Syntheses of 7-Alkyl-1,3,6-trimethylpyrrolo[2,3-*d*]pyrimidines and 4-Alkylamino-2,5-dimethyl-2,3-dihydrofuro[3,2-*e*]pyrimidines

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7-Alkyl-1,3,6-trimethylpyrrolo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones were readily synthesized by treatment of 6-alkylamino-5-allyl-1,3-dimethyluracils, which were derived from 5-allyl-6-chloro-1,3-dimethyluracil and alkylamines, with bis(acetonitrile) palladium (II) chloride. In addition, 4-alkylamino-2,5-dimethyl-2,3-dihydrofuro[3,2-*e*]pyrimidin-6-ones were easily synthesized by treatment of 5-allyl-6-chloro-1-methyluracil with alkylamines.

Keywords pyrrolo[2,3-*d*]pyrimidine; 5-allylbarbituric acid; 5-allyl-6-chlorouracil; palladium-catalyzed cyclization; PdCl₂·(CH₃CN)₂; furo[3,2-*e*]pyrimidine

6-Functionalized 5-allylpyrimidines can be used as starting materials for the synthesis of condensed pyrimidine rings.²⁾ Some of which have interesting biological activities. For example, 6-chlorouracils containing allyl and alkyl groups display virostatic and cytostatic activities.³⁾ Our interest in the 1,3-dialkyl-5-allyl-6-chlorouracils as potential bioactive substances and as starting materials for the syntheses of pyrrolo[2,3-*d*]pyrimidines, which can be regarded as analogues of antitumor antibiotics, tubercidin (1),⁴⁾ sangivamycin (2),⁵⁾ and toyocamycin (3),⁶⁾ prompted us to investigate possible pathways for the syntheses of condensed nitrogenous heterocycles.

5-Allylbarbituric acid (4) has been synthesized by cyclization reaction between urea and ethyl allylmalonate in 37% yield.⁷⁾ We could raise the yield of 4 to 60% by the use of equimolar dry sodium methoxide (instead of 2 molar eq of ethanolic sodium ethoxide) in acetone. 1-Methyl- or 1,3-dimethylurea, however, failed to react with the above ester under similar conditions. Because *N*-unsubstituted 6-chlorouracil has usually been obtained by partial hydrolysis of 2,4,6-trichloropyrimidine,⁸⁾ we attempted the synthesis of 5-allyl-2,4,6-trichloropyrimidine (5)⁹⁾ by chlorination of 4 with POCl₃ in the presence of *N,N*-diethylaniline. It turned out that this reaction afforded only 5 in 50% yield. Alkaline hydrolysis of 5 with 4 molar eq excess of NaOH in water gave 41% yield of 5-allyl-6-chlorouracil (6). In the case of added water (0.56 mol), the reaction of 4 (0.10 mol) with POCl₃ (1.07 mol) and *N,N*-dimethylaniline (0.08 mol) proceeded smoothly, giving rise to 6 as the sole isolable product in 54% yield. Under the above conditions, pyrophosphoryl chloride that was formed by the reaction of POCl₃ and water¹⁰⁾ may be the actual chlorinating reagent. The structure of 6 was supposed to be 5-allyl-6-chlorouracil

because a series of reactions starting with 6 gave rise to 11a via 8. Spectral data of 6 are also consistent with the assigned structure (*vide infra*).

Alkylation of 6 with an excess of MeI in the presence of K₂CO₃ in dimethylsulfoxide (DMSO) at 70 °C gave rise to 5-allyl-6-chloro-1,3-dimethyluracil (7) in 75% yield. When an equimolar amount of MeI was used under similar conditions, the yield of 5-allyl-6-chloro-1-methyluracil (8)

Fig. 1

Chart 3

Chart 4

was 20%. A satisfactory result (71% yield of **8**) was obtained when MeI and K₂CO₃ were used in a molar ratio of 1.5 to 0.5 in acetone instead of DMSO. The structure of **8** was supported by its ultraviolet (UV) spectra in alkaline media. As is well established,¹¹⁾ 1- and 3-alkyluracil each have characteristic UV spectra, the latter absorbing at longer wavelength. The UV spectrum of **6** was quite similar to that of 1-alkyluracil and not to that of 3-alkyluracil. Treatment of **7** with several alkylamines furnished the required 6-aminouracils **9a-f** in good yields.

Hegedus and co-workers¹²⁾ have prepared indole derivatives from 2-allylanilines by using a palladium catalyst. For our cyclization (from **9** and **10**) we applied their method of palladium-catalyzed cyclization to obtain pyrrolo[2,3-*d*]pyrimidines. Thus, the 6-aminouracils **9a-e** were treated with 1 molar eq of benzoquinone and 10 molar eq of LiCl in tetrahydrofuran (THF) in the presence of a catalytic amount of PdCl₂(CH₃CN)₂, at room temperature to give the required 7-alkylpyrrolo[2,3-*d*]pyrimidines **10a-e** in poor or moderate yields. In the case of unsubstituted 6-aminouracil **9f**, this reaction proceeded at 40–50 °C under palladium-catalyzed conditions and gave the pyrrolo[2,3-*d*]pyrimidine derivative **10f** in 55% yield.

On the other hand, treatment of **8** with alkylamines gave the 2,3-dihydrofuro[3,2-*e*]pyrimidines **11a-c** in moderate yields. The mass spectra (MS) and proton nuclear magnetic resonance (¹H-NMR) spectra of these compounds are consistent with those of the assigned bicyclic structure. In order to confirm the structure, we carried out X-ray crystal structure analysis of **11a**.

The structures of other newly synthesized compounds were confirmed by MS, high-resolution mass spectra (High MS), ¹H-NMR, and elemental analysis.

The results may be summarized as follows. i) The modified conditions allowed us to obtain 5-allylbarbituric acid in high yields. ii) Chlorination of 5-allylbarbituric acid was

investigated and a procedure was developed to obtain 5-allyl-6-chlorouracil directly from 5-allylbarbituric acid. iii) Methylation of 5-allyl-6-chlorouracil was studied. iv) A synthetic procedure for pyrrolo[2,3-*d*]pyrimidines was developed. v) 2,3-Dihydrofuro[3,2-*e*]pyrimidines were prepared easily from 5-allyl-6-chloro-1-methyluracil with alkylamines, and the structure of the key compound (**11a**) was confirmed by means of X-ray analysis.

Experimental

General Melting points were determined in a capillary tube and are uncorrected. MS and High MS were recorded on JMS-DX 300 and JMA 3500 instruments. ¹H-NMR spectra were recorded on a Varian VXR-300 spectrometer in CDCl₃ or in DMSO-*d*₆. Chemical shifts are expressed in terms of δ values. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; qu, quintet; se, sextet; m, multiplet; br, broad. Microanalyses were performed by the staff in the Microanalytical Laboratory of this school. Thin layer chromatography (TLC) was performed on Kieselgel 60 GF₂₅₄ (Merck) and spots were detected under UV light. Unless otherwise stated, the solvents were removed with a rotary evaporator and a water aspirator (ca. 20 mmHg).

5-Allylbarbituric Acid (4) A mixture of dry sodium methoxide [prepared from sodium (5.75 g, 0.25 atom) and methanol (150 ml)], urea (15 g, 0.25 mol), diethyl allylammonate (50 g, 0.25 mol), and acetone (50 ml) was stirred under reflux for 7 h. The precipitate was collected by filtration, washed with acetone, suspended in water (100 ml), and acidified with concentrated aqueous HCl to pH 1–2. The precipitate was filtered off and recrystallized from EtOH to give 25 g (60%) of **4** as colorless needles, mp 170 °C (lit.⁷⁾ mp 167 °C). MS *m/z*: 168 (M⁺). Anal. Calcd for C₇H₈N₂O₃: C, 50.00; H, 4.80; N, 16.66. Found: C, 49.87; H, 4.95; N, 16.51.

5-Allyl-2,4,6-trichloropyrimidine (5) A mixture of **4** (16.8 g, 0.1 mol), *N,N*-diethylaniline (10 ml), and POCl₃ (75 ml) was boiled for 3 h. The excess POCl₃ was removed under reduced pressure, and the residue was poured onto ice (200 g), extracted with CHCl₃ (100 ml $\times$ 3), and dried over Na₂SO₄. The solvent was removed and the residue was distilled at 120–122 °C/5 mmHg to give **5** (11.2 g, 50%) as a colorless oil, which spontaneously crystallized on standing, mp 38–40 °C (lit.⁹⁾ mp 39 °C). MS *m/z*: 222, 224, 226, and 228 (M⁺). Anal. Calcd for C₇H₅Cl₃N₂: C, 37.62; H, 2.25; N, 12.57; Cl, 47.59. Found: C, 37.48; H, 2.39; N, 12.36; Cl, 47.71.

5-Allyl-6-chlorouracil (6) i) A mixture of **5** (4.5 g, 0.02 mol), NaOH (3.2 g, 0.08 mol), and water (50 ml) was boiled with stirring for 10–12 h, until a clear solution was obtained. After cooling, the solution was washed with ether (50 ml) and the water phase was acidified with concentrated aqueous HCl to pH 3–4. The crystals formed after standing for 12 h at 10 °C were collected by filtration, and recrystallized from EtOH to give **6** (1.5 g, 41%) as colorless needles, mp 214–216 °C. ii) POCl₃ (100 ml) added dropwise to a mixture of **4** (16.8 g, 0.1 mol), *N,N*-dimethylaniline (10 ml), and water (10 ml) during 1 h. The mixture was boiled for 45 min, the excess POCl₃ was removed *in vacuo*, and the residue was poured onto ice (270 g). After cooling, the precipitate was collected by filtration, washed with ether (100 ml), and dried at 100 °C to give **6** (10.1 g, 54%) as colorless needles, mp 215–217 °C (EtOH). MS *m/z*: 186 and 188 (M⁺). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (log ϵ): 262 (3.67). UV $\lambda_{\text{max}}^{0.1 \text{ N aq. NaOH-EtOH}(1:10)}$ nm (log ϵ): 290 (3.98). ¹H-NMR (DMSO-*d*₆) δ : 3.00–3.07 (2H, br, –CH₂CH=CH₂), 4.97 (1H, d, –CH₂CH=CH₂, *J*=4.0 Hz), 5.00 (1H, d, –CH₂CH=CH₂, *J*=5.8 Hz), 5.74 (1H, ddt, –CH₂CH=CH₂, *J*=2.5, 4.0, 5.8 Hz), 11.35 (1H, br s, NH),

11.90 (1H, br, NH). *Anal.* Calcd for $C_7H_7ClN_2O_2$: C, 45.16; H, 3.76; N, 15.05; Cl, 19.09. Found: C, 44.91; H, 3.80; N, 14.93; Cl, 18.87.

5-Allyl-6-chloro-1,3-dimethyluracil (7) A mixture of **6** (9.3 g, 50 mmol), K_2CO_3 (13.8 g, 0.1 mol), and MeI (17.7 g, 0.125 mol) in DMSO (50 ml) was stirred at 60–70 °C for 1 h, then cooled. A 4% (w/v) aqueous solution (100 ml) of NaOH was added, and the mixture was extracted with ether (50 ml $\times$ 3). The organic phase was dried over Na_2SO_4 , the solvent was removed, and the residue was distilled at 120–130 °C/3 mmHg to give **7** (8.0 g, 75%) as an oil, which crystallized on standing, mp 38–40 °C. High MS Calcd for $C_9H_{11}ClN_2O_2$: 214.051, 216.048. Found: 214.049, 216.048. 1H -NMR ($CDCl_3$) δ : 3.24 (2H, dt, $-CH_2CH=CH_2$, $J=1.5$, 6.0 Hz), 3.32, 3.55 (3H each, s, NCH_3), 5.01 (1H, ddd, $-CH_2CH=CH_2$, $J=1.5$, 1.5, 10.0 Hz), 5.07 (1H, ddd, $-CH_2CH=CH_2$, $J=1.5$, 1.5, 17.0 Hz), 5.77 (1H, ddt, $-CH_2CH=CH_2$, $J=6.0$, 10.0, 17.0 Hz).

5-Allyl-6-chloro-1-methyluracil (8) A mixture of **6** (3.72 g, 20 mmol), K_2CO_3 (1.38 g, 10 mmol), and MeI (4.26 g, 30 mmol) in acetone (100 ml) was stirred with boiling for 10 h. The mixture was filtered, and the filtrate was evaporated to dryness. The residue was recrystallized from AcOEt to give **8** (2.83 g, 71%) as colorless needles, mp 186–188 °C. MS m/z : 200 and 202 (M^+). UV λ_{max}^{EtOH} nm (log ϵ): 267 (4.05). UV $\lambda_{0.1N aq. NaOH-EtOH(1:10)}$ nm (log ϵ): 266 (3.91). 1H -NMR ($CDCl_3$) δ : 3.25 (2H, dt, $-CH_2CH=CH_2$, $J=1.5$, 6.0 Hz), 3.45 (3H, s, NCH_3), 5.03 (1H, ddd, $-CH_2CH=CH_2$, $J=1.5$, 10.0 Hz), 5.10 (1H, ddd, $-CH_2CH=CH_2$, $J=1.5$, 1.5, 17.0 Hz), 5.79 (1H, ddt, $-CH_2CH=CH_2$, $J=6.0$, 10.0, 17.0 Hz), 9.96 (1H, br, NH). *Anal.* Calcd for $C_8H_9ClN_2O_2$: C, 47.89; H, 4.52; N, 14.46; Cl, 17.67. Found: C, 47.90; H, 4.65; N, 14.24; Cl, 17.52.

5-Allyl-1,3-dimethyl-6-methylaminouracil (9a) A mixture of **7** (2.15 g, 10 mmol), 40% aqueous solution of methylamine (4 ml), and water (10 ml) was refluxed for 1 h, then extracted with $CHCl_3$ (15 ml $\times$ 2). The organic phase was dried over Na_2SO_4 , the solvent was removed, and the residue was recrystallized from ether to give **9a** (1.6 g, 76%) as colorless needles, mp 73–75 °C. MS m/z : 209 (M^+). 1H -NMR ($CDCl_3$) δ : 2.79 (3H, d, $NHCH_3$, $J=5.5$ Hz), 3.20 (2H, d, $-CH_2CH=CH_2$, $J=5.5$ Hz), 3.30, 3.40 (3H each, s, NCH_3), 3.94 (1H, br q, $NHCH_3$, $J=5.5$ Hz), 5.03 (1H, br d, $-CH_2CH=CH_2$, $J=9.5$ Hz), 5.04 (1H, br d, $-CH_2CH=CH_2$, $J=17.0$ Hz), 5.81 (1H, ddt, $-CH_2CH=CH_2$, $J=5.5$, 9.5, 17.0 Hz). *Anal.* Calcd for $C_{10}H_{15}N_3O_2$: C, 57.40; H, 7.22; N, 20.08. Found: C, 57.16; H, 7.19; N, 19.98.

5-Allyl-6-ethylamino-1,3-dimethyluracil (9b) A mixture of **7** (1.50 g, 7 mmol) and 70% aqueous solution of ethylamine (3.5 ml) was refluxed for 2 h. The reaction mixture was worked up in a manner similar to that described above for **9a**, giving **9b** (1.4 g, 89%) as colorless needles, mp 99–101 °C. MS m/z : 223 (M^+). 1H -NMR ($CDCl_3$) δ : 1.20 (3H, t, CH_2CH_3 , $J=7.0$ Hz), 3.06 (2H, dq, $-NHCH_2CH_3$, $J=7.0$, 7.0 Hz), 3.21 (2H, dt, $-CH_2CH=CH_2$, $J=1.5$, 6.0 Hz), 3.32, 3.40 (3H each, s, NCH_3), 3.70 (1H, br t, $-NHCH_2CH_3$, $J=7.0$ Hz), 5.04 (1H, ddd, $-CH_2CH=CH_2$, $J=1.2$, 1.5, 10.0 Hz), 5.06 (1H, ddd, $-CH_2CH=CH_2$, $J=1.2$, 1.5, 17.0 Hz), 5.82 (1H, ddt, $-CH_2CH=CH_2$, $J=6.0$, 10.0, 17.0 Hz). *Anal.* Calcd for $C_{11}H_{17}N_3O_2$: C, 59.17; H, 7.68; N, 18.82. Found: C, 58.98; H, 7.72; N, 18.71.

5-Allyl-1,3-dimethyl-6-propylaminouracil (9c) A mixture of **7** (1.5 g, 7 mmol) and propylamine (3.5 ml) was refluxed for 2 h. The reaction mixture was worked up in a manner similar to that described above for **9a** to give **9c** (1.3 g, 81%) as colorless needles, mp 103–105 °C. MS m/z : 237 (M^+). 1H -NMR ($CDCl_3$) δ : 0.97 (3H, t, $-CH_2CH_2CH_3$, $J=7.0$ Hz), 1.60 (2H, m, $-CH_2CH_2CH_3$), 2.98 (2H, q, $-NHCH_2CH_2CH_3$, $J=7.0$ Hz), 3.23 (2H, dt, $-CH_2CH=CH_2$, $J=1.5$, 6.0 Hz), 3.33, 3.41 (3H each, s, NCH_3), 3.78 (1H, br t, $-NHCH_2CH_2CH_3$, $J=7.0$ Hz), 5.05 (1H, ddd, $-CH_2CH=CH_2$, $J=1.5$, 1.5, 9.5 Hz), 5.07 (1H, ddd, $-CH_2CH=CH_2$, $J=1.5$, 1.5, 17.0 Hz), 5.83 (1H, ddt, $-CH_2CH=CH_2$, $J=6.0$, 9.5, 17.0 Hz). *Anal.* Calcd for $C_{12}H_{19}N_3O_2$: C, 60.73; H, 8.07; N, 17.71. Found: C, 60.51; H, 7.82; N, 17.67.

5-Allyl-6-(β -hydroxyethyl)amino-1,3-dimethyluracil (9d) A mixture of **7** (1.07 g, 5 mmol) and β -hydroxyethylamine (3.5 ml) was refluxed for 1 h. The reaction mixture was worked up in a manner similar to that described above for **9a**, giving **9d** (0.72 g, 60%) as colorless needles, mp 80–82 °C. MS m/z : 239 (M^+). 1H -NMR ($CDCl_3$) δ : 2.56 (1H, br, $-CH_2CH_2OH$), 3.18 (2H, dt, $-NHCH_2CH_2OH$, $J=4.5$, 5.5 Hz), 3.24 (2H, dt, $-CH_2CH=CH_2$, $J=1.5$, 6.0 Hz), 3.33, 3.43 (3H each, s, NCH_3), 3.75 (2H, br t, $-CH_2CH_2OH$, $J=4.5$ Hz), 4.42 (1H, br t, $-NHCH_2CH_2OH$, $J=5.5$ Hz), 5.03 (1H, ddd, $-CH_2CH=CH_2$, $J=1.5$, 1.8, 10.0 Hz), 5.09 (1H, ddd, $-CH_2CH=CH_2$, $J=1.5$, 1.8, 17.0 Hz), 5.83 (1H, ddt, $-CH_2CH=CH_2$, $J=6.0$, 10.0, 17.0 Hz). *Anal.* Calcd for $C_{11}H_{17}N_3O_3$: C, 55.21; H, 7.16; N, 17.56. Found: C, 55.35; H, 7.06; N, 17.27.

5-Allyl-6-benzylamino-1,3-dimethyluracil (9e) A mixture of **7** (2.14 g,

10 mmol) and benzylamine (4 ml) was refluxed for 2 h, then cooled. Water (15 ml) was added, and the precipitate filtered off and recrystallized from EtOH to give **9e** (2.0 g, 70%) as colorless plates, mp 145–147 °C. MS m/z : 285 (M^+). 1H -NMR ($DMSO-d_6$) δ : 3.01 (2H, dt, $-CH_2CH=CH_2$, $J=1.5$, 5.8 Hz), 3.13, 3.37 (3H each, s, NCH_3), 4.32 (2H, d, $-CH_2C_6H_5$, $J=7.0$ Hz), 4.91 (1H, ddd, $-CH_2CH=CH_2$, $J=1.5$, 2.0, 10.0 Hz), 4.94 (1H, ddd, $-CH_2CH=CH_2$, $J=1.5$, 2.0, 17.0 Hz), 5.76 (1H, ddt, $-CH_2CH=CH_2$, $J=5.8$, 10.0, 17.0 Hz), 5.98 (1H, br t, $-NHCH_2C_6H_5$, $J=7.0$ Hz), 7.23–7.38 (5H, m, $CH_2C_6H_5$). *Anal.* Calcd for $C_{16}H_{19}N_3O_2$: C, 67.34; H, 6.71; N, 14.72. Found: C, 67.52; H, 6.82; N, 14.66.

5-Allyl-6-amino-1,3-dimethyluracil (9f) A mixture of **7** (1.07 g, 5 mmol) and 30% ethanolic ammonia (30 ml) was placed in a steel autoclave and heated at 150–160 °C for 7 h. After cooling of the mixture, the solvent was removed and water (30 ml) was added to the residue. Crystals were collected by filtration and recrystallized from EtOH to give **9f** (0.8 g, 82%) as colorless needles, mp 108–110 °C. High MS Calcd for $C_9H_{13}N_3O_2$: 195.101. Found: 195.101. 1H -NMR ($DMSO-d_6$) δ : 3.03 (2H, br d, $-CH_2CH=CH_2$, $J=6.0$ Hz), 3.11, 3.30 (3H each, s, NCH_3), 4.87 (1H, d, $-CH_2CH=CH_2$, $J=10.0$ Hz), 5.01 (1H, d, $-CH_2CH=CH_2$, $J=17.0$ Hz), 5.71 (1H, ddt, $-CH_2CH=CH_2$, $J=6.0$, 10.0, 17.0 Hz), 6.38 (2H, br s, $-NH_2$).

General Procedure for the Catalytic Cyclization of 6-Alkylamino-5-allyl-1,3-dimethyluracils (9a–f) A mixture of $PdCl_2 (CH_3CN)_2$ (0.1 eq), benzoquinone (1 eq), LiCl (10 eq), and THF (20 ml/mmol substrate) was stirred for 5 min. The substrate in THF (5 ml/mmol of substrate, 1 eq) was added, and the solution was stirred from 2 to 40 h at room temperature. The THF was removed on a rotary evaporator, and the residue was diluted with water (10 ml/mmol of substrate). The solution was extracted with $CHCl_3$ (20 ml $\times$ 3). The $CHCl_3$ layer was washed three times with 20 ml portions of 1 N aqueous NaOH and dried over Na_2SO_4 . The solvent was removed on a rotary evaporator. The residue was purified by preparative TLC (benzene–acetone, 1 : 1) and recrystallized from AcOEt or EtOH.

1,3,6,7-Tetramethylpyrrolo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (10a) According to the general procedure, the crude product was obtained from **9a** (210 mg, 1 mmol), $PdCl_2 (CH_3CN)_2$ (26 mg, 0.1 mmol), benzoquinone (110 mg, 1 mmol), LiCl (420 mg, 10 mmol), and THF (25 ml). The mixture was stirred for 2 h at room temperature. The usual isolation, followed by recrystallization from EtOH gave **10a** (70 mg, 33%) as colorless needles, mp 176–178 °C. High MS Calcd for $C_{10}H_{13}N_3O_2$: 207.101. Found: 207.101. UV λ_{max}^{EtOH} nm (log ϵ): 218 (4.44), 248 (3.97), 280 (3.90). 1H -NMR ($CDCl_3$) δ : 2.21 (3H, s, CCH_3), 3.36, 3.71, 3.75 (3H each, s, NCH_3), 6.21 (1H, s, 5-H). *Anal.* Calcd for $C_{10}H_{13}N_3O_2 \cdot H_2O$: C, 53.32; H, 6.71; N, 18.65. Found: C, 53.22; H, 6.57; N, 18.68.

7-Ethyl-1,3,6-trimethylpyrrolo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (10b) According to the general procedure, the crude product was obtained from **9b** (670 mg, 3 mmol), $PdCl_2 (CH_3CN)_2$ (78 mg, 0.3 mmol), benzoquinone (330 mg, 3 mmol), LiCl (1.26 g, 30 mmol), and THF (45 ml). The mixture was stirred for 20 h. The usual isolation, followed by preparative TLC (benzene–acetone, 1 : 1) gave **10b** (200 mg, 30%) as colorless needles, mp 154–156 °C. High MS Calcd for $C_{11}H_{15}N_3O_2$: 221.116. Found: 221.117. UV λ_{max}^{EtOH} nm (log ϵ): 218 (4.34), 248 (3.88), 282 (3.82). 1H -NMR ($CDCl_3$) δ : 1.36 (3H, t, CH_2CH_3 , $J=7.0$ Hz), 2.25 (3H, d, CCH_3 , $J=1.0$ Hz), 3.39, 3.76 (3H, each, s, NCH_3), 4.13 (2H, q, CH_2CH_3 , $J=7.0$ Hz), 6.30 (1H, q, 5-H, $J=1.0$ Hz). *Anal.* Calcd for $C_{11}H_{15}N_3O_2 \cdot 3/5H_2O$: C, 56.93; H, 7.03; N, 18.10. Found: C, 56.83; H, 6.80; N, 18.03.

1,3,6-Trimethyl-7-propylpyrrolo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (10c) According to the general procedure, the crude product was obtained from **9c** (711 mg, 3 mmol), $PdCl_2 (CH_3CN)_2$ (78 mg, 0.3 mmol), benzoquinone (330 mg, 3 mmol), LiCl (1.26 g, 30 mmol), and THF (45 ml). The mixture was stirred for 30 h. The usual isolation, followed by preparative TLC (benzene–acetone, 1 : 1) gave **10c** (220 mg, 31%) as colorless needles, mp 94–96 °C. High MS Calcd for $C_{12}H_{17}N_3O_2$: 235.131. Found: 235.132. UV λ_{max}^{EtOH} nm (log ϵ): 218 (4.28), 248 (3.83), 280 (3.79). 1H -NMR ($CDCl_3$) δ : 0.95 (3H, t, $-CH_2CH_2CH_3$, $J=7.5$ Hz), 1.72 (2H, m, $-CH_2CH_2CH_3$), 2.25 (3H, d, CCH_3 , $J=1.0$ Hz), 3.40, 3.74 (3H each, s, NCH_3), 4.00 (2H, t, $-CH_2CH_2CH_3$, $J=7.5$ Hz), 6.30 (1H, q, 5-H, $J=1.0$ Hz). *Anal.* Calcd for $C_{12}H_{17}N_3O_2 \cdot H_2O$: C, 56.90; H, 7.56; N, 16.58. Found: C, 56.82; H, 7.32; N, 16.60.

7-(β -Hydroxy)ethyl-1,3,6-trimethylpyrrolo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (10d) According to the general procedure, the crude product was obtained from **9d** (239 mg, 1 mmol), $PdCl_2 (CH_3CN)_2$ (26 mg, 0.1 mmol), benzoquinone (110 mg, 1 mmol), LiCl (420 mg, 10 mmol), and THF (25 ml). The mixture was stirred for 40 h. The usual isolation (but without washing the $CHCl_3$ layer with 1 N NaOH), followed by preparative TLC (benzene–acetone, 1 : 1) gave **10d** (40 mg, 17%) as colorless needles,

mp 173–175 °C. MS m/z : 237 (M^+). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (log ϵ): 218 (4.29), 248 (3.86), 280 (3.79). $^1\text{H-NMR}$ (DMSO- d_6) δ : 2.23 (3H, d, CCH_3 , $J=1.0$ Hz), 3.20, 3.72 (3H each, s, NCH_3), 3.62 (2H, q, $-\text{NCH}_2\text{CH}_2\text{OH}$, $J=5.5$ Hz), 4.23 (2H, t, $-\text{NCH}_2\text{CH}_2\text{OH}$, $J=5.5$ Hz), 5.09 (1H, br t, $-\text{CH}_2\text{OH}$, $J=5.5$ Hz), 6.16 (1H, q, 5-H, $J=1.0$ Hz). Anal. Calcd for $\text{C}_{11}\text{H}_{15}\text{N}_3\text{O}_3$: C, 55.68; H, 6.35; N, 17.21. Found: C, 55.42; H, 6.37; N, 17.40.

7-Benzyl-1,3,6-trimethylpyrrolo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (10e) According to the general procedure, the crude product was obtained from **9e** (285 mg, 1 mmol), $\text{PdCl}_2(\text{CH}_3\text{CN})_2$ (26 mg, 0.1 mmol), benzoquinone (110 mg, 1 mmol), LiCl (420 mg, 10 mmol), and THF (25 ml). The mixture was stirred for 3 h. The usual isolation followed by recrystallization from AcOEt gave **10e** (110 mg, 39%) as colorless plates, mp 160–162 °C. MS m/z : 283 (M^+). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (log ϵ): 216 (4.62), 246 (4.10), 280 (4.03). $^1\text{H-NMR}$ (CDCl_3) δ : 2.16 (3H, d, CCH_3 , $J=1.0$ Hz), 3.36, 3.56 (3H each, s, NCH_3), 5.33 (2H, s, $\text{CH}_2\text{C}_6\text{H}_5$), 6.37 (1H, q, 5-H, $J=1.0$ Hz), 6.85–6.89, 7.23–7.36 (5H, m, $\text{CH}_2\text{C}_6\text{H}_5$). Anal. Calcd for $\text{C}_{16}\text{H}_{17}\text{N}_3\text{O}_2$: C, 67.82; H, 6.05; N, 14.83. Found: C, 67.61; H, 6.04; N, 14.66.

1,3,6-Trimethylpyrrolo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (10f) A mixture of **9f** (195 mg, 1 mmol), $\text{PdCl}_2(\text{CH}_3\text{CN})_2$ (26 mg, 0.1 mmol), benzoquinone (110 mg, 1 mmol), LiCl (420 mg, 10 mmol), and THF (25 ml) was stirred at 40–50 °C for 2 h, then cooled. The precipitate was collected by filtration and purified by column chromatography on silica gel eluted with CHCl_3 -EtOH (10:1). The fraction containing the product was collected, and concentrated to dryness, then the residue was recrystallized from MeOH to give **10f** (107 mg, 55%) as colorless prisms, mp 268–270 °C. High MS Calcd for $\text{C}_9\text{H}_{11}\text{N}_3\text{O}_2$: 193.085. Found: 193.084. UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (log ϵ): 210 (4.38), 244 (3.84), 278 (3.78). $^1\text{H-NMR}$ (DMSO- d_6) δ : 2.21 (3H, d, CCH_3 , $J=1.0$ Hz), 3.19, 3.41 (3H each, s, NCH_3), 6.01 (1H, q, 5-H, $J=1.0$ Hz), 11.52 (1H, br, NH). Anal. Calcd for $\text{C}_9\text{H}_{11}\text{N}_3\text{O}_2 \cdot \text{H}_2\text{O}$: C, 51.17; H, 6.20; N, 19.89. Found: C, 50.95; H, 6.32; N, 19.74.

4-Benzylamino-2,5-dimethyl-2,3-dihydrofuro[3,2-*e*]pyrimidin-6-one (11a) A mixture of **8** (1.0 g, 5 mmol) and benzylamine (1.6 g, 15 mmol) was refluxed for 10 min, then cooled. Water (10 ml) was added, and the precipitate was collected by filtration and recrystallized from EtOH to give **11a** (0.85 g, 63%) as colorless plates, mp 140–142 °C. MS m/z : 271 (M^+). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (log ϵ): 288 (3.91). $^1\text{H-NMR}$ (DMSO- d_6) δ : 1.17 (3H, d, CCH_3 , $J=6.0$ Hz), 2.55 (1H, dd, 3-H, $J=6.0$, 13.5 Hz), 3.09 (1H, dd, 3-H, $J=8.5$, 13.5 Hz), 3.40 (3H, s, NCH_3), 4.57 (2H, br d, $\text{CH}_2\text{C}_6\text{H}_5$, $J=6.5$ Hz), 4.60–4.72 (1H, m, 2-H), 7.23–7.41 (5H, m, $\text{CH}_2\text{C}_6\text{H}_5$), 7.55 (1H, br t, NHCH_2 , $J=6.5$ Hz). Anal. Calcd for $\text{C}_{15}\text{H}_{17}\text{N}_3\text{O}_2$: C, 66.40; H, 6.32; N, 15.49. Found: C, 66.20; H, 6.29; N, 15.42.

X-Ray Crystallographic Analysis of 11a A crystal of **11a** with the dimensions of $0.7 \times 0.3 \times 0.3 \text{ mm}^3$ was used for the analysis. The cell dimensions and diffraction intensities were measured with a Rigaku four-circle diffractometer (AFC-5R), using graphite-monochromated Mo $K\alpha$ radiation ($\lambda=0.71069 \text{ \AA}$) at $20 \pm 1^\circ \text{C}$.

Crystal Data: $\text{C}_{15}\text{H}_{17}\text{N}_3\text{O}_2$, M_r 289.33, monoclinic, space group $P2_1/a$, $a=10.48$ (6), $b=8.61$ (1), $c=16.29$ (7) $\text{\AA}$, $\beta=92.4$ (4)°, $V=0000$ (1) $\text{\AA}^3$, $Z=4$, $D_c=1.308 \text{ g/cm}^3$, $\mu(\text{Mo } K\alpha)=0.87 \text{ cm}^{-1}$. The ω - 2θ scan mode with a scan rate of $16^\circ/\text{min}$ was employed with the ω scan range ($1.20+0.30 \tan\theta$)°. A total of 3686 reflections were collected up to 2θ of 55.1° . The collected reflection intensities were corrected for Lorentz and polarization factors, but not for absorption. The structures were solved by direct methods using the program MITHRIL.¹³ The non-hydrogen atoms were refined by the full-matrix least-squares method with anisotropic temperature factors. In the difference Fourier map, one molecule of water was found. The positions of all hydrogen atoms were calculated but not refined. At the final stage of refinement, 2018 reflections with $|F_o| > 3\sigma(|F_o|)$ out of 3686 unique reflections were used. Final R was 0.045 ($R_w=0.052$). The function minimized was $\sum_w(|F_o|-|F_c|)^2$, where w was taken as $4F_o^2/\sigma^2(F_o^2)$. Atomic scattering factors were taken from the International Tables for X-ray Crystallography (1974).¹⁴ No peak larger than $0.23 \text{ e \AA}^{-3}$ was found in the last difference electron density map. All calculations were performed using the TEXSAN¹⁵ crystallographic software package of Molecular Structure Corporation.

The perspective drawing of **11a** and the numbering scheme of atoms are shown in Fig. 2. The final positional and thermal parameters are listed in Table I. The bond distances and angles are presented in Table II and III, respectively.

The bond lengths and angles are within normal ranges. As shown in Fig. 2, the methyl group attached to the 2-position and the phenyl group are situated on the same side of the plane of the furopyrimidine skeleton.

2,5-Dimethyl-4-methylamino-2,3-dihydrofuro[3,2-*e*]pyrimidin-6-one (11b) A mixture of **8** (0.60 g, 3 mmol) and a 40% aqueous solution of

Fig. 2. Perspective Drawing of the Molecule **11a** with the Atomic Numbering

TABLE I. The Positional Parameters and Equivalent Isotropic Thermal Parameters with Their Estimated Standard Deviations in Parentheses

Atom	$x (\times 10^4)$	$y (\times 10^4)$	$z (\times 10^4)$	$B_{\text{eq}} (\text{\AA}^2)$
O1	5113 (2)	1907 (2)	7370 (1)	3.71 (8)
O2	1582 (2)	1454 (2)	5603 (1)	3.76 (8)
O3	4121 (2)	3356 (2)	4426 (1)	4.3 (1)
N1	3353 (2)	1553 (2)	6483 (1)	3.10 (8)
N2	2255 (2)	3846 (2)	6025 (1)	2.52 (8)
N3	2801 (2)	6339 (2)	6446 (1)	3.08 (9)
C1	5275 (5)	2913 (5)	8739 (2)	6.5 (2)
C2	5686 (3)	3148 (3)	7884 (2)	3.9 (1)
C3	5189 (3)	4682 (3)	7494 (2)	3.5 (1)
C4	4049 (2)	4117 (2)	6970 (1)	2.7 (1)
C5	3066 (2)	4811 (2)	6496 (1)	2.45 (9)
C6	2387 (2)	2220 (2)	6024 (1)	2.8 (1)
C7	4111 (2)	2513 (2)	6913 (1)	2.7 (1)
C8	1189 (3)	4505 (3)	5520 (2)	3.6 (1)
C9	3465 (3)	7531 (3)	6943 (2)	3.0 (1)
C10	3015 (2)	7684 (2)	7806 (1)	2.9 (1)
C11	2142 (3)	6674 (3)	8148 (2)	4.2 (1)
C12	1766 (3)	6899 (4)	8937 (2)	5.7 (2)
C13	2261 (4)	8122 (4)	9409 (2)	5.8 (2)
C14	3109 (3)	9130 (4)	9066 (2)	5.5 (2)
C15	3479 (3)	8911 (3)	8290 (2)	4.2 (1)

TABLE II. Bond Lengths ($\text{\AA}$) with Their Standard Deviations in Parentheses

O1-C2	1.470 (6)	C2-C3	1.548 (6)
O1-C7	1.366 (7)	C3-C4	1.520 (8)
O2-C6	1.253 (6)	C4-C5	1.397 (7)
N1-C6	1.361 (7)	C4-C7	1.386 (4)
N1-C7	1.326 (6)	C9-C10	1.507 (7)
N2-C5	1.395 (7)	C10-C11	1.396 (7)
N2-C6	1.407 (3)	C10-C15	1.393 (6)
N2-C8	1.474 (8)	C11-C12	1.374 (7)
N3-C5	1.347 (4)	C12-C13	1.391 (7)
N3-C9	1.465 (6)	C13-C14	1.378 (7)
C1-C2	1.490 (8)	C14-C15	1.351 (7)

methylamine (6 ml) was stirred under reflux for 1 h. After evaporation of the solvent, the residue was subjected to silica gel column chromatography with CHCl_3 -EtOH (5:1) and the product was recrystallized from CHCl_3 -AcOEt (2:1) to give **11b** (0.38 g, 65%) as a white powder, mp 172–173 °C. MS m/z : 195 (M^+). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (log ϵ): 286 (4.13). $^1\text{H-NMR}$ (DMSO- d_6) δ : 1.33 (3H, d, CCH_3 , $J=6.0$ Hz), 2.92 (1H, dd, 3-H, $J=6.5$,

TABLE III. Bond Angles (°) with Their Standard Deviations in Parentheses

C2-O1-C7	108.6 (3)	O2-C6-N1	123.2 (3)
C6-N1-C7	116.3 (3)	O2-C6-N2	117.4 (3)
C5-N2-C6	122.4 (3)	N1-C6-N2	119.4 (3)
C5-N2-C8	120.5 (3)	O1-C7-N1	118.6 (3)
C6-N2-C8	117.1 (3)	O1-C7-C4	112.5 (3)
C5-N3-C9	124.0 (3)	N1-C7-C4	128.9 (3)
O1-C2-C1	107.8 (4)	N3-C9-C10	114.5 (4)
O1-C2-C3	105.3 (3)	C9-C10-C11	123.6 (4)
C1-C2-C3	113.3 (4)	C9-C10-C15	118.5 (4)
C2-C3-C4	101.6 (4)	C11-C10-C15	117.9 (4)
C3-C4-C5	136.0 (3)	C10-C11-C12	120.3 (4)
C3-C4-C7	108.6 (4)	C11-C12-C13	120.5 (4)
C5-C4-C7	115.2 (3)	C12-C13-C14	119.1 (4)
N2-C5-N3	115.5 (3)	C13-C14-C15	120.5 (4)
N2-C5-C4	117.8 (3)	C10-C15-C14	121.8 (4)
N3-C5-C4	126.7 (3)		

13.5 Hz), 2.98 (3H, d, NHCH_3 , $J=4.0$ Hz), 3.24 (3H, s, NCH_3), 3.50 (1H, dd, 3-H, $J=8.5$, 13.5 Hz), 4.72–4.84 (1H, m, 2-H), 7.10 (1H, br q, NHCH_3 , $J=4.0$ Hz). *Anal.* Calcd for $\text{C}_9\text{H}_{13}\text{N}_3\text{O}_2$: C, 55.37; H, 6.71; N, 21.52. Found: C, 55.19; H, 6.71; N, 21.27.

4-Amino-2,5-dimethyl-2,3-dihydrofuro[3,2-*e*]pyrimidin-6-one (11c) A mixture of **8** (0.40 g, 2 mmol) and a 25% aqueous solution of ammonia (10 ml) was stirred under reflux for 3 h. After concentration of the mixture, the residue was purified by silica gel column chromatography, eluted with CHCl_3 -EtOH (5:1), and the product was recrystallized from CHCl_3 -EtOH (10:1) to give **11c** (0.22 g, 61%) as a white powder, mp 122–124 °C. High MS Calcd for $\text{C}_8\text{H}_{11}\text{N}_3\text{O}_2$: 181.085. Found: 181.085. UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (log ϵ): 280 (4.12). $^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ : 1.34 (3H, d, CCH_3 , $J=6.0$ Hz), 2.40 (1H, dd, 3-H, $J=6.0$, 14.0 Hz), 3.01 (1H, dd, 3-H, $J=8.5$, 14.0 Hz), 3.22 (3H, s, NCH_3), 4.79–4.91 (1H, m, 2-H), 7.10 (2H, s, NH_2). *Anal.* Calcd for $\text{C}_8\text{H}_{11}\text{N}_3\text{O}_2 \cdot 2\text{H}_2\text{O}$: C, 44.23; H, 6.95; N, 19.34. Found: C, 44.27; H, 6.85; N, 19.21.

Acknowledgement We are grateful to Mrs. H. Hatano, Mrs. A.

Nakatani, Miss A. Nakagawa, Mrs. C. Sakabe, and Mrs. N. Satoh, School of Pharmaceutical Sciences, Kitasato University, for microanalyses and spectral measurements. This work was supported in part by Grants-in-Aid for Cancer Research (No. 61010096, No. 62010033, and No. 63010031) from the Ministry of Education, Science and Culture, Japan.

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