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Simple Syntheses of 1,3-Dialkylpyrrolo- and Furopyrimidines[1)]

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Simple and efficient syntheses of 7-deazacaffeines, 9-deazatheophyllines, furo[2,3-*d*]pyrimidines and furo[3,2-*d*]pyrimidines from 5- or 6-substituted pyrimidines by means of intramolecular cyclization reactions are described.

Keywords——1,3-dialkylallylaminouracil; 1,3-dialkylpropargylaminouracil; furo[2,3-*d*]-pyrimidine; furo[3,2-*d*]pyrimidine; pyrrolo[2,3-*d*]pyrimidine; pyrrolo[3,2-*d*]pyrimidine; palladium complex; thermal reaction; acid-catalyzed cyclization

As a part of our synthetic studies on heterocyclic compounds, we recently reported a new and convenient synthesis of 1,3-dialkylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)diones from 6-allylamino- and 6-(substituted allyl)aminouracils by using a palladium complex or by thermal cyclization.[2)] Furthermore, we found that 5- or 6-substituted uracils undergo an acid-catalyzed cyclization reaction to give the substituted pyrrolo- and furopyrimidines in fairly good yields.[1)] In this report, we present additional information and complete experimental details of our work.

1,3-Dimethyl-5-(substituted allyl)aminouracils (**2a**,**c**,**d**) were prepared from the reaction of 5-bromo-1,3-dimethyluracil (**1**) and substituted allylamines and were heated under reflux in tetralin to give the Claisen rearrangement products, 5-amino-1,3-dimethyl-6-(substituted allyl)uracils (**3a** and **3c**), and cyclization products (**4** and **5**[3)]), but **3d** was not obtained by this thermal reaction.

5-Amino-6-crotyl-1,3-dimethyluracil (**3b**) was directly prepared by reflux of **1** and α-methyl allylamine but **2b** was not isolated in this reaction. Cyclization products (**4**, **5** and **6**) were also prepared by the pyrolysis of **3a** or **3b** in tetralin in low yield. It is reasonable to suppose that the cyclization compounds were formed *via* intermediate (**3**) as shown in Chart 1.

1,3-Dimethylpyrido[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)dione derivatives were not obtained from 5-allylaminouracils (**2**) by using a palladium complex similar to that used for the preparation of 1,3-dimethylpyrido[2,3-*d*]pyrimidines from 6-(substituted allyl)aminouracils.[2)]

6-Chloro-1,3-dimethyluracil (**7**)[4)] was warmed with sodium in allyl alcohol to give 6-allyloxy-1,3-dimethyluracil (**8**) which afforded the Claisen rearrangement product, 5-allyl-6-hydroxy-1,3-dimethyluracil (**9**), in 82.2% yield under reflux in dioxane and 1,3,6-trimethyl-5,6-dihydrofuro[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)dione (**10**) in 6.9% yield under reflux in dimethylformamide (DMF). The mass and nuclear magnetic resonance (NMR, ^1H and ^{13}C) spectral data and elemental analysis were consistent with the indicated structure (**10**).

Heating of **9** in DMF under reflux gave **10** in low yield, while treatment of **9** in conc. H_2SO_4 at room temperature (method A) afforded the same dihydrofuro compound (**10**) in 74.4% yield (73.3% yield by reflux of **9** in 48% HBr solution; method B). On the other hand, an expected methyl ketone, 1,3-dimethyl-6-(2-oxo-propoxy)uracil (**11**), was obtained as the

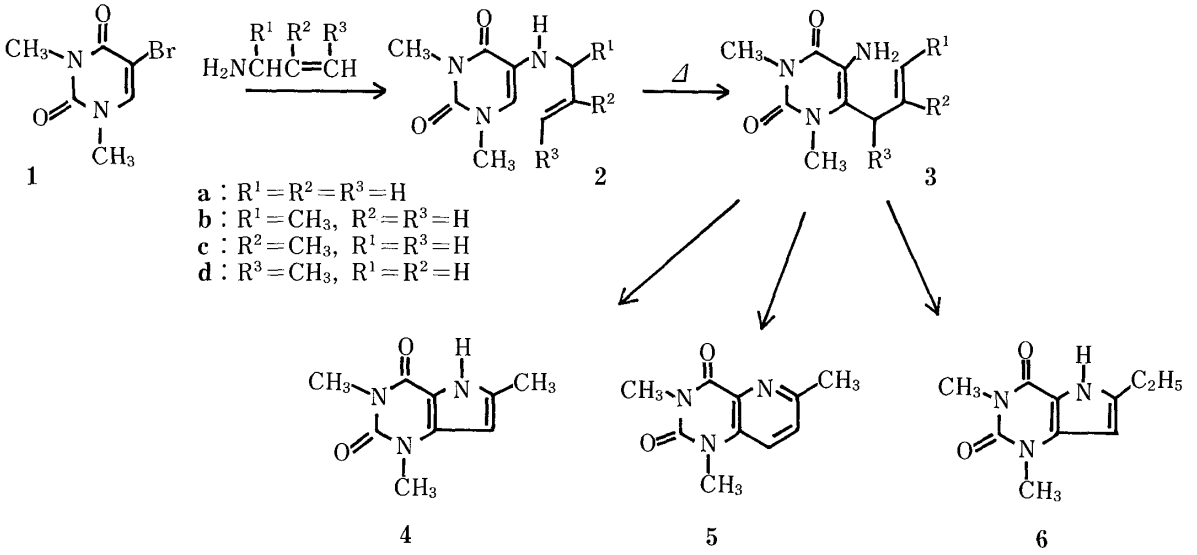


Chart 1

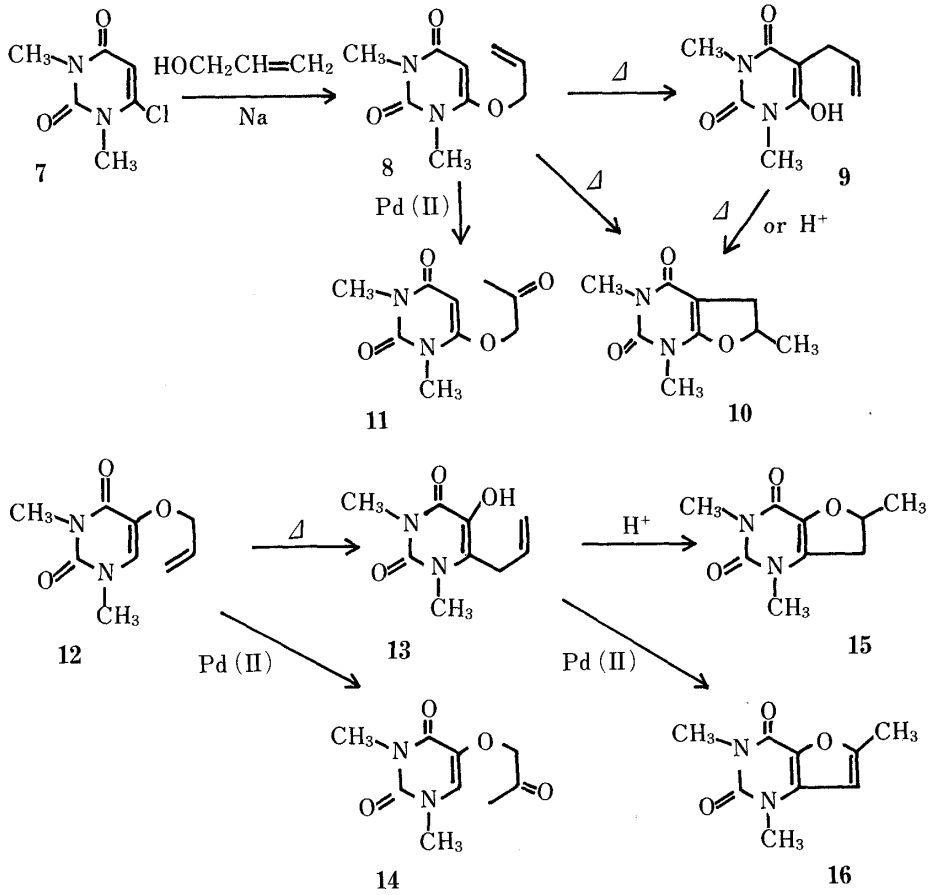
only isolable product in low yield by the $PdCl_2$–CuCl–O_2 oxidation[5] of **8**.

5-Allyloxy-1,3-dimethyluracil (**12**)[6] was prepared from the reaction of 5-hydroxy-1,3-dimethyluracil[7] and allyl bromide and gave the Claisen rearrangement compound (**13**) on pyrolysis.[6] Acid treatment of **13** in the same manner as for **9** afforded the expected 1,3,6-trimethyl-6,7-dihydrofuro[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)dione (**15**) in 59.2% yield (78.4% yield by reflux of **13** in 48% HBr solution). This compound (**15**) was also obtained by similar acid treatment of **12** in low yield (3.7%) together with **13**.

Moreover, treatment of **13** with palladium (II) acetate or the $PdCl_2$–CuCl–O_2 combination gave the furopyrimidine (**16**)[8] in 11.1% and 6.1% yields, respectively. On the other hand, 1,3-dimethyl-5-(2-oxo-propoxy)uracil (**14**) was obtained from **12** in 9.6% yield by using the $PdCl_2$–CuCl–O_2 system.

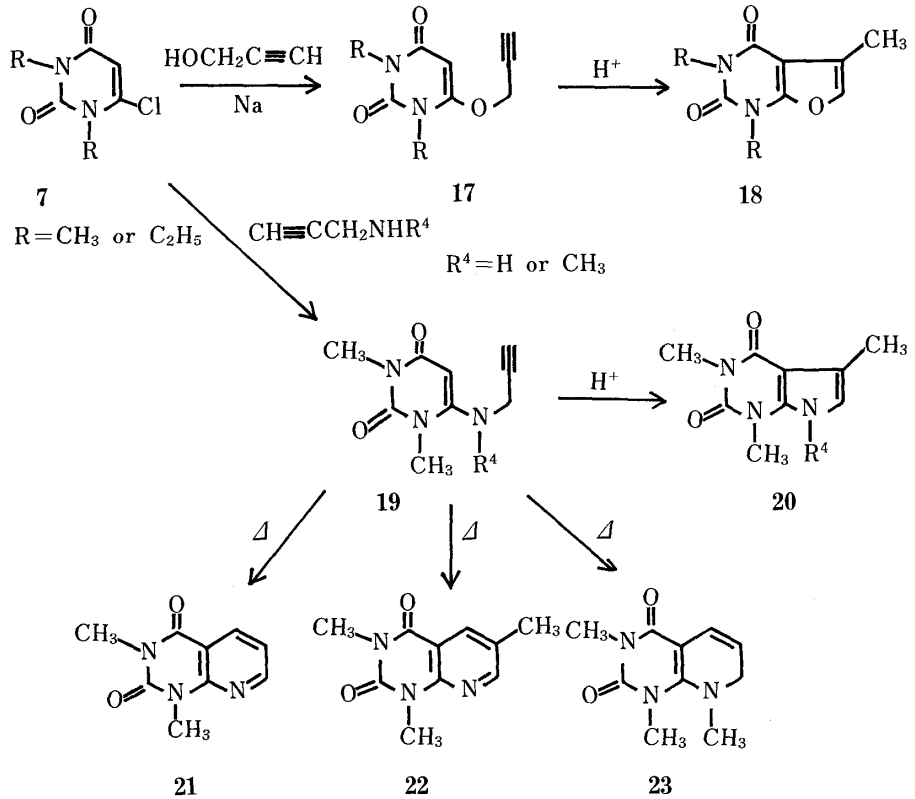
The results of these reactions (Chart 2) show that the dihydrofuropyrimidines are easily prepared from 5- or 6-allyl-substituted hydroxyuracils (**9** and **13**) by means of the acid-catalyzed cyclization reactions. Next, we attempted to synthesize furopyrimidines, 7-deazacaffeines and 9-deazatheophyllines by the method described above and obtained satisfactory results.

By similar acid treatment (method A), 1,3-dialkyl-6-propargyloxyuracils (**17**, R=CH_3 or C_2H_5), prepared by the reaction of 1,3-dialkyl-6-chlorouracils (**7**) and propargyl alcohol, afforded the expected 1,3-dialkyl-5-methyl-furo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)diones (**18**, R=CH_3 or C_2H_5) in 62.2% (R=CH_3) and 88.7% (R=C_2H_5) yields, respectively. The ^{1}H-NMR spectrum of this compound (**18**, R=CH_3) clearly indicated the presence of an aromatic proton (δ 7.00, 1H, s) and a methyl group on a furan ring (δ 2.26, 3H, s). The ^{13}C-NMR spectrum of **18** (R=CH_3) shows a signal due to aromatic carbon at δ 134.83 (doublet) and an aromatic methyl carbon at δ 8.82 (singlet). In the same way, 1,3-dimethyl-6(*N*-methyl-*N*-propargyl)aminouracil (**19**, R^4=CH_3), obtained by the reaction of **7** (R=CH_3) and *N*-methylpropargylamine, was treated with acid to give the desired 1,3,5,7-tetramethylpyrrolo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)dione (**20**, R=CH_3; 9-methyl-7-deazacaffeine) in 77.5% yield. Furthermore, 7-deazacaffeine (**20**, R=H)[9] was also prepared by similar acid treatment of 1,3-dimethyl-6-propargylaminouracil (**19**, R=H) in 71.0% yield. The structural features of **20** are supported by the spectral data. This method for the preparation of alkylated furo[2,3-*d*]pyrimidines and pyrrolo[2,3-*d*]pyrimidines, described



7 8 9 10 11 12 13 14 15 16

Chart 2



7 17 18 19 20 21 22 23

Chart 3

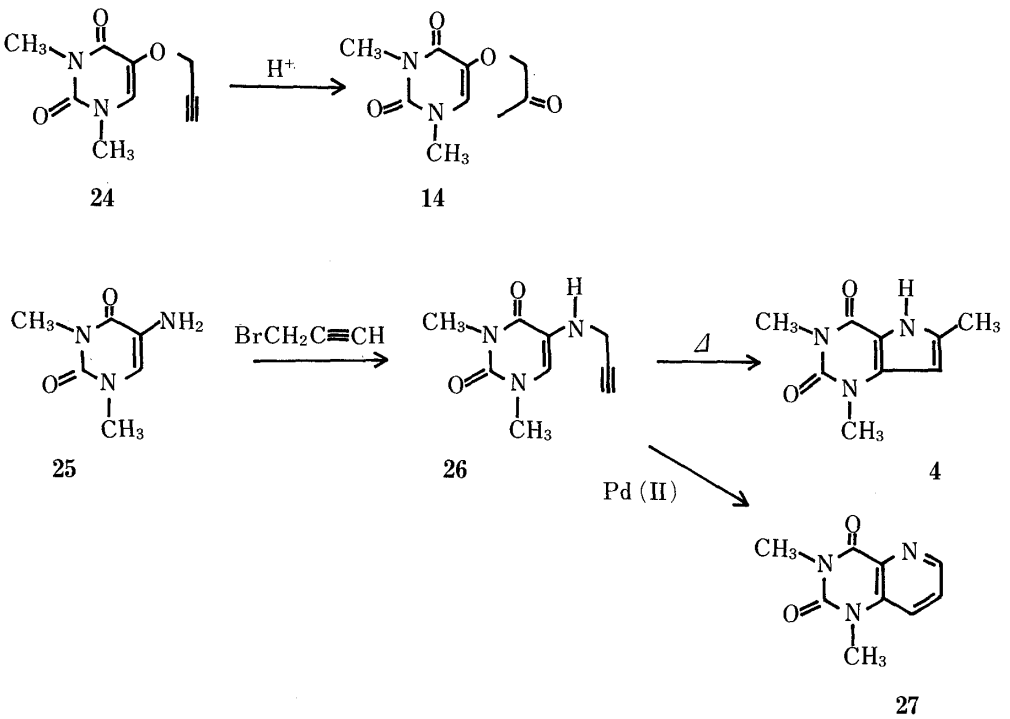
herein, is quite simple and efficient.

Heating of **19** ($R^4 = H$) in DMF under reflux gave 1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)dione (**21**)[2] in 11.0% yield. However, treatment of **19** ($R^4 = CH_3$) in tetralin under reflux gave 1,3,6-trimethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)dione (**22**)[2] in 38.0% yield and 7,8-dihydro-1,3,8-trimethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)dione (**23**) in 12.2% yield. The structure of **23**, which is the expected cyclization product, was assigned on the basis of the spectral data. The formation of **22** shows that the methyl group migrates from the N_8 position to C_6 during the thermal reaction.

Treatment of 1,3-dimethyl-5-propargyloxyuracil (**24**), which was prepared from 5-hydroxy-1,3-dimethyluracil and propargyl bromide, in DMF under reflux gave the same results as reported by Fox *et al.*[8] The methyl ketone (**14**) was obtained by acid treatment (method A) of **24** in 57.5% yield.

1,3-Dimethyl-5-propargylaminouracil (**26**), prepared by the reaction of 5-amino-1,3-dimethyluracil (**25**) and propargyl bromide, afforded the desired 1,3,6-trimethylpyrrolo-[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)dione (**4**; 8-methyl-9-deazatheophylline) in 64.6% yield on reflux in DMF, but the starting material (**26**) was completely recovered after acid treatment in the same manner as described above. This compound (**4**) was also obtained by pyrolysis of **2a** in low yield.

The structure of **4** was elucidated on the basis of the spectral data. Moreover, treatment of **26** with palladium (II) acetate afforded 1,3-dimethylpyrido[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)dione (**27**) in 40.3% yield as shown in Chart 4.



24 14 25 26 4 27

Chart 4

Thus, several fused pyrimidines were easily prepared from 1,3-dialkyl-5-(or -6-) substituted uracils by the cyclization reactions described herein.

Experimental

All melting points were determined on a micro hot-stage apparatus (Mitamura, Tokyo) and are uncorrected. Infrared (IR) spectra (ν_{max}) in KBr disks were recorded on a Hitachi 215 infrared spectrophotometer and are

expressed in cm^{-1}. NMR spectra (^1H and ^{13}C) were measured on a JNM-FX 100 spectrometer (JEOL, Tokyo) at 100 MHz and chemical shifts are expressed relative to 1% tetramethylsilane (TMS) as an internal standard; s=singlet, d=doublet, t=triplet, br=broad and m=multiplet. Mass spectra (MS) were obtained on a GCMS-9000 spectrometer (Shimadzu, Tokyo) and a JMS-DX 300 instrument. Elemental analyses were done by the staff of the Analytical Center of the School of Pharmaceutical Sciences, Kitasato University (Tokyo), to whom our thanks are due. Thin-layer chromatography (TLC) was performed on Merck precoated Silica gel 60 F_{254} plates.

Preparative TLC was done with the same commercial product, 20×20 cm, with a thickness of 0.25, 0.5 or 2.0 mm. All the chemicals used were of reagent grade, and were used without further purification.

General Procedure for the Synthesis of 1,3-Dimethyl-5-(substituted allyl)aminouracils (2c,d)——A gently stirred solution of 5-bromo-1,3-dimethyluracil and a substituted allylamine was refluxed for 5 h. The reaction mixture was concentrated *in vacuo*, then the residue was extracted with EtOAc or CH_2Cl_2 and the organic layer was washed with two portions (small amounts) of water and saturated aqueous NaCl, and dried over $MgSO_4$. After removal of the solvent, the residue was purified by crystallization from an appropriate solvent.

1,3-Dimethyl-5-(β-methylallyl)aminouracil (2c)——According to the general procedure, the crude product was obtained from 1,3-dimethyl-5-bromouracil (**1**, 4.07 g) and β-methylallylamine (40 ml), and recrystallized from EtOAc–ether to give a pale yellow powder, mp 59—60 °C. Yield 2.15 g (55.2%). ^1H-NMR ($CDCl_3$) δ: 1.75 (3H, s, $-CH_3$), 3.36, 3.39 (each 3H, s, NCH_3), 3.51 (2H, s, br, $NHCH_2-$), 4.24 (1H, br, NH), 4.92 (2H, s, br, $C=CH_2$), 6.15 (1H, s, H-6). MS *m/z*: 209 (M^+). *Anal.* Calcd for $C_{10}H_{15}N_3O_2$: C, 57.40; H, 7.23; N, 20.08. Found: C, 57.39; H, 7.32; N, 20.38.

5-Crotylamino-1,3-dimethyluacil (2d)——According to the general procedure, the crude product was obtained from **1** (7.3 g) and crotylamine (48 ml), and recrystallized from EtOAc to give a colorless powder, mp 76—77 °C. Yield 4.41 g (61.9%). ^1H-NMR ($CDCl_3$) δ: 1.73 (3H, d, J=6 Hz, $=CHCH_3$), 3.38, 3.41 (each 3H, s, NCH_3), 3.48 (2H, br, $-NHCH_2$), 4.00 (1H, br, NH), 5.52—5.74 (2H, m, $-CH=CH-$), 6.08 (1H, s, H-6). MS *m/z*: 209 (M^+). *Anal.* Calcd for $C_{10}H_{15}N_3O_2$: C, 57.40; H, 7.23; N, 20.08. Found: C, 57.42; H, 7.29; N, 20.14.

5-Amino-6-crotyl-1,3-dimethyluracil (3b)——A solution of **1** (6.0 g) in α-methylallylamine (24 ml) was refluxed overnight. The reaction mixture was concentrated *in vacuo*, then the residue was extracted with EtOAc and the organic layer was washed with saturated aqueous NaCl, and dried over $MgSO_4$. After removal of the solvent, the residue was crystallized from ether and purified by recrystallization from EtOAc to give a white powder mp 101 °C. Yield 1.82 g (31.7%). ^1H-NMR ($CDCl_3$) δ: 1.70 (3H, s, $-CH_3$), 3.30 (2H, br, $C-CH_3$), 2.46—3.20 (2H, br, NH_2), 3.42 (6H, s, 2×NCH_3), 5.48 (2H, dd, J=4 Hz, $-CH=CH-$). ^{13}C-NMR ($CDCl_3$) δ: 17.79 (q), 28.51 (q), 30.51 (t), 31.67 (q), 118.95 (s), 122.90 (d), 128.16 (d), 131.81 (s), 150.72 (s), 160.37 (s). MS *m/z*: 209 (M^+). *Anal.* Calcd for $C_{10}H_{15}N_3O_2$: C, 57.40; H, 7.23; N, 20.08. Found: C, 57.12; H, 7.25; N, 19.80.

Thermal Reaction of 2a[6]——A solution of **2a** (1.00 g) in tetralin (10.0 ml) was refluxed for 48 h under a nitrogen atmosphere. Then CH_2Cl_2 (10 ml) was added, and the mixture was extracted with 0.01 N aqueous HCl. The extract was neutralized with 20% aqueous NaOH, and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with water, dried over anhydrous $MgSO_4$, and evaporated *in vacuo*. The residue was purified by silica gel column chromatography with benzene–ether as an eluent to give **3a** (0.0368 g, 3.6%, colorless solid)[6] and **4** (0.07 g, 7.1%, mp 279—280 °C). The spectral and analytical data for **4** are described later.

Thermal Reaction of 2c——A solution of **2c** (0.50 g) in tetralin (5.0 ml) was refluxed for 12 h under a nitrogen atmosphere. The procedure described in the case of the thermal reaction of **2a** yielded a crude product, which was purified by preparative TLC (EtOAc) to give pale yellow needles (**3c**), mp 80—81 °C (from ether). Yield 0.10 g (20%). ^1H-NMR ($CDCl_3$) δ: 1.86 (3H, s, $-CH_3$), 3.30 (4H, m, $-CH_2-$ and NH_2), 3.37, 3.42 (each 3H, s, NCH_3), 4.64 and 4.90 (2H, $=CH_2$). MS *m/z*: 209 (M^+). The high-resolution MS showed *m/z*: 209.11806 (Calcd 209.11646). *Anal.* Calcd for $C_{10}H_{15}N_3O_2$: C, 57.40; H, 7.23; N, 20.08. Found: C, 57.72; H, 7.25; N, 19.93.

Thermal Reaction of 2d——A solution of **2d** (2.0 g) in tetralin (20 ml) was refluxed for 8 d under a nitrogen atmosphere. The procedure described in the case of the thermal reaction of **2a** yielded a crude product, which was purified by recrystallization from EtOAc to give colorless plates (**5**), mp 249—251 °C (lit.[3] mp 248 °C). Yield 0.4025 g (20.5%). ^1H-NMR (DMSO-d_6) δ: 2.54 (3H, s, $C-CH_3$), 3.31, 3.48 (each 3H, s, 2×NCH_3), 7.62 (1H, d, J=8.6 Hz, =CH), 7.87 (1H, d, J=8.6 Hz). This compound (**5**) was shown to be identical with an authentic sample prepared from 5-amino-1,3-dimethyluracil and crotonaldehyde.[3]

Thermal Reaction of 3b——A solution of **3b** (0.50 g) in tetralin (5.0 ml) was refluxed for 50 h under a nitrogen atmosphere. The procedure described in the case of the thermal reaction of **2a** yielded a crude solid, which was filtered off and recrystallized from MeOH to give **5** (1.7 mg). On the other hand, the mother liquor was purified by preparative TLC (benzene: EtOAc=1 : 1) to give a white powder **6**, mp 247 °C (from EtOAc). Yield 0.051 g (10.5%). ^1H-NMR ($CDCl_3$) δ: 1.34 (3H, t, J=7.7 Hz, $C-CH_3$), 2.74 (2H, q, J=7.7 Hz, $-CH_2-$), 3.46, 3.49 (each 3H, s, 2×NCH_3), 5.77 (1H, s, =CH), 11.42 (1H, br, −NH). ^{13}C-NMR ($CDCl_3$) δ: 13.45 (q), 21.49 (t), 27.92 (q), 32.06 (q), 92.25 (d), 109.30 (s), 136.54 (s), 145.46 (s), 151.74 (s), 155.69 (s). MS *m/z*: 207 (M^+). *Anal.* Calcd for $C_{10}H_{13}N_3O_2$: C, 57.96; H, 6.32; N, 20.28. Found: C, 57.84; H, 6.13; N, 20.26.

Thermal Reaction of 3a[6]——A solution of **3a** (35.9 mg) in tetralin (2.0 ml) was refluxed for 22 h under a nitrogen atmosphere. The procedure described in the case of the thermal reaction of **2a** yielded a crude product, which was

purified by recrystallization from MeOH to give **4** (6.1 mg).

6-Allyloxy-1,3-dimethyluracil (8)——6-Chloro-1,3-dimethyluracil (5.22 g) was added to allyl alcohol (30 ml) containing 1.5 g of sodium. The solution was heated at 30—40 °C under a nitrogen atmosphere with stirring for 30 min, then cooled and evaporated *in vacuo*. The residue was partitioned between water and EtOAc, and the organic layer was dried over $MgSO_4$. After removal of the solvent, the crystals that resulted were washed with ether and recrystallized from CH_2Cl_2–ether to give white needles, mp 124—125 °C. Yield 3.35 g (57.2%). IR ν_{max}^{KBr}: 1710, 1650, 1620. MS *m/z*: 196 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 3.32 (3H, s, NCH_3), 3.38 (3H, s, NCH_3), 4.56 (2H, d, J=5.4 Hz), 5.12 (1H, s, =CH–), 5.36—5.52 (2H, m, $=CH_2$), 5.80—6.22 (1H, m, =CH–). ^{13}C-NMR ($CDCl_3$) δ: 27.78 (q), 28.80 (q), 70.56 (t), 78.50 (d), 119.88 (t), 130.11 (d), 151.26 (s), 160.12 (s), 163.05 (s). *Anal.* Calcd for $C_9H_{12}N_2O_3$: C, 55.09; H, 6.17; N, 14.28. Found: C, 55.43; H, 6.16; N, 14.34.

Thermal Reaction of 8——1) A solution of **8** (1.0 g) in dioxane (80 ml) was stirred at 100 °C for 4 h under a nitrogen atmosphere. The reaction mixture was evaporated to dryness and purified by preparative TLC (EtOAc: MeOH = 4 : 1). The solid was filtered off and recrystallized from CH_2Cl_2–ether to give white needles (**9**), mp 55—60 °C. Yield 0.822 g (82.2%). Further purification of this compound could not be achieved because of its lability. IR ν_{max}^{KBr}: 3375, 1680, 1440. ^{1}H-NMR ($CDCl_3$) δ: 2.67 (2H, d, J=7.32 Hz, $-CH_2-$), 3.29 (6H, s, 2 × NCH_3), 4.01 (1H, br, OH), 5.04—5.25 (2H, m, $=CH_2$), 5.43—5.50 (1H, m, =CH–). ^{13}C-NMR ($CDCl_3$) δ: 28.80 (q), 46.68 (t), 75.97 (s), 121.92 (t), 128.35 (d), 150.68 (s), 169.97 (s). MS *m/z*: 196 (M^+). The high-resolution MS showed *m/z* 196.08550 (Calcd 196.08480).

2) A solution of **8** (0.5 g) in DMF (20 ml) was heated at 150 °C with stirring overnight under a nitrogen atmosphere. The reaction mixture was evaporated to dryness and purified by preparative TLC (EtOAc: MeOH = 4 : 1) to give **10** (0.035 g, 6.9%).

Thermal Reaction of 9——A solution of **9** (0.82 g) in DMF (20 ml) was stirred at 130—140 °C for 5 h under a nitrogen atmosphere. The reaction mixture was evaporated to dryness and purified by preparative TLC (EtOAc) to give **10** (0.040 g, 4.8%).

1,3,6-Trimethyl-5,6-dihydrofuro[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)dione (10)——Method A: A solution of **9** (0.8 g) in conc. H_2SO_4 (20 ml) was stirred at room temperature for 4 d. After neutralization with aqueous NH_3, the reaction mixture was extracted with CH_2Cl_2. The extract was washed with H_2O and dried over $MgSO_4$. After removal of the solvent, the residue was recrystallized from CH_2Cl_2–ether to give white prisms, mp 85—87 °C. Yield 0.595 g (74.4%). IR ν_{max}^{KBr}: 1700, 1620. ^{1}H-NMR ($CDCl_3$) δ: 1.53 (3H, d, J=6.1 Hz, C–CH_3), 2.17 (1H, dd, J=13.43 Hz, $-CH_2-$), 2.68 (1H, dd, J=13.43 Hz, $-CH_2-$), 3.31, 3.33 (each 3H, s, 2 × NCH_3), 5.00—5.20 (1H, m, –CH–). ^{13}C-NMR ($CDCl_3$) δ: 21.39 (q), 27.34 (q), 28.99 (q), 32.80 (t), 84.01 (d), 85.23 (s), 151.11 (s), 159.78 (s), 161.01 (s). MS *m/z*: 196 (M^+). *Anal.* Calcd for $C_9H_{12}N_2O_3$: C, 55.09; H, 6.17; N, 14.28. Found: C, 55.29; H, 6.13; N, 14.44.

Method B: A solution of **9** (0.386 g) in 48% HBr (20 ml) was heated at 80 °C for 20 min. The reaction mixture was poured into ice-H_2O, neutralized with aqueous NH_3, and extracted with CH_2Cl_2. The organic solution was dried over $MgSO_4$ and evaporated to dryness. The solid that resulted was recrystallized from CH_2Cl_2–ether to give **10** (0.285 g, 73.3%).

1,3-Dimethyl-6-(2-oxo-propoxy)uracil (11)——A mixture of CuCl (0.5 g) and $PdCl_2$ (0.18 g) in DMF (5.0 ml) and H_2O (0.6 ml) was stirred under a stream of oxygen at room temperature for 3 h. Compound **8** (0.99 g) was added and the mixture was stirred under oxygen for 1 h at 80—90 °C. The reaction mixture was evaporated to dryness and the residue was extracted with $CHCl_3$. Evaporation of the organic layer gave a crude mixture, which was isolated by column chromatography. The major product (0.029 g) eluted with ether–benzene (2 : 8) was recrystallized from EtOAc to give white needles, mp 124—125 °C. Yield 0.0196 g (1.84%). IR ν_{max}^{KBr}: 1680, 1610, 1460. ^{1}H-NMR ($CDCl_3$) δ: 2.32 (3H, s, $COCH_3$), 3.37, 3.48 (each 3H, s, 2 × NCH_3), 4.71 (2H, s, $-CH_2-$), 5.01 (1H, s, =CH–). ^{13}C-NMR ($CDCl_3$) δ: 26.30 (q), 27.95 (q), 29.12 (q), 72.80 (t), 78.73 (d), 151.18 (s), 159.69 (s), 162.86 (s), 199.26 (s). MS *m/z*: 212 (M^+). *Anal.* Calcd for $C_9H_{12}N_2O_4$: C, 50.94; H, 5.70; N, 13.20. Found: C, 50.80; H, 5.85; N, 13.16.

Pd (II) Oxidation of 12[6]——A mixture of CuCl (0.5 g) and $PdCl_2$ (0.18 g) in DMF (5.0 ml) and H_2O (0.6 ml) was stirred in a stream of oxygen at room temperature for 3 h. A solution of **12** (0.495 g) in DMF (6 ml) was added and the mixture was stirred under oxygen for 10 min at 80—90 °C, then evaporated *in vacuo*. The residue was extracted with CH_2Cl_2 and evaporation of the CH_2Cl_2 gave a crude product, which was separated by preparative TLC (EtOAc: benzene = 1 : 1). The major product was recrystallized from CH_2Cl_2–ether to give white needles (**14**), mp 100—101 °C. Yield 0.051 g (9.6%). IR ν_{max}^{KBr}: 1735, 1640, 1460. ^{1}H-NMR ($CDCl_3$) δ: 2.19 (3H, s, $COCH_3$), 3.35, 3.38 (each 3H, s, NCH_3), 4.62 (2H, s, $-CH_2-$), 7.23 (1H, s, =CH–). ^{13}C-NMR ($CDCl_3$) δ: 26.18 (q), 28.24 (q), 37.05 (q), 75.85 (t), 132.04 (d), 132.98 (s), 150.53 (s), 160.16 (s), 204.55 (s). MS *m/z*: 212 (M^+). *Anal.* Calcd for $C_9H_{12}N_2O_4$: C, 50.94; H, 5.70; N, 13.20. Found: C, 51.00; H, 5.70; N, 13.16. The Pd (II) acetate oxidation of **13** in AcOH at room temperature afforded **15** in 9.1% yield.

Pd (II) Oxidation of 13[6]——Palladium (II) acetate (0.112 g) was added to a solution of **14** (0.098 g) in AcOH (10 ml). The reaction mixture was heated at 80 °C for 10 min with stirring under a nitrogen atmosphere. The reaction mixture was poured into ice-H_2O and neutralized with 20% aqueous NaOH, then extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried over $MgSO_4$ and evaporated *in vacuo*. The resulting products were separated by preparative TLC (EtOAc: benzene = 1 : 1) and the major product was recrystallized from EtOH to give

16 [10.8 mg, 11.1%, mp 212—213 °C (lit.[8] mp 210—211 °C)]. This compound (**16**) was also obtained by $PdCl_2$–$CuCl$–O_2-catalyzed oxidative cyclization in 6.1% yield.

1,3,6-Trimethyl-6,7-dihydrofuro[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)dione (15). Acid Treatment of 12 or 13——1) According to the general procedure (method A, stirring at room temperature (r.t.) for 2 d), the crude product was obtained from a solution of **13** (98 mg) in conc. H_2SO_4 (10 ml), and recrystallized from CH_2Cl_2–ether to give white needles, mp 139—141 °C. Yield 58 mg (59.2%). IR ν_{max}^{KBr}: 1705, 1680. ^{1}H-NMR ($CDCl_3$) δ: 1.52 (3H, d, J=5.86 Hz, C–CH_3), 2.83 (1H, dd, J=16.60 Hz, –CH_2–), 3.36 (1H, dd, J=16.60 Hz, –CH_2–), 3.35, 3.37 (each 3H, s, 2 × NCH_3), 4.80—5.20 (1H, m, –CH_2–). ^{13}C-NMR ($CDCl_3$) δ: 21.68 (q), 28.36 (q), 33.19 (q), 37.18 (t), 78.31 (d), 132.35 (s), 134.11 (s), 151.35 (s), 155.40 (s). MS *m/z*: 196 (M^+). *Anal.* Calcd for $C_9H_{12}N_2O_3$: C, 55.09; H, 6.17; N, 14.28. Found: C, 55.04; H, 5.99; N, 14.03.

2) According to the general procedure (method B, stirring at 100 °C for 5 h), the crude product was obtained from a solution of **13** (0.3 g) in 47% HBr (20 ml), and separated by preparative TLC (EtOAc: benzene = 1 : 1). The major product was recrystallized from CH_2Cl_2–ether to give **15** (0.151 g, 78.4%).

3) According to the general procedure (method B, stirring at 80 °C for 1 h), the crude product was obtained from a solution of **12** (0.2 g) in 47% HBr (20 ml) and separated by preparative TLC (EtOAc: benzene = 1 : 1). After recrystallization, **15** (7.4 mg, 3.7%) and **14** (35.4 mg, 17.7%) were obtained.

1,3-Dimethyl-6-(2-propynyloxy)uracil (17, R = Me)——6-Chloro-1,3-dimethyluracil (**7**, R = Me, 5.22 g) was added to propargyl alcohol (30 ml) containing 1.5 g of sodium under a nitrogen atmosphere. The solution was stirred at room temperature for 30 min, and evaporated *in vacuo*. The residue was partitioned between H_2O and CH_2Cl_2, and the CH_2Cl_2 solution was dried over $MgSO_4$. After removal of the solvent, the crystals that resulted were washed with ether and recrystallized from CH_2Cl_2–isopropyl ether to give white needles, mp 150—151 °C. Yield 4.18 g (72.0%). IR ν_{max}^{KBr}: 1700, 1660, 1620. ^{1}H-NMR ($CDCl_3$) δ: 2.69 (1H, t, J=3.6 Hz, ≡CH), 3.36, 3.39 (each 3H, s, 2 × NCH_3), 4.76 (2H, d, J=3.2 Hz, –CH_2–), 5.26 (1H, s, =CH–). ^{13}C-NMR ($CDCl_3$) δ: 27.92 (q), 28.88 (q), 57.60 (t), 75.19 (d), 78.36 (d), 79.09 (d), 151.21 (s), 159.49 (s), 162.85 (s). MS *m/z*: 194 (M^+). *Anal.* Calcd for $C_9H_{10}N_2O_3$: C, 55.66; H, 5.19; N, 14.43. Found: C, 55.60; H, 5.20; N, 14.55.

1,3-Diethyl-6-(2-propynyloxy)uracil (17, R = Et)——According to the method used in the synthesis of 1,3-dimethyl-6-(2-propynyloxy)uracil (**17**, R = Me), the crude product was obtained from 6-chloro-1,3-diethyluracil (**7**, R = Et, 4.05 g) and propargyl alcohol (40 ml), and recrystallized from CH_2Cl_2–isopropyl ether to give colorless needles, mp 102—103 °C. Yield 1.787 g (68.8%). IR ν_{max}^{KBr}: 1640, 1470, 1435. ^{1}H-NMR ($CDCl_3$) δ: 1.22 (3H, t, J=7.08 Hz, C–CH_3), 1.24 (3H, t, J=7.08 Hz, C–CH_3), 2.72 (1H, t, J=2.2 Hz, ≡CH), 3.97 (4H, q, J=7.08 Hz, 2 × –CH_2–), 4.75 (2H, d, J=2.2 Hz, O–CH_2–), 5.22 (1H, s, =CH–). ^{13}C-NMR ($CDCl_3$) δ: 12.96 (q), 13.84 (q), 36.30 (t), 37.72 (t), 57.45 (t), 75.34 (d), 78.31 (d), 79.33 (d), 150.43 (s), 159.35 (s), 162.57 (s). MS *m/z*: 222 (M^+). *Anal.* Calcd for $C_{11}H_{14}N_2O_3$: C, 59.45; H, 6.35; N, 12.60. Found: C, 59.20; H, 6.35; N, 12.67.

1,3,5-Trimethylfuro[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)dione (18, R = Me). Acid Treatment of 17 (R = Me)—— According to the general procedure (method A, stirring at r.t. for 2 d), the crude product was obtained from a solution of **17** (R = Me, 0.7 g) in conc. H_2SO_4 (20 ml), and recrystallized from CH_2Cl_2–ether to give white needles (**18**, R = Me), mp 143—144 °C. Yield 0.446 g (62.2%). IR ν_{max}^{KBr}: 1660, 1520, 1420. ^{1}H-NMR ($CDCl_3$) δ: 2.26 (3H, d, J=1.22 Hz, C–CH_3), 3.39, 3.53 (each 3H, s, 2 × NCH_3), 7.00 (1H, d, J=1.22 Hz, =CH–). ^{13}C-NMR ($CDCl_3$) δ: 8.82 (q), 27.97 (q), 29.19 (q), 97.02 (s), 119.97 (s), 134.83 (d), 150.68 (s), 155.49 (s), 158.86 (s). MS *m/z*: 194 (M^+). *Anal.* Calcd for $C_9H_{10}N_2O_3$: C, 55.66; H, 5.19; N, 14.43. Found: C, 55.92; H, 5.06; N, 14.22.

1,3-Diethyl-5-methylfuro[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)dione (18, R = Et). Acid Treatment of 17 (R = Et)—— According to the general procedure (method A, stirring at r.t. for 2 weeks), the crude product was obtained from a solution of **17** (R = Et, 0.666 g) in conc. H_2SO_4 (20 ml), and recrystallized from ether–*n*-hexane to give white needles (**18**, R = Et), mp 83—84 °C. Yield 0.59 g (88.7%). IR ν_{max}^{KBr}: 1690, 1650, 1520. ^{1}H-NMR ($CDCl_3$) δ: 1.24 (3H, t, J=7.08 Hz, C–CH_3), 1.35 (3H, t, J=7.08 Hz, C–CH_3), 2.26 (3H, d, J=1.47 Hz, C–CH_3), 4.05 (2H, q, J=7.08 Hz, –CH_2–), 4.07 (2H, q, J=7.08 Hz, –CH_2–), 6.97 (1H, d, J=1.47 Hz, =CH–). ^{13}C-NMR ($CDCl_3$) δ: 8.87 (q), 13.21 (q), 13.74 (q), 36.50 (t), 38.40 (t), 97.31 (s), 119.97 (s), 134.78 (d), 149.84 (s), 155.40 (s), 158.71 (s). MS *m/z*: 222 (M^+). *Anal.* Calcd for $C_{11}H_{14}N_2O_3$: C, 59.45; H, 6.35; N, 12.60. Found: C, 59.74; H, 6.27; N, 12.55.

1,3-Dimethyl-6-propargylaminouracil (19, R^4 = H)——A solution of 1,3-dimethyl-6-chlorouracil (**7**, R = Me, 5.0 g) in propargylamine (40 ml) was stirred at room temperature. A solid was gradually deposited from the reaction mixture. The pale yellow crystals that appeared in the reaction flask were collected and washed with a solution of ether and MeOH (4 : 1). The crude product was recrystallized from MeOH to give white needles, mp 225—227 °C. Yield 4.37 g (79.0%). IR ν_{max}^{KBr}: 3260, 1690, 1600, 1460. ^{1}H-NMR (DMSO-d_6) δ: 2.50 (1H, br, ≡CH), 3.13, 3.26 (each 3H, s, 2 × NCH_3), 3.89 (2H, br, –CH_2–), 4.77 (1H, s, =CH–), 7.24 (1H, s, NH). ^{13}C-NMR (DMSO-d_6) δ: 27.24 (q), 29.34 (q), 31.67 (t), 74.36 (d), 74.90 (d), 79.77 (d), 151.40 (s), 152.91 (s), 161.64 (s). MS *m/z*: 193 (M^+). *Anal.* Calcd for $C_9H_{11}N_3O_2$: C, 55.95; H, 5.74; N, 21.75. Found: C, 55.82; H, 5.71; N, 21.90.

1,3-Dimethyl-6-(*N*-methyl-*N*-propargyl)aminouracil (19, R^4 = Me)——A solution of 1,3-dimethyl-6-chlorouracil (**7**, R = Me, 4.0 g) in *N*-methylpropargylamine (25 ml) was stirred at room temperature for 6 h. The reaction mixture was concentrated *in vacuo* to leave a crystalline solid, which was recrystallized from EtOH–ether to give pale yellow plates, mp 112—113 °C. Yield 4.16 g (87.7%). ^{1}H-NMR ($CDCl_3$) δ: 2.52 (2H, t, J=2.2 Hz, ≡CH), 2.82, 3.29 and 3.41

(each 3H, s, 3 × NCH_3), 3.79 (2H, d, J=2.2 Hz, –CH_2–), 5.38 (1H, s, =CH–). ^{13}C-NMR ($CDCl_3$) δ: 27.68 (q), 33.09 (q), 38.79 (q), 43.37 (t), 74.90 (d), 76.65 (d), 88.64 (d), 152.82 (s), 158.52 (s), 162.81 (s). MS *m/z*: 207 (M^+). *Anal.* Calcd for $C_{10}H_{13}N_3O_2$: C, 57.96; H, 6.32; N, 20.28. Found: C, 57.90; H, 6.22; N, 19.99.

1,3,5,7-Tetramethylpyrrolo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)dione (20, R^4=Me). Acid Treatment of 19 (R^4=Me)——According to the general procedure (method A, stirring at r.t. for 1 d), the crude product was obtained from a solution of **19** (R^4=Me, 0.4 g) in conc. H_2SO_4 (20 ml), and recrystallized from $CHCl_3$–ether to give colorless needles (**20**, R^4=Me), mp 224—225 °C. Yield 0.388 g (77.5%). IR ν_{max}^{KBr}: 1680, 1640, 1580, 1540. ^{1}H-NMR ($CDCl_3$) δ: 2.27 (3H, s, C–CH_3), 3.36, 3.74 (each 3H, s, 2 × NCH_3), 3.81 (3H, s, NCH_3), 6.10 (1H, s, =CH–). ^{13}C-NMR ($CDCl_3$) δ: 10.77 (q), 27.92 (q), 31.97 (q), 36.00 (q), 100.97 (s), 116.42 (s), 120.66 (d), 137.76 (s), 152.04 (s), 159.54 (s). MS *m/z*: 207 (M^+). *Anal.* Calcd for $C_{10}H_{13}N_3O_2$: C, 57.96; H, 6.32; N, 20.28. Found: C, 58.01; H, 6.27; N, 20.29.

1,3,5-Trimethylpyrrolo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)dione (7-Deazacaffeine, 20, R^4=H). Acid Treatment of 19 (R^4=H)——According to the general procedure (method A, stirring at r.t. for 1 d), the crude product was obtained from a solution of **19** (R^4=H, 0.3 g) in conc. H_2SO_4 (5 ml), and recrystallized from MeOH to give a white powder (**20**, R^4=H), mp >300 °C. Yield 0.251 g (71.0%). IR ν_{max}^{KBr}: 3150, 1680, 1620, 1540, 1430. ^{1}H-NMR (DMSO-d_6) δ: 2.18 (3H, s, C–CH_3), 3.19, 3.39 (each 3H, s, 2 × NCH_3), 6.50 (1H, s, –CH=), 11.36 (1H, br, NH). ^{13}C-NMR (DMSO-d_6) δ: 10.96 (q), 27.29 (q), 30.16 (q), 97.61 (s), 113.69 (d), 115.30 (s), 138.73 (s), 150.72 (s), 158.91 (s). MS *m/z*: 193 (M^+). *Anal.* Calcd for $C_9H_{11}N_3O_2$: C, 55.95; H, 5.74; N, 21.75. Found: C, 56.11; H, 5.66; N, 21.85.

Thermal Reaction of 19 (R^4=H)——A solution of **19** (R^4=H, 0.6 g) in DMF (20 ml) was stirred at 110 °C overnight under a nitrogen atmosphere. The reaction mixture was evaporated to dryness *in vacuo* and the major product was isolated by preparative TLC (EtOAc) and recrystallized from MeOH to give **21** [0.066 g, 11.0%, mp 164—165 °C (lit[2] mp 164—164.5 °C)].

Thermal Reaction of 19 (R^4=Me)——A solution of **19** (R^4=Me, 0.6 g) in tetralin (20 ml) was stirred at 200 °C for 5 h under a nitrogen atmosphere. The reaction mixture was evaporated to dryness *in vacuo* and the products were purified by preparative TLC (EtOAc) and recrystallized from MeOH to give **22** [0.225 g, 38.0%, mp 161—162 °C (lit.[2] mp 159 °C)], and **23** (0.073 g, 12.2%, mp 107—114 °C. Recrystallized from CH_2Cl_2–ether), ^{1}H-NMR ($CDCl_3$) δ: 2.73, 3.36 and 3.42 (each 3H, s, 3 × NCH_3), 3.79 (2H, dd, J=4.1 Hz, –CH_2–), 5.40 (1H, m, J=9 and 4.1 Hz, =CH–), 6.63 (1H, d, J=9 Hz, =CH–). MS *m/z*: 207 (M^+). *Anal.* Calcd for $C_{10}H_{13}N_3O_2$: C, 57.94; H, 6.32; N, 20.28. Found: C, 58.24; H, 6.35; N, 19.16. The high-resolution MS showed *m/z* 207.09870 (Calcd 207.10070).

Acid Treatment of 24[8]——According to the general procedure (method A, stirring at r.t. for 3 d), the crude product was obtained from a solution of **24** (0.1 g) in conc. H_2SO_4 (10 ml), and recrystallized from CH_2Cl_2–ether to give white needles (**14**, 0.063 g, 57.5%, mp 100—101 °C).

1,3,-Dimethyl-5-propargylaminouracil (26)——Propargyl bromide (1.0 ml) was added to a solution of 1,3-dimethyl-5-aminouracil (**25**, 1.0 g) in MeOH (10 ml) and CH_2Cl_2 (10 ml). The reaction mixture was stirred at room temperature overnight, and evaporated to dryness *in vacuo*. The residue was purified by preparative TLC (EtOAc) and the crystalline product was recrystallized from EtOAc to give white needles, mp 140—142 °C. Yield 0.52 g (41.0%). IR ν_{max}^{KBr}: 3350, 1620, 1410. ^{1}H-NMR ($CDCl_3$) δ: 2.30 (1H, t, J=2.44 Hz, ≡CH), 3.39, 3.41 (each 3H, s, 2 × NCH_3), 3.84 (2H, d, J=2.44 Hz, –CH_2–), 4.25 (1H, br, NH), 6.41 (1H, s, =CH–). ^{13}C-NMR ($CDCl_3$) δ: 28.26 (q), 33.53 (t), 36.94 (q), 72.17 (d), 79.48 (d), 117.49 (d), 122.95 (s), 149.79 (s), 160.62 (s). MS *m/z*: 193 (M^+). *Anal.* Calcd for $C_9H_{11}N_3O_2$: C, 55.95; H, 5.74; N, 21.75. Found: C, 55.89; H, 5.71; N, 21.53.

1,3,6-Trimethylpyrrolo[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)dione (8-Methyl-9-deazatheophylline, 4)——A solution of **26** (0.61 g) in DMF (20 ml) was refluxed for 40 h under a nitrogen atmosphere. The reaction mixture was evaporated to dryness *in vacuo* to leave crystals, which were recrystallized from MeOH to give yellow plates, mp 279—280 °C. Yield 0.498 g (64.6%). IR ν_{max}^{KBr}: 3170, 1685, 1630, 1560, 1520. ^{1}H-NMR ($CDCl_3$) δ: 2.44 (3H, s, C–CH_3), 3.46 (6H, s, 2 × NCH_3), 5.75 (1H, s, =CH–), 11.60 (1H, br, NH). ^{13}C-NMR ($CDCl_3$) δ: 13.50 (q), 27.92 (q), 32.64 (q), 93.61 (d), 109.25 (s), 136.73 (s), 139.42 (s), 151.70 (s), 155.64 (s). MS *m/z*: 193 (M^+). *Anal.* Calcd for $C_9H_{11}N_3O_2$: C, 55.95; H, 5.74; N, 21.75. Found: C, 55.86; H, 5.78; N, 21.93.

1,3-Dimethylpyrido[3,2-*d*]pyrimidine (27)——Palladium (II) acetate (0.112 g) was added to a solution of **26** (0.0965 g) in AcOH (21 ml). The reaction mixture was stirred at room temperature overnight under a nitrogen atmosphere. Distilled water was added to the reaction mixture, and the resulting solution was neutralized with 20% aqueous NaOH, then extracted with $CHCl_3$. The $CHCl_3$ extract was dried over $MgSO_4$ and evaporated *in vacuo*. The residue was separated by preparative TLC (EtOAc: MeOH=4:1) and the major product was recrystallized from $CHCl_3$–ether to give white needles, mp 240—241 °C. Yield 0.0504 g (40.3%). IR ν_{max}^{KBr}: 1700, 1650, 1575. ^{1}H-NMR ($CDCl_3$) δ: 3.55, 3.63 (each 3H, s, 2 × NCH_3), 7.62 (1H, s, =CH–), 7.64 (1H, s, =CH–), 8.65 (1H, dd, J=3.6 Hz and J=3.6 Hz, –N=CH–). MS *m/z*: 191 (M^+). *Anal.* Calcd for $C_9H_9N_3O_3$: C, 56.54; H, 4.75; N, 21.98. Found: C, 56.26; H, 4.73; N, 21.77.

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