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Pyrimidine Derivatives and Related Compounds. XXIII.[1] Synthesis and Pharmacological Properties of 9-Deazaxanthine Derivatives[2]

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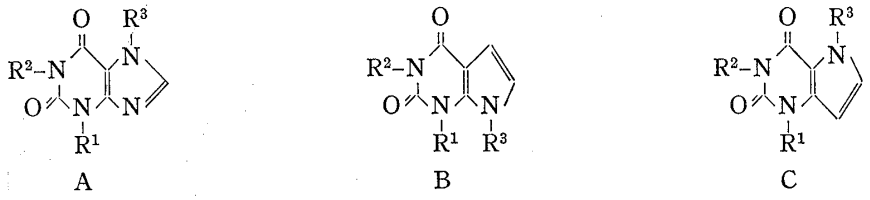
For investigation of the structure-activity relationship of xanthine derivatives, two new synthetic routes to 9-deazaxanthines have been found. Catalytical reduction of 6-(2-dimethylaminovinyl)-5-nitrouracils (**2**), which were prepared by condensation of 5-nitro-6-methyluracils (**1**) with dimethylformamide (DMF)-diethylacetal or DMF-dimethyl sulfate complex, gave the 2,4-dioxo-1,2,3,4-tetrahydropyrrolo[3,2-*d*]pyrimidines (**3**) and its 6-dimethylamino relatives (**4**). Heating 5-formylamino-1,3,6-trimethyluracil (**15a**) also gave pyrrolo[3,2-*d*]pyrimidine derivative (**3a**). Diuretic, cardiac, and central nervous system stimulating activities of the 9-deazaxanthines (**3**, **6**, **9**) were weeker than those of caffeine.

In the course of investigating the structure-activity relationship of xanthine derivatives (A) and related compounds, we previously reported[1] the synthesis and pharmacology of 7-deazaxanthine derivatives (B) whose structure is theoretically derived by a replacement of the nitrogen atom at 7-position of xanthine ring with a methine group, and found that the compounds (B) have diuretic activity comparable to that of caffeine. In this connection, this paper describes the synthesis of 9-deazaxanthine derivatives (C) and their diuretic, cardiac, and central nervous system (CNS) stimulating activities which were tested in order to research a role of the nitrogen atoms at 7- and 9-positions of xanthines (A) in their pharmacological properties.



A B C

Chart 1

Chemistry

A few reports[4] have already been published on the synthesis of 9-deazaxanthine derivatives (C), or 2,4-dioxo-1,2,3,4-tetrahydropyrrolo[3,2-*d*]pyrimidine derivatives. We have studied a new synthetic rout to the pyrrolo[3,2-*d*]pyrimidines in which 6-methyl-5-nitrouracils were used as starting materials.

Thus, 6-methyl-5-nitrouracils (**1**) were treated with dimethylformamide(DMF)-diethylacetal or DMF-DMS complex[5] to give 6-(2-dimethylaminovinyl)-5-nitrouracils (**2**). Catalytic

1) Part XXII: S. Senda and K. Hirota, *Chem. Pharm. Bull.* (Tokyo), **22**, 1459 (1974).
2) This work was presented at the First Symposium on Drug Activity, Tokushima, 1972, Abstract Papers, p.93 and the Sixth Congress of Heterocyclic Chemistry, Nagoya, 1973, Abstract Papers, p. 171.
3) Location: *492–36, Mitahora, Gifu.*
4) *a*) W. Pfleiderer and H. Mosthaf, *Chem. Ber.*, **90**, 738 (1957); *b*) K. Imai, *Chem. Pharm. Bull.* (Tokyo), **12**, 1030 (1964); *c*) E.C. Taylor and E.E. Garcia, *J. Org. Chem.*, **30**, 655 (1965); *d*) H. Fenner and H. Mostschall, *Tetrahedron Letters*, **1971**, 4175; *e*) T. Murata and K. Ukawa, *Chem. Pharm. Bull.* (Tokyo), **22**, 240 (1974).
5) H. Bredereck, F. Effenbereger, and G. Simchen, *Chem. Ber.*, **96**, 1354 (1963); DMS: dimethyl sulfate.

hydrogenation of **2** in an autoclave under 50—60 atm gave 2,4-dioxo-1,2,3,4-tetrahydropyrrolo[3,2-*d*]pyrimidines (**3**) and by-products (**4**). The structure of the by-product (**4a**) was assigned as 6-dimethylamino-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrrolo[3,2-*d*]pyrimidine (**4a**) on the basis of nuclear magnetic resonance (NMR) and mass spectra. The NMR spectrum showed a sharp singlet at 3.53 ppm (6 protons, 6-dimethylamino group) and a doublet at 5.32 ppm (1 proton, hydrogen at C-7), which was changed to a singlet after treatment with deuteriumoxide. The mass spectrum showed a molecular ion peak at *m/e* 222. The main product (**3a**) was identified by comparison with an authentic sample prepared by decarboxylating 6-carboxy-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrrolo[3,2-*d*]pyrimidine (**5**) which was synthesized by the procedure of Pfleiderer.[4a] Methylation of the NH at 5-position of **3a** was not successful with dimethyl sulfate or diazomethane, only recovering the starting material, but it was accomplished by treating **3a** with methyl iodide in the presence of potassium carbonate in DMF, yielding the desired 5-methyl derivative (**6**), which was also prepared as follows; 6-ethoxycarbonyl-1,3,5-trimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrrolo[3,2-*d*]pyrimidine (**7**)[4a] was hydrolyzed under an alkaline condition to obtain the carboxylic compound (**8**) which was then decarboxylated to give **6**. In methylation with dimethyl sulfate, the 3-butyl compound (**3c**) was methylated only at 1-position giving 3-butyl-1-methyl compound (**9**), while in that with methyl iodide it was methylated both at 1- and 5-positions producing 3-butyl-1,5-dimethyl compound (**10**) (Chart 2).

The mechanism for the formation of **3** and **4** which are obtained by catalytic hydrogenation of **2**, is outlined in Chart 3. In the course of successive reduction ($NO \rightarrow NHOH \rightarrow NH_2$)

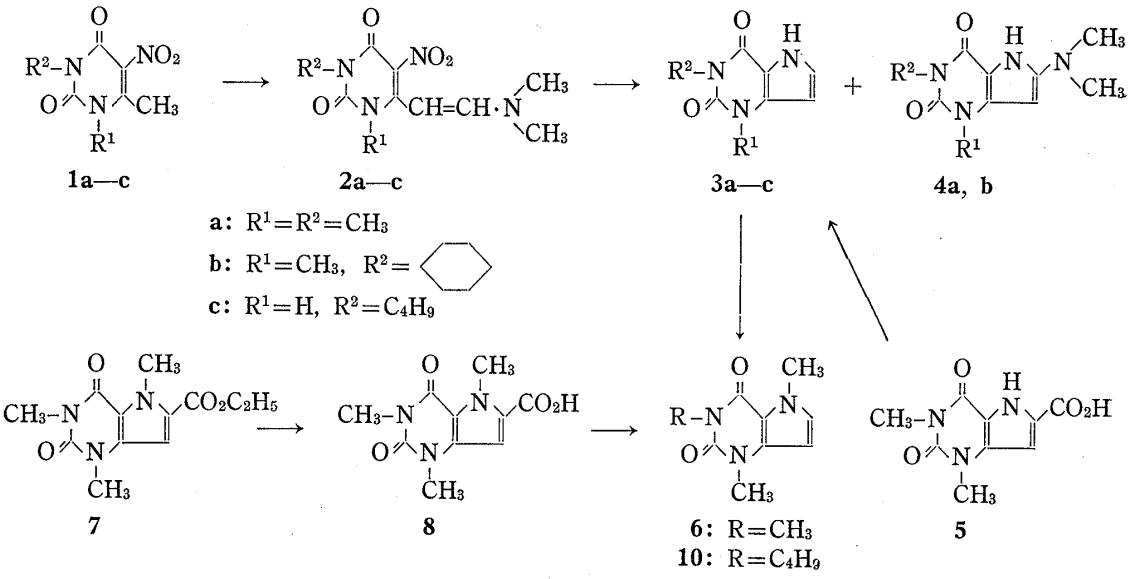


Chart 2

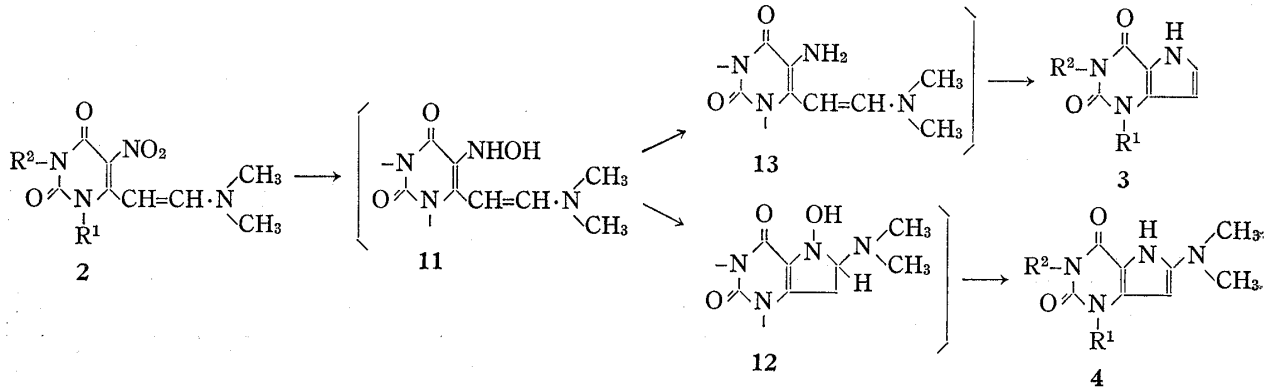


Chart 3

of the 5-nitro group of **2**, the 5-hydroxyamino compound (**11**) is cyclized to form **12**, which is then dehydrated to give the 6-dimethylamino compound (by-product) (**4**). In the above reduction process, on the other hand, the 5-amino compound (**13**) is cyclized and then dedimethylaminated to give the main product (**3**).

Another new synthesis of the pyrrolo[3,2-*d*]pyrimidine derivatives was studied as follows. Thus, 3-substituted 5-amino-1,6-dimethyluracils (**14**) [substituent: 3-CH_3 (**a**); 3-phenyl (**b**)] were formylated with formic acid to afford the 5-formylamino compounds (**15**). Heating **15a** at 270—300° formed pyrrolo[3,2-*d*]pyrimidine (**3a**) in a low yield, whereas under the same conditions the cyclization of **15b** did not proceed, only recovering the deformylated compound (**14b**). In a similar process, **14** was allowed to react with ethyl orthoformate to give 5-ethoxy methyleneamino compound (**16**), which was heated in a manner described above, but only to recover the starting material.

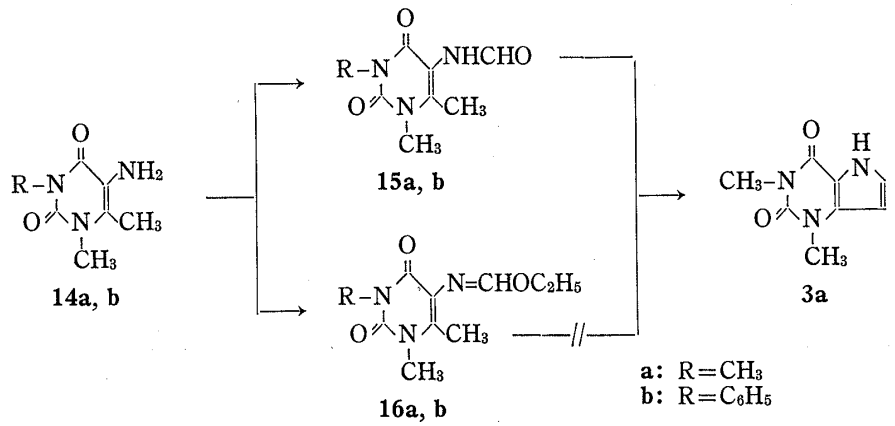


Chart 4

Table I. Diuretic, Cardiac, and CNS Stimulating Activities and Acute Toxicity of 9-Deazaxanthine Derivatives

Compd. No.	Diuretic activity[a] 50 mg/kg	100 mg/kg	200 mg/kg	Cardiac[b] activity (chronotropic) 50 mg/kg	100 mg/kg	CNS[c] stimulating activity (spontaneous motor activity) 50 mg/kg	100 mg/kg	Acute toxicity[d] LD_{50} (mg/kg)
3a	92			14(+)		261		100(67—149)
3c		134	161		28(++)		134	>1600
6		88			15(+)		261	200(134—299)
9			113		29(++)			1130
Caffeine		168			57(+++)	402		238(170—339)
Theophylline	144	156			31(++)	462		200(134—299)

a) Weight of urine for 3 hours in mice (*p.o.*) compared with control (100).[6]
b) effects on the ECG of pentobarbitalized mice (per cent increase in heart rate)[7]
c) Postexploratory activity compared with control (100) by the Animex apparatus (A.B. Farad Co.).[8]
d) in mice (*i.p.*)

Pharmacology

Diuretic activity (weight of urine collected for 3 hours in mice),[6] cardiac activity (chronotropic activity),[7] CNS stimulating activity (spontaneous motor activity),[8] and acute toxicity

6) T. Mineshita, S. Matsumura, S. Kimoto, and O. Uno, *Pharmacometrics*, **4**, 33 (1970).
7) S. Chiba and K. Kubota, *European J. Pharmacol.*, **21**, 281 (1973).
8) T.H. Svensson and G. Thieme, *Psychopharmacologia*, **14**, 157 (1969); *idem*, *J. Pharmacol.*, **22**, 639 (1970).

(LD_{50}) were studied concerning the 9-deazaxanthine derivatives. The results are summarized in Table I.

Generally the 9-deazaxanthine derivatives did not show diuretic activity except 1-butyl-9-deazaxanthine (**3c**) which had diuretic activity weaker than that of caffeine. The fact that the 9-deazaxanthine derivatives have very weak diuretic activity in comparison with the xanthine and 7-deazaxanthine derivatives, supports the view that the nitrogen atom at 9-position of xanthine ring plays a very important role in showing the diuretic activity as described in the preceeding paper.[1)]

As to the CNS stimulating activity (spontaneous motor activity), the 1,3-dimethyl and 1,3,5-trimethyl compounds (**3a** and **6**) were active. For the cardiac activity (positive chronotropic activity), the butyl compounds (**3c** and **9**) showed activity similar to that of theophylline. However these activities were much weaker than those of caffeine.

Experimental[9)]

General Procedure of N-Substituted 6-Methyl-5-nitrouracil Derivatives (1a, 1b, 1c)——To a solution of 20 ml of conc. H_2SO_4 and 20 ml of fuming nitric acid, was added 10 g of N-substituted 6-methyluracil gradually with stirring and cooling at 0° to 5°. The reaction mixture was poured carefully over ice, the precipitated product was filtered, washed with H_2O, and recrystallized from a suitable solvent.

1,3,6-Trimethyl-5-nitrouracil (**1a**) and 3-cyclohexyl-1,6-dimethyl-5-nitrouracil (**1b**) have been already reported,[10)] but melting point of **1b** was corrected into 212° (recrystallized from MeOH) (lit.[10a)] mp 138°). *Anal.* Calcd. for $C_{12}H_{17}O_4N_3$: C, 53.92; H, 6.41; N, 15.72. Found: C, 53.88; H, 6.50; N, 15.76.

3-Butyl-1-methyl-5-nitrouracil (**1c**) was recrystallized from benzene to give 66% of colorless leaflets, mp 176°. *Anal.* Calcd. for $C_9H_{13}O_4N_3$: C, 47.57; H, 5.77; N, 18.49. Found: C, 47.76; H, 5.89; N, 18.50.

6-(2-Dimethylaminovinyl)-1,3-dimethyl-5-nitrouracil (2a)——a) To a solution of 1,3,6-trimethyl-5-nitrouracil (**1a**) (4 g, 0.02 mole) in 10 ml of DMF was added 4.8 g of DMF-dimethyl sulfate complex.[5)] The mixture was kept at 0°, and 2.4 g of triethylamine was gradually dropped thereinto with stirring. The mixture was stirred at room temperature for 2 hr, after cooling the precipitated crystals were filtered off, and recrystallized from MeOH to give 2.5 g (49%) of reddish leaflets, mp 185—186°. NMR ($CDCl_3$) δ: 3.02 (6H, s, $N(CH_3)_2$), 3.37 and 3.48 (each 3H, each s, $NCH_3 \times 2$), 4.52 (1H, d, J=13 Hz, $CH{=}CHN\langle$), 6.98 (1H, d, J=13 Hz, $-CH{=}CHN\langle$). *Anal.* Calcd. for $C_{10}H_{14}O_4N_4$: C, 47.24; H, 5.55; N, 22.04. Found: C, 47.32; H, 5.67; N, 22.27.

b) To a solution of 4 g (0.02 mole) of **1a** in 10 ml of DMF was added 4.5 g (0.03 mol) of DMF-diethylacetal. The solution was stirred at room temperature for 30 min and concentrated *in vacuo*. Ether was added to the residue and the crude product was filtered and recrystallized from MeOH to give 5.0 g (98%) of reddish leaflets, mp 185°, identical with the compound (**2a**) prepared above.

3-Cyclohexyl-6-(2-dimethylaminovinyl)-1-methyl-5-nitrouracil (2b)——a) To a mixture of 3-cyclohexyl-1,6-dimethyl-5-nitrouracil (**1b**) (5.3 g, 0.02 mole) and 10 ml of DMF was added 9.6 g of DMF-dimethyl sulfate complex. Triethylamine (4.8 g) was gradually dropped with stirring at room temperature and the mixture was further stirred for 30 min. After cooling, the resulting precipitate was filtered and recrystallized from MeOH to give 3.5 g (54%) of orange needles, mp 209—210°. NMR ($CDCl_3$) δ: 2.98 (6H, s, $N(CH_3)_2$), 3.43 (3H, s, NCH_3), 4.47 (1H, d, J=13 Hz, $CH{=}CHN\langle$), 6.95 (1H, d, J=13 Hz, $CH{=}CHN\langle$). *Anal.* Calcd. for $C_{15}H_{22}O_4N_4$: C, 55.88; H, 6.88; N, 17.38. Found: C, 55.98; H, 7.04; N, 17.46.

b) A solution of **1b** (5.3 g, 0.02 mole) and DMF-diethylacetal (4.5 g, 0.03 mole) in 30 ml of benzene was heated under reflux for 30 min. The solvent was evaporated off, ether was added to the residue, and the crude product was filtered. Recrystallization from MeOH gave 4.8 g (75%) of **2b**, mp 209—210°, identical with the compound (**2b**) prepared above.

3-Butyl-6-(2-dimethylaminovinyl)-5-nitrouracil (2c)——a) To a mixture of 3-butyl-6-methyl-5-nitrouracil (**1c**) (4.6 g, 0.02 mole) and 10 ml of DMF was added 9.6 g of DMF-dimethyl sulfate complex. Triethylamine (4.8 g) was gradually dropped with stirring at room temperature and the mixture was further stirred for 30 min. After the reaction, the resulting precipitate was filtered and recrystallized from EtOH to give 3.5 g (62%) of **2c**, mp 253°. *Anal.* Calcd. for $C_{12}H_{18}O_4N_4$: C, 51.05; H, 6.43; N, 19.85. Found: C, 51.23; H, 6.60; N, 20.12.

9) All melting points were measured with a Yanagimoto Micro Melting Point Apparatus and are uncorrected. NMR spectra were recorded on a Hitachi Perkin-Elmer Model R-20B spectrometer using tetramethylsilane as internal reference.

10) *a*) S. Senda, A. Suzui, M. Honda, and H. Fujimura, *Chem. Pharm. Bull.*, (Tokyo), **6**, 482 (1958); *b*) W. Pfleiderer and H. Mosthaf, *Chem. Ber.*, **90**, 728 (1957).

b) A solution of 4.6 g (0.02 mole) of **1c** and 4.5 g (0.03 mole) of DMF-diethylacetal in 30 ml of benzene was refluxed for 5 min. After cooling, the resulting precipitate was filtered, washed with ether, and recrystallized from EtOH to give 4.6 g (82%) of **2c**, mp 253°, identical with the compound (**2c**) prepared above.

Catalytic Reduction of 6-(2-Dimethylaminovinyl)-1,3-dimethyl-5-nitrouracil (2a)——A solution of **2a** (5.1 g, 0.02 mole) in DMF (50 ml) was hydrogenated in an autoclave at 50 atm and 60° using Pd-C (0.5 g) as a catalyst. After 2 hr, activated carbon was added to the reaction solution and the catalyst was removed by filtration. The filtrate was evaporated to dryness under reduced pressure. Benzene was added to the residue and an insoluble material was filtered and recrystallized from EtOH to give 0.7 g (16%) of 6-dimethyl-amino-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrrolo[3,2-*d*]pyrimidine (**4a**), mp >300°. NMR (DMSO-d_6) δ: 2.92 (6H, s, $N(CH_3)_2$), 3.22 and 3.35 (each 3H, each s, $NCH_3 \times 2$), 5.32 (1H, d, $J=3$ Hz, 7-H, changed to a singlet by addition of D_2O), 10.90 (1H, br, NH, disappeared by addition of D_2O). Mass Spectrum *m/e*: 222 (M^+). *Anal.* Calcd. for $C_{10}H_{14}O_2N_4$: C, 54.02; H, 6.35; N, 25.21. Found: C, 54.07; H, 6.38; N, 25.31.

The filtrate of benzene solution was evaporated under reduced pressure. The residue was recrystallized from benzene to give 2.2 g (62%) of 1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrrolo[3,2-*d*]pyrimidine (**3a**), mp 210°. NMR ($CDCl_3$) δ: 3.47 and 3.52 (6H, each s, $NCH_3 \times 2$), 6.00(1H, t, 7-H), 7.17 (1H, t, 6-H), 10.90—11.35 (1H, br, NH). *Anal.* Calcd. for $C_8H_9O_2N_3$: C, 53.62; H, 5.06; N, 23.45. Found: C, 53.55; H, 5.13; N, 23.32.

Catalytic Reduction of 3-Cyclohexyl-6-(2-dimethylaminovinyl)-1-methyl-5-nitrouracil (2b)——A solution of **2b** (9.7 g, 0.03 mole) in DMF (100 ml) was hydrogenated in an autoclave at 50 atm and 80° using Pd-C (0.5 g) as a catalyst. After 3 hr, activated carbon was added to the reaction solution and the catalyst was removed by filtration. The filtrate was evaporated under reduced pressure. Ether was added to the residue and the crude product was filtered and subjected to column chromatography on activated alumina eluting with benzene to give 1.1 g (13%) of 3-cyclohexyl-6-dimethylamino-1-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrrolo[3,2-*d*]pyrimidine (**4b**), mp 260°, which was recrystallized from EtOH. NMR (DMSO-d_6) δ: 2.89 (6H, s, $N(CH_3)_2$), 3.28 (3H, s, NCH_3), 5.24 (1H, d, $J=3$ Hz, 7-H). *Anal.* Calcd. for $C_{15}H_{22}O_2N_4$: C, 62.04; H, 7.64; N, 19.30. Found: C, 62.15; H, 7.69; N, 19.25. From the fraction eluted with AcOEt, 3-cyclohexyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrrolo[3,2-*d*]pyrimidine (**3b**) (2.3 g, 31%) was obtained. Recrystallization from AcOEt gave colorless prisms of mp 219°. *Anal.* Calcd. for $C_{13}H_{17}O_2N_3$: C, 63.14; H, 6.93; N, 16.99. Found: C, 63.05; H, 6.93; N, 17.04.

Catalytic Reduction of 3-Butyl-6-(2-dimethylaminovinyl)-5-nitrouracil (2c)——A mixture of **2c** (8.5 g, 0.03 mole), Pd-C (0.5 g), and DMF (100 ml) was treated as described in the reduction of **2a** to give 5.2 g (84%) of a crude product. Recrystallization from EtOH afforded colorless needles of 3-butyl-2,4-dioxo-1,2,3,4-tetrahydropyrrolo[3,2-*d*]pyrimidine (**3c**), mp >300°. NMR (CF_3CO_2H) δ: 6.35 (1H, t, $J=2.6$ Hz, 7-H), 7.50 (1H, t, $J=2.6$ Hz, 6-H). *Anal.* Calcd. for $C_{10}H_{13}O_2N_3$: C, 57.96; H, 6.32; N, 20.28. Found: C, 57.86; H, 6.44; N, 20.03.

1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrrolo[3,2-*d*]pyrimidine (3a)——a) A mixture of 6-carboxy-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrrolo[3,2-*d*]pyrimidine (**5**)[4a] (5 g) and Cu powder (0.5 g) was heated on a salt bath at 280—320°. After cease of evolution of CO_2 was confirmed by $Ba(OH)_2$ solution, the reaction mixture was extracted with benzene, and the extract was evaporated. The residue was recrystallized from benzene to give 1.6 g (40%) of **3a**, mp 212°, identical with the compound (**3a**) prepared in the reduction of **2a**.

b) 5-Formylamino-1,3,6-trimethyluracil (**15a**) (1.0 g) was heated on a salt bath at 270—300° for 10 min. After the reaction, the residue was recrystallized from benzene to give 0.14 g (15%) of **3a**, mp 212°, identical with the compound (**3a**) prepared in the reduction of **2a**.

1,3,5-Trimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrrolo[3,2-*d*]pyrimidine (6)——a) A mixture of **3a** (2 g, 0.01 mole), methyl iodide (7.1 g), and anhydrous potassium carbonate (1.3 g) in 50 ml of DMF was heated at 80° with stirring for 4 hr. The solvent was evaporated off under reduced pressure and H_2O was added to the residue. The resulting crude product was filtered and recrystallized from ligroin to give 1.4 g (73%) of **6**, mp 170°. NMR ($CDCl_3$) δ: 3.43 and 3.48 (each 3H, each s, $NCH_3 \times 2$), 4.03 (3H, s, 5-NCH_3), 5.90 (1H, d, $J=3$ Hz, 7-H), 6.89 (1H, d, $J=3$ Hz, 6-H). *Anal.* Calcd. for $C_9H_{11}O_2N_3$: C, 55.95; H, 5.74; N, 21.75. Found: C, 56.16; H, 5.71; N, 21.88.

b) A mixture of **8** (0.7 g) and Cu powder (0.7 g) was heated on a salt bath at 260—310°. After cease of evolution of CO_2 was confirmed by $Ba(OH)_2$ solution, the reaction mixture was extracted with AcOEt, and the extract was evaporated. The residue was recrystallized from ligron to give 0.3 g (53%) of **6**, mp 168°, identical with the compound (**6**) prepared above.

6-Carboxy-1,3,5-trimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrrolo[3,2-*d*]pyrimidine (8)——A mixture of 6-ethoxycarbonyl-1,3,5-trimethyl-2,4-dioxo-1,2,3,4-tetrahydro[3,2-*d*]pyrimidine (**7**)[4a] (2.5 g, 0.01 mole), NaOH (3 g), H_2O (5 ml), and EtOH (50 ml) was heated on a water bath for 30 min. EtOH was evaporated under reduced pressure, a small amount of H_2O was added to the residue, and the solution was acidified with conc. HCl. The resulting precipitate was filtered and recrystallized from DMF–EtOH to give 1.9 g (85%) of **8**, mp >300°. NMR (DMSO-d_6) δ: 3.25 and 3.39 (each 3H, each s, $NCH_3 \times 2$), 4.22 (3H, s, 5-NCH_3), 6.80 (1H, s, 7-H). *Anal.* Calcd. for $C_9H_9O_4N_3$: C, 48.43; H, 4.06; N, 18.83. Found: C, 48.13; H, 4.22; N, 18.70.

3-Butyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrrolo[3,2-*d*]pyrimidine (9)——In 20 ml of 5% aq. solution of NaOH was dissolved 1.4 g of **3c**, 3.1 g of dimethyl sulfate was added dropwise thereinto and the

mixture was stirred for 1 hr. The resulting precipitate was filtered and recrystallized from H_2O to give 1.0 g (67%) of colorless prisms, mp 167°. NMR ($CDCl_3$) δ: 3.53 (3H, s, NCH_3), 6.03 (1H, t, J=3 Hz, 6-H), 7.18 (1H, t, J=3 Hz, 7-H), 11.15—11.66 (1H, br. NH). *Anal.* Calcd. for $C_{11}H_{15}O_2N_3$: C, 59.71; H, 6.83; N, 18.99. Found: C, 59.81; H, 7.03; N, 19.02.

3-Butyl-1,5-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrrolo[3,2-*d*]pyrimidine (10)——A mixture of **3c** (2.1 g, 0.01 mole), methyl iodide (8.4 g, 0.06 mole), and anhydrous potassium carbonate (1.3 g, 0.01 mole) in 50 ml of DMF was heated at 80° with stirring for 4 hr. The solvent was evaporated off under reduced pressure and H_2O was added to the residue. The resulting crude product was filtered and recrystallized from ligroin to give 2.0 g (85%) of **10**, mp 96—98°. NMR ($CDCl_3$) δ: 3.47 (3H, s, 1-NCH_3), 4.03 (3H, s, 5-NCH_3), 5.90 (1H, d, J=3 Hz, 6-H), 6.89 (1H, d, J=3 Hz, 7-H). *Anal.* Calcd. for $C_{12}H_{17}O_2N_3$: C, 61.25; H, 7.28; N, 17.86. Found: C, 61.07; H, 7.42; N, 17.99.

5-Formylamino-1,3,6-trimethyluracil (15a)——5-Amino-1,3,6-trimethyluracil (**14a**)[4a,10a] (3.4 g, 0.02 mole) in 15 ml of 98% formic acid was refluxed for 2 hr. The excess formic acid was removed by evaporation under reduced pressure and ether was added to the residue. The resulting crude product was filtered and recrystallized from benzene to give 3.5 g (89%) of colorless needles, mp 152°. NMR ($CDCl_3$) δ: 2.27 (3H, s, 6-CH_3), 3.39 and 3.51 (each 3H, each s, $NCH_3\times2$), 7.60—7.92 (1H, br, NH), 8.37 (1H, d, J=1.5 Hz, CHO). *Anal.* Calcd. for $C_8H_{11}O_3N_5$: C, 48.72; H, 5.62; N, 21.31. Found: C, 49.09; H, 5.84; N, 21.44.

5-Formylamino-1,6-dimethyl-3-phenyluracil (15b)——5-Amino-1,6-dimethyl-3-phenyluracil (**14b**)[11] (2.3 g, 0.01 mole) was treated as described in the preparation of **15a** to give 2.2 g (85%) of **15b**, mp 160°, which was recrystallized from AcOEt. NMR ($CDCl_3$) δ: 2.22 (3H, s, 6-CH_3), 3.45 (3H, s, NCH_3), 7.00—7.60 (5H, multiplet, C_6H_5), 7.95 (1H, br, NH), 8.14 (1H, d, J=1.5 Hz, CHO). *Anal.* Calcd. for $C_{13}H_{13}O_3N_3$: C, 60.22; H, 5.07; N, 16.21. Found: C, 60.37; H, 5.13; N, 16.33.

5-Ethoxymethyleneamino-1,3,6-trimethyluracil (16a)——A solution of **14a** (1.5 g) in 5 ml of ethyl orthoformate was refluxed for 10 min. The excess ethyl orthoformate was removed by evaporation *in vacuo* and ether was added to the residue. The resulting crude product was filtered and recrystallized from ligroin to give 1.5 g (75%) of colorless needles, mp 117°. NMR ($CDCl_3$) δ: 1.35 (3H, t, J=4.7 Hz, $CH_2\underline{CH_3}$), 2.41 (3H, s, 6-CH_3), 3.40 and 3.49 (each 3H, each s, $NCH_3\times2$), 4.26 (2H, q, J=4.7 Hz, $C\underline{H_2}CH_3$), 8.71 (1H, s, –N=CH–O). *Anal.* Calcd. for $C_{10}H_{15}O_3N_3$: C, 53.32; H, 6.71; N, 18.66. Found: C, 53.35; H, 6.62; N, 18.57.

5-Ethoxymethyleneamino-1,6-dimethyl-3-phenyluracil (16b)——A solution of **14a** (4.6 g, 0.02 mole) in 15 ml of ethyl orthoformate was treated as described in the preparation of **16a** to give 4.5 g (78%) of **16b**, mp 164°, which was recrystallized from ligroin. *Anal.* Calcd. for $C_{15}H_{17}O_3N_3$: C, 62.70; H, 5.96; N, 14.63. Found: C, 62.86; H, 6.02; N, 14.83.

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11) S. Senda, K. Hirota, and K. Banno, *J. Med. Chem.*, **15**, 471 (1972).