Synthesis of Pyrimidine Derivatives Using *N*-Bis(methylthio)methylenecyanamide

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N-Bis(methylthio)methylenecyanamide (**1**) was allowed to react with active methylene compounds (methyl cyanoacetate, dimethyl malonate, ethyl acetoacetate, ethyl phenylacetate) in the presence of potassium carbonate or potassium hydroxide in dimethyl sulfoxide followed by the treatment using appropriate a base or an acid to give the corresponding 6-methylthiouracil derivatives in 15-80% yields.

These uracil derivatives are found to be useful intermediates for the synthesis of 6-aminouracils and fused pyrimidine derivatives.

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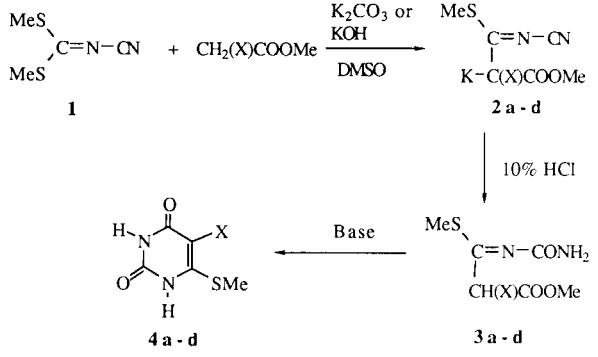
N-Bis(methylthio)methyleneamide derivatives are important and versatile reagents in the synthesis of biologically active heterocyclic compounds [1]. Among these compounds, *N*-bis(methylthio)methylenecyanamide (**1**), is an extremely interesting electrophilic reagent for the introduction of not only an aminomethylene group of amines and active methylene compounds but also a C=N-C=N unit in the synthesis of heterocyclic compounds [2-7]. We now wish to report the synthesis of 6-methylthiouracil derivatives using the reaction of **1** with active methylene compounds and the reaction of these products with nucleophiles such as amines.

We have previously found that the potassium carbonate as a base in the study on reaction of ketene dithioacetals with the various active methylene compounds gives the satisfactory results [8]. Therefore, we first attempted using potassium carbonate as a base in the reaction of **1** with methyl cyanoacetate. When the reaction was conducted at room temperature in the presence of potassium carbonate in dimethyl sulfoxide (DMSO) followed by treatment with 10% hydrochloric acid, the expected displacement product of methylthio group in **1** was obtained in 94% yield. This product was found to be urea derivative, 6-cyano-β-methoxycarbonyl-α-methylthioethylideneurea (**3a**), from elemental analysis and ir, uv, and ^{1}H-nmr spectral data. Treatment of this amide **3a** with 10% sodium hydroxide gave the expected uracil derivative **4a** in 92% yield. In the case of this reaction, treatment with hydrochloric acid did not give the corresponding potassium salt **2a** which is a very stable substance and can be recrystallized from methanol to give colorless needles, mp >360°. The treatment of this salt with 10% hydrochloric acid gave the corresponding amide **3a**. Similarly, the reaction of **1** with dimethyl malonate afforded the desired urea derivative **3b** which was also easily converted to **4b** by treatment of triethylamine as a base in 75% yield. However, the reaction of **1** with ethyl acetoacetate under similar conditions did not give the corresponding salt and the urea derivatives. After treatment of the reaction mixture with 10% hydrochloric acid, 5-acetyl-6-methylthiouracil (**4c**) was obtained in poor yield. On the other hand, the reaction of **1** with ethyl phenylacetate did not occur by using potassium carbonate in DMSO. When the reaction was conducted at room temperature in the presence of pulverized potassium hydroxide in DMSO followed by treatment with 10% hydrochloric acid, the expected 5-phenyl-6-methylthiouracil (**4d**) was obtained in 31% yield.

Scheme 1

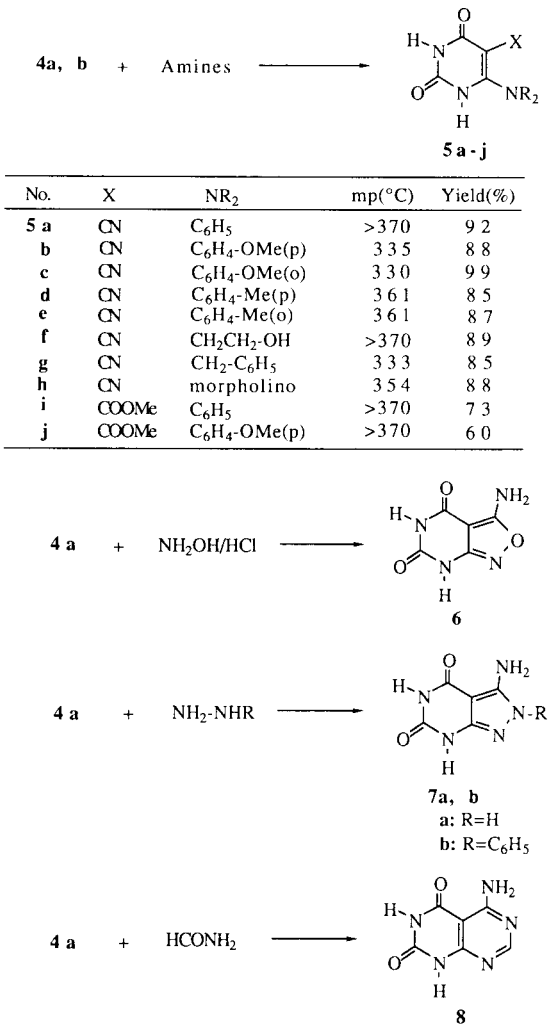


No.	X	mp(°C)	Yield(%)
4a	CN	307	80
b	COOMe	277	75
c	COMe	333	15
d	C_6H_5	293	31

Some 6-aminouracil derivatives display high antitumor activity [9-12]. Therefore the synthesis of 6-aminouracil derivatives by the aminolysis of **4a-d** with various amines is highly desired and was readily achieved because of the high activity of the methylthio group toward nucleophilic reagents. The reaction of **4a,b** with amines afforded the corresponding 6-aminouracils **5a-j** in good yields. This aminolysis is applied to prepare fused pyrimidines. The reaction of **4a** with hydroxylamine hydrochloride, hydrazine hydrate and formamide gave the corresponding isox-

azolo[3,4-*d*]pyrimidine **6**, pyrazolo[3,4-*d*]pyrimidines **7a,b** and the pyrimido[4,5-*d*]pyrimidine **8** with good results [13].

Scheme 2



In conclusion, 6-methylthiouracils obtained in this paper, are found to be useful intermediates for the synthesis of 6-aminouracils and fused pyrimidines.

EXPERIMENTAL

All melting points were determined in a capillary tube and are uncorrected. Infrared (ir) spectra were recorded in potassium bromide pellets on a JASCO IRA-2 spectrometer and ultraviolet (uv) absorption spectra were determined in 95% ethanol on a Hitachi EP-S2 spectrometer. Nuclear magnetic resonance (nmr) spectra were obtained on JNM-PS-100(100 MHz) and JNM-FX-90Q(90 MHz) spectrometers with tetramethylsilane as an internal standard. Mass spectra (ms) were recorded on a JEOL-01SG mass spectrometer.

Potassium 1-Cyano-1-methoxycarbonyl-1-[*N*-cyanoimino(α-methylthio)methyl]methylide (**2a**).

A mixture of 14.6 g (0.1 mole) of *N*-bis(methylthio)methylenecyanamide (**1**), 14.8 g (0.15 mole) of methyl cyanoacetate, 56.0 g (0.2 mole) of potassium carbonate, and 200 ml of dimethyl sulfoxide was stirred at room temperature for 4 hours. This reaction mixture was poured portionwise into 500 ml of ice-water under cooling with ice. The resulting precipitate was collected by filtration and recrystallized from methanol to give colorless needles, mp >360°, in 93% yield; ir (potassium bromide): ν max cm^{-1}; 2202, 2160 (CN), 1660 (CO); uv (ethanol, insufficient solubility): λ max nm 220, 268, 320; λ min nm 240, 287; ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 2.24 (3H, s, SMe), 3.51 (3H, s, OMe).

Anal. Calcd. for $C_7H_6N_3O_2SK$: C, 35.73; H, 2.57; N, 17.86; S, 13.63. Found: C, 35.89; H, 2.56; N, 17.91; S, 13.61.

6-Cyano-β-methoxycarbonyl-α-methylthioethylideneurea (**3a**).

A mixture of 14.6 g (0.1 mole) of *N*-bis(methylthio)methylene cyanamide (**1**), 14.8 g (0.15 mole) of methyl cyanoacetate, 56.0 g (0.2 mole) of potassium carbonate, and 200 ml of dimethyl sulfoxide was stirred at room temperature for 4 hours. This reaction mixture was poured portionwise into 500 ml of 10% hydrochloric acid under cooling with ice. The precipitate that appeared was collected by filtration and recrystallized from methanol to give 20.1 g (93.5 mmoles) of colorless needles, mp 204°, in 93% yield; ir (potassium bromide): ν max cm^{-1} 3430, 3340 (NH), 2205 (CN), 1692 (CO); uv (ethanol): λ max nm (log ε) 240 (3.67), 267 (3.80), 322 (4.20); ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 2.46 (3H, s, SMe), 3.64 (3H, s, OMe), 7.08 (2H, bs, CH or NH), 10.30 (1H, bs, CH or NH).

Anal. Calcd. for $C_7H_9N_3O_3S$: C, 39.06; H, 4.21; N, 19.52; S, 14.90. Found: C, 39.02; H, 4.23; N, 19.47; S, 14.81.

6-Methoxycarbonyl-β-methoxycarbonyl-α-methylthioethylideneurea (**3b**).

This compound (1.11 g, 4.48 mmoles) was prepared from **1** (0.73 g, 5.0 mmoles) and dimethyl malonate (0.92 g, 7.0 mmoles) in 90% yield in a manner similar to that described for the preparation of **3a**. An analytical sample was recrystallized from methanol to give colorless needles, mp 160°; ir (potassium bromide): ν max cm^{-1} 3420, 3220 (NH), 1720, 1670 (CO); uv (ethanol): λ max nm (log ε) 243 (4.04), 302 (4.15).

Anal. Calcd. for $C_8H_{12}O_5N_2S$: C, 38.71; H, 4.87; N, 11.28; S, 12.92. Found: C, 38.65; H, 4.84; N, 11.27; S, 13.03.

6-Methylthiouracil-5-carbonitrile (**4a**).

A solution of 2.15 g (10.0 mmoles) of **3a** in 20 ml of 10% sodium hydroxide aqueous solution was stirred at room temperature for 2 hours and then heated at 70° for 10 minutes. After cooling, this solution was acidified with 10% hydrochloric acid. The precipitate that appeared was collected by filtration and recrystallized from methanol to give 1.68 g (9.2 mmoles, 92%) of colorless needles, mp 305° (lit [3] mp 299°); ir (potassium bromide): ν max cm^{-1} 3400-2600 (broad, NH or OH), 2200 (CN), 1750-1600 (broad, C=O); uv (ethanol, insufficient solubility): λ max nm 243, 315, 340 (shoulder): λ min nm 226, 284.

Methyl 6-Methylthiouracil-5-carboxylate (**4b**).

A solution of **3b** (0.93 g, 4.30 mmoles) and 1.0 ml of triethylamine in 30 ml of methanol was refluxed for 4 hours. After removal of the solvent and triethylamine, 10 ml of 10% hydrochloric acid was added to the residue. The precipitate that appeared was collected by the filtration and recrystallized from

methanol to give 0.87 g (3.35 mmoles) of colorless needles, mp 277°, in 87% yield; ir (potassium bromide): ν max cm^{-1} 3080, 2290, 2800 (NH or OH), 1730, 1674, 1630 (CO); uv (ethanol): λ max nm (log ϵ) 240 (4.16), 297 (4.19); ^{1}H-nmr (deuteriochloroform + trifuluoroacetic acid): δ 2.17 (3H, s, SMe), 3.81 (3H, s, OMe).

Anal. Calcd. for $C_7H_8O_4N_2S$: C, 38.89; H, 3.73; N, 12.96; S, 14.83. Found: C, 38.87; H, 3.73; N, 12.75; S, 14.99.

5-Acety-6-methylthiouracil (**4c**).

A mixture of 14.6 g (0.1 mole) of *N*-bis(methylthio)methylene cyanamide (**1**), 13.2 g (0.15 mole) of ethyl acetyacetate, 27.6 g (0.2 mole) of potassium carbonate, and 200 ml of dimethyl sulfoxide was stirred at room temperature for 4 hours. This reaction mixture was poured portionwise into 500 ml of 10% hydrochloric acid under cooling with ice. This solution was allowed to stand over for one day to yield colorless solid. This precipitate that appeared was collected by filtration and recrystallized from methanol to give 3.0 g (15.0 mmoles) of colorless needles, mp 333°, in 15% yield; ir (potassium bromide): ν max cm^{-1} 3250, 2920, 2810 (NH or OH), 1708, 1620 (CO); uv (ethanol, insufficient solubility): λ max nm 238, 307; λ min nm 268; ^{1}H-nmr (trifuluoroacetic acid): δ 2.32 (3H, s, Ac or SMe), 2.61 (3H, s, Ac or SMe).

Anal. Calcd. for $C_7H_8N_2O_3S$: C, 41.99; H, 4.03; N, 13.99; S, 16.01. Found: C, 41.83; H, 4.06; N, 14.09; S, 15.77.

5-Phenyl-6-methylthiouracil (**4d**).

A mixture of 1.64 g (10 mmoles) of ethyl phenylacetate, 1.46 g (10 mmoles) of **1**, 2.20 g (40 mmoles) of potassium hydroxide, and 30 ml of dimethyl sulfoxide was heated at 70° for 6 hours. The reaction mixture was poured into 200 ml of ice-water and then heated at 100° for 30 minutes. After cooling, the mixture was allowed to stand over for 5 hours. The precipitate that appeared was collected by filtration and recrystallized from methanol to give 0.73 g (3.11 mmoles) of the colorless needles, mp 293°, in 31% yield; ir (potassium bromide): ν max cm^{-1} 3280-2400 (broad NH or OH), 1730, 1705, 1650, 1620 (CO); uv (ethanol): λ max nm (log ϵ) 238 (4.05), 299 (4.11).

Anal. Calcd. for $C_{11}H_{10}N_2O_2S$: C, 56.40; H, 4.32; N, 11.96; S, 13.69. Found: C, 56.53; H, 4.19; N, 11.92; S, 13.73.

6-Anilinouracil-5-carbonitrile (**5a**).

A mixture of 6-methylthiouracil-5-carbonitrile (0.183 g, 1 mmole) and aniline (0.372 g, 4 mmoles) was heated at 100° for 2 hours. The reaction mixture was washed with 10 ml of methanol to give a colorless crude product (0.21 g, 0.92 mmole), mp >350°. An analytical sample was recrystallized from methyl cellosove to give colorless needles, mp 366° dec; ir (potassium bromide): ν max cm^{-1} 3150, 3100, 3000 (NH or OH), 2200 (CN), 1720, 1650 (CO); uv (ethanol, efficient solubility): λ max nm 242, 281; λ min nm 228, 256.

Anal. Calcd. for $C_{11}H_8N_4O_2$: C, 57.89; H, 3.53; N, 24.55. Found: C, 57.89; H, 3.47; N, 24.35.

6-(*p*-Anisidino)uracil-5-carbonitrile (**5b**).

This compound (0.42 g, 1.63 mmoles) was prepared from **4a** (0.37 g, 2 mmoles) and *p*-anisidine (0.492 g, 4 mmoles) in 82% yield in a manner similar to that described for the preparation of **5a**. An analytical sample was recrystallized from methanol to give colorless prisms, mp 335°; ir (potassium bromide): ν max cm^{-1} 3100, 2980, 2830 (NH or OH), 2200 (CN), 1650, 1635 (CO); uv (ethanol): λ max nm (log ϵ) 239 (4.36), 301 (4.15), 335 (4.06).

Anal. Calcd. for $C_{12}H_{10}N_4O_3$: C, 55.81; H, 3.90; N, 21.70. Found: C, 55.84; H, 3.88; N, 21.41.

6-(*o*-Anisidino)uracile-5-carbonitrile (**5c**).

A mixture of 0.37 g (2 mmoles) of **4a** and 0.491 g (4 mmoles) of *o*-anisidine was heated at 200° for 20 minutes. After cooling, the reaction mixture was washed with 10 ml of methanol to give a white solid. An analytical sample was recrystallized from methyl cellosolve to give 0.51 g (1.98 mmoles) of colorless needles, mp 330°, in 99% yield; ir (potassium bromide): ν max cm^{-1} 3140, 3000 (NH or OH), 2190 (CN), 1680 (CO); uv (ethanol, insufficient solubility): λ max nm 225, 285; λ min nm 240, 258.

Anal. Calcd. for $C_{12}H_{10}N_4O_3$: C, 55.81; H, 3.90; N, 21.70. Found: C, 55.79; H, 3.81; N, 21.65.

6-(*p*-Toluidino)uracil-5-carbonitrile (**5d**).

This compound (0.41 g, 1.69 mmoles) was prepared from **4a** (0.37 g, 2 mmoles) and *p*-toluidine (0.968 g, 4 mmoles) in 85% yield in a manner similar to that described for the preparation of **5c**. An analytical sample was recrystallized from methanol to give colorless needles, mp 361° dec; ir (potassium bromide): ν max cm^{-1} 3200, 3040, 2990 (NH or OH), 2210 (CN), 1725, 1685, 1660, 1625 (CO); uv (ethanol): λ max nm (log ϵ) 242 (4.18), 280 (4.30).

Anal. Calcd. for $C_{12}H_{10}N_4O_2$: C, 59.90; H, 4.16; N, 23.13. Found: C, 59.11; H, 4.09; N, 23.24.

6-(*o*-Toluidino)uracil-5-carbonitrile (**5e**).

This compound (0.42 g, 1.74 mmoles) was prepared from **4a** (0.37 g, 2 mmoles) and *o*-toluidine (0.421 g, 0.421 mmoles) in 87% yield in a manner similar to that described for the preparation of **3a**. An analytical sample was recrystallized from methanol to give colorless leaflets, mp 361°; ir (potassium bromide): ν max cm^{-1} 3100, 3000 (NH or OH), 2205 (CN), 1715, 1650, 1610 (CO); uv (ethanol): λ max nm (log ϵ) 238 (shoulder, 4.22), 273 (4.22).

Anal. Calcd. for $C_{12}H_{10}N_4O_2$: C, 59.32; H, 4.15; N, 23.13. Found: C, 59.31; H, 4.09; N, 23.24.

6-Ethanolaminouracil-5-carbonitrile (**5f**).

This compound (0.35 g, 1.79 mmoles) was prepared from **4a** (0.37 g, 2 mmoles) and ethanolamine (0.244 g, 4 mmoles) in 89% yield in a manner similar to that described for the preparation of **5a**. An analytical sample was recrystallized from methanol to give colorless needles, mp >370°; ir (potassium bromide): ν max cm^{-1} 3340, 3250, 3140, 3000 (NH or OH), 2200 (CN), 1715, 1655, 1635 (CO); uv (ethanol, insufficient solubility): λ max nm 226, 269; λ min nm 245.

Anal. Calcd. for $C_7H_8N_4O_3$: C, 42.86; H, 4.11; N, 28.56. Found: C, 42.75; H, 4.07; N, 28.18.

6-Benzylaminouracil-5-carbonitrile (**5g**).

A mixture of 0.37 g (2 mmoles) of **4a** and 0.231 g (3 mmoles) was heated at 180° for 30 minutes. The reaction mixture was dissolved in 5 ml of methanol and then 10 ml of 10% hydrochloric acid solution was added. The precipitate that appeared was collected by filtration and recrystallized from acetic acid to give 0.41 g (1.69 mmoles, 85%) of colorless needles, mp 333°; ir (potassium bromide): ν max cm^{-1} 3400, 3250, 2940 (NH or OH), 2200 (CN), 1715, 1650-1600 (broad, CO); uv (ethanol): λ max nm (log ϵ) 227 (4.48), 270 (4.29).

Anal. Calcd. for $C_{12}H_{10}N_4O_2$: C, 59.50; H, 4.16; N, 23.13. Found: C, 59.07; H, 4.15; N, 23.17.

6-Morpholinouracil-5-carbonitrile (**5h**).

This compound (0.39 g, 1.76 mmoles) was prepared from **4a** (0.37 g, 2 mmoles) and morpholine (0.348 g, 4 mmoles) in 88% yield in a manner similar to that described for the preparation of **5h**. An analytical sample was recrystallized from methanol to give colorless needles, mp 354°; ir (potassium bromide): ν max cm^{-1} 3150, 3020 (NH or OH), 2200 (CN), 1725, 1640 (CO); uv (ethanol, insufficient solubility): λ max nm 234, 280; λ min nm 258.

Anal. Calcd. for $C_9H_{10}N_4O_3$: C, 48.65; H, 4.54; N, 25.21. Found: C, 48.35; H, 4.65; N, 25.11.

Methyl 6-Anilinouracil-5-carboxylate (**5i**).

A mixture of 0.432 g (2 mmoles) of **4b** and 0.465 g (5 mmoles) was heated at 180° for 1 hour. The reaction mixture was washed with 1% hydrochloric acid. The product was recrystallized from methanol to give 0.38 g (1.46 mmoles, 74%) of colorless needles, mp 380°; ir (potassium bromide): ν max cm^{-1} 3360, 3200, 3100 (NH or OH), 1715, 1695, 1628 (CO); uv (ethanol): λ max nm (log ϵ) 254 (4.31), 273 (4.33), 292 (shoulder, 4.30); ^{1}H-nmr (deuteriochloroform): δ 3.71 (3H, s, OMe), 7.39 (5H, s, Phenyl-H).

Anal. Calcd. for $C_{12}H_{11}N_3O_4$: C, 55.17; H, 4.24; N, 16.08. Found: C, 55.15; H, 4.21; N, 16.00.

Methyl 6-(*p*-Methoxyphenyl)aminouracil-5-carboxylate (**5j**).

This compound (0.35 g, 1.20 mmoles) was prepared from **4b** (0.432 g, 2 mmoles) and *p*-anisidine (0.615 g, 5 mmoles) in 60% yield in a manner similar to that described for the preparation of **5j**. An analytical sample was recrystallized from methanol to give colorless needles, mp >400°; ir (potassium bromide): ν max cm^{-1} 3100, 2920, 2830 (NH or OH), 2200 (CN), 1640, 1610 (CO).

Anal. Calcd. for $C_{13}H_{13}N_3O_5$: C, 53.61; H, 4.50; N, 14.43. Found: C, 53.55; H, 4.61; N, 14.42.

3-Aminoisoxazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (**6**).

A mixture of 0.916 g (5 mmoles) of **4a**, 1.39 g (20 mmoles) of hydroxyamine hydrochloride, 2 ml of triethylamine, and 50 ml of ethanol was refluxed for 4 hours. After evaporation of ethanol and excess triethylamine, the residue was washed with water and recrystallized from water to give 0.79 g (4.7 mmoles, 93%) of colorless needles, mp 360° (lit [14] mp >360°); ir (potassium bromide): ν max cm^{-1} 3400, 3080, 3150 (NH or OH), 1730, 1650 (CO); uv (ethanol, insufficient solubility): λ max nm 240 (shoulder), 259; λ min nm 219.

3-Amino-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (**7a**).

A mixture of 0.37 g (2 mmoles) of **4a**, 1 ml of hydrazine hydrate, and 15 ml of water was refluxed for 1 hour. After removal of the water, the residue was recrystallized from a mixture of benzene and methanol to give 0.31 g (1.76 mmoles) of colorless powder, mp >370°. An analytical sample was recrystallized from methanol to give colorless needles, mp >370°; ir (potassium bromide): ν max cm^{-1} 3360, 3300, 3160, 3050 (NH or OH), 1700, 1665, 1620 (CO); uv (ethanol, insufficient solubility): λ max nm 256; λ min nm 235.

Anal. Calcd. for $C_5H_5N_5O_2 \cdot 1/2H_2O$: C, 34.09; H, 3.43; N, 39.76. Found: C, 33.99; H, 3.49; N, 39.61.

3-Amino-2-phenyl-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (**7b**).

A mixture of 0.37 g (2 mmoles) of **4b** and 0.216 g (2 mmoles) of phenylhydrazine was heated at 150° for 4 hours. The product was recrystallized from a mixture of methanol and benzene to give 0.104 g (1.77 mmoles, 88%) of colorless powder, mp 345-347° dec; ir (potassium bromide): ν max cm^{-1} 3350, 3300, 3140, 3030 (NH or OH), 1700-1660, 1620 (CO); uv (ethanol): λ max nm 242 (4.17), 280 (4.28).

Anal. Calcd. for $C_{11}H_9N_5O_2$: C, 54.32; H, 3.73; N, 28.79. Found: C, 54.11; H, 3.69; N, 28.56.

4-Aminopyrimido[4,5-*d*]pyrimidine-5,7(6*H*,8*H*)-dione (**8**).

A mixture of 0.304 g (2.0 mmoles) of **4a** and 3 ml of formamide was heated at 180° for 4 hours. After cooling, 10 ml of methanol was added to the reaction mixture and the resulting precipitate was collected by filtration to give 0.30 g (1.68 mmoles, 84%) of colorless solid. An analytical sample was recrystallized from acetic acid to give colorless needles, mp >360°; ir (potassium bromide): ν max cm^{-1} 3360, 3260, 3180 (NH or OH), 1710, 1675, 1620 (CO); uv (ethanol, insufficient solubility): λ max nm 232, 250 (shoulder), 294; λ min nm 270.

Anal. Calcd. for $C_6H_5N_5O_2 \cdot 1/2H_2O$: C, 38.30; H, 3.21; N, 37.20. Found: C, 38.63; H, 2.94; N, 37.20.

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