Synthesis of Methyl 9-Benzylguanine-8-carbamate: A Convenient Synthesis of Oxazolo[5,4-*d*]pyrimidines and Their Conversion into Imidazo[4,5-*d*]pyrimidines via a Carbodiimide-Mediated Rearrangement[1]

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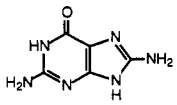
The reaction of 2,5-diamino-4-(benzylamino)pyrimidin-6(1*H*)-one (**5**) with *N*-(methoxycarbonyl)-*S*-methylpseudothiourea furnished 2-amino-4-(benzylamino)-5-[1-[3-(methoxycarbonyl)guanidino]]pyrimidin-6(1*H*)-one (**6**). Although compound **6** should be a precursor for the synthesis of the title compound **4**, the cyclization of compound **6** could not be effected by using standard conditions. Cyclodesulfurization of 2-amino-4-(benzylamino)-5-[1-[3-(methoxycarbonyl)thioureido]]pyrimidin-6(1*H*)-one (**7**), with dicyclohexylcarbodiimide in *N*,*N*-dimethylformamide, furnished methyl 6-amino-4-(benzylamino)oxazolo[5,4-*d*]pyrimidine-2-carbamate (**9**) in 88% yield. The title compound **4** was synthesized via a thermal or base-catalyzed rearrangement of compound **9**, or from 2-amino-4-(benzylamino)-5-[1-[3-(methoxycarbonyl)-*S*-methylpseudothioureido]]pyrimidin-6(1*H*)-one (**8**) by using base catalysis.

The importance of purine nucleoside phosphorylase (PNP; nucleoside phosphorylase; purine nucleoside; orthophosphate ribosyltransferase; EC 2.4.2.1) in immunodevelopment has generated a strong interest in the development of PNP inhibitors as well as nucleoside substrate analogues that are resistant to cleavage by PNP.[2] Numerous analogues of inosine and guanosine, with modifications in the heterocyclic base or in the ribose moiety, have been studied as inhibitors of PNP.[3,4] 8-Aminoguanine (**1**) and 8-aminoguanosine (**2**) are very



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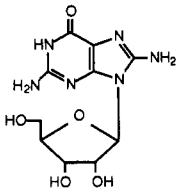

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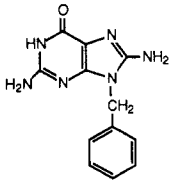

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promising inhibitors[5] of PNP, but since both compounds are also substrates for the enzyme, their activity as inhibitors is limited. It was of interest to determine the effect that a variation of the substituent at the N-9 position of 8-aminoguanine might have on the binding at the active site of the enzyme, especially if this substituent at N-9 provided a compound resistant to phosphorolytic scission by PNP. On this premise, we prepared 8-amino-9-benzylguanine (**3**) by a classical approach,[8] involving bromination of 9-benzylguanine followed by treatment of the 8-bromo derivative with ammonia. Compound **3** has proved to be a very potent inhibitor of PNP,[8] and we now describe our efforts toward a more general synthesis of **3** and some derivatives.

Our initial strategy involved the preparation of a 4-(6)-amino-5-guanidinopyrimidine derivative which would cyclize under the reaction conditions to afford an 8-substituted purine.[6] However, the treatment of 2,5-diamino-4-(benzylamino)pyrimidin-6(1*H*)-one (**5**)[7] with *N*-(methoxycarbonyl)-*S*-methylpseudothiourea produced the intermediate guanidinopyrimidin-6(1*H*)-one **6**. Several attempts to effect a ring closure of compound **6** were unsuccessful (Scheme I).

The reaction of ethoxycarbonyl isothiocyanate with *o*-phenylenediamines readily produces *N*-(ethoxycarbonyl)thiourea derivatives[10] which in many cases cyclize, upon heating, with the loss of hydrogen sulfide to afford 2-[*N*-(ethoxycarbonyl)amino]benzimidazoles.[10] This cyclization can also be effected by treatment with cupric acetate in acetic acid[11] or by alkylation of the thione group derivative.[12] Applying the latter methodology, 4-(benzylamino)-2,5-diaminopyrimidin-6(1*H*)-one (**5**)[7,13] was suspended in acetonitrile and then treated with methoxycarbonyl isothiocyanate[9] to afford the desired intermediate thioureidopyrimidine **7** in 38% overall yield. Treatment of **7** with methyl iodide afforded the (*S*-methylpseudothioureido)pyrimidine **8** in 87% yield. However, very little cyclized product was observed when **8** was heated in methanol at reflux temperature. Treatment of **8** with anhydrous potassium carbonate or sodium methoxide in

† National Defense Medical Center.

(1) Presented in part at the 10th International Congress of Heterocyclic Chemistry, University of Waterloo, Ontario, Canada, Aug 11–16, 1985; P6-263. Chern, J.-W.; Wise, D. S.; Townsend, L. B. *J. Heterocycl. Chem.* **1984**, *21*, 1245. Chern, J.-W.; Wise, D. S.; Townsend, L. B. *Heterocycles* **1984**, *22*, 2439.

(2) Giblett, E. R.; Ammann, A. J.; Sandman, R.; Wara, D. W.; Diamond, L. K. *Lancet* **1975**, *1*, 1010. Stoeckler, J. D.; Cambor, C.; Burgess, F. W.; Erban, S. B.; Parks, R. E., Jr. *Pharmacologist* **1979**, *22*, 99.

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(4) Townsend, L. B.; Cline, B. L.; Panzica, R. P.; Fagerness, P. E.; Roti Roti, L. W.; Stoeckler, J. D.; Crabtree, G. W.; Parks, R. E., Jr. In *Lectures in Heterocyclic Chemistry*; Castle, R. N., Lalizari, I., Eds.; Heterocorp: Orem, UT, 1978; p S-79. Stoeckler, J. D. In *Developments in Cancer Chemotherapy*; Glazer, R. I., Ed.; CRC: Boca Raton, FL.

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(6) Raeymakers, A. H. M.; Van Gelder, J. L. H.; Roevens, L. F. C.; Janssen, P. A. J. *Arzneim.-Forsch./Drug Res.* **1978**, *28*, 586.

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(8) Daddona, P. E.; Wiesmann, W. P.; Milhouse, W.; Chern, J.-W.; Townsend, L. B.; Hershield, M. S.; Webster, H. K. *J. Biol. Chem.* **1986**, *261*, 11667.

(9) Methoxycarbonyl isothiocyanate was prepared by adding methyl chloroformate dropwise to a suspension of potassium thiocyanate in acetonitrile. For a review on this reagent, see: (a) Esmail, R.; Kruger, F. *Synthesis* **1975**, 301. (b) George, B.; Papadopoulos, E. P. *J. Heterocycl. Chem.* **1983**, *20*, 1127.

(10) Matsu, T.; Nagano, M.; Tobitsuka, J.; Oyamada, K. *Yakugaku Zasshi* **1973**, *93*, 977; *Chem. Abstr.* **1973**, *79*, 105139.

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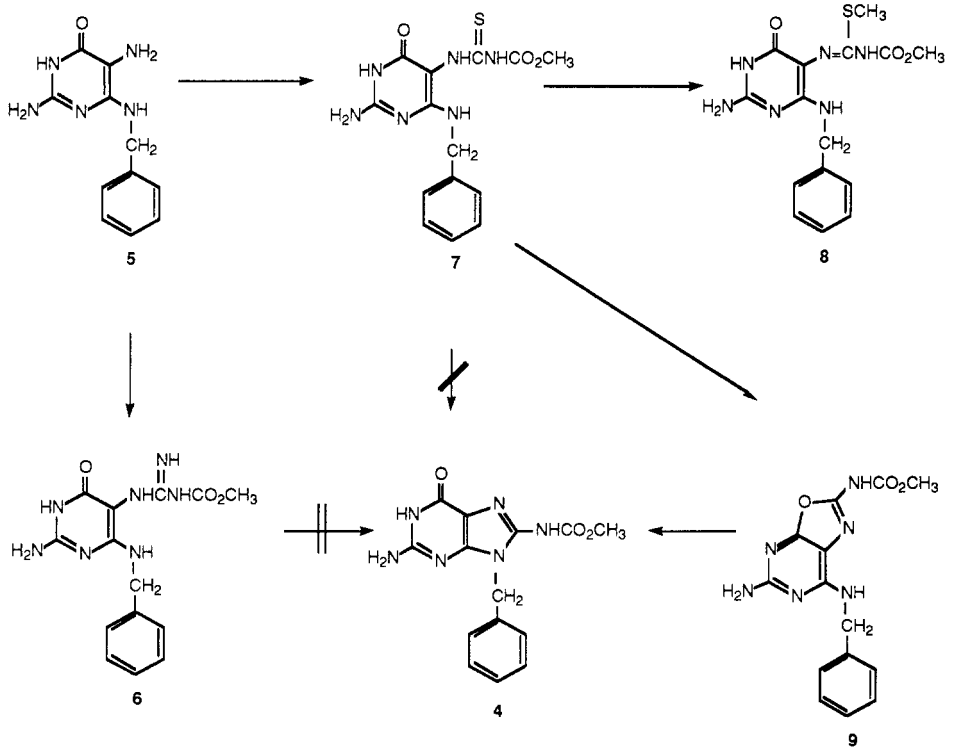
0022-3263/88/1953-5617$01.50/0

Scheme I

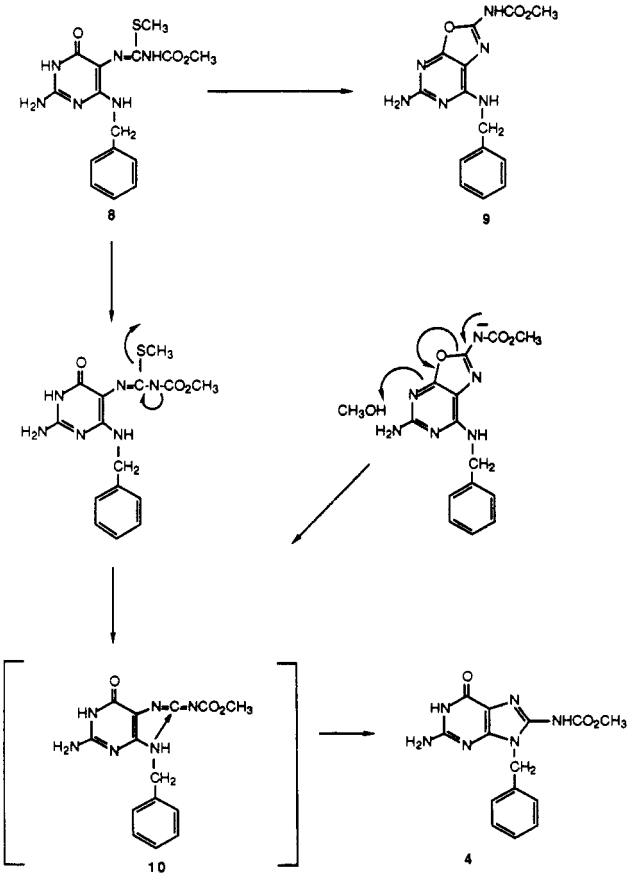


methanol at reflux temperature smoothly converted 8 into methyl 9-benzylguanine-8-carbamate (4) in 82% yield accompanied by a trace of 3. The formation of methyl 6-amino-4-(benzylamino)oxazolo[5,4-*d*]pyrimidine-2-carbamate (9), isolated in a subsequent reaction, vide infra, was also observed by TLC near the beginning of the reaction. Compound 9 was then slowly converted into 4.

Two plausible mechanisms for this reaction are as follows (Scheme II). (1) Base abstraction of the proton on the *S*-methylpseudothioureido side chain of compound 8 is followed by the formation of a short-lived carbodiimide intermediate 10 and the subsequent formation of 9 and/or 4. Compound 9 then undergoes a rearrangement to furnish 4. (2) Elimination of the methylthio group of 8 takes place by a nucleophilic attack of the oxygen anion at C-6 to form 9. This is then followed by a ring transformation mediated by sodium methoxide to form compound 4.

Since a carbodiimide may be an intermediate in the synthesis of 4 from 8, we sought reaction conditions that would favor the formation of a carbodiimide. Dicyclohexylcarbodiimide (DCC) is known to form *N,N'*-disubstituted carbodiimides from *N,N'*-disubstituted thioureas in a reversible equilibrium reaction,[14] and it was reasoned that DCC might facilitate the formation of the carbodiimide 10. A subsequent intramolecular attack on the carbodiimide by the exocyclic nitrogen of the benzylamino group would then afford 4. However, when 7 was treated with DCC in DMF at room temperature, only 9 was obtained (88% yield) (Scheme III). The formation of 4 was not observed. That 9 was obtained in the reaction indicated that the reaction must occur as expected via the initial formation of an adduct 11 between DCC and compound 7.[14,15] *N,N'*-Dicyclohexylthiourea must have been eliminated either by a direct nucleophilic attack of the C-6 oxygen or by the abstraction of a proton from the pseudothioureido side chain to form a carbodiimide intermediate with a subsequent ring closure through a nucleophilic attack of the 6-oxygen.

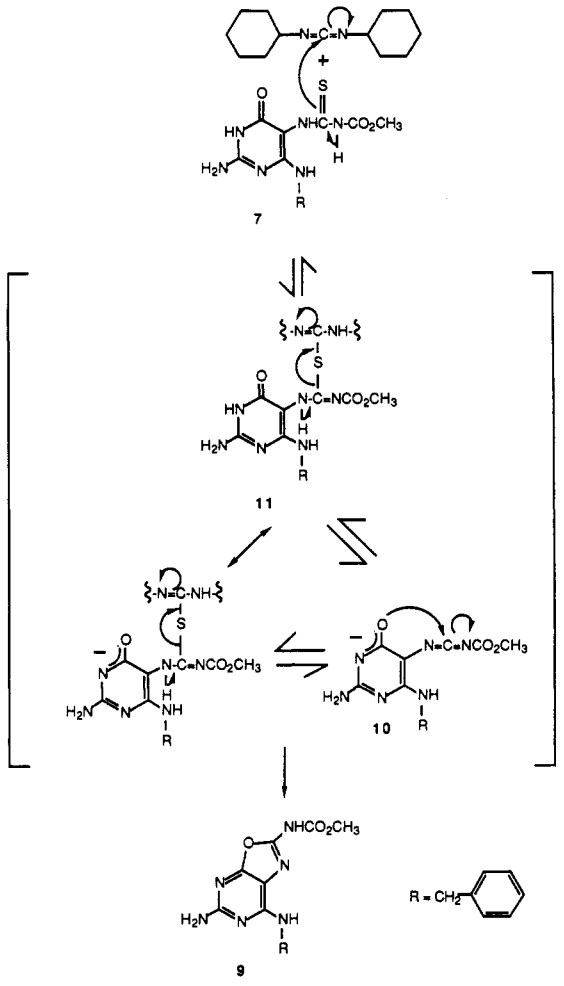
Scheme II



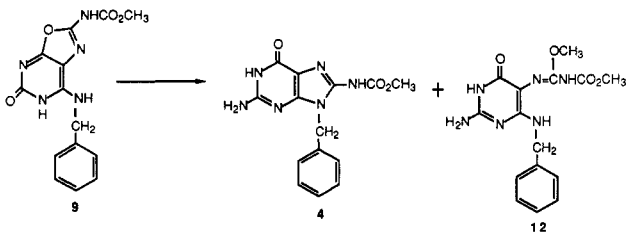
Oxazolo[5,4-*d*]pyrimidines are known to undergo rearrangement to purines on heating in formamide or dilute sodium hydroxide.[16,17] The mechanism postulated for

(14) Wragg, R. T. *Tetrahedron Lett.* **1970**, 3931.
(15) This kind of adduct has been proposed in the following: (a) Pfitzner, K. E.; Moffatt, J. G. *J. Am. Chem. Soc.* **1965**, *87*, 5661; (b) *Ibid.* **1965**, *87*, 5670. See also ref 13.

Scheme III

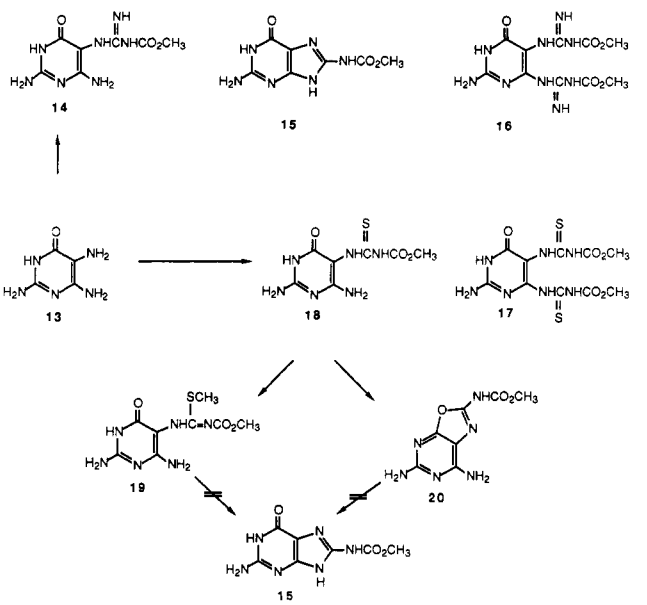


Scheme IV



these rearrangements assumes an initial nucleophilic reaction at the 2-carbon of the oxazole ring, resulting in a ring opening of the oxazole ring to a 4-amino-5-formamidopyrimidin-6(1*H*)-one anion intermediate, which then recyclizes to the purine ring system. Following this approach, treatment of **9** under basic conditions effected a smooth conversion of **9** into **4**, contaminated with only a trace amount of **3**. A reasonable mechanism for this transformation would involve the initial abstraction of a proton from the 2-carbamoyl moiety of **9**, rather than an initial nucleophilic reaction at the 2-carbon of the oxazole ring, followed by an opening of the oxazole ring to furnish a carbodiimide intermediate which on ring closure affords **4**. When **9** was heated at reflux in methanol for 3 days, **4** and compound **12** were isolated in 46% and 42% yields,

Scheme V



respectively (Scheme IV). Once again, two possible mechanisms may be postulated to explain this result. First, nucleophilic attack by methanol on the C-2 position of the oxazolo[5,4-*d*]pyrimidine derivative may have occurred to form **12**, which subsequently ring-closed to afford **4**. Alternatively, the oxazole ring of **9** may have opened thermally to the carbodiimide **10**, which then underwent competitive nucleophilic attack by either methanol or the C-4 exocyclic benzylamine nitrogen. To clarify this point, we heated compound **9** at reflux in acetonitrile instead of methanol. In this case, only **4** was obtained. Heating compound **12** at reflux in methanol or acetonitrile effected no reaction. This result indicates that the ring transformation of an oxazolo[5,4-*d*]pyrimidine into an imidazo[4,5-*d*]pyrimidine derivative most likely proceeds through a short-lived carbodiimide intermediate (**10**) and not by a nucleophilic attack of methanol on the oxazole ring. That only **9** was obtained from the reaction of **7** with DCC in DMF at room temperature provides some support that **9** is the kinetically controlled product in the reaction and **4** is the thermodynamically controlled product.

The unsuccessful cyclization of **6** to form **4** prompted us to determine if this was caused by steric hindrance of the 4-benzylamino group or by a decreased nucleophilicity of this amine due to a delocalization of its lone pair of electrons into the pyrimidine ring.[18] Treatment of 2,4,5-triaminopyrimidin-6(1*H*)-one sulfate (**13**) with 1 equiv of *N*-(methoxycarbonyl)-*S*-methylpseudothiourea afforded **14** (86% yield) rather than the expected bicyclic methyl guanine-8-carbamate (**15**) (Scheme V). The formation of **16** was not detected in this reaction. Similarly, the reaction of **13** with 2 equiv of methoxycarbonyl isothiocyanate did not afford **17** but, instead, furnished **18** in 63% yield. Therefore, it would seem that the nucleophilicity of the exocyclic nitrogen at C-4 is not sufficient to effect a reaction. This is most likely the reason for the observed results and would indicate that the steric effect of the 4-benzyl moiety in **8** was not responsible for the unsuc-

(16) Brown, D. J. "Fused Pyrimidines (Part II Purines)" in the series *The Chemistry of Heterocyclic Compounds*; Wiley-Interscience: New York, 1971; Vol. 24, pp 81–83.

(17) Ohtsuka, Y. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 187. Ohtsuka, Y. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 954. Ohtsuka, Y. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 3909. Ohtsuka, Y. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 506.

(18) For a detailed discussion of pyrimidine chemistry, see the following: Brown, D. J. "The Pyrimidines", Vol. XVI in the series *The Chemistry of Heterocyclic Compounds*; Weissberger, A., Taylor, E. C., Eds.; Wiley-Interscience: New York, 1962. Brown, D. J. "The Pyrimidines Supplement 5", 1970, in the same series. Broom, A. D.; Shim, J. L.; Anderson, G. L. *J. Org. Chem.* **1976**, *41*, 1095. Anderson, G. L.; Broom, A. D. *J. Org Chem.* **1977**, *42*, 4159.

cessful ring cyclization. This prompted us to attempt a ring cyclization of **18** to obtain the methyl guanine-8-carbamate (**15**).

The reaction of **18** with methyl iodide afforded the (*S*-methylpseudothioureido)pyrimidine **19** in 78% yield, while the treatment of **18** with DCC led to the formation of the oxazolo[5,4-*d*]pyrimidine **20** in 84% yield. Several attempts to obtain compound **15** by a reaction of **19** or **20** with sodium methoxide or potassium carbonate were not successful.

In summary, two facile approaches for the synthesis of methyl 9-benzylguanine-8-carbamate (**4**) have been developed. The first approach involved a base-catalyzed cyclization of an *S*-methylpseudothioureido derivative. The second procedure involved the cyclodesulfurization of a (methoxycarbonyl)thioureido derivative with DCC to obtain an oxazolo[5,4-*d*]pyrimidine-2-carbamate. Subsequent ring opening of this oxazolo[5,4-*d*]pyrimidine followed by cyclization produced **4**. It also should be noted that a short-lived carbodiimide intermediate is most likely involved in the mechanism for both of these two methods. The procedure described herein should be adaptable to the synthesis of other bicyclic heterocyclic systems such as imidazopyridines or thiazolopyrimidines, and studies in this area are being investigated in our laboratory. The successful synthesis of **4** has also provided a facile method for the future synthesis of potential PNP inhibitors.

Experimental Section

General Methods. Proton nuclear magnetic resonance (^{1}H NMR) spectra were obtained by using a Varian EM-360 spectrometer (60 MHz) or Brucker Wm 360 spectrometer (360 MHz). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a JEOL FX-90Q. The following abbreviations were used to designate the multiplicity of individual signals: s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, m = muliplet. Melting points are uncorrected and were determined either on a Thomas-Hoover or on an Electrothermal melting point apparatus. UV spectra were recorded on a Hewlett-Packard UV 8450 spectrometer. IR spectra were recorded on a Perkin-Elmer 281 spectrophotometer, and elemental analyses were obtained from M-H-W Laboratories, Phoenix, AZ 85013. Thin-layer chromatography (TLC) was performed with Analtech silica gel GHLF TLC plates (250 μm).

Methyl 9-Benzylguanine-8-carbamate (4). A mixture of methyl 6-amino-4-(benzylamino)oxazolo[5,4-*d*]pyrimidine-2-carbamate (**9**, 2.45 g, 7.8 mmol), anhydrous potassium carbonate (2.2 g, 15.6 mmol), and anhydrous methanol (50 mL) was heated at reflux in an oil bath. After 4 h, the solvent was removed in vacuo (water pump) and the residual solid was dissolved in water (20 mL). Ammonium chloride (1.68 g, 21.2 mmol) in water (20 mL) was added to this solution. The solid was collected by filtration and then washed with water (10 mL) and methanol (5 mL) to give compound **4** (2.13 g, 87%). An analytical sample was prepared by recrystallization from a mixture of DMF and methanol (v/v, 1/1) in a freezer for 2 days. The collected solid was then dried in vacuo (oil pump) at the reflux temperature of toluene for 24 h. Mp: 321–322 °C. UV λ_{max} (nm) ($\epsilon \times 10^4$): (methanol) 266 (1.7); (pH 1) 259 (1.8); (pH 11) 264 (1.4), 273 (1.3), 289 (1.4). IR (KBr): 3450, 3280, 2920, 1740 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 3.4 (s, 3 H, CH_3), 5.1 (s, 2 H, CH_2), 6.58 (s, 2 H, NH_2, D_2O exchangeable), 7.3 (m, 5 H, Ar H), 9.8 (br, 1 H, NH, D_2O exchangeable), 10.7 (s, 1 H, NH, D_2O exchangeable).

Anal. Calcd for $C_{14}H_{14}N_6O_3$ (314.305): C, 53.50; H, 4.49; H, 26.74. Found: C, 53.21; H, 4.57; N, 26.60.

2-Amino-4-(benzylamino)-5-[1-[3-(methoxycarbonyl)-guanidino]]pyrimidin-6(1*H*)-one (6). Sodium nitrite (3 g, 43 mmol) in water (10 mL) was added to a mixture of 2-amino-4-(benzylamino)pyrimidin-6(1*H*)-one[7] (3.26 g, 15 mmol), glacial acetic acid (10 mL), and water (50 mL). The mixture was stirred at room temperature for 4 h, and the red solid was then collected and washed with water (30 mL). The solid was then suspended in water (100 mL) in a 500-mL Erlenmeyer flask and the flask placed on a steam bath. Sodium dithionite (7.5 g) was added to this hot stirring mixture in small portions over a period of 1 h. When the color of the mixture remained a pale yellow, the mixture was cooled in an ice bath at once. After cooling to room temperature, the solid **5** was collected by filtration, washed with water (10 mL), and then mixed at once with 2 equiv of *N*-(methoxycarbonyl)-*S*-methylpseudothiourea which had been prepared as follows.[6] A 10% sodium hydroxide solution was added dropwise to a mixture of *S*-methylpseudothiourea sulfate (4.17 g, 15 mmol) and methyl chloroformate (2.3 mL, 30 mmol) in water (20 mL) in an ice bath with stirring until the pH of the solution was approximately 8. The pH of the solution was adjusted to 5 by use of glacial acetic acid (5 mL).

Sodium acetate monohydrate (2.07 g, 15 mmol) was then added to the mixture of **5**, *N*-(methoxycarbonyl)-*S*-methylpseudothiourea, and water (100 mL), and the mixture was heated in an oil bath at 80 °C for 4 h. After the mixture was cooled to room temperature, the solid was collected by filtration and washed with water (50 mL) and methanol (10 mL). Activated charcoal (0.2 g) was added to a solution of this crude product in a 10% HCl solution (75 mL), and the mixture was filtered. The filtrate was neutralized with a solution of 58% ammonium hydroxide and hydrazine (v/v, 3/1) to give a colorless solid. The solid was collected by filtration, washed with water (50 mL) and methanol (20 mL), and then dried at 70 °C over sodium hydroxide for 24 h in vacuo (water pump), to give compound **6** (1.87 g, 36%). An analytical sample was dried over P_2O_5 at the reflux temperature of toluene in vacuo (oil pump) for 12 h. Mp: 255–257 °C. UV λ_{max} (nm) ($\epsilon \times 10^4$): (methanol) 273 (1.8); (pH 1) 268 (2.1); (pH 11) 267 (1.7). ^{1}H NMR (DMSO-d_6): δ 3.5 (s, 3 H, CH_3), 4.5 (d, 2 H, CH_2), 6.4 (s, 2 H, NH_2, D_2O exchangeable), 6.8 (t, 1 H, NH, D_2O exchangeable), 7.3 (s, 5 H, Ar H), 7.5–10 (br, 4 H, NH, D_2O exchangeable).

Anal. Calcd for $C_{14}H_{17}N_7O_3 \cdot H_2O$ (349.351): C, 48.13; H, 5.48; N, 28.07. Found: C, 48.36; H, 5.53; N, 28.17.

2-Amino-4-(benzylamino)-5-[1-[3-(methoxycarbonyl)-thioureido]]pyrimidin-6(1*H*)-one (7). Sodium nitrite (6.9 g, 100 mmol) in water (30 mL) was added to a mixture of 2-amino-4-(benzylamino)pyrimidin-6(1*H*)-one[7] (7.41 g, 34 mmol), glacial acetic acid (20 mL), and water (100 mL) with stirring at room temperature. After 4 h, the red solid was collected by filtration and washed with water (100 mL). The solid was suspended in water (200 mL) and heated on a steam bath with stirring. Sodium dithionite (15 g) was added to the hot stirring mixture in small portions over a period of 1 h. The mixture was cooled in an ice bath as soon as the mixture had turned to a permanent pale yellow color. The solid was collected by filtration, washed with water (20 mL), and then mixed with 2 equiv of fresh methoxycarbonyl isothiocyanate in acetonitrile (50 mL).[9] The mixture was heated for 4 h at reflux in an oil bath. After the mixture was cooled to room temperature, the solid was collected by filtration and then washed with water (100 mL) and methanol (20 mL). The solid was dried over sodium hydroxide at 70 °C for 24 h in vacuo (water pump) to give a pure compound **7** (4.51 g, 38%), mp 234–236 °C. UV λ_{max} (nm) ($\epsilon \times 10^4$): (methanol) 268 (2.4); (pH 1) 268 (2.7); (pH 11) 267 (2.4). IR (KBr): 3490, 3390, 3330, 3230, 3180, 3030, 2960, 1740 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 3.7 (s, 3 H, CH_3), 4.55 (d, 2 H, CH_2), 6.35 (s, 2 H, NH_2, D_2O exchangeable), 6.85 (t, 1 H, NH, D_2O exchangeable), 7.30 (s, 5 H, Ar H), 10.10 (s, 1 H, NH, D_2O exchangeable), 10.20 (s, 1 H, NH, D_2O exchangeable), 11.15 (s, 1 H, NH, D_2O exchangeable).

Anal. Calcd for $C_{14}H_{16}N_6SO_3$ (348.38): C, 48.27; H, 4.62; N, 24.12. Found: C, 48.15; H, 4.83; N, 23.87.

2-Amino-4-(benzylamino)-5-[1-[3-(methoxycarbonyl)-*S*-methylpseudothioureido]]pyrimidin-6(1*H*)-one (8). Methyl iodide (0.59 mL, 5.5 mmol) was added to a mixture of 2-amino-4-(benzylamino)-5-[1-[3-(methoxycarbonyl)pseudothioureido]]-pyrimidin-6(1*H*)-one (**7**, 1.92 g, 5.5 mmol) and anhydrous potassium carbonate (0.8 g, 5.7 mmol) in DMF (30 mL). The mixture was stirred at room temperature for 2.5 h, and the solvent was then evaporated to dryness in vacuo (oil pump). The solid which was formed by adding water (30 mL) was collected by filtration and washed with water (20 mL) and methanol (3 mL). The solid was then dried over sodium hydroxide at 60 °C for 12 h in vacuo (water pump) to give compound **8** (1.76 g, 88%). This crude

product was dissolved in warm methanol (30 mL), treated with 0.2 g of activated charcoal, and then filtered. The cloud point was induced by adding water (40 mL) to the filtrate. The mixture was allowed to stand in the freezer for 12 h, and the solid was collected by filtration and washed with water (5 mL) and methanol (2 mL). The solid was then dried over sodium hydroxide at 60 °C for 24 h, to give compound **8** (1.36 g, 68%). An analytical sample was prepared by recrystallization twice using the above procedure. R_f: 0.59 (methanol/methylene chloride, 1/9). Mp 310 °C dec. UV λ_{max} (nm) ($\epsilon \times 10^4$): (methanol) 248 (2.3); (pH 1) 274 (2.6); (pH 11) 250 (2.8). ^{1}H NMR (DMSO-d_6): δ 2.35 (s, 3 H, CH_3), 3.70 (s, 3 H, CH_3), 4.60 (d, 2 H, CH_2), 5.35 (t, 1 H, NH, D_2O exchangeable), 6.00 (s, 2 H, NH_2, D_2O exchangeable), 7.35 (s, 5 H, Ar H), 9.8 (br s, 1 H, NH, D_2O exchangeable), 11.10 (br s, 1 H, NH, D_2O exchangeable).

Anal. Calcd for $C_{15}H_{18}N_6SO_3$ (362.405): C, 49.71; H, 5.01; N, 23.19. Found: C, 49.67; H, 5.16; N, 22.96.

Methyl 6-Amino-4-(benzylamino)oxazolo[5,4-*d*]pyrimidine-2-carbamate (9). Dicyclohexylcarbodiimide (0.62 g, 3.18 mmol) was added to a mixture of 2-amino-4-(benzylamino)-5-[1-[3-(methoxycarbonyl)thioureido]]pyrimidin-6(1*H*)-one (**7**, 0.37 g, 1.06 mmol) and DMF (20 mL). The mixture was stirred at room temperature for 5 h, and the solvent was then evaporated to an oily residue at 50 °C in vacuo (oil pump). The residue solidified upon the addition of ether (10 mL). This solid was collected by filtration, washed with ether (10 mL), and dried at 70 °C for 18 h to give compound **9** (0.29 g, 88%). An analytical sample was prepared by recrystallization from a mixture of methanol and water (v/v, 1/1). R_f: 0.64 (methanol/chloroform, 1/9). Mp 278–280 °C. UV λ_{max} (nm) ($\epsilon \times 10^4$): (methanol) 284 (2.2); (pH 1) 268 (2.5), 306 (1.4); (pH 11) 297 (2.5). IR (KBr): 3500, 3420, 3300, 3180, 3080, 2950, 1770 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 3.70 (s, 3 H, CH_3), 4.65 (d, 2 H, CH_2), 6.20 (s, 2 H, NH_2, D_2O exchangeable), 7.32 (s, 5 H, Ar H), 7.9 (t, 1 H, NH, D_2O exchangeable), 11.08 (s, 1 H, NH, D_2O exchangeable).

Anal. Calcd for $C_{14}H_{14}N_6O_3$ (314.305): C, 53.50; H, 4.49; N, 26.74. Found: C, 53.53; H, 4.64; N, 26.63.

2-Amino-4-(benzylamino)-5-[1-[3-(methoxycarbonyl)-*O*-methylpseudoureido]]pyrimidin-6(1*H*)-one (12). A solution of methyl 6-amino-4-(benzylamino)oxazolo[5,4-*d*]pyrimdine-2-carbamate (**9**, 1.77 g, 5.46 mmol) in methanol (100 mL) was heated at refulx in an oil bath for 3 days. The precipitate was collected by filtration and washed with water (10 mL) to give compound **4** (0.81 g, 47%), which was identical with **4** prepared by the previous method. The filtrate was evaporated in vacuo at 70 °C to afford a residue, which was chromatographed on silica gel (20 × 2 cm i.d. column) by eluting with a mixture of methanol and chloroform (v/v, 1/4). Fractions were collected, and those that contained compound **12** (TLC, methanol/chloroform, 1/4) were pooled and evaporated to a solid, which was recrystallized from a mixture of 80% methanol and water to afford compound **12** (0.31 g, 43%); mp 195–196 °C. ^{1}H NMR (DMSO-d_6): δ 3.58 (s, 3 H, CH_3), 3.66 (s, 3 H, CH_3), 4.47 (d, 2 H, CH_2), 6.88 (s, 2 H, NH_2), 7.04 (t, 1 H, NH), 7.24 (br s, 5 H, Ar H), 9.03 (s, 1 H, NH), 10.07 (br s, 1 H, NH).

Anal. Calcd for $C_{15}H_{18}N_6O_4 \cdot H_2O$: C, 49.45; H, 5.53; N, 23.07. Found: C, 49.53; H, 5.48; N, 22.90.

2,4-Diamino-5-[1-[3-(methoxycarbonyl)guanidino]]pyrimidin-6(1*H*)-one (14). To a mixture of *S*-methylpseudothiourea sulfate (2.78 g, 10 mmol) and methyl chloroformate (1.54 mL, 20 mmol) was added a 10% sodium hydroxide solution dropwise below 15 °C, to adjust the pH of the solution to 8. The pH of the solution was then adjusted to 5 with glacial acetic acid (1.8 mL). This solution was added to a mixture of 2,4,5-triaminopyrimidin-6(1*H*)-one sulfate (**13**, 2.39 g, 10 mmol) and sodium acetate monohydrate (2.72 g, 20 mmol) in water (50 mL). The mixture was heated in an oil bath at 85 °C for 3 h and then allowed to cool to room temperature. The solid was collected by filtration and washed with water (20 mL) and then methanol (10 mL). The sample was dried over sodium hydroxide in vacuo (water pump) at 70 °C for 24 h to furnish compound **14** (2.09 g, 86%). An analytical sample was prepared by dissolving the sample in hot 10% hydrochloric acid solution and then effecting a reprecipitation by adding a mixture of 58% ammonium hydroxide and hydrazine (v/v, 3/1), to give colorless needles, mp >360 °C. UV λ_{max} (nm) ($\epsilon \times 10^4$): (methanol) 266 (1.3); (pH 1) 261 (1.5); (pH 11) 260 (1.3). IR (KBr): 3520, 3360, 3250, 2940, 1690 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 3.5 (s, 3 H, CH_3), 6.0 (s, 2 H, NH_2, D_2O exchangeable), 6.4 (s, 2 H, NH_2, D_2O exchangeable), 6.5–9.0 (br, 4 H, NH, D_2O exchangeable).

Anal. Calcd for $C_7H_{11}N_7O_3$ (241.209): C, 34.86; H, 4.60; N, 40.65. Found: C, 34.90; H, 5.12; N, 40.80.

2,4-Diamino-5-[1-[3-(methoxycarbonyl)thioureido]]pyrimidin-6(1*H*)-one (18). 2,4,5-Triaminopyrimidin-6(1*H*)-one sulfate (**13**, 2.38 g, 10 mmol) and sodium acetate monohydrate (5.52 g, 40 mmol) were suspended in water (75 mL). To this suspension was added acetonitrile (20 mL) containing 2 equiv of freshly prepared methoxycarbonyl isothiocyanate which was prepared in acetonitrile (50 mL). The mixture was heated to reflux in an oil bath at 100 °C for 4 h. After cooling to room temperature, the solid was collected by filtration, washed with water (20 mL) and methanol (10 mL), and then dried at 70 °C for 24 h in vacuo (water pump), to give compound **18** (1.62 g, 63%). R_f: 0.2 (methanol/methylene chloride, v/v, 1/9). Mp: >360 °C. IR (KBr): 3480, 3440, 3370, 3320, 1740 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 3.70 (s, 3 H, CH_3), 5.95 (s, 2 H, NH_2, D_2O exchangeable), 6.20 (s, 3 H, CH_3), 5.95 (s, 2 H, NH_2, D_2O exchangeable), 6.20 (s, 2 H, NH_2, D_2O exchangeable), 10.05 (s, 1 H, NH, D_2O exchangeable), 10.20 (s, 1 H, NH, D_2O exchangeable), 11.12 (s, 1 H, NH, D_2O exchangeable).

Anal. Calcd for $C_7H_{10}N_6SO_3$ (258.26): C, 32.56; H, 3.90; N, 32.54. Found: C, 32.51; H, 4.07; N, 32.30.

2,4-Diamino-5-[1-[3-(methoxycarbonyl)-*S*-methylpseudothioureido]]pyrimidin-6(1*H*)-one (19). Methyl iodide (0.13 mL, 2.0 mmol) was added to a mixture of 2,4-diamino-5-[1-[3-(methoxycarbonyl)thioureido]]pyrimidin-6(1*H*)-one (**18**, 0.516 g, 2.0 mmol) and anhydrous potassium carbonate (2.8 g, 2.02 mmol) in anhydrous DMF (50 mL). The mixture was stirred at room temperature for 5 h, and the solvent was then evaporated to dryness at 50 °C in vacuo (oil pump). The residue was allowed to stand at 5 °C for 18 h, and the solid was collected by filtration and then washed with methanol (3 mL). The solid was dried at 70 °C in vacuo (water pump) for 12 h to give compound **19** (0.43 g, 78%). An analytical sample was prepared by recrystallization from methanol. R_f: 0.56 (methanol/chloroform, v/v, 2/8). Mp: 210 °C dec. UV λ_{max} (nm) ($\epsilon \times 10^4$): (methanol) 245 (1.9), 269 (1.3); (pH 1) 258 (1.8); (pH 11) 247 (2.3). ^{1}H NMR (DMSO-d_6): δ 2.25 (d, 3 H, CH_3), 3.6 (s, 3 H, CH_3), 6.2 (s, 2 H, NH_2, D_2O exchangeable), 6.3 (s, 2 H, NH_2, D_2O exchangeable), 9.7 (s, 1 H, NH, D_2O exchangeable), 10.2 (s, 1 H, NH, D_2O exchangeable).

Anal. Calcd for $C_8H_{12}N_6O_3S \cdot {}^1/_4H_2O$ (276.790): C, 34.72; H, 4.55; N, 30.36. Found: C, 34.72; H, 4.53; N, 30.34.

Methyl 4,6-Diaminooxazolo[5,4-*d*]pyrimidine-2-carbamate (20). To 2,4-diamino-5-[1-[3-(methoxycarbonyl)thioureido]]pyrimidin-6(1*H*)-one (**18**, 2.3 g, 8.9 mmol) suspended in DMF (100 mL) was added dicyclohexylcarbodiimide (1.84 g, 27 mmol), and the mixture was stirred at room temperature for 1 week. After filtration, the filtrate was evaporated to dryness at 50 °C in vacuo (oil pump). The residue was triturated with ether (30 mL), collected by filtration, and then washed with water (5 mL) and methanol (3 mL). The solid was suspended in toluene (50 mL) and the suspension heated at 80 °C. After 30 min, the solid was collected by filtration and dried at 70 °C for 10 h in vacuo (water pump) to furnish compound **20** (1.81 g, 84%). An analytical sample was prepared by dissolving the sample in methanol, slowly adding water to the cloud point, and allowing the solution to stand at 5 °C for 18 h. R_f: 0.45 (methanol/methylene chloride, v/v, 1/9). Mp: >300 °C. UV λ_{max} (nm) ($\epsilon \times 10^4$): (methanol) 269 (1.8); (pH 1) 264 (2.2), 296 (1.0); (pH 11) 282 (2.1). IR (KBr): 3580, 3450, 3350, 2960, 1760 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 3.7 (s, 3 H, CH_3), 6.10 (s, 2 H, NH_2, D_2O exchangeable), 6.90 (s, 2 H, NH_2, D_2O exchangeable), 11.10 (br s, 1 H, NH, D_2O exchangeable).

Anal. Calcd for $C_7H_8N_6O_3 \cdot H_2O$ (242.2): C, 34.71; H, 4.16; N, 34.70. Found: C, 34.97; H, 4.25; N, 34.85.

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Synthesis of 5-Substituted Uracils, Uridines, and 2'-Deoxyuridine Analogues[1]

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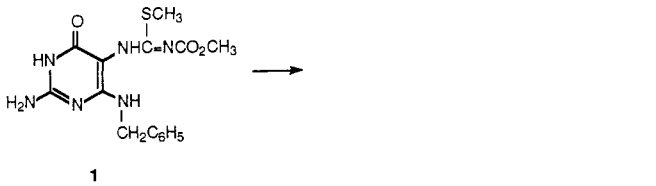
Reactions of 5-aminouracil (**4**), 5-aminouridine (**19a**), and 2'-deoxy-5-aminouridine (**19b**) with methoxycarbonyl isothiocyanate afforded 5-[1-[3-(methoxycarbonyl)thioureido]]uracil (**5**), 5-[1-[3-(methoxycarbonyl)thioureido]]uridine (**20a**), and 5-[1-[3-(methoxycarbonyl)thioureido]]-2'-deoxyuridine (**20b**) in near quantitative yields. Treatment of compound **5** or **20a** with 1 equiv of methyl iodide furnished 5-[1-[3-(methoxycarbonyl)-*S*-methylpseudothioureido]]uracil (**6**) and 3-methyl-5-[1-[3-(methoxycarbonyl)-*S*-methylpseudothioureido]]uridine (**21**), respectively. Compound **5** reacted with alcohols, amines, and ethanethiol in the presence of dicyclohexylcarbodiimde (DCC) to afford several 5-[1-[3-(methoxycarbonyl)-*O*-alkylpseudoureido]]uracils, 5-[1-[3-(methoxycarbonyl)guanidino]]uracil (**15**), and 5-[1-[3-(methoxycarbonyl)-*S*-ethylpseudothioureido]]uracil (**17**), respectively. Similar, reactions with **20a** resulted in the formation of 5-[1-[3-(methoxycarbonyl)-*O*-ethylpseudoureido]]uridine (**22**), 5-[1-[3-(methoxycarbonyl)ureido]]uridine (**23**), and 5-[1-[3-(methoxycarbonyl)-*S*-ethylpseudothioureido]]uridine (**24a**). The synthesis of 5-[1-[3-(methoxycarbonyl)-*S*-ethylpseudothioureido]]-2'-deoxyuridine (**24b**) was accomplished by the treatment of compound **20b** with ethanethiol in the presence of DCC. The ^{1}H NMR and ^{13}C NMR spectra of these compounds and the X-ray crystallography of compounds **13** and **17** are discussed.

Recently we reported that methyl 9-benzylguanine-8-carbamate (**2**) may be readily formed from either 2-amino-4-(benzylamino)-5-[1-[3-(methoxycarbonyl)-*S*-methylpseudothioureido]pyrimidin-6-one (**1**) or methyl 6-amino-4-(benzylamino)oxazolo[5,4-*d*]pyrimidine-2-carbamate (**3**)[2] via a short-lived carbodiimide intermediate.[3]



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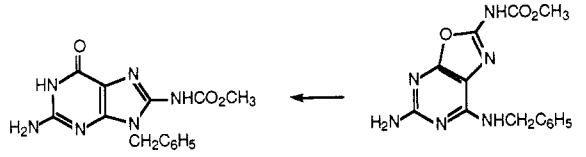

2 **3**

In connection with these studies,[2,3] it was considered that possibly a pyrimidine or pyrimidine nucleoside that contained a 5-[1-[3-(methoxycarbonyl)-*S*-methylpseudoureido]] group or a nucleoside with a methyl oxazolo[5,4-*d*]pyrimidine-2-carbamate aglycon might have good potential for biological activity due to the reactivity of these systems toward nucleophiles. This paper describes our synthetic efforts in this area.

5-Aminouracil (**4**) was reacted with methoxycarbonyl isothiocyanate[4] to furnish 5-[1-[3-(methoxycarbonyl)thioureido]]uracil (**5**) in near quantitative yield. Treatment of **5** with 1 equiv of methyl iodide gave a modest yield of 5-[1-[3-(methoxycarbonyl)-*S*-methylpseudothioureido]]-uracil (**6**). Treatment of **5** with dicyclohexylcarbodiimide (DCC), under conditions which in our previous studies[2,3] readily furnished oxazolo[4,5-*d*]pyrimidines from a series of 4-amino-5-thioureidopyrimidin-6-ones, effected no reaction in this case. Performing the reaction under high-temperature conditions afforded a complex mixture. To determine the influence of DMF on the course of this reaction, the reaction of **5** with DCC was repeated with methanol as the solvent at reflux temperature. In this case, only a single product was isolated from this reaction. The spectral data for this compound exhibited: (1) a UV spectrum with an absorption pattern very similar to that observed for **3** and (2) a ^{1}H NMR spectrum that contained, in addition to the expected peak at δ 3.8 (singlet) for the methyl moiety of the methoxycarbonyl group, an additional peak at δ 3.6 (singlet), which was suggestive of another methyl group. A methanol adduct at the C-6 position of the pyrimidine ring of the desired compound **8**, such as compound **9**, was ruled out since the chemical shift for the C-6 proton of this compound was at δ 7.58, which would suggest that the uracil ring system in this compound was still a conjugated system. In addition the ^{13}C NMR spectra of this compound revealed that the chemical shift of the carbon atoms of the uracil ring system remained relatively

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