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Pyrimidine Derivatives and Related Compounds. XXXIII.[1] Reactions of 6-Bromomethyl-5-formyl-1,3-dimethyluracil and Its Hydrazones with Nucleophiles. Synthesis of Pyrrolo[3,4-*d*]pyrimidines and Pyrimido[4,5-d]pyridazines[2]

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The reactions of 6-bromomethyl-5-formyl-1,3-dimethyluracil (**1**) and its hydrazones (**6a** and **6b**) with nucleophiles were investigated. Treatment of **1** with primary amines or hydrazines afforded pyrrolo[3,4-*d*]pyrimidines or pyrimido[4,5-*d*]pyridazines, respectively. When 6-bromomethyl-1,3-dimethyluracil-5-carboxaldehyde tosylhydrazone (**6a**) was treated with hydrazine hydrate, it was readily converted into pyrrolo[3,4-*d*]pyrimidine (**7**) and pyrimido[4,5-*d*]pyridazine (**8**). The reaction of 6-bromomethyl-1,3-dimethyluracil-5-carboxaldehyde acetylhydrazone (**6b**) with hydrazine hydrate gave N-aminopyrrolo[3,4-*d*]-pyrimidine (**9**).

Keywords——pyrrolo[3,4-*d*]pyrimidine; pyrimido[4,5-*d*]pyridazine; quinazoline-2,4-dione; 5-formyluracils; nucleophilic substitution; 1,4-cycloaddition

In the preceding papers, we reported the reactions of 6-bromomethyl-1,3-dimethyl-5-nitrouracil with nucleophiles.[3–5] These investigations also included the discovery of a facile synthesis of pyrazolo[4,3-*d*]pyrimidine 1-oxides by the reaction of the 6-bromomethyl-5-nitrouracil with primary alkylamines[4] and that of a new type of ring transformation of the resulting oxides into pyrimido[5,4-*d*]pyrimidines.[5] Our studies on the reactions of the 6-bromomethyl-5-nitrouracil have led us to an interest in studying those of 6-bromomethyl-5-formyl-1,3-dimethyluracil (**1**). In addition, our interest in the possible physiological activity of pyrrolo[3,4-*d*]pyrimidine[6] and pyrimido[4,5-*d*]pyridazine,[7,8] deaza and aza analogs of purine and pterine, has led to the investigation of convenient methods for the synthesis of 6-substituted pyrrolo[3,4-*d*]pyrimidines and 7-substituted pyrimido[4,5-*d*]pyridazines.

Though there are already many reports on syntheses of pyrrolo[3,4-*d*]pyrimidines, most of them deal with the annelation of pyrrole precursors to the fused pyrimidine ring system.[9]

In this paper we wish to describe the reactions of **1** and its hydrazones with nucleophiles and also a convenient method for the synthesis of 6-substituted pyrrolo[3,4-*d*]pyrimidines and 7-substituted pyrimido[4,5-*d*]pyridazines from the pyrimidine ring system.

The key intermediate, 6-bromomethyl-5-formyl-1,3-dimethyluracil (**1**), was prepared in 88% yield by warming 5-formyl-1,3,6-trimethyluracil[10] with bromine in chloroform. Treatment of **1** with aliphatic amines or benzylamine in ethyl acetate at 0° afforded the corresponding 6-substituted pyrrolo[3,4-*d*]pyrimidines (**2a—e**) in good yields. Reactions of arylamines with **1** were carried out in methanol at room temperature and the corresponding products (**2f—i**) were obtained. The structures of **2a—i** were established by their elemental analyses and spectral data.

Compound **1** reacted smoothly with dialkylamines in ethyl acetate at 0° to give the corresponding 6-dialkylaminomethyl-5-formyluracils (**3a** and **3b**). Similarly, the reaction of **1** with potassium thiocyanate in methanol at room temperature gave **3c**. When a methanolic solution of **1** was treated with thiophenols or glycine ethylester hydrochloride in the presence of triethylamine the corresponding acetals (**4a—c**) were obtained. Compound **4a** was easily hydrolyzed with formic acid to give the aldehyde, 5-formyl-1,3-dimethyl-6-phenylthiomethyl-

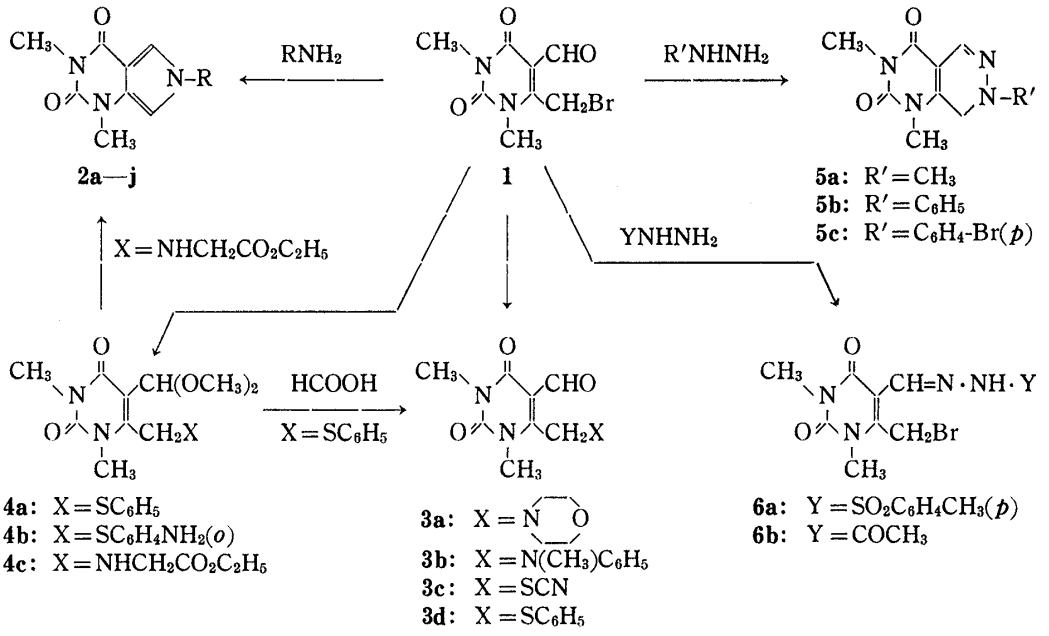

Chart 1

TABLE I. Formation of 6-Substituted 6*H*-Pyrrolo[3,4-*d*]pyrimidine-2,4(1*H*,3*H*)-diones (**2**)

Compd.	R	Method[a]	Reaction time	Recryst. solvent	Yield (%)	mp (°C)
2a	CH_3	A	0.5	Ligroin	70	174—176
2b	iso-C_3H_7	A	0.5	Ether	60	129—130
2c	$CH_2CH{=}CH_2$	A	2	Ether	60	129—131
2d	*n*-C_4H_9	A	0.5	Ligroin	47	118—120
2e	$C_6H_5CH_2$	A	1	Ligroin	73	128—129
2f	C_6H_5	B	2	2-Propanol	78	194—196
2g	4-$CH_3C_6H_4$	B	1	2-Propanol	56	229—230
2h	3,4-$(CH_3)_2C_6H_3$	B	1	Ethanol	70	220—221
2i	4-BrC_6H_4	B	2	Methanol	55	299—300

a) See "Experimental."

uracil (**3d**). Similar treatment of **4c** with formic acid resulted in ring closure after hydrolysis, and the pyrrolo[3,4-*d*]pyrimidine (**2j**) was formed.

Reaction of **1** with some hydrazines as nucleophiles was also examined in the expectation of obtaining 6-aminopyrrolo[3,4-*d*]pyrimidines or pyrimido[4,5-*d*]pyridazines. Thus, treatments of **1** with hydrazine hydrate in various solvents, such as methanol and ethyl acetate, afforded a complicated mixture. However, the reaction with methylhydrazine in ethyl acetate at 0° gave the 7-methylpyrimido[4,5-*d*]pyridazine (**5a**). Other 7-substituted pyrimido[4,5-*d*]-pyridazines (**5b** and **5c**) were similarly obtained by the reaction of **1** with arylhydrazines in acetic acid at room temperature followed by refluxing in an appropriate solvent. On the other hand, when **1** was allowed to react with *p*-toluenesulfonyl(tosyl)hydrazine and acetylhydrazine at room temperature, the 6-bromomethyluracil-5-carboxaldehyde hydrazones (**6a** and **6b**) were obtained, respectively.

The reactions of **6a** and **6b** with hydrazines and amines were then carried out to prepare the fused pyrimidines. Thus, treatment of **6a** with hydrazine hydrate in methanol at room temperature caused a conversion into 1,3-dimethyl-6-tosylamino-6*H*-pyrrolo[3,4-*d*]-pyrimidine-2,4-(1*H*,3*H*)-dione (**7**) and 1,3-dimethyl-7-tosyl-7,8-dihydropyrimido[4,5-*d*]pyridazine-2,4(1*H*, 3*H*)-

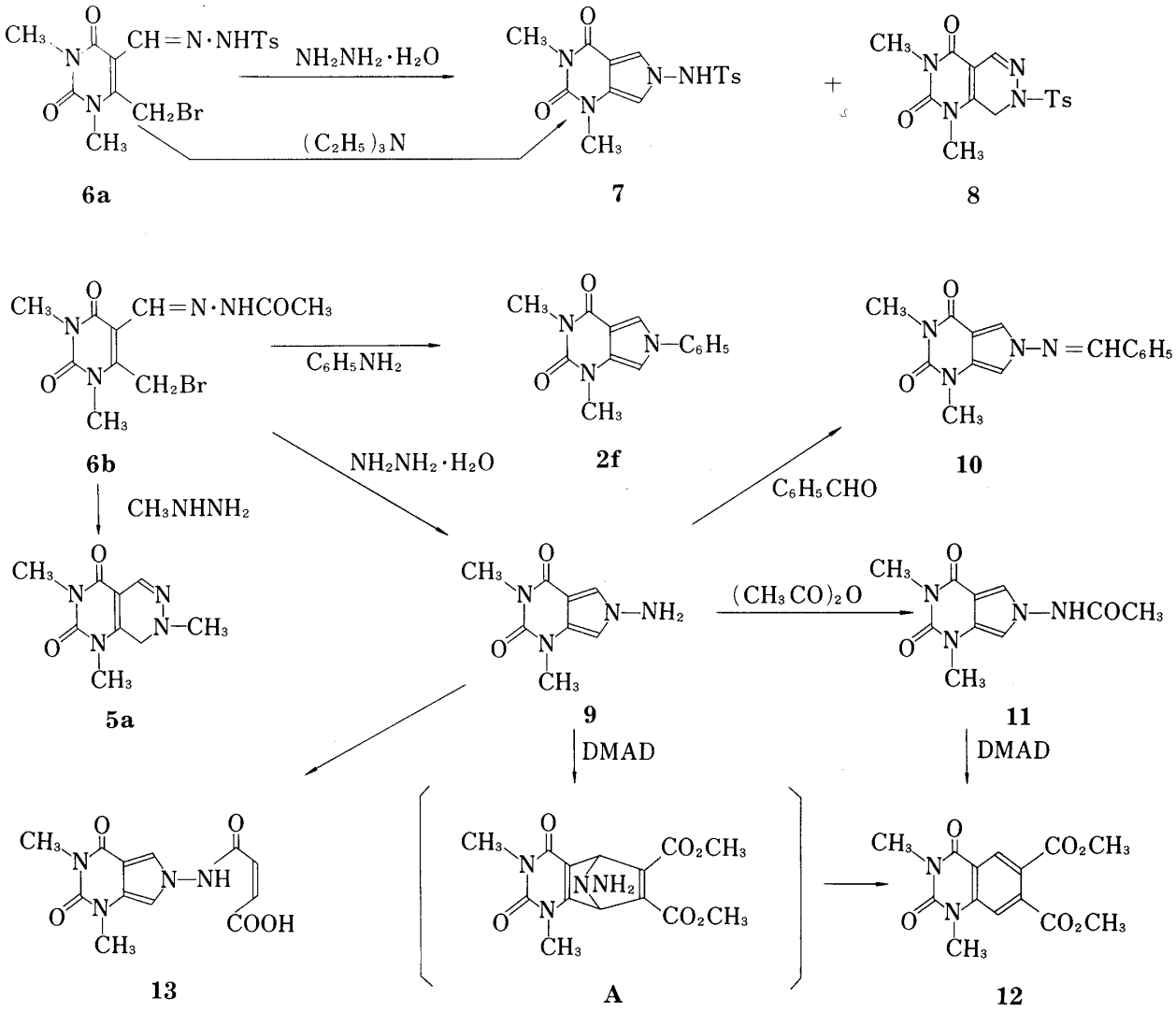

Chart 2

dione (**8**) at the same time. In this reaction, hydrazine hydrate did not act as a nucleophile but as a base. Accordingly similar treatment of **6a** with triethylamine afforded only **7**.

Compound **6b** was treated with aniline in methanol in the presence of triethylamine to afford the pyrrolo[3,4-*d*]pyrimidine (**2f**). The treatment of **6b** with methylhydrazine gave the pyrimido[4,5-*d*]pyridazine (**5a**). However, similar reaction of **6b** with hydrazine hydrate did not afford the expected pyrimido[4,5-*d*]pyridazine[11] and the sole product isolated was 6-amino-1,3-dimethyl-6*H*-pyrrolo[3,4-*d*]pyrimidine-2,4(1*H*, 3*H*)-dione (**9**). The structure of **9** was confirmed by spectral data and further by the conversion of **9** into the Schiff's base (**10**) using benzaldehyde.

Deamination of **9** with sodium nitrite in dilute hydrochloric acid failed to give the expected 6-unsubstituted pyrrolo[3,4-*d*]pyrimidine. The compound (**9**) was easily acetylated by warming in acetic anhydride, giving **11**. Furthermore, the compound (**9**), having a cyclic 1,3-diene moiety, is expected to undergo 1,4-cycloaddition across the 5,7-positions with dienophiles.[12] When a solution of **9** and dimethyl acetylenedicarboxylate (DMAD) in acetonitrile was heated to reflux for 1 hour, ring transformation occurred to yield 6,7-dimethoxycarbonyl-1,3-dimethylquinazoline-2,4(1H, 3H)-dione (**12**). This reaction presumably involves the formation of a cycloadduct intermediate (A). Compound **12** was also obtained by the similar reaction of **11** with DMAD. However, attempts to react other N-alkylpyrrolo[3,4-*d*]pyri-

midines such as **2a** (R=CH_3) and **2b** (R=iso-C_3H_7) with DMAD resulted in the recovery of the starting materials. Further, the reaction of **9** with other dienophiles, *e.g.* acetylenecarboxylic acid and dimethyl maleate, under the same conditions failed and the starting material was recovered. Refluxing of **9** with maleic anhydride in acetonitrile gave the acylated product (**13**) only.

Reaction mechanisms for the conversion of the hydrazones (**6a** and **6b**) into the pyrimido-[4,5-*d*]pyridazines (**5a** and **8**) and the pyrrolo[3,4-*d*]pyrimidines (**2f**, **7**, and **9**) are suggested in Chart 3. The proposed mechanism for the cyclization of **6a** to **7** and **8** is based on the formation of only **7** by use of triethylamine, which is more basic than hydrazine hydrate. Thus, an initial proton abstraction from the 6-bromomethyl group by a base affords a nitrogen anion, which undergoes intramolecular cyclization and subsequent elimination of hydrogen bromide, yielding **7**.

The proposed reaction mechanism for the conversion of **6b** into **2f**, **9** or **5a** is closely related to the mechanism[13] of pyrazolo[3,4-*d*]pyrimidine synthesis by the reaction of 6-chloro-1,3-dimethyluracil-5-carboxaldehyde phenylhydrazone with methylhydrazine. The formation of **2f**, **9** or **5a** presumably proceeds by an initial nucleophilic substitution of **6b** with amines or hydrazines, followed by cyclization and subsequent elimination of acetylhydrazine.

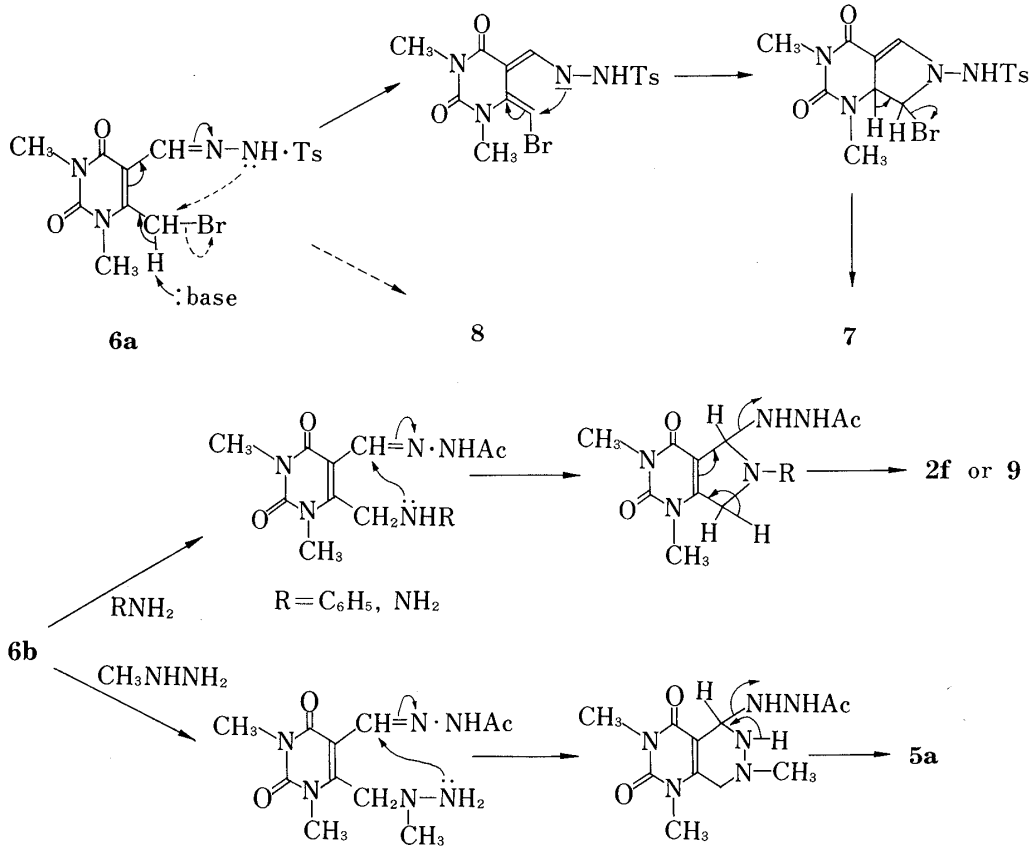

Chart 3

Experimental

Melting points were determined on a Yanagimoto hot-stage apparatus and are uncorrected. ^1H Nuclear magnetic resonance (NMR) spectra were recorded on a Hitachi Perkin-Elmer R-20B 60 MHz spectrometer with tetramethylsilane as an internal standard. Infrared (IR) spectra were obtained with a Hitachi 215 instrument as KBr pellets. Ultraviolet (UV) spectra were measured on a Hitachi 323 spectrophotometer.

6-Bromomethyl-5-formyl-1,3-dimethyluracil (1)——A solution of 4.8 g (0.03 mol) of bromine in 20 ml of chloroform was added dropwise to a stirred solution of 5.5 g (0.03 mol) of 5-formyl-1,3,6-trimethyluracil in

TABLE II. Spectral and Analytical Data for 6-Substituted 6*H*-Pyrrolo[3,4-*d*]-pyrimidine-2,4(1*H*,3*H*)-diones (2)

	UV λmax nm (log ε)	NMR ($CDCl_3$) δ C_5–H	C_7–H	$J_{5,7}$ (Hz)	Formula	Analysis (%) Calcd (Found) C	H	N
2a	221, 257, 293 (4.38, 3.83, 3.45)	7.14	6.22	2.3	$C_9H_{11}N_3O_2$	55.95 (55.89	5.74 5.73	21.75 21.62)
2b	221, 257, 293 (4.38, 3.89, 3.49)	7.27	6.30	2.7	$C_{11}H_{15}N_3O_2$	59.71 (59.57	6.83 6.89	18.99 18.81)
2c	222, 256, 293 (4.40, 3.89, 3.46)	7.18	6.23	2.4	$C_{11}H_{13}N_3O_2$	60.26 (60.15	5.89 6.08	19.15 18.86)
2d	222, 257, 294 (4.40, 3.89, 3.46)	7.16	6.22	2.4	$C_{12}H_{17}N_3O_2$	61.25 (60.95	7.26 7.28	17.86 17.93)
2e	225, 256, 262 (sh), 295 (4.44, 3.98, 3.95, 3.45)	a)	6.25	2.7	$C_{15}H_{15}N_3O_2$	66.90 (66.80	5.61 5.49	15.61 15.40)
2f	236, 271, 305 (sh) (4.36, 4.20, 3.84)	7.58	6.55	2.4	$C_{14}H_{13}N_3O_2$	65.87 (65.83	5.13 4.99	16.46 16.37)
2g	238, 273, 305 (sh) (4.37, 4.24, 3.90)	7.52	6.57	2.7	$C_{15}H_{15}N_3O_2$	66.90 (67.08	5.61 5.64	15.61 15.61)
2h	238, 275, 306 (sh) (4.37, 4.24, 3.92)	7.50	6.58	2.7	$C_{16}H_{17}N_3O_2$	67.82 (67.68	6.05 6.12	14.83 14.84)
2i	242, 250 (sh), 275, 306 (sh) (4.30, 4.29, 4.37, 3.96)	b)			$C_{14}H_{12}BrN_3O_2$	50.31 (50.37	3.62 3.60	12.57 12.75)

a) Not observed: overlapped by other signals.
b) Could not be determined.

80 ml of chloroform at 50°. The solvent was evaporated off *in vacuo*. Water was added to the residue and the resulting precipitate was separated by filtration and dried to give 6.9 g (88%) of **1**. Recrystallization from water gave colorless needles, mp 129—130°. *Anal.* Calcd for $C_8H_9BrN_2O_3$: C, 36.81; H, 3.48; N, 10.73. Found: C, 36.97; H, 3.43; N, 10.74. IR ν_{max} cm^{-1}: 1710, 1640 (C=O). UV λ_{max}^{EtOH} nm (log ε): 234 (4.01), 313 (4.01). NMR ($CDCl_3$) δ: 3.37 (3H, s, NCH_3), 3.60 (3H, s, NCH_3), 4.88 (2H, s, CH_2Br), 10.12 (1H, s, CHO).

6-Substituted 1,3-Dimethyl-6*H*-pyrrolo[3,4-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (2a—i); General Procedures——Method A: An amine (0.004 mol) was added to a stirred solution of 0.52 g (0.002 mol) of **1** in 20 ml of ethyl acetate with cooling in an ice bath. Stirring was continued for the time given in Table I. The mixture was filtered and evaporated to dryness *in vacuo*. Water (10 ml) was added to the residue, and the precipitate was separated by filtration. The product was recrystallized from an appropriate solvent as given in Table I.

Method B: An arylamine (0.008 mol) was added to a solution of 1.04 g (0.004 mol) of **1** in 20 ml of methanol at room temperature with stirring. Stirring was continued for the time given in Table I, and then the methanol was evaporated off *in vacuo*. Water (10 ml) was added to the residue, and the precipitate was separated by filtration. The product was recrystallized from an appropriate solvent as given in Table I.

1,3-Dimethyl-6-phenyl-6*H*-pyrrolo[3,4-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (2f)——To a mixture of 0.64 g (0.002 mol) of **6b** and 0.5 ml of triethylamine suspended in 25 ml of methanol was added 0.19 g (0.002 mol) of aniline at room temperature. Stirring was continued for 2 hr and then the solvent was evaporated off *in vacuo*. Water was added to the residue, and the precipitate was filtered off and dried to give 0.36 g (70%) of **2f**, which was identical with a sample prepared by Method B described above.

6-Ethoxycarbonylmethyl-1,3-dimethyl-6*H*-pyrrolo[3,4-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (2j)——A solution of 0.66 g (0.002 mol) of **4c** in 10 ml of formic acid was heated at 90° for 1 hr. The solvent was evaporated off *in vacuo*. Water was added to the residue, and the precipitate was collected and dried to give 0.47 g (88%) of **2j**. Recrystallization from ligroin afforded colorless needles, mp 156—158°. *Anal.* Calcd for $C_{12}H_{15}N_3O_4$: C, 54.33; H, 5.76; N, 15.84. Found: C, 54.10; H, 5.64; N, 15.82. IR ν_{max} cm^{-1}: 1740, 1700, 1660 (C=O). UV λ_{max}^{EtOH} nm (log ε): 221 (4.38), 254 (3.88), 260 sh (3.85), 294 (3.49). NMR ($CDCl_3$) δ: 1.30 (3H, t, CH_3), 3.36 (6H, s, $NCH_3 \times 2$), 4.22 (2H, q, CH_2), 4.64 (2H, s, CH_2), 6.30 (1H, d, J=2.3 Hz, C_7–H), 7.22 (1H, d, J=2.3 Hz, C_5–H).

5-Formyl-1,3-dimethyl-6-morpholinomethyluracil (3a)——To a stirred solution of 0.52 g (0.002 mol) of **1** in 15 ml of ethyl acetate was added 0.35 g (0.004 mol) of morpholine with cooling in an ice bath. The mixture was stirred for 0.5 hr, then the solvent was evaporated off *in vacuo*. Water was added to the residue, and the precipitate was filtered off and dried to give 0.31 g (58%) of **3a**. Recrystallization from ether afforded colorless needles, mp 144—146°. *Anal.* Calcd for $C_{12}H_{17}N_3O_4$: C, 53.92; H, 6.41; N, 15.72. Found: C, 53.87; H, 6.43; N, 15.45. IR ν_{max} cm^{-1}: 1720, 1690, 1650 (C=O).

5-Formyl-1,3-dimethyl-6-(N-methylanilino)methyluracil (3b)——The reaction of **1** and methylaniline by the procedure described above afforded **3b** in 87% yield. Recrystallization from 2-propanol afforded colorless needles, mp 140—141°. *Anal.* Calcd for $C_{15}H_{17}N_3O_3$: C, 62.70; H, 5.96; N, 14.63. Found: C, 62.70; H, 5.98; N, 14.63. IR ν_{max} cm^{-1}: 1710, 1690, 1640 (C=O).

6-Cyanothiomethyl-5-formyl-1,3-dimethyluracil (3c)——To a stirred solution of 2.08 g (0.008 mol) of **1** in 30 ml of methanol was added 1.55 ml of 50% potassium thiocyanate (0.008 mol) at room temperature. The mixture was stirred for 1.5 hr, then the solvent was evaporated off *in vacuo*. Water was added to the residue, and the precipitate was filtered off and dried to give 1.7 g (89%) of **3c**. Recrystallization from 2-propanol gave yellow needles, mp 122—123°. *Anal.* Calcd for $C_9H_9N_3O_3S$: C, 45.19; H, 3.79; N, 17.57. Found: C, 44.94; H, 3.79; N, 17.33. IR ν_{max} cm^{-1}: 2150 (CN), 1720, 1690, 1650 (C=O). NMR ($CDCl_3$) δ: 3.40, 3.65 (3H×2, s×2, N-CH_3×2), 4.54 (2H, s, CH_2), 10.13 (1H, s, CH).

5-Formyl-1,3-dimethyl-6-phenylthiomethyluracil (3d)——A solution of 0.67 g (0.002 mol) of **4a** in 8 ml of formic acid was heated at 90° for 30 min. The solvent was evaporated off *in vacuo*, and the residue was purified by column chromatography on silica gel with chloroform as the eluent to afford 0.25 g (43%) of **3d**. Recrystallization from ether gave colorless needles, mp 111—112°. *Anal.* Calcd for $C_{14}H_{14}N_3O_3S$: C, 57.91; H, 4.87; N, 9.65. Found: C, 57.96; H, 4.87; N, 9.45. IR ν_{max} cm^{-1}: 1720, 1690, 1640 (C=O).

1,3-Dimethyl-6-phenylthiomethyl-5-carboxaldehyde Dimethyl Acetal (4a)——To a stirred solution of 0.52 g (0.002 mol) of **1** and 0.5 ml of triethylamine in 15 ml of methanol was added 0.22 g (0.002 mol) of thiophenol with cooling in an ice bath. Stirring was continued for 1 hr, then the methanol was evaporated off *in vacuo*. Water was added to the residue, and the precipitate was filtered off and dried to give 0.6 g (89%) of **4a**. Recrystallization from ether gave yellow needles, mp 157°. *Anal.* Calcd for $C_{16}H_{21}N_3O_3S$: C, 54.69; H, 6.02; N, 11.96. Found: C, 54.87; H, 6.02; N, 12.12. IR ν_{max} cm^{-1}: 3450, 3350 (NH_2), 1690, 1650 (C=O).

6-(2-Aminophenylthio)methyl-1,3-dimethyluracil-5-carboxaldehyde Dimethyl Acetal (4b)——A solution of 0.52 g (0.002 mol) of **1**, 0.25 g (0.002 mol) of 2-aminothiophenol, and 0.5 ml of triethylamine in 20 ml of methanol was stirred at room temperature for 2 hr. The precipitate was collected by filtration and dried to give 0.65 g (92%) of **4b**. Recrystallization from 2-propanol gave yellow needles, mp 157°. *Anal.* Calcd for $C_{16}H_{21}N_3O_3S$: C, 54.69; H, 6.02; N, 11.96. Found: C, 54.87; H, 6.02; N, 12.12. IR ν_{max} cm^{-1}; 3450, 3350 (NH_2), 1690, 1650 (C=O).

6-Ethoxycarbonylmethylaminomethyl-1,3-dimethyluracil-5-carboxaldehyde Dimethyl Acetal (4c)——A mixture of 0.52 g (0.002 mol) of **1**, 0.28 g (0.002 mol) of glycine ethylester hydrochloride, and 1 ml of triethylamine in 15 ml of methanol was stirred at room temperature for 4 hr. The solvent was evaporated off *in vacuo*. Water was added to the residue, and the precipitate was filtered off and dried to afford 0.2 g (30%) of **4c**. Recrystallization from ether gave colorless needles, mp 97.5—99°. *Anal.* Calcd for $C_{16}H_{20}N_2O_4S$: C, 57.13; H, 5.99; N, 8.33. Found: C, 57.25; H, 5.85; N, 8.11. IR ν_{max} cm^{-1}; 1700, 1630 (C=O).

1,3,7-Trimethyl-7,8-dihydropyrimido[4,5-*d*]pyridazine-2,4(1*H*,3*H*)-dione (5a)——Method A: To a stirred solution of 0.26 g (0.001 mol) of **1** in 15 ml of ethyl acetate was added 0.1 g (0.002 mol) of methylhydrazine with cooling in an ice bath. The mixture was stirred for 0.5 hr, then the solvent was evaporated off *in vacuo*. Water (10 ml) was added to the residue and the mixture was extracted with chloroform (5 ml×3). The chloroform solution was dried and concentrated to give 0.12 g (58 g) of **5a**. Recrystallization from ligroin afforded yellow needles, mp 142—144°. *Anal.* Calcd for $C_9H_{12}N_4O_2$: C, 51.91; H, 5.85; N, 26.91. Found: C, 52.09; H, 5.78; N, 26.80. IR ν_{max} cm^{-1}: 1710, 1650 (C=O). UV λ_{max}^{EtOH} nm (log ε): 263 (4.02), 346 (3.49). NMR ($CDCl_3$) δ: 2.98 (3H, s, N-CH_3), 3.35 (3H, s, N-CH_3), 3.41 (3H, s, N-CH_3), 3.83 (2H, s, -CH_2N), 7.40 (1H, s, CH=N).

Method B: To a stirred suspension of 0.55 g (0.0017 mol) of **6b** in 25 ml of methanol was added 0.17 g (0.0036 mol) of methylhydrazine with cooling in an ice bath. The mixture was stirred for 1.5 hr, then the solvent was evaporated off *in vacuo*. Water (5 ml) was added to the residue and the mixture was extracted with chloroform (5 ml×3). The chloroform solution was dried and concentrated *in vacuo*. Ether was added to the residue and the precipitate was filtered off and dried to give 0.18 g (50%) of **5a**, which was identical with a sample prepared by method A.

1,3-Dimethyl-7-phenyl-7,8-dihydropyrimido[4,5-*d*]pyridazine-2,4(1*H*,3*H*)-dione(5b)——To a solution of 0.52 g (0.002 mol) of **1** in 5 ml of acetic acid was added 0.22 g (0.002 mol) of phenylhydrazine at room temperature. The precipitate was collected, washed with ether and water, and heated under reflux in 100 ml of methanol for 10 min. The solution was allowed to stand at room temperature and the resulting precipitate was filtered off to give 0.3 g (59%) of pure **5b**, mp 192—193° (dec.). *Anal.* Calcd for $C_{14}H_{14}N_4O_2$: C, 62.21; H, 5.22; N, 20.73. Found: C, 62.12; H, 5.10; N, 20.63. IR ν_{max} cm^{-1}: 1700, 1650 (C=O). UV λ_{max}^{EtOH} nm (log ε); 278 (4.22), 287 sh (4.18). NMR (CF_3COOH) δ: 3.55 (3H, s, NCH_3), 3.71 (3H, s, NCH_3), 5.23 (2H, s, CH_2N), 8.67 (1H, s, CH=N).

7-(4-Bromophenyl)-1,3-dimethyl-7,8-dihydropyrimido[4,5-*d*]pyridazine-2,4(1*H*,3*H*)-dione (5c)——A mixture of 1.04 g (0.004 mol) of **1** and 0.89 g (0.004 mol) of 4-bromophenylhydrazine hydrochloride in 20 ml of acetic acid was stirred at room temperature for 2.5 hr. The precipitate was collected, washed with ether and water, and heated under reflux in 20 ml of dimethylformamide for 10 min. The solution was allowed to stand at room temperature and the resulting precipitate was filtered off to give 0.14 g (10%) of pure **5c**,

mp 197—199° (dec.). *Anal.* Calcd for $C_{14}H_{13}BrN_4O_2$: C, 48.15; H, 3.75; N, 16.05. Found: C, 48.27; H, 3.72; N, 16.15. IR ν_{max} cm^{-1}: 1710, 1660 (C=O).

6-Bromomethyl-1,3-dimethyluracil-5-carboxaldehyde Tosylhydrazone (6a)——A mixture of 0.52 g (0.002 mol) of 1 and 0.38 g (0.002 mol) of tosylhydrazine in 20 ml of methanol was stirred at room temperature for 1 hr. The solvent was evaporated off *in vacuo*. Water was added to the residue, and the precipitate was filtered off and dried to give 0.6 g (69%) of **6a**. Recrystallization from methanol gave yellow needles, mp 177—178° (dec.). *Anal.* Calcd for $C_{15}H_{17}BrN_4O_4S$: C, 41.99; H, 3.99; N, 13.06. Found: C, 42.03; H, 3.96; N, 13.33. IR ν_{max} cm^{-1}: 3150 (NH), 1700, 1630 (C=O). NMR (DMSO-d_6) δ: 2.38 (3H, s, CH_3), 3.15 (3H, s, NCH_3), 3.45 (3H, s, NCH_3), 4.86 (2H, s, CH_2Br), 7.52 (4H, m, aromatic), 7.95 (1H, s, CH=N).

6-Bromomethyl-1,3-dimethyluracil-5-carboxaldehyde Acetylhydrazone (6b)——To a stirred solution of 0.52 g (0.002 mol) of **1** in 5 ml of acetic acid was added 0.15 g (0.002 mol) of acetylhydrazine at 15° and the mixture was stirred for 1 hr then diluted with 50 ml of ice/water. The resulting precipitate was collected, washed with water, and dried to give 0.58 g (92%) of **6b**. Recrystallization from 2-propanol afforded yellow needles, mp 173—175° (dec.). *Anal.* Calcd for $C_{10}H_{13}BrN_4O_3$: C, 37.87; H, 4.13; N, 17.67. Found: C, 38.08; H, 4.18; N, 17.78. IR ν_{max} cm^{-1}: 3400, 3220 (NH), 1700, 1660, 1620 (C=O). NMR ($CDCl_3$) δ: 2.33 (3H, s, $COCH_3$), 3.40 (3H, s, NCH_3), 3.63 (3H, s, NCH_3), 4.85 (2H, s, CH_2Br), 8.18 (1H, s, CH=N), 9.78 (1H, bs, N–NH).

1,3-Dimethyl-6-tosylamino-6*H*-pyrrolo[3,4-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (7) and 1,3-Dimethyl-7-tosyl-7,8-dihydropyrimido[4,5-*d*]pyridazine-2,4(1*H*,3*H*)-dione (8)——To a suspension of 0.86 g (0.002 mol) of **6a** in 50 ml of methanol was added 0.2 g (0.004 mol) of hydrazine hydrate at room temperature. The mixture was stirred for 5 hr, then the precipitate was filtered off and dried to give 0.114 g (16%) of **8**. Recrystallization from methanol gave yellow needles, mp 152—153°. *Anal.* Calcd for $C_{15}H_{16}N_4O_4S$: C, 51.72; H, 4.63; N, 16.09. Found: C, 51.86; H, 4.61; N, 15.98. IR ν_{max} cm^{-1}: 1710, 1660 (C=O). UV λ_{max}^{EtOH} nm (log ε): 226 (4.26), 253 (4.18). NMR (DMSO-d_6) δ: 2.39 (3H, s, CH_3), 3.11 (3H, s, NCH_3), 3.31 (3H, s, NCH_3), 4.46 (2H, s, CH_2N), 7.45 (1H, s, CH–N), 7.55 (4H, m, aromatic). The filtrate was evaporated to dryness *in vacuo*. Water was added to the residue, and the precipitate was collected and dried to give 0.5 g (71%) of **7**. Recrystallization from methanol gave colorless prisms, mp 267—270. *Anal.* Calcd for $C_{15}H_{16}N_4O_4S$; C, 51.72; H, 4.63; N, 16.09. Found: C, 51.73; H, 4.53; N, 16.17. IR ν_{max} cm^{-1}: 3140 (NH), 1690, 1630 (C=O). UV λ_{max}^{EtOH} nm (log ε): 222 (4.48), 254 (4.04), 290 sh (3.59). NMR (DMSO-d_6) δ: 2.40 (3H, s, CH_3), 3.13 (6H, s, $NCH_3 \times 2$), 6.43 (1H, d, J=2.4 Hz, C_7–H), 6.82 (1H, d, J=2.4 Hz, C_5–H), 7.48 (4H, m, aromatic).

Preparation of 7 by the Reaction of 6a with Triethylamine——To a suspension of 0.43 g (0.001 mol) of **6a** in 25 ml of methanol was added 0.5 ml of triethylamine with cooling in an ice bath. After being stirred for 1 hr, the mixture was filtered and the filtrate was concentrated *in vacuo*. Water was added to the residue and the mixture was acidified with acetic acid. The precipitate was collected and dried to give 0.245 g (70%) of **7**, which was identical with a sample prepared by the method described above.

6-Amino-1,3-dimethyl-6*H*-pyrrolo[3,4-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (9)——To a stirred suspension of 16 g (0.05 mol) of **6b** in 500 ml of methanol was added 5 g (0.1 mol) of hydrazine hydrate at room temperature. Stirring was continued for 2 hr, then a pure sample of 5.45 g of **9** was collected by filtration. An additional crop of product was obtained from the concentrated mother liquor. Total yield: 7.8 g (80%). Recrystallization from 2-propanol gave colorless needles, mp 220—222°. *Anal.* Calcd for $C_8H_{10}N_4O_2$: C, 49.48; H, 5.19; N, 28.85. Found: C, 49.43; H, 5.14; N, 28.62. IR ν_{max} cm^{-1}: 3320, 3220 (NH_2), 1700, 1640 (C=O). UV λ_{max}^{EtOH} nm (log ε): 221 (4.37), 261 (3.86), 289 sh (3.53). NMR (DMSO-d_6) δ: 3.18 (3H, s, NCH_3), 3.25 (3H, s, NCH_3), 6.32 (2H, bs, NH_2), 6.60 (1H, d, J=2.7 Hz, C_7–H), 7.20 (1H, d, J=2.7 Hz, C_5–H).

6-Benzylidenamino-1,3-dimethyl-6*H*-pyrrolo[3,4-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (10)——A mixture of 0.19 g (0.001 mol) of **9** and 0.11 g (0.001 mol) of benzaldehyde in 10 ml of ethanol was stirred at room temperature for 2 hr. The precipitate was filtered off and dried to give 0.24 g (85%) of **10**. Recrystallization from ethanol afforded colorless needles, mp 244—245°. *Anal.* Calcd for $C_{15}H_{14}N_4O_2$: C, 63.82; H, 5.00; N, 19.85. Found: C, 63.69; H, 4.96; N, 19.59. IR ν_{max} cm^{-1}: 1690, 1660 (C=O). NMR ($CDCl_3$) δ: 3.38 (3H, s, NCH_3), 3.40 (3H, s, NCH_3), 7.50 (7H, m, C_5–H, C_7–H, and aromatic), 8.40 (1H, s, CH=N).

6-Acetylamino-1,3-dimethyl-6*H*-pyrrolo[3,4-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (11)——A mixture of 0.194 g (0.001 mol) of **9** in 2 ml of acetic anhydride was heated at 90° for 1 min. The precipitate was collected and washed with ether to give 0.19 g (80%) of **11**. Recrystallization from ethyl acetate afforded colorless needles, mp 233—234°. *Anal.* Calcd for $C_{10}H_{12}N_4O_3$: C, 50.84; H, 5.12; N, 23.72. Found: C, 50.74; H, 5.09; N, 23.45. IR ν_{max} cm^{-1}: 3280 (NH), 1710, 1690, 1650 (C=O). UV λ_{max}^{EtOH} nm (log ε): 218 sh (4.40), 254 (3.89), 293 (3.50). NMR (DMSO-d_6) δ: 2.99 (3H, s, $COCH_3$), 3.18 (3H, s, NCH_3), 3.24 (3H, s, NCH_3), 6.82 (1H, d, J=2.4 Hz, C_7–H), 7.39 (1H, d, J=2.4 Hz, C_5–H), 11.40 (1H, bs, NH).

6,7-Dimethoxycarbonyl-1,3-dimethylquinazoline-2,4(1*H*,3*H*)-dione (12)——Method A: A mixture of 0.39 g (0.002 mol) of **9** and 0.29 g (0.002 mol) of dimethyl acetylenedicarboxylate in 20 ml of acetonitrile was refluxed for 1 hr then the solvent was evaporated off *in vacuo*. Ether was added to the residue and the precipitate was collected by filtration to give 0.51 g (83%) of **12**. Recrystallization from methanol afforded colorless needles, mp 196°. *Anal.* Calcd for $C_{14}H_{14}N_2O_6$: C, 54.90; H, 4.61; N, 9.15. Found: C, 54.86; H, 4.48; N, 9.23. IR ν_{max} cm^{-1}: 1740, 1710, 1660 (C=O). UV λ_{max}^{EtOH} nm (log ε); 235 (4.20), 277 (3.81), 325 (3.18). NMR ($CDCl_3$) δ: 3.45 (3H, s, NCH_3), 3.59 (3H, s, NCH_3), 3.88 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 7.27 (1H, s,

C_8–H), 8.58 (1H, s, C_5–H).

Method B: A mixture of 0.39 g (0.002 mol) of **11** and 0.29 g (0.002 mol) of dimethyl acetylenedicarboxylate in 20 ml of acetonitrile was refluxed for 1 hr then the solvent was evaporated off *in vacuo*. Ether was added to the residue and the precipitate was collected by filtration to give 0.30 g (49%) of **12**, which was identical with a sample prepared by Method A described above.

Reaction of 6-Amino-1,3-dimethyl-6*H*-pyrrolo[3,4-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (9) with Maleic Anhydride——A mixture of 0.39 g (0.002 mol) of **9** and 0.2 g (0.002 mol) of maleic anhydride in 20 ml of acetonitril was refluxed for 4 hr. The solution was allowed to stand at room temperature, and the precipitate was filtered off and dried to give 0.3 g (51%) of **13**. Recrystallization from methanol gave colorless needles, mp>300°. *Anal.* Calcd for $C_{12}H_{12}O_5N_4$: C, 49.31; H, 4.14; N, 19.17. Found: C, 49.26; H, 4.24; N, 19.02. IR ν_{max} cm^{-1}: 3400—2700 (NH and COOH), 1750, 1690, 1650 (C=O). NMR (DMSO-d_6) δ: 3.22 (3H, s, CH_3), 3.28 (3H, s, CH_3), 6.75 (1H, d, J=16 Hz, CH=C), 6.90 (1H, d, J=2.5 Hz, C_7–H), 6.92 (1H, d, J=16 Hz, CH=C), 7.60 (1H, d, J=2.5 Hz, C_5–H), 12.20 (1H, b, NH).

References and Notes

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