3H, d, J=6.2) CH_3 1.31 (3H, d, J=6.2)	5.72 (1H, s)	3.6—4.2[c] (4H, m)		3.41 (3H, s)
3e	OCH_2 4.2 (2H, m) CH 5.9 (1H, tdd, J=5.5, 9.9, 17.1) CH_2 5.1—5.4 (2H, m)	5.65 (1H, s)	3.5—4.5 (4H, m)		3.42 (3H, s)
3f	OCH_2 4.42 (2H, d, J=2.4) CH 2.55 (1H, t, J=2.4)	5.82 (1H, s)	3.5—4.4 (4H, m)		3.42 (3H, s)

a) All spectra were obtained in $CDCl_3$ solution. *b*) Spectrum was recorded on a GX-400 instrument. *c*) It is difficult to discriminate between OCH and OCH_2CH_2N absorption peaks.

(C(9)), 144.01 (C(9a)), 150.59 (C(6)), 158.70 (C(8)).

9-Bromo-3,4-dihydro-7-methyl-1-propoxy-1*H*-pyrimido[6,1-*c*][1,4]-oxazine-6,8(7*H*)-dione (**3c**): *Anal.* Calcd for $C_{11}H_{15}BrN_2O_4$: C, 41.40; H, 4.74; Br, 25.04; N, 8.78. Found: C, 41.17; H, 4.56; Br, 23.95; N, 8.78.

9-Bromo-3,4-dihydro-7-methyl-1-isopropoxy-1*H*-pyrimido[6,1-*c*][1,4]-oxazine-6,8(7*H*)-dione (**3d**): *Anal.* Calcd for $C_{11}H_{15}BrN_2O_4$: C, 41.40; H, 4.74; Br, 25.04; N, 8.78. Found: C, 41.53; H, 4.63; Br, 25.18; N, 8.74.

1-Allyloxy-9-bromo-3,4-dihydro-7-methyl-1*H*-pyrimido[6,1-*c*][1,4]-oxazine-6,8(7*H*)-dione (**3e**): *Anal.* Calcd for $C_{11}H_{13}BrN_2O_4$: C, 41.66; H, 4.13; Br, 25.20; N, 8.83. Found: C, 41.46; H, 3.99; Br, 25.59; N, 8.76.

9-Bromo-3,4-dihydro-7-methyl-1-(2-propynyloxy)-1*H*-pyrimido[6,1-*c*][1,4]oxazine-6,8(7*H*)-dione (**3f**): *Anal.* Calcd for $C_{11}H_{11}BrN_2O_4$: C, 41.93; H, 3.52; Br, 25.36; N, 8.89. Found: C, 42.01; H, 3.45; Br, 25.28; N, 8.91.

3,4-Dihydro-7-methyl-1*H*-pyrimido[6,1-*c*][1,4]oxazine-6,8(7*H*)-dione (5) A suspension of **3a** (1.53 g, 5.0 mmol) and 10% Pd–C (0.3 g) in EtOH (100 ml) was stirred at room temperature for 6 h under a hydrogen atmosphere. After the reaction, Pd–C was filtered off and the filtrate was concentrated to dryness *in vacuo*. The residue was neutralized with 5% $NaHCO_3$ and the mixture was extracted with $CHCl_3$ (3 times). The crystalline residue was recrystallized from acetone to give 0.62 g (68%) of colorless needles, mp 152—153 °C. *Anal.* Calcd for $C_8H_{10}N_2O_3$: C, 52.74; H, 5.53; N, 15.38. Found: C, 52.63; H, 5.46; N, 15.28. IR (KBr): 1703, 1660 (C=O) cm^{-1}. UV λ_{max}^{EtOH} nm (log ε): 208 (3.89), 267 (3.98). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.34 (3H, s, N–CH_3), 3.81 (2H, dd, J=5.1, 5.9 Hz, N–CH_2), 4.04 (2H, dd, J=5.1, 5.9 Hz, O–CH_2), 4.54 (2H, d, J=1.5 Hz, C(1)-H_2), 5.50 (1H, t, J=1.5 Hz, C(9)-H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 27.53 (N–CH_3), 41.27 (C(4)), 64.47 (C(3)), 64.82 (C(1)), 96.07 (C(9)), 147.87 (C(9a)), 151.81 (C(6)), 161.93 (C(8)). MS *m/z*: 182 (M^+).

9-Bromo-3,4-dihydro-1-hydroxy-7-methyl-1*H*-pyrimido[6,1-*c*][1,4]-oxazine-6,8(7*H*)-dione (6) A solution of **3a** (0.9 g, 3.0 mmol) in 47% HBr (5 ml) was heated at 140—150 °C for 2 h. After removal of the solvent *in vacuo*, the residue was neutralized with 5% $NaHCO_3$ and the separated crystalline mass was collectted. The product was purified from MeOH to give 0.68 g (82%) of colorless leaflets, mp 228—230 °C. *Anal.* Calcd for $C_8H_9BrN_2O_4$: C, 34.68; H, 3.27; Br, 28.84; N, 10.11. Found: C, 34.71; H, 3.21; Br, 28.62; N, 10.22. IR (KBr): 3360 (OH), 1695, 1630 (C=O) cm^{-1}. UV λ_{max}^{EtOH} nm (log ε): 215 (3.93), 283 (3.96). ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 3.50 (3H, s, N–CH_3), 3.6–4.6 (4H, m, N–CH_2 and O–CH_2), 6.13 (1H, s, C(1)-H). MS *m/z*: 278 (M^+ for ^{81}Br), 276 (M^+ for ^{79}Br).

9-Bromo-3,4-dihydro-7-methyl-1*H*-pyrimido[6,1-*c*][1,4]oxazine-1,6,8-(7*H*)-trione (7) PDC (7.34 g, 20 mmol) was added portionwise to a solution of **6** (0.55 g, 2 mmol) in dimethylformamide (12 ml) with stirring at room temperature, and the mixture was stirred for 3 d, diluted with water (60 ml), and extracted with $CHCl_3$ (3 times). The residue was extracted with acetone (3 times), and the solvent was evaporated off. This residue was chromatographed on a silica gel column with $CHCl_3$. The resulting crystalline mass was recrystallized from AcOEt to give 0.38 g (69%) of colorless needles, mp 240—241 °C. *Anal.* Calcd for $C_8H_7BrN_2O_4$: C, 34.93; H, 2.57; Br, 29.05; N, 10.18. Found: C, 35.07; H, 2.57; Br, 28.88; N, 10.11. IR (KBr): 1743, 1700, 1650 (C=O) cm^{-1}. UV λ_{max}^{EtOH} nm (log ε): 212 (3.87), 315 (3.66). ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 3.46 (3H, s, N-CH_3), 4.22 (2H, m, N-CH_2), 4.58 (2H, m, O-CH_2), MS *m/z*: 276 (M^+ for ^{81}Br), 274 (M^+ for ^{79}Br).

3,4-Dihydro-7-methyl-1*H*-pyrimido[6,1-*c*][1,4]oxazine-1,6,8(7*H*)-trione (8) A suspension of **7** (0.25 g, 0.9 mmol) and 10% Pd–C (0.14 g) in MeOH (300 ml) was stirred at room temperature for 5 h under hydrogen atmosphere. After the reaction, Pd–C was filtered off and the filtrate was concentrated to dryness *in vacuo*. The residue was neutralized with 5% $NaHCO_3$ and the mixture was extracted with $CHCl_3$ (4 times, total 500 ml). The crystalline residue was recrystallized from MeOH to give 0.15 g (84%) of colorless needles, mp 265—268 °C (lit.,[2] mp 259 °C (H_2O)). *Anal.* Calcd for $C_8H_8N_2O_4$: C, 48.98; H, 4.11; N, 14.28. Found: C, 49.23; H, 4.06; N, 14.38. IR (KBr): 1743, 1703, 1660 (C=O) cm^{-1}. UV λ_{max}^{EtOH} nm (log ε): 204 (3.61), 294 (3.37). ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 3.38 (3H, s, N-CH_3), 4.14 (2H, m, N-CH_2), 4.63 (2H, m, O-CH_2), 6.69 (1H, s, C(9)-H). MS *m/z*: 196 (M^+).

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