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Studies on Pyrimidine Derivatives. XXXII.[1] Reaction of 4-Substituted 2,6-Dimethylpyrimidine 1-Oxides with Phosphoryl Chloride

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The reaction of 2,6-dimethyl-4-phenylpyrimidine 1-oxide with phosphoryl chloride gave 4-chloromethyl-2-methyl-6-phenylpyrimidine exclusively. In contrast, 2,6-dimethyl-4-methoxypyrimidine 1-oxide and 2,6-dimethyl-4-dimethylaminopyrimidine 1-oxide reacted with the same reagent to give the corresponding 2-chloromethylpyrimidines predominantly.

Keywords——pyrimidine *N*-oxide; chloromethylpyrimidine; phosphoryl chloride; site-selective reaction; substituent effect

As reported in the preceding paper,[1] pyrimidine *N*-oxides having a methyl group at their 2- or 4-position reacted with phosphoryl chloride to give the corresponding 2-chloromethyl or 4-chloromethyl derivatives without the formation of ring-chlorinated products. The present paper deals with site-selectivity in the side-chain chlorination of 4-substituted 2,6-dialkylpyrimidine 1-oxides with phosphoryl chloride.

Throughout this investigation, the following standard procedure was used in order to observe the results under similar conditions. An *N*-oxide and three molecular equivalents of phosphoryl chloride were dissolved in dioxane, and the resulting solution was heated under reflux for an appropriate time.

The approximate ratio of the two isomers, 2-chloromethyl- and 4-chloromethylpyrimidines was determined by two methods. One was the direct analysis of chloromethylpyrimidine fractions obtained by vacuum distillation of the crude products by proton magnetic resonance (^{1}H-NMR) spectroscopy. The other was similar spectrometric analysis of methoxymethylpyrimidine fractions derived by treatment of the reaction products with excess sodium methoxide in methanol. The values from the latter method were considered to be more reliable, because, in some cases, chloromethylpyrimidines partially resinified during vacuum distillation.

When 2,6-dimethyl-4-phenylpyrimidine 1-oxide (**1a**) was allowed to react with phosphoryl chloride, 4-chloromethyl-2-methyl-6-phenylpyrimidine (**3a**) was obtained as a sole product. In contrast, the reactions of 4-methoxy-2,6-dimethyl- (**1b**) and 2,6-dimethyl-4-dimethylaminopyrimidine 1-oxide (**1c**) gave the corresponding 2-chloromethylpyrimidines (**2b**, **c**) as major products. In the reactions of other 4-substituted 2,6-dimethylpyrimidine *N*-oxides, however, the clear site-selectivity was not observed. Namely, pyrimidine *N*-oxides such as 4-chloro-2,6-dimethyl- (**1d**), 2,4,6-trimethyl- (**1e**), 2,6-dimethyl- (**1f**), and 2,4-dimethylpyrimidine 1-oxide (**1g**) reacted with phosphoryl chloride to give a mixture of the corresponding 2-chloromethyl- (**2d**—**f**) and 4-chloromethylpyrimidine (**3d**—**f**), although the ratio of these isomers was strongly affected by the substituents at the 4-position.

The isomer ratios in the chloromethylpyrimidines (**2** and **3**) and methoxymethylpyrimidines (**2′** and **3′**) are listed in Table I. The authentic specimens which were necessary for the spectral analysis of the products were obtained by alternative syntheses. Since the syntheses of all the specimens were accomplished by routine methods, the procedures are describ-

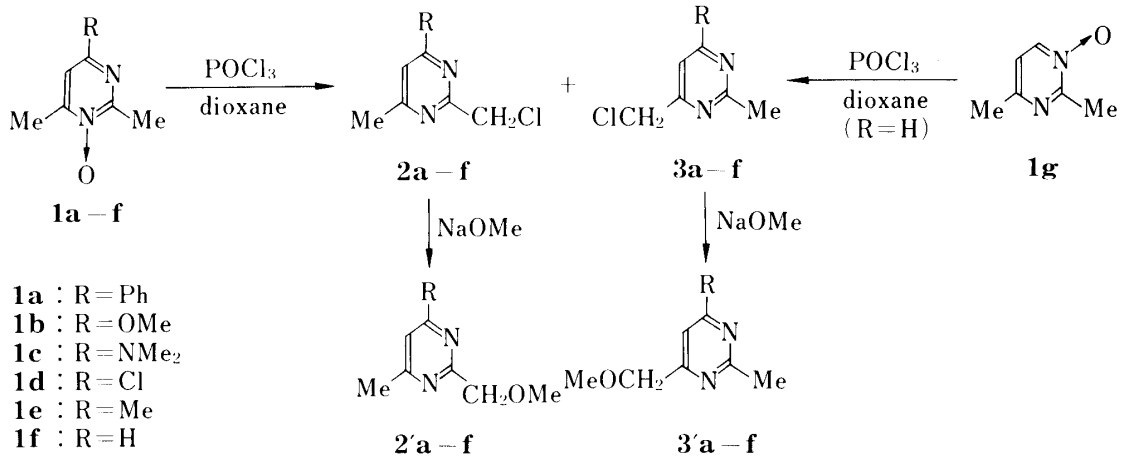
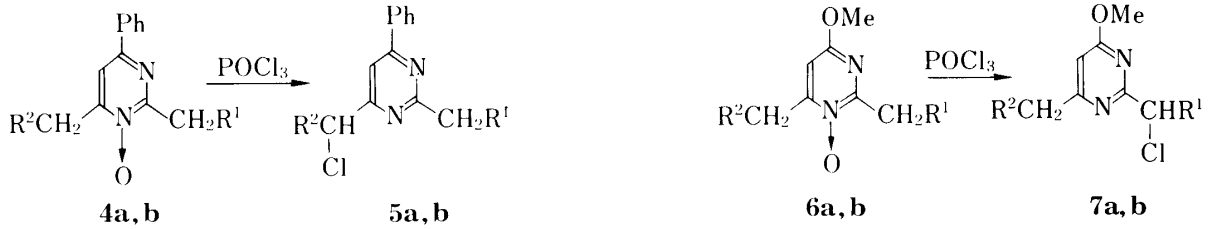


Chart 1

TABLE I. Reaction of 2,6-Dimethylpyrimidine *N*-Oxides (**1a**—**g**) with Phosphoryl Chloride

Pyrimidine 1-oxide	Chloromethylpyrimidine		Ratio determined by ^{1}H-NMR	
	bp [mmHg] (°C)	Yield (%)	Chloromethylpyrimidine 2-Isomer : 4-Isomer	Methoxymethylpyrimidine 2-Isomer : 4-Isomer
1a	145—146 [2]	70	0 : 100	0 : 100
1b	85—86 [2]	48	93 : 7	91 : 9
1c	80—84 [7]	37	100 : 0	85 : 15
1d	80—85 [2]	54	42 : 58	40 : 60[a]
1e	60—70 [2]	32	69 : 31	67 : 33
1f	61—62 [4]	53	0 : 100	20 : 80
1g	45—48 [2]	35	20 : 80	36 : 64

a) Analyzed after conversion to 4-methoxy derivatives.



4a : R^1=Me, R^2=H
4b : R^1=H, R^2=Me

Chart 2

ed briefly in the experimental section and not illustrated in the charts.

The site-selective reaction caused by the presence of 4-methoxyl and 4-phenyl groups appears to be general. The reaction of 2-ethyl-6-methyl-4-phenyl- (**4a**) or 6-ethyl-2-methyl-4-phenylpyrimidine 1-oxide (**4b**) with phosphoryl chloride in dioxane afforded 4-chloromethyl-2-ethyl-6-phenyl- (**5a**) or 4-(1-chloroethyl)-2-methyl-6-phenylpyrimidine (**5b**) in good yield, respectively. On the other hand, 2-ethyl-4-methoxy-6-methyl- (**6a**) and 6-ethyl-4-methoxy-2-methyl pyrimidine 1-oxide (**6b**) reacted with phosphoryl chloride to give the corresponding 2-chloroalkylpyrimidines (**7a**, **b**) exclusively. No formation of the isomeric chloroalkylpyrimidines was observed in any of these cases.

Experimental

All melting points and boiling points are uncorrected. Infrared (IR) spectra were measured with a JASCO IRA-1 spectrometer. ^{1}H-NMR spectra were taken at 60 MHz with a JEOL JNM-PMX 60 spectrometer. Chemical shifts are expressed in δ value. The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, and br=broad.

The following pyrimidine *N*-oxides were synthesized according to the literature: 2,6-dimethyl-4-phenyl- (**1a**),[2] 4-methoxy-2,6-dimethyl- (**1b**),[3] 4-chloro-2,6-dimethyl- (**1d**),[4] 2,4,6-trimethyl- (**1e**),[5] and 2-ethyl-4-methoxy-6-methylpyrimidine 1-oxide (**6a**).[3]

2,6-Dimethylpyrimidine 1-Oxide (1f) and 3-Oxide (1g)[6]——2,4-Dimethylpyrimidine (3.24 g, 30 mmol) was added to a solution of *m*-chloroperbenzoic acid (6.21 g, 36 mmol) in $CHCl_3$ (50 ml). The mixture was allowed to stand for 24 h at room temperature and then was washed with 30% K_2CO_3. The aqueous layer was extracted continuously with $CHCl_3$ for 12 h. The crude product obtained from the combined $CHCl_3$ layer was purified by SiO_2 column chromatography using $CHCl_3$ and acetone as eluents. The $CHCl_3$ fraction gave a colorless solid (**1f**), bp 76—77 C (3 mmHg), mp 49—52 °C. Yield 1.2 g (32%). IR ν_{max}^{KBr} cm^{-1}: 1240. ^{1}H-NMR ($CDCl_3$): 2.57 (3H, s), 2.78 (3H, s), 7.27 (1H, d, J=5 Hz), 8.10 (1H, d, J=5 Hz). *Anal.* Calcd for $C_6H_8N_2O$: C, 58.05; H, 6.50; N, 22.57. found: C, 58.34; H, 6.70; N, 22.25.

The acetone fraction gave a colorless solid (**1g**), bp 85—88 °C (3 mmHg), mp 83—85 °C. Yield 1.30 g (35%). IR ν_{max}^{KBr} cm^{-1}: 1240. ^{1}H-NMR ($CDCl_3$): 2.50 (3H, s), 2.72 (3H, s), 7.10 (1H, d, J=7 Hz), 8.35 (1H, d, J=7 Hz). *Anal.* Calcd for $C_6H_8N_2O$: C, 58.05; H, 6.50; N, 22.57. Found: C, 57.95; H, 6.70; N, 22.49.

2,6-Dimethyl-4-dimethylaminopyrimidine 1-Oxide (1c)——A mixture of **1b** (0.77 g, 5 mmol) and 50% aq. Me_2NH (5 ml) was heated at 100 °C for 20 h in a sealed tube. After removal of the excess Me_2NH, the residue was made alkaline with aq. K_2CO_3 and extracted continuously with $CHCl_3$ for 24 h. The crude product obtained from the $CHCl_3$ extract was recrystallized from AcOEt to give colorless plates, mp 97—99 °C. Picrate: yellow prisms (EtOH), mp 153—154 °C. IR ν_{max}^{KBr} cm^{-1}: 1270. ^{1}H-NMR ($CDCl_3$): 2.46 (3H, s), 2.63 (3H, s), 3.08 (6H, s), 6.23 (1H, s). *Anal.* Calcd for $C_{14}H_{16}N_6O_8$ (picrate): C, 42.43; H, 4.07; N, 21.21. Found: C, 42.23; H, 4.05; N, 21.04.

2-Ethyl-4-methyl-6-phenylpyrimidine——A solution of 2-chloro-4-methyl-6-phenylpyrimidine (2.0 g, 10 mmol) in dry ether (20 ml) containing dichloro(1,3-diphenylphosphinopropane)nickel [Ni(dppp)Cl_2] (0.1 g, 0.2 mmol) was added under an N_2 atmosphere with stirring to a solution of EtMgBr prepared from Mg (0.485 g, 20 mmol) and EtBr (2.1 g, 20 mmol) in dry ether (20 ml), and the mixture was refluxed for 5 h. After addition of 3 N HCl, the aqueous layer was taken and made alkaline with K_2CO_3, and the oil that separated was extracted with $CHCl_3$. The $CHCl_3$ extract was distilled under reduced pressure to give a colorless liquid, bp 134—136 °C (2 mmHg). Yield 1.31 g (66%). Picrate: yellow needless (EtOH), mp 211—212 °C. ^{1}H-NMR ($CDCl_3$): 1.43 (3H, t, J=7 Hz), 2.53 (3H, s), 3.02 (2H, q, J=7 Hz), 7.4—7.5 (4H, m), 8.0—8.2 (2H, m). *Anal.* Calcd for $C_{19}H_{17}N_5O_7$ (picrate): C, 53.39; H, 4.01; N, 16.39. Found: C, 53.21; H, 4.26; N, 16.10.

6-Ethyl-2-methyl-4(3*H*)-pyrimidinone——An MeONa–MeOH solution [prepared from Na (3.85 g, 167 mmol) and dry MeOH (100 ml)] was added to a mixture of acetamidine hydrochloride (15.8 g, 167 mmol) and ethyl 3-oxopentanoate[7] (24.1 g, 167 mmol) in dry MeOH (100 ml), and the mixture was stirred overnight at room temperature. After removal of the MeOH, the residue was extracted with hot $CHCl_3$. The crude product from the $CHCl_3$ extract was recrystallized from ether to give colorless needles, mp 125—126 °C (lit.[8] mp 122—123 °C). Yield 18.8 g (82%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3100—2900 (br), 1675. ^{1}H-NMR ($CDCl_3$): 1.26 (3H, t, J=7 Hz), 2.55 (3H, s), 2.60 (2H, q, J=7 Hz), 6.34 (1H, s), 12.8—13.5 (1H, br).

4-Chloro-6-ethyl-2-methylpyrimidine——A mixture of 6-ethyl-2-methyl-4(3*H*)-pyrimidinone (18.8 g, 136 mmol) and $POCl_3$ (100 ml) was refluxed for 2 h. After removal of the excess $POCl_3$, the residue was poured into dil. NH_4OH under cooling, and the resulting mixture was extracted with $CHCl_3$. The residue obtained from the $CHCl_3$ extract was passed through a short column of Al_2O_3 using $CHCl_3$ as an eluent. The crude product was distilled under reduced pressure to give a colorless liquid, bp 70—75 °C (2 mmHg). Yield 8.8 g (41%). ^{1}H-NMR ($CDCl_3$): 1.30 (3H, t, J=7 Hz), 2.67 (3H, s), 2.75 (2H, q, J=7 Hz), 7.05 (1H, s). *Anal.* Calcd for $C_7H_9ClN_2$: C, 53.70; H, 5.76; Cl, 22.65; N, 17.89. found: C, 53.91; H, 5.77; Cl, 22.24; N, 17.80.

4-Ethyl-2-methyl-6-phenylpyrimidine——A solution of 4-chloro-6-ethyl-2-methylpyrimidine (4.8 g, 31 mmol) in dry ether (20 ml) containing Ni(dppp)Cl_2 (0.34 g, 0.62 mmol) was added under an N_2 atmosphere with stirring to a solution of PhMgBr [prepared from Mg (1.51 g, 62 mmol) and PhBr (9.7 g, 62 mmol)] in dry ether (60 ml), and the mixture was refluxed for 6 h. After addition of 3 N HCl, the aqueous layer was made alkaline with K_2CO_3, and the oil that separated was extracted with $CHCl_3$. The $CHCl_3$ extract was distilled under reduced pressure to give a colorless liquid, bp 120—121 °C (2 mmHg). Yield 5.15 g (84%). Picrate: yellow needles (EtOH), mp 195—196 °C. ^{1}H-NMR ($CDCl_3$): 1.33 (3H, t, J=7 Hz), 2.74 (3H, s), 2.81 (2H, q, J=7 Hz), 7.3—7.5 (4H, m), 8.0—8.2 (2H, m). *Anal.* Calcd for $C_{19}H_{17}N_5O_7$ (picrate): C, 53.39; H, 4.01; N, 16.39. Found: C, 53.25; H, 3.92; N, 16.33.

4-Ethyl-6-methoxy-2-methylpyrimidine——A mixture of 4-chloro-6-ethyl-2-methylpyrimidine (4.0 g, 26 mmol) and MeONa–MeOH [prepared from Na (1.18 g, 51 mmol) and dry MeOH (100 ml)] was refluxed for 2 h. After removal of the MeOH, H_2O was added to the residue, and the resulting mixture was extracted with $CHCl_3$. The

$CHCl_3$ extract was distilled under reduced pressure to give a colorless liquid, bp 57—58 °C (2 mmHg). Yield 3.13 g (81%). ^{1}H-NMR ($CDCl_3$): 1.26 (3H, t, J=7 Hz), 2.57 (3H, s), 2.68 (2H, q, J=7 Hz), 3.95 (3H, s), 6.40 (1H, s). *Anal.* Calcd for $C_8H_{12}N_2O$: C, 63.13; H, 7.95; N, 18.41. Found: C, 62.97; H, 8.39; N, 18.00.

2-Ethyl-6-methyl-4-phenylpyrimidine 1-oxide (**4a**) was prepared according to the reported procedure[3] from 2-ethyl-4-methyl-6-phenyl-pyrimidine (2.07 g, 10 mmol) as colorless needles, mp 121—122 °C, which were recrystallized from ether. Yield 0.99 g (44%). IR ν_{max}^{KBr} cm^{-1}: 1260. ^{1}H-NMR ($CDCl_3$): 1.43 (3H, t, J=7 Hz), 2.59 (3H, s), 3.18 (2H, q, J=7 Hz), 7.4—7.6 (4H, m), 8.0—8.2 (2H, m). *Anal.* Calcd for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.08. Found: C, 73.03; H, 6.56; N, 13.01.

6-Ethyl-2-methyl-4-phenylpyrimidine 1-oxide (**4b**) was similarly prepared from 6-ethyl-2-methyl-4-phenyl-pyrimidine (3.98 g, 20 mmol) as colorless prisms, mp 85—86 °C, which were recrystallized from hexane. Yield 1.55 g (31%). IR ν_{max}^{KBr} cm^{-1}: 1210. ^{1}H-NMR ($CDCl_3$): 1.36 (3H, t, J=Hz), 2.79 (3H, s), 2.97 (2H, q, J=7 Hz), 7.3—7.5 (4H, m), 7.9—8.1 (2H, m). *Anal.* Calcd for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.08. Found: C, 72.88; H, 6.56; N, 13.01.

6-Ethyl-4-methoxy-2-methylpyrimidine 1-oxide (**6b**) was similarly prepared from 4-ethyl-6-methoxy-2-methylpyrimidine (3.1 g, 20 mmol) as a colorless liquid, bp 100—104 °C (2 mmHg), which solidified at room temperature. Yield 1.5 g (44%). Picrate: yellow prisms (EtOH), mp 100—101 °C. IR ν_{max}^{Nujol} cm^{-1}: 1220. ^{1}H-NMR ($CDCl_3$): 1.26 (3H, t, J=7 Hz), 2.69 (3H, s), 2.83 (2H, q, J=7 Hz), 3.92 (3H, s), 6.58 (1H, s). *Anal.* Calcd for $C_{14}H_{15}N_5O_9$ (picrate): C, 42.32; H, 3.81; N, 17.63. Found: C, 42.24; H, 3.76; N, 17.56.

General Procedure for Reaction of Pyrimidine *N*-Oxides with Phosphoryl Chloride in Dioxane——A solution of a pyrimidine *N*-oxide (5 mmol) and $POCl_3$ (15 mmol) in dioxane (10 ml) was refluxed for 1—7 h until the spot of starting material was no longer detectable on thin-layer chromatography (TLC) (SiO_2). After removal of the dioxane, the residue was poured into dil. NH_4OH under cooling, and the resulting mixture was extracted with $CHCl_3$. The $CHCl_3$ extract was distilled under reduced pressure to give the corresponding chloromethylpyrimidine as a liquid. The chloromethylpyrimidines were converted to the methoxymethylpyrimidines by treatment with excess MeONa in dry MeOH.

4-Chloromethyl-2-ethyl-6-phenylpyrimidine (5a)——According to the general procedure, **5a** was obtained from **4a** as a colorless liquid, bp 136—138 °C (2 mmHg). Yield 0.72 g (77%). ^{1}H-NMR ($CDCl_3$): 1.45 (3H, t, J=7 Hz), 3.07 (2H, q, J=7 Hz), 4.66 (2H, s), 7.5—7.6 (3H, m), 7.76 (1H, s), 8.1—8.3 (2H, m). *Anal.* Calcd for $C_{13}H_{13}ClN_2$: C, 67.09; H, 5.63; N, 12.04. Found: C, 67.39; H, 5.74; N, 12.00.

4-(1-Chloroethyl)-2-methyl-6-phenylpyrimidine (5b)——According to the general procedure, **5b** was obtained from **4b** as a colorless liquid, bp 144—146 °C (2 mmHg). Picrate: yellow needles (EtOH), mp 144—145 °C. Yield 0.52 g (46%). ^{1}H-NMR ($CDCl_3$): 1.89 (3H, d, J=7 Hz), 2.81 (3H, s), 5.08 (1H, q, J=7 Hz), 7.4—7.6 (3H, m), 7.74 (1H, s), 8.0—8.2 (2H, m). *Anal.* Calcd for $C_{19}H_{16}ClN_5O_7$ (picrate): C, 49.41; H, 3.49; N, 15.17. Found: C, 49.20; H, 3.37; N, 14.71.

2-(1-Chloroethyl)-4-methoxy-6-methylpyrimidine (7a)——According to the general procedure, **7a** was obtained from **6a** as a colorless liquid, bp 64—66 °C (2 mmHg). Picrolonate: yellow needles (EtOH), mp 115—116 °C (dec.). Yield 0.33 g (35%). ^{1}H-NMR ($CDCl_3$): 1.89 (3H, d, J=7 Hz), 2.46 (3H, s), 3.97 (3H, s), 5.07 (1H, q, J=7 Hz), 6.45 (1H, s). *Anal.* Calcd for $C_{18}H_{19}ClN_6O_6$ (picrolonate): C, 47.95; H. 4.25; N, 18.64. Found: C, 48.38; H, 4.52; N, 18.73.

2-Chloromethyl-4-ethyl-6-methoxypyrimidine (7b)——According to the general procedure, **7b** was obtained from **6b** as a colorless liquid, bp 76—78 °C (2 mmHg). Yield 0.55 g (59%). ^{1}H-NMR ($CDCl_3$): 1.26 (3H, t, J=7 Hz), 2.69 (2H, q, J=7 Hz), 3.96 (3H, s), 4.56 (2H, s), 6.46 (1H, s). *Anal.* Calcd for $C_8H_{11}ClN_2O$: C, 51.48; H, 5.94; N, 15.01. Found: C, 50.98; H, 5.87; N, 14.85.

2-Chloromethyl-4-methyl-6-phenylpyrimidine (2a)——A solution of 4-methyl-6-phenyl-2-pyrimidinemethanol[9] (2.0 g, 10 mmol) and $POCl_3$ (4.6 g, 30 mmol) in $CHCl_3$ (30 ml) was refluxed for 30 min. The mixture was poured into ice-water, made alkaline with conc. NH_4OH, and extracted with $CHCl_3$. The $CHCl_3$ extract was distilled under reduced pressure to give a colorless liquid. Yield 1.6 g (73%).

4-Chloromethyl-2-methyl-6-phenylpyrimidine (**3a**) was similarly synthesized from 2-methyl-6-phenyl-4-pyrimidinemethanol[9] (0.51 g, 2.5 mmol) as a colorless liquid. Yield 0.49 g (90%).

4-Chloromethyl-2,6-dimethylpyrimidine (**3e**) was similarly synthesized from 2,6-dimethyl-4-pyrimidine-methanol[10] (1.4 g, 10 mmol) as a colorless liquid. Yield 0.8 g (51%).

2-Methoxymethyl-4-methyl-6-phenylpyrimidine (2'a)——Compound **2a** (1.1 g, 5 mmol) was added to an MeONa–MeOH solution prepared from dry MeOH (10 ml) and Na (0.23 g, 10 mmol), and the mixture was refluxed for 1 h. After removal of the MeOH, H_2O was added to the residue, and the mixture was extracted with $CHCl_3$. The $CHCl_3$ extract was distilled under reduced pressure to give a colorless liquid. Yield 0.9 g (84%).

4-Methoxymethyl-2-methyl-6-phenylpyrimidine (**3'a**) was similarly prepared from **3a** (0.44 g, 2 mmol) as a colorless liquid. Yield 0.37 g (86%).

2-Methoxymethyl-4,6-dimethylpyrimidine (**2'e**) was similarly prepared from 2-chloromethyl-4,6-dimethyl-pyrimidine[10] (0.78 g, 5 mmol) as a colorless liquid. Yield 0.6 g (79%).

4-Methoxymethyl-2,6-dimethylpyrimidine (**3'e**) was similarly prepared from **3e** (0.7 g, 4.5 mmol) as a colorless liquid. Yield 0.54 g (79%).

2-Methoxymethyl-6-methyl-4(3*H*)-pyrimidinone——3-Chloroacetylaminocrotonamide[11] (1.0 g, 5.67 mmol) was added to an MeONa–MeOH solution [prepared from dry MeOH (30 ml) and Na (0.5 g, 20 mmol)], and the mixture was refluxed for 3 h. After removal of the MeOH, the residue was dissolved in 3 N HCl. The aq. solution was neutralized with 1 N $NaHCO_3$, and concentrated to dryness under reduced pressure. The residue was extracted with hot $CHCl_3$. The crude product obtained from the $CHCl_3$ extract was recrystallized from cyclohexane to give colorless needles, mp 96—98 °C. Yield 0.7 g (78%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3350, 1680. ^{1}H-NMR ($CDCl_3$): 2.30 (3H, s), 3.50 (3H, s), 4.30 (2H, s), 6.20 (1H, s), 10.7—11.4 (1H, br). *Anal.* Calcd for $C_7H_{10}N_2O_2$: C, 54.53; H, 6.54; N, 18.17. Found: C, 54.28; H, 6.57; N, 18.15.

6-Methoxymethyl-2-methyl-4(3*H*)-pyrimidinone——An MeONa–MeOH solution [prepared from dry MeOH (50 ml) and Na (3.45 g, 150 mmol)] was added to a mixture of ethyl 4-methoxy-3-oxobutanoate[12] (13 g, 100 mmol) and acetamidine hydrochloride (14.2 g, 150 mmol) in dry MeOH (50 ml) with stirring, and the whole was stirred for 1 h at room temperature. After removal of the MeOH, the residue was heated at 100 °C for 1 h under reduced pressure (30 mmHg), and then dissolved in H_2O. The aqueous solution was neutralized with 3 N HCl and extracted continuously with $CHCl_3$ for 24 h. The crude product obtained from the $CHCl_3$ extract was recrystallized from MeOH to give colorless scales, mp 169 °C. Yield 11 g (71%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3200—2800 (br), 1670. ^{1}H-NMR ($CDCl_3$): 2.48 (3H, s), 3.47 (3H, s), 4.30 (2H, s), 6.45 (1H, s), 13.3—13.7 (1H, br). *Anal.* Calcd for $C_7H_{10}N_2O_2$: C,

TABLE II. Chloromethyl- (**2a** and **3a, e**) and Methoxymethylpyrimidines (**2′a—f** and **3′a—f**)

Compd. No.	bp (°C) [mmHg]	^{1}H-NMR ($CDCl_3$) δ		Formula	Analysis (%) Calcd (Found)		
		$-CH_2-$	Other protons		C	H	N
2a	140—143 [2]	4.60 (2H, s)	2.50 (3H, s), 7.60 (4H, m) 7.9—8.2 (2H, m)	$C_{12}H_{11}ClN_2$	65.90 (65.96)	5.03 (5.06)	12.81 (12.52)
3a	130 [2]	4.65 (2H, s)	2.80 (3H, s), 7.3—7.6 (3H, m) 7.67 (1H, s), 7.8—8.3 (2H, m)	$C_{13}H_{11}ClN_2$	65.90 (66.02)	5.03 (4.97)	12.81 (12.95)
3e	94 [15]	4.45 (2H, s)	2.46 (3H, s), 2.58 (3H, s) 7.31 (1H, s)	$C_7H_9ClN_2$	53.67 (53.83)	5.75 (6.04)	17.89 (17.80)
2′a	134 [2]	4.53 (2H, s)	2.45 (3H, s), 3.47 (3H, s) 7.3—7.7 (4H, m), 7.9—8.2 (2H, m)	$C_{13}H_{14}N_2O$	72.87 (72.74)	6.59 (6.62)	13.08 (12.93)
3′a	128 [2]	4.42 (2H, s)	2.66 (3H, s), 3.47 (3H, s) 7.3—7.5 (3H, m), 7.57 (1H, s) 8.0—8.2 (2H, m)	$C_{13}H_{14}N_2O$	72.87 (72.84)	6.59 (6.54)	13.08 (13.03)
2′b	110—114 [20]	4.40 (2H, s)	2.37 (3H, s), 3.33 (3H, s) 3.93 (3H, s), 6.33 (1H, s)	$C_8H_{12}N_2O_2$	57.13 (56.88)	7.19 (7.26)	16.66 (16.59)
3′b	110 [19]	4.30 (2H, s)	2.50 (3H, s), 3.43 (3H, s) 3.92 (3H, s), 6.52 (1H, s)	$C_{14}H_{15}N_5O_9$ (Picrate)[a]	42.32 (42.47)	3.82 (3.79)	17.63 (17.74)
2′c	145—150 [25]	4.25 (2H, s)	2.25 (3H, s), 3.00 (6H, s) 3.35 (3H, s), 6.00 (1H, s)	$C_9H_{15}N_3O$	59.64 (59.81)	8.34 (8.44)	23.19 (23.44)
3′c	136—137 [15]	4.25 (2H, s)	2.30 (3H, s), 3.27 (6H, s) 3.45 (3H, s), 6.27 (1H, s)	$C_9H_{15}N_3O$	59.64 (59.45)	8.34 (8.21)	23.19 (23.01)
2′d	115 [15]	4.45 (2H, s)	2.45 (3H, s), 3.42 (3H, s) 7.03 (1H, s)	$C_7H_9ClN_2O$	48.70 (48.52)	5.22 (5.21)	16.23 (16.14)
3′d	105—106 [16]	4.42 (2H, s)	2.60 (3H, s), 3.42 (3H, s) 7.22 (1H, s)	$C_7H_9ClN_2O$	48.70 (48.43)	5.22 (5.24)	16.23 (16.14)
2′e	102—103 [13]	4.43 (2H, s)	2.44 (6H, s), 3.45 (3H, s) 6.78 (1H, s)	$C_8H_{12}N_2O$	63.13 (62.92)	7.95 (7.82)	18.41 (18.20)
3′e	96 [17]	4.33 (2H, s)	2.40 (3H, s), 2.57 (3H, s) 3.40 (3H, s), 6.97 (1H, s)	$C_8H_{12}N_2O$	63.13 (63.28)	7.95 (8.05)	18.41 (18.49)
2′f	99 [15]	4.46 (2H, s)	2.45 (3H, s), 3.42 (3H, s) 7.00 (1H, d, J=5 Hz), 8.48 (1H, d, J=5 Hz)	$C_7H_{10}N_2O$	60.85 (60.85)	7.30 (7.30)	20.28 (20.12)
3′f	82—83 [15]	4.40 (2H, s)	2.60 (3H, s), 3.43 (3H, s) 7.15 (1H, d, J=5 Hz), 8.50 (1H, d, J=5 Hz)	$C_{13}H_{13}N_5O_8$ (Picrate)[b]	42.51 (42.81)	3.57 (3.46)	19.07 (19.17)

a) Yellow prisms (C_6H_6), mp 105 °C. *b*) Yellow needles (C_6H_6), mp 125—126 °C (dec.).

54.53; H, 6.54; N, 18.17. Found: C, 54.27; H, 6.46; N, 18.00.

4-Chloro-2-methoxymethyl-6-methylpyrimidine (2'd)——A mixture of 2-methoxymethyl-6-methyl-4(3*H*)-pyrimidinone (1.1 g, 7 mmol) and $POCl_3$ (10 ml) was refluxed for 1 h. After removal of the excess $POCl_3$, the residue was poured into ice–conc. NH_4OH and extracted with $CHCl_3$. The $CHCl_3$ extract was passed through a short column of Al_2O_3 using C_6H_6 as an eluent, and the C_6H_6 eluate was distilled under reduced pressure to give a colorless liquid. Yield 1.1 g (92%).

4-Chloro-6-methoxymethyl-2-methylpyrimidine (**3'd**) was similarly prepared from 6-methoxymethyl-2-methyl-4(3*H*)-pyrimidinone (2.0 g, 13 mmol) as a colorless liquid. Yield 1.8 g (80%).

4-Methoxy-2-methoxymethyl-6-methylpyrimidine (2'b)——Compound **2'd** (0.86 g, 5 mmol) was added to an MeONa–MeOH solution [prepared from dry MeOH (10 ml) and Na (0.23 g, 10 mmol)], and the mixture was refluxed for 1 h. After removal of the MeOH, the residue was dissolved in H_2O and extracted with $CHCl_3$. The $CHCl_3$ extract was distilled under reduced pressure to give a colorless liquid. Yield 0.74 g (88%).

4-Methoxy-6-methoxymethyl-2-methylpyrimidine (**3'b**) was similarly prepared from **3'd** (0.86 g, 5 mmol) as a colorless liquid. Yield 0.75 g (89%).

4-Dimethylamino-2-methoxymethyl-6-methylpyrimidine (2'c)——A mixture of **2'd** (0.86 g, 5 mmol) and 40% aq. Me_2NH (2.25 g, 20 mmol) was heated in a sealed tube at 120 °C for 24 h. After dilution with H_2O, the mixture was extracted with $CHCl_3$. The $CHCl_3$ extract was distilled under reduced pressure to give a colorless liquid. Yield 0.8 g (88%).

4-Dimethylamino-6-methoxymethyl-2-methylpyrimidine (**3'c**) was similarly prepared from **3'd** (0.86 g, 5 mmol) as a colorless liquid. Yield 0.84 g (93%).

2-Methoxymethyl-4-methylpyrimidine (2'f)——A solution of **2'd** (1.2 g, 7 mmol) and conc. NH_4OH (5 ml) in MeOH (50 ml) was hydrogenated over 10% Pd-C (0.5 g) at atmospheric pressure. After filtration to remove the catalyst, the filtrate was acidified with conc.HCl, and the mixture was concentrated to dryness under reduced pressure. The residue was made alkaline with aq. K_2CO_3, and the resulting mixture was extracted with $CHCl_3$. The $CHCl_3$ extract was distilled under reduced pressure to give a colorless liquid. Yield 0.8 g (83%).

4-Methoxymethyl-2-methylpyrimidine (**3'f**) was similarly prepared from **3'd** (1.2 g, 7 mmol) as a colorless liquid. Yield 0.57 g (59%).

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