# Synthesis and Unusual Chemical Reactivity of Certain Novel 4,5-Disubstituted 7-Benzylpyrrolo[2,3-*d*][1,2,3]triazines

Michael T. Migawa† and Leroy B. Townsend*

*Department of Chemistry, College of Literature, Sciences and Arts, Department of Medicinal Chemistry, College of Pharmacy, University of Michigan, Ann Arbor, Michigan 48109-1065*

*leroy.townsend@umich.edu*

*Received October 18, 2000*

The fact that only two pyrrolo[2,3-*d*][1,2,3]triazines heterocycles had been reported in the literature prompted us to initiate studies designed to provide additional members of this ring system. Initial attempts to prepare additional derivatives of the 7-unsubstituted pyrrolo[2,3-*d*][1,2,3]triazin-4-ones were limited by their low chemical reactivity. Subsequently, 7-benzyl-5-carboxamidopyrrolo-[2,3-*d*][1,2,3]triazin-4-one (**16**) was prepared from diethyl 2-nitropyrrole-3,4,-dicarboxylate via an alkylation, ammonolysis, reduction and intramolecular diazocoupling sequence. Conversion of **16** into 7-benzyl-4-(1,2,4-triazol-1-yl)pyrrolo[2,3-*d*][1,2,3]triazine-5-carbonitrile (**17**) was accomplished, and nucleophilic displacements of the 4-triazol-1-yl group were studied. Treatment of **17** with $NH_3$/$CH_3CN$ gave a mixture of 4-amino-7-benzylpyrrolo[2,3-*d*][1,2,3]triazine-5-carbonitrile (**19**) and 2-amino-1-benzylpyrrole-3,4-dicarbonitrile (**21**). A mechanism to account for the formation of this mixture is described along with studies on the effect that ammonia concentration and a TFA catalyst have on the product ratio. Compound **19** was converted into the 5-carboxamide and 5-thioamide derivatives of **19**.

## Introduction

Many structural analogues of the naturally occurring purine nucleosides, adenosine and guanosine, have been synthesized and subsequently demonstrated to be useful chemotherapeutic agents. These discoveries have prompted an exceptional growth of research resulting in the preparation of a vast number of purine ribo- and 2-deoxyribonucleoside analogs.[1] While modifications of the sugar moiety, the heterocylic base and the exocyclic substituents have been reported, our major research interests have been focused on modifications of the purine ring per se. The preparation of these base-modified nucleosides are synthetically challenging and can result in the discovery of new classes of chemotherapeutic agents, potentially with novel biological modes of action.[2,3]

In view of the important biological activity of many purine analogues, it was of considerable interest that an entire class of aza-deazapurine nucleoside analogs, the pyrrolo[2,3-*d*][1,2,3]triazine nucleosides, had not been reported in the literature. These pyrrolo[2,3-*d*][1,2,3]-triazines are similar in structure to the imidazo[4,5-*d*]-pyrimidines (2-azapurines), differing only in a carbon−nitrogen ring substitution at C-5, and to the pyrrolo[2,3-*d*]pyrimidine nucleosides, differing only in a nitrogen−carbon ring substitution at C-2. In fact, only two pyrrolo[2,3-*d*][1,2,3]triazine heterocycles had been reported[4,5] in the literature (**1** and **2**, Figure 1).


**Figure 1.**

However, the synthetic route for the preparation of **1** and **2** is very limited in regards to exocyclic functional groups. This fact prompted us to initiate studies designed to provide pyrrolo[2,3-*d*][1,2,3]triazines amenable toward functional group modifications at the C-4, C-5, C-6, and N-7 positions.

## Results and Discussion

A retrosynthetic disconnection of the pyrrolo[2,3-*d*]-[1,2,3]triazine ring system (**4**) suggests two potential ring disconnections (Scheme 1). First, disconnection of the pyrrole ring gives the 1,2,3-triazine precursor (**3**) from which the pyrrole portion could be constructed via a cyclization reaction. Second, disconnection of the 1,2,3-triazine ring gives a pyrrole precursor (**5**) from which the 1,2,3-triazine portion could be constructed. The first route was rejected since a suitably substituted precursor would be difficult to obtain[6] and the monocyclic 1,2,3-triazines are much more unstable than pyrroles.[7] On the other

† Present address: Ibis Therapeutics, a Division of Isis Pharmaceuticals, Inc., 2292 Faraday Avenue, Carlsbad, CA 92008.

(1) (a) *Chemistry of Nucleosides and Nucleotides*; Townsend, L. B., Ed.; Plenum Press: New York, 1994; Vol. 3. (b) *Chemistry of Nucleosides and Nucleotides*; Townsend, L. B., Ed.; Plenum Press: New York, 1991; Vol. 2.

(2) Kosalka, G. W.; Chamberlain, S. D.; Daluge, S. M.; Boyd, F. L.; Tidwell, J. H.; Martin, M. T.; Harvey, R. J.; Frick, L. W.; Perkins, D. G.; Wang, L. H.; Drach, J. C.; Townsend, L. B.; Biron, K. K. *XII International Roundtable: Nucleosides, Nucleotides and their Biological Application*; La Jolla, CA, September, 1996.

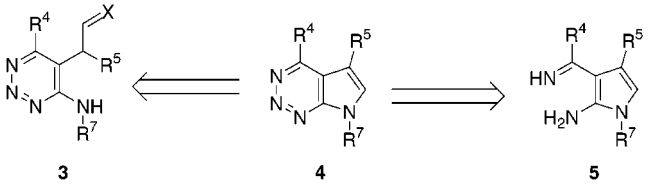
(3) Ptak, R. G.; Borysko, K. Z.; Porcari, A. R.; Buthod, J. L.; Holland, L. E.; Shipman, C., Jr.; Townsend, L. B.; Drach, J. C. *AIDS Res. Hum. Retroviruses* **1998**, *14*, 11315−1322.

(4) Roth, H. J.; Eger, K. *Arch. Pharm. (Weinheim, Ger.)* **1975**, *308*, 186−189.

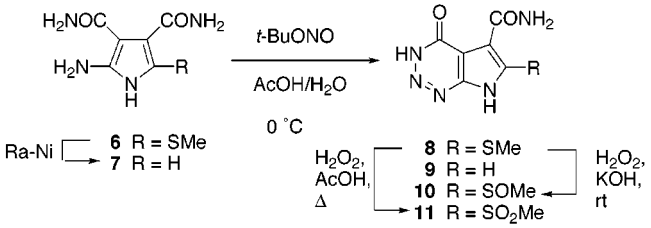
(5) Steinhilber, D.; Schmidt, K.; Eger, K.; Roth, H. J. *Pharm. Res.* **1986**, *3*, 271−277.

10.1021/jo001499i CCC: $20.00 
Published on Web 06/16/2001

**Scheme 1**



**Scheme 2**



hand, the chemistry of the pyrrole ring system has been well explored, and the success of an intramolecular diazo-coupling strategy, in the preparation of several 5:6 fused systems, supported this method[8−11] as our first choice for the key step in the preparation of pyrrolo[2,3-*d*][1,2,3]-triazines (**4**).

Initially we chose to explore the reactivity of the N-1-unsubstituted pyrrole, 2-amino-5-(methylthio)pyrrole-3,4-dicarboxamide (**6**),[12] toward the reported[8] diazo-coupling conditions. However, diazotization of pyrrole **6** under 6 N HCl/$NaNO_2$ conditions resulted in significant decomposition. By changing the conditions to *tert*-butylnitrite/AcOH, we obtained reasonable yields of the pyrrolo[2,3-*d*][1,2,3]triazin-4-one **8** (Scheme 2). Raney nickel reductive desulfurization of **6** gave the 5-unsubstituted pyrrole **7** and diazotization of **7** gave the $N^7$-unsubstituted pyrrolo-[2,3-*d*][1,2,3]triazin-4-one **9**.

Treatment of the pyrrolotriazine **8** and pyrrolotriazine **9** individually under a variety of conditions, e.g., $POCl_3$, $POCl_3/PCl_5$, $POCl_3$/1,2,3-triazole/base, alkylation and glycosylation, failed to give any functionalized product. It was subsequently found that the 6-methylthio moiety of pyrrolotriazine **8** could be converted to the sulfoxide **10** with hydrogen peroxide in the presence of KOH or to the sulfone **11** with hydrogen peroxide in acetic acid at reflux temperature (Scheme 3). Attempts to displace either the sulfone with a nucleophile (e.g., $NaN_3$, $RNH_2$) or convert **10** or **11** to a precursor suitable for glycosylation failed under a variety of conditions.

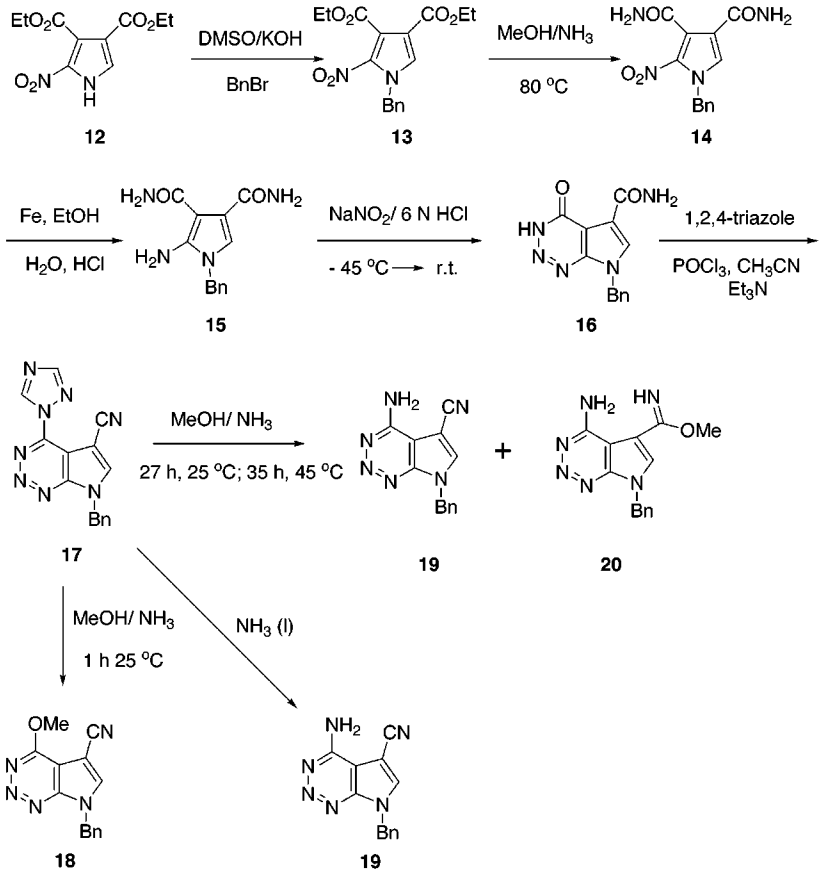
As a result of some difficulty in functionalizing the N-7-unsubstituted pyrrolo[2,3-*d*][1,2,3]triazines (i.e., **8**, **10**, **11**), we elected to install a N-7 substituent prior to the diazo-coupling step. Preliminary attempts at N-1 alkylation[13] of pyrrole **6** resulted in very poor yields and some decomposition of starting material. This is not surprising since 2-aminopyrroles are well-known to undergo various side reactions (oxidation, polymerization).[14] We then initiated an alternative approach for the preparation of N-1-substituted 2-aminopyrrole-3,4-dicarboxamides. In this approach, the amino group of the 2-amino-3-carboxamide precursor would be masked as a nitro group, and then reduced immediately before the intramolecular diazo-coupling reaction.

Therefore, diethyl 1-benzyl-2-nitropyrrole-3,4-dicarboxylate (**13**) was prepared by an alkylation of the potassium salt of diethyl 2-nitropyrrole-3,4-dicarboxylate (**12**) with benzyl bromide. The pyrrole diester **13** was then treated with methanolic ammonia at 80 °C for 45 h to obtain the desired dicarboxamide precursor, 1-benzyl-2-nitropyrrole-3,4-dicarboxamide (**14**). The structural assignment for this compound as the diamide was based on four $D_2O$ exchangeable protons in the $^1H$ NMR spectrum. A reduction of the nitro group of **14** was then accomplished to give 2-amino-1-benzylpyrrole-3,4-dicarboxamide (**15**) in a 94% yield. The presence of two additional $D_2O$ exchangeable resonances in the $^1H$ NMR spectrum of **15** was used to determine that a complete reduction of the nitro group had occurred.

Compound **15** was diazotized[15] at −45 °C using sodium nitrite in 6 N HCl and then allowed to reach room temperature. The precipitate was collected by filtration and dried to give a 93% yield of 7-benzyl-5-carboxamidopyrrolo[2,3-*d*][1,2,3]triazin-4-one (**16**) without the need for further workup. Lower yields were obtained when the initial reaction temperature was allowed to rise above −30 °C. Concomitant functionalization of both the 4- and the 5-position of pyrrolo[2,3-*d*][1,2,3]triazine **16** was then attempted under a variety of conditions. Treatment of compound **16** with $POCl_3$ and DMAP in acetonitrile[15−17] for 10 min at room temperature, followed by quenching with methanolic ammonia, produced only a trace of a compound tentatively assigned the structure 7-benzyl-5-cyanopyrrolo[2,3-*d*][1,2,3]triazin-4-one, based on the lack of $D_2O$ exchangeable protons in the $^1H$ NMR spectrum and the presence of a characteristic cyano group resonance at 115 ppm in the $^{13}C$ NMR spectrum. Alternatively, quenching the aforementioned reaction, after 4 h, with methanolic ammonia or sodium methoxide/methanol produced very low yields of 7-benzyl-4-methoxypyrrolo[2,3-*d*][1,2,3]triazine-5-carbonitrile (**18**, vida infra). Since $POCl_3$/DMAP had proved unsuccessful, we opted to try an alternative procedure[18] in which a heterocycle is added to a premixed suspension of $POCl_3$, 1,2,4-triazole and triethylamine. Subjecting **16** to this procedure gave a 49% yield of 7-benzyl-4-(1,2,4-triazol-1-yl)pyrrolo[2,3-*d*][1,2,3]triazine-5-carbonitrile (**17**). The presence of two separate triazole proton resonances in the $^1H$ NMR spectrum indicated that the 4-(triazol-1-yl)

(6) Itoh, T.; Matsuya, Y.; Hasegawa, H.; Nagata, K.; Okada, M.; Ohsawa, A. *Chem. Pharm. Bull.* **1995**, *43*, 881−883.
(7) Neunhoeffer, H. 1,2,3-Triazines. In *The Chemistry of 1,2,3-Triazines and 1,2,4-Triazines, Tetrazines, and Pentazines*; Neunhoeffer, H., Ed.; Wiley: New York, 1978.
(8) Montgomery, J. A.; Thomas, H. J. 4-Amino-7-β-D-ribofuranosyl-7*H*-imidazo[4,5-*d*]-*v*-triazine (2-azaadenosine). In *Nucleic Acid Chemistry, Improved and New Synthetic Procedures, Methods and Techniques*; Townsend, L. B., Tipson, R. S., Eds.; Wiley and Sons: New York, 1978; Vol. 2.
(9) Woolley, D. W.; Shaw, E. *J. Biol. Chem.* **1951**, *189*, 401−410.
(10) Panzica, R. P.; Townsend, L. B. *J. Heterocycl. Chem.*, **1972**, *9*, 623−628.
(11) Biraldi, P. G.; Garuti, L.; Roberti, M. *Synthesis* **1994**, 1437−1440.
(12) Gewalt, V. K.; Kleinert, M.; Thiele, B.; Hentschel, M. *J. Prakt. Chem.* **1972**, *2*, 303−314.
(13) Bennett, S. M.; Nguyen-Ba, N.; Ogilvie, K. K. *J. Med. Chem.* **1990**, *33*, 2162−2173.
(14) *Aminopyrroles*, Pyrroles. Part Two.; Cirrincione, G., Almerico, A. M., Aiello, E., Dattolo, G., Eds.; John Wiley & Sons: New York, 1992.
(15) Kelly, J. L.; Wilson, D. C.; Styles, V. L.; Soroko, F. E.; Cooper, B. R. *J. Heterocycl. Chem.* **1995**, *32*, 1417−1421.
(16) Adamiak, R. W.; Biala, E.; Skalski, B. *Nucleic Acids Res.* **1985**, *13*, 2989−3003.
(17) Adamiak, R. W.; Biala, E.; Skalaski, B. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1054−1055.
(18) Perbost, M.; Hoshiko, T.; Morvan, F.; Swayze, E.; Griffey, R. H.; Sanghvi, Y. S. *J. Org. Chem.* **1995**, *60*, 5150−5156.

**Scheme 3**



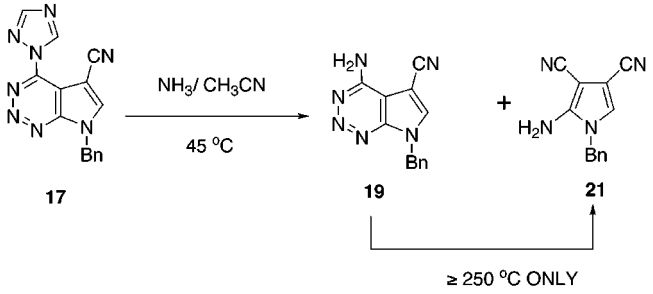

regioisomer rather than the 4-(triazol-4-yl) regioisomer was obtained.

We then initiated studies designed to explore the reactivity of the 4-triazol-1-yl group toward nucleophilic displacement. We reasoned that treatment of **17** with ammonia should give an amino group at the 4-position of the pyrrolo[2,3-*d*][1,2,3]triazine ring. However, treatment of the pyrrolotriazine **17** with methanolic ammonia at room temperature for 1 h gave 7-benzyl-4-methoxypyrrolo[2,3-*d*][1,2,3]triazine-5-carbonitrile (**18**) as the only product. Morever, treatment of compound **17** with methanolic ammonia for 27 h at room temperature, followed by 35 h at 45 °C, gave a 19% yield of 4-amino-7-benzylpyrrolo[2,3-*d*][1,2,3]triazine-5-carbonitrile (**19**) and a 34% yield of methyl 4-amino-7-benzylpyrrolo[2,3-*d*]-[1,2,3]triazine-5-imidate (**20**), along with some decomposition products. Longer reaction times and higher temperatures resulted in lower yields of compounds **19** and **20**. On the other hand, treatment of **17** with liquid ammonia in a sealed tube at room temperature for 2 h gave a 61% yield of 4-amino-7-benzylpyrrolo[2,3-*d*][1,2,3]-triazine-5-carbonitrile (**19**) as the only product.

It was of some interest that during our studies to establish optimum reaction conditions for a clean conversion of **17** to **19**, we found that when the pyrrolo[2,3-*d*]-[1,2,3]triazine **17** was treated with a dilute solution of ammonia in acetonitrile, a mixture of pyrrolo[2,3-*d*][1,2,3]-triazine **19** and 2-amino-1-benzylpyrrole-3,4-dicarbonitrile (**21**) was obtained (Scheme 4).

We have recently reported[19] that compound **19** undergoes a thermal elimination of nitrogen at 250 °C to give

**Scheme 4**

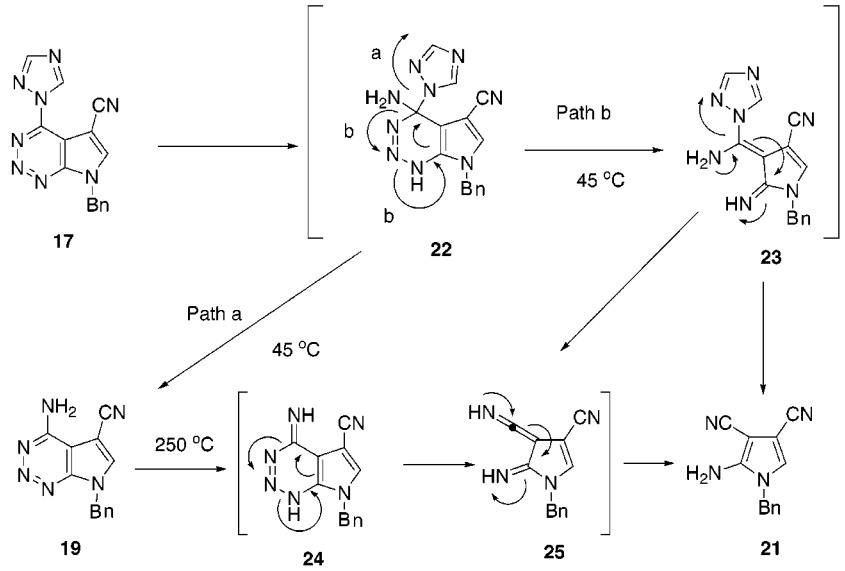



the pyrrole **21**. Therefore, $^{15}$N-labeling studies[19] have suggested that this reaction may proceed by a retro Diels−Alder reaction involving the elimination of N-2 and N-3 from the imino tautomer of compound **19**. This prompted us to determine whether the 4-aminopyrrolotriazine **19** was being converted directly into the pyrrole **21** under milder conditions than we had previously[19] used, i.e., close to room temperature rather than heating at ≥250 °C. Therefore, we subjected the 4-aminopyrrolo-[2,3-*d*][1,2,3]triazine **19** to essentially the same reaction conditions that produced the mixture of **19** and **21** from **17**, i.e., a 0.5 M solution of ammonia in acetonitrile at 45 °C. To our surprise, we recovered only the starting material. This would suggest that both **19** and **21** arise from a common intermediate. A mechanism that takes these facts into account is proposed in Scheme 5.

Nucleophilic addition of ammonia results in the formation of a Meisenheimer complex (**22**). The formation of this intermediate is followed by nitrogen elimination (**22** to **23** (path b)) and 1,2,4-triazole elimination to give pyrrole **21** or a simple elimination of the 1,2,4-triazole

(19) Migawa, M. T.; Townsend, L. B. *Org. Lett.* **1999**, *1*, 537−539.

**Scheme 5**




(path a) to give 4-aminopyrrolotriazine **19**. In the case of the thermal elimination, the aromaticity of the pyrrolotriazine ring must be disrupted in order to undergo the concerted thermal elimination, while in the case of the Meisenheimer complex, the 1,2,3-triazine portion of the heterocycle already has disrupted aromaticity, allowing a nitrogen elimination to occur at a lower temperature. Similar to the thermal elimination, the reaction that proceeds through the Meisenheimer complex is assumed to lose nitrogen from the 2- and 3-positions of compound **17**.

We next initiated studies to ascertain the effect that a change in the ammonia concentration would have on the pyrrolo[2,3-*d*][1,2,3]triazine **19**/ pyrrole **21** product ratio (Figure 2). As higher concentrations of ammonia were used, the 4-aminopyrrolotriazine formation was favored over pyrrole formation. In fact, a variation of the product ratio (**19/21**) of 4 to 14 was observed over a concentration range of 0.16−0.62 M.

Additionally, we sought to determine the effect that an acid catalyst would have on the product ratios. The results of subjecting compound **17** to various concentrations of trifluoroacetic acid (TFA) in a 0.4 M $NH_3$/ acetonitrile solution are shown in Figure 3. Adding TFA as an acid catalyst dramatically increases the **19**/**21** product ratio. When 4 equiv of TFA was used, the **19**/**21** product ratio increased to 47:1 without any significant change in total yield.

The mechanism proposed in Scheme 6 accounts for the observed variation in the **19**/**21** product ratio (Figure 2) resulting from an increased ammonia concentration and the observed increase in the **19**/**21** product ratio resulting from the addition of TFA (Figure 3).

A protonation or deprotonation (or both) of intermediate **22** would result in the formation of intermediates **26** or **27**, respectively. This catalytic effect would favor triazole elimination (i.e., path a) over nitrogen elimination (i.e., path b).

Therefore, the mechanism proposed in Scheme 5 successfully accounts for the conversion of the pyrrolo[2,3-*d*][1,2,3]triazine **17** into 4-aminopyrrolo[2,3-*d*][1,2,3]-triazine **19** and pyrrole **21** and explains the apparent

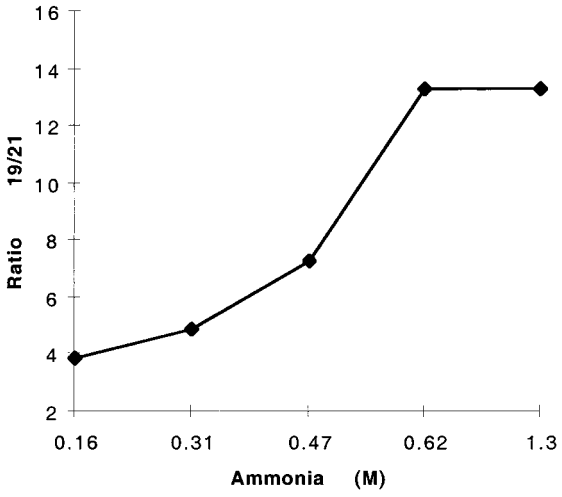



**Figure 2.** Reaction was run at 45 °C for 7 days. Ratios were determined by integration of the $^1$H NMR methylene resonances. Starting material was recovered in the case where [$NH_3$] is 0.16 (32%) and 0.31 (6%).

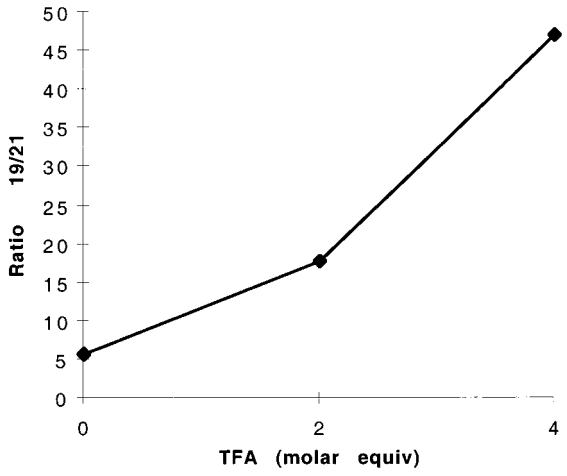
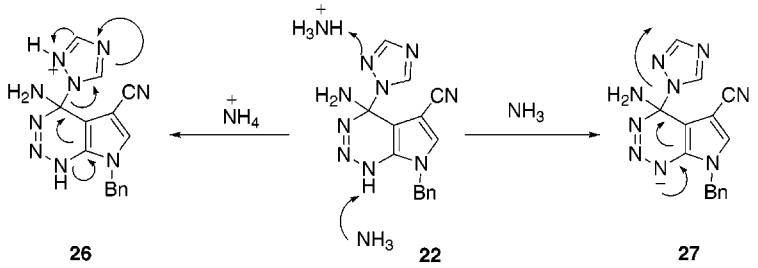
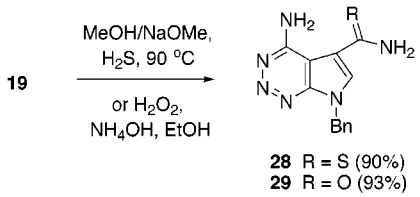



**Figure 3.** Reaction was run in 0.4 M $NH_3$ at 45 °C for 7 days. Ratios and yields were determined by integration of the $^1$H NMR methylene resonances. Total yields were 80% ± 5% with starting material being recovered in each case (8% ± 3%).

**Scheme 6**



**Scheme 7**



discrepancy between the previously reported[19] thermal elimination of compound **19** and this recent observation.

Finally, two additional modifications of the 5-position of the pyrrolo[2,3-*d*][1,2,3]triazine system were accomplished. Compound **19** was treated with a presaturated solution of hydrogen sulfide gas, in a mixture of methanol and sodium methoxide, in a sealed vial at 90 °C to give the thioamide **28** as a hemihydrate (Scheme 7). Alternatively, the preparation of the amide **29** has been accomplished in excellent yield by treating the 4-aminopyrrolotriazine **19** with 30% hydrogen peroxide in ethanol and ammonium hydroxide.

In conclusion, we have developed a general route for the synthesis of 4,5-disubstituted 7-benzylpyrrolo[2,3-*d*][1,2,3]triazines. Additionally, a novel nitrogen elimination was discovered which may serve to explain some of the interesting chemical reactivity of this novel ring system. We are currently expanding this methodology to prepare novel pyrrolo[2,3-*d*][1,2,3]triazine nucleosides.

## Experimental Section

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Silica gel, SilicAR 40−63 $\mu$m 230−400 mesh was used for chromatography. Flash column chromatography refers to the chromatography technique described by Still et al. (*J. Org. Chem.* **1978**, *43*, 2923−2925). (*X*% EtOAc/Hex, *Y* cm × *Z* cm) means the solvent system that is used as the eluent, the diameter of the column (*Y*) and the height of silica gel (*Z*). Solvent systems are expressed as a percentage of the more polar component with respect to total volume (v/v %). Thin-layer chromatography (TLC) was performed on prescored SilicAR 7GF plates (Analtech, Newark, DE). Compounds were visualized by illuminating with UV light (254 nm) or by spraying with 10% methanolic sulfuric acid followed by charring on a hot plate. Evaporations were carried out under reduced pressure (water aspirator) with the bath temperature not exceeding 50 °C, unless specified otherwise. The $^1$H (300 MHz) and $^{13}$C (75 MHz) NMR spectra were recorded and the chemical shifts are expressed in parts per one million relative to the standard chemical shift of the solvent for DMSO-$d_6$, 2.50 ppm ($^1$H NMR), 39.50 ppm ($^{13}$C NMR), and relative to tetramethylsilane as an internal standard for $CDCl_3$ ($^1$H NMR), and relative to the standard chemical shift of the solvent for $^{13}$C NMR (77.0 ppm). Mass spectroscopy and elemental analyses were performed by the University of Michigan Chemistry Department or by MHW Laboratories, Phoenix, AZ.

**2-Aminopyrrole-3,4-dicarboxamide (7).** A stirred mixture of isopropyl alcohol (110 mL), commercial grade Raney nickel (10 g), and 2-amino-5-(methylthio)pyrrole-3,4-dicarboxamide[12] (**6**, 2.14 g, 10.0 mmol) was heated at reflux temperature for 24 h. At that time, the reaction mixture was filtered (hot) through Celite. The Celite was resuspended in 2-propanol (70 mL) and then filtered through another bed of Celite. The solvent portions were combined and evaporated under reduced pressure, and the resultant solid was dried under reduced pressure at 78 °C for 16 h to yield 1.10 g (65%) of a dark product. This solid was recrystallized from hot water and dried under reduced pressure at 78 °C for 24 h to yield 0.79 g (47%) of **7** as purple needles: mp > 210 °C (dec); $R_f$ = 0.46 (40:9:1, EtOAc/MeOH/$H_2O$); $^1$H NMR (DMSO-$d_6$, 300 MHz) $\delta$ 10.51 (bs, 1H, $D_2O$ exchangeable, NH), 9.83 (bs, 1H, $D_2O$ exchangeable, $CONH_2$), 7.51 (bs, 1H, $D_2O$ exchangeable, $CONH_2$), 6.97 (bs, 2H, collapses to s, 1H upon $D_2O$ addition, $CONH_2$ and ArH), 6.44 (bs, 1H, $D_2O$ exchangeable, $CONH_2$), 6.11 (bs, 2H, $D_2O$ exchangeable, $NH_2$); $^{13}$C NMR (DMSO-$d_6$, 75 MHz) $\delta$ 168.6, 168.4, 147.8, 116.4, 113.6, 93.2. Anal. Calcd for $C_6H_8N_4O_2$: C, 42.86; H, 4.80; N, 33.32. Found: C, 42.89; H, 4.77; N, 32.94.

**5-Carboxamido-6-(methylthio)pyrrolo[2,3-*d*][1,2,3]triazin-4-one (8).** A stirred mixture of 2-amino-5-(methylthio)pyrrole-3,4-dicarboxamide[12] (**6**, 2.14 g, 10.0 mmol), AcOH (glacial, 100 mL), and $H_2O$ (50 mL) was cooled to 0 °C (ice bath), and *tert*-butylnitrite (3.17 mL, 24.0 mmol) was added over a 5 min period. The reaction was allowed to stir at 0 °C for 15 min and then at room temperature for 90 min. At that time, the flask was covered and allowed to stand for 16 h. The resultant mixture was then reduced to one-half of its original volume and cooled at 10 °C for 1 h, and the precipitate was collected by filtration, washed with $H_2O$ (100 mL), and dried under reduced pressure at 78 °C for 24 h to give 1.41 g (64%) of **8** as a purple solid. An analytical sample was prepared by dissolving 530 mg of **8** in $NH_4OH$ (conc, 60 mL), treating with charcoal, filtering, and reprecipitating with HCl (conc). The precipitate was collected by filtration and dried under reduced pressure at 78 °C for 24 h to give 236 mg (45% recovery) of **8** as a white solid: mp > 200 °C (dec); $^1$H NMR (DMSO-$d_6$, 300 MHz) $\delta$ 15.03 (bs, 1H, $D_2O$ exchangeable, NH),13.31 (bs, 1H, $D_2O$ exchangeable, NH), 9.31 (bs, 1H, $D_2O$ exchangeable, $CONH_2$), 7.29 (bs, 1H, $D_2O$ exchangeable, $CONH_2$), 2.60 (s, 3H, $CH_3$); $^{13}$C NMR (DMSO-$d_6$, 75 MHz) $\delta$ 164.1, 156.0, 145.8, 144.7, 108.6, 107.4, 12.26; IR (KBr) 3386, 3333, 1598 cm$^{-1}$; Anal. Calcd for $C_7H_7N_5O_2S$: C, 37.33; H, 3.13; N, 31.09. Found: C, 37.50; H, 2.86; N, 30.85.

**5-Carboxamidopyrrolo[2,3-*d*][1,2,3]triazin-4-one (9).** Compound **9** was prepared in a 38% (673 mg) yield from **7** following the procedure used for the preparation of **8**: mp > 200 °C (dec); $^1$H NMR (DMSO-$d_6$, 300 MHz) $\delta$ 15.11 (bs, 1H, $D_2O$ exchangeable, NH),13.60 (bs, 1H, $D_2O$ exchangeable, NH), 9.21 (bs, 1H, $D_2O$ exchangeable, $CONH_2$), 8.06 (s, 1H, H-6), 7.48 (bs, 1H, $D_2O$ exchangeable, $CONH_2$); $^{13}$C NMR (DMSO-$d_6$, 75 MHz) $\delta$ 162.8, 157.0, 145.6, 130.7, 114.9, 105.5; HRMS (70 eV) calcd for $C_6H_5N_5O_2$ 179.0443, found 179.0450.

**5-Carboxamido-6-sulfinylpyrrolo[2,3-*d*][1,2,3]triazin-4-one (10).** A solution of 5-carboxamido-6-(methylthio)pyrrolo-[2,3-*d*][1,2,3]triazin-4-one (**8**, 500 mg, 2.2 mmol), 1 N KOH (10

(20) Duffy, T. D.; Wibberley, D. G. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1921−1929.

mL) and 30% $H_2O_2$ (2 mL) was allowed to stir at room temperature. After 1 h, an additional portion of 30% $H_2O_2$ (2 mL) was added, then another portion of 30% $H_2O_2$ (2 mL) was added after 2 h, and the reaction was allowed to stir for an additional 1 h. At that time, the pH of the reaction mixture was adjusted to 5 with 5 N HCl. The precipitate was collected by filtration and dried under reduced pressure at 50 °C for 24 h to give 361 mg (67%) of **10** which was slightly colored but pure by $^1$H NMR. An analytical sample was prepared by dissolving 210 mg in 1 N KOH (30 mL), treating with charcoal, filtering, and reprecipitating with 4 N HCl. The precipitate was collected by filtration and dried under reduced pressure at 50 °C for 48 h to give 140 mg (67% recovery) of **10** as a white solid: mp > 250 °C (dec); $^1$H NMR (DMSO-$d_6$, 300 MHz) $\delta$ 15.28 (bs, 1H, $D_2O$ exchangeable, NH),14.38 (bs, 1H, $D_2O$ exchangeable, NH), 9.30 (bs, 1H, $D_2O$ exchangeable, $CONH_2$), 7.81 (bs, 1H, $D_2O$ exchangeable, $CONH_2$), 3.02 (s, 3H, $CH_3$); $^{13}$C NMR (DMSO-$d_6$, 75 MHz) $\delta$ 162.9, 156.6, 147.5, 145.8, 111.9, 107.0, 42.2. Anal. Calcd for $C_7H_7N_5O_3S$: C, 34.85; H, 2.92; N, 29.03. Found: C, 34.73; H, 3.14; N, 28.86.

**5-Carboxamido-6-methylsulfonylpyrrolo[2,3-*d*][1,2,3]-triazin-4-one (11).** A solution of 5-carboxamido-6-(methylthio)pyrrolo[2,3-*d*][1,2,3]triazin-4-one (**8**, 1.29 g, 5.73 mmol), AcOH (glacial, 20 mL) and 30% $H_2O_2$ (10 mL) was heated at reflux temperature for 3 h. At that time, the reaction mixture was cooled to 10 °C. The precipitate was collected by filtration, washed with $H_2O$ (20 mL) and MeOH (20 mL). and dried under reduced pressure at 50 °C for 48 h to give 910 mg (62%) of **11** as a white solid: mp > 200 °C (dec); $^1$H NMR (DMSO-$d_6$, 300 MHz) $\delta$ 15.31 (bs, 1H, $D_2O$ exchangeable, NH),14.0 (bs, 1H, $D_2O$ exchangeable, NH), 9.37 (bs, 1H, $D_2O$ exchangeable, $CONH_2$), 7.81 (bs, 1H, $D_2O$ exchangeable, $CONH_2$), 3.66 (s, 3H, $CH_3$); $^{13}$C NMR (DMSO-$d_6$, 75 MHz) $\delta$ 161.6, 156.6, 143.7, 137.6, 115.9, 107.0, 43.5. Anal. Calcd for $C_7H_7N_5O_4S$: C, 32.69; H, 2.74; N, 27.23. Found: C, 32.72; H, 2.80; N, 27.15.

**Diethyl 1-Benzyl-2-nitropyrrole-3,4-dicarboxylate (13).** A suspension of DMSO (20 mL) and KOH (powdered, 499 mg, 8.9 mmol) was stirred for 75 min under argon, at which time a clear solution was observed. Diethyl 2-nitropyrrole-3,4-dicarboxylate[20] (**12**, 1.5 g, 5.9 mmol) was added to the solution in one portion, followed by the dropwise addition of benzyl bromide (1.06 mL, 8.9 mmol) over a 5 min period. After 2.5 h, the reaction mixture was poured onto $H_2O$ (150 mL), extracted with EtOAc (2 × 75 mL), dried ($MgSO_4$), and filtered. The filtrate was evaporated under reduced pressure, hexanes (20 mL) was added to the oil, and the resulting precipitate was collected by filtration. Drying this solid under reduced pressure at 50 °C for 24 h gave a quantitative yield of **13** as a yellow powder. Recrystallization of this powder from methanol and drying under reduced pressure at 78 °C for 48 h yielded 1.21 g (61%) of a white solid. An additional 505 mg (25%) of **13** was obtained from the mother liquor for a total yield of 1.72 g (86%): mp 118−119 °C; $R_f$ = 0.45 (30% EtOAc/hexanes); $^1$H NMR (DMSO-$d_6$, 300 MHz) $\delta$ 8.22 (s, 1H, ArH), 7.4−7.2 (m, 5H, Ph), 5.64 (q, 2H, $CH_2$), 5.60 (s, 2H, $CH_2$), 4.24 (q, 2H, $CH_2$), 1.27 (t, 3H, $CH_3$), 1.25 (t, 3H, $CH_3$); $^{13}$C NMR (DMSO-$d_6$, 75 MHz) $\delta$ 162.3, 161.0, 135.9, 132.9, 132.7, 128.8, 128.0, 126.8, 121.3, 112.3, 61.7, 60.7, 53.3, 14.0, 13.7. Anal. Calcd for $C_{17}H_{18}N_2O_6$: C, 58.96;, 5.24; N, 8.09. Found: C, 58.83; H, 5.16; N, 8.02.

**1-Benzyl-2-nitropyrrole-3,4-dicarboxamide (14).** Diethyl 1-benzyl-2-nitropyrrole-3,4-dicarboxylate (**13**, 1.05 g, 3.03 mmol) in methanolic ammonia (40 mL, saturated at 0 °C) was heated in a sealed vial at 80 °C for 45 h. The reaction was then cooled to −15 °C, and the precipitate was collected by filtration, washed with methanol (20 mL), and dried under reduced pressure at 78 °C for 2 days to give 726 mg (83%) of **14** as white crystals: mp > 295 °C (dec); $^1$H NMR (DMSO-$d_6$, 300 MHz) $\delta$ 8.03 (bs, 1H, $CONH_2$, $D_2O$ exchangeable), 7.90 (s, 1H, ArH), 7.68 (bs, 1H, $CONH_2$, $D_2O$ exchangeable), 7.4−7.2 (m, 7H, Ph, 2-$CONH_2$, collapses to 5H upon addition of $D_2O$), 5.56 (s, 2H, $CH_2$); $^{13}$C NMR (DMSO-$d_6$, 75 MHz) $\delta$ 164.8, 162.8, 136.3, 133.1, 130.6, 128.8, 127.9, 126.9, 123.3, 117.1, 53.0. Anal. Calcd for $C_{13}H_{12}N_4O_4$: C, 54.17; H, 4.20; N, 19.44. Found: C, 54.11; H, 4.33; N, 19.39.

**2-Amino-1-benzylpyrrole-3,4-dicarboxamide (15).** Five drops of 12 N HCl was added to a stirred mixture of 1-benzyl-2-nitropyrrole-3,4-dicarboxamide (**14**, 726 mg, 2.52 mmol), iron (reduced, 844 mg, 15 mmol), and 50% ethanol (aq, 25 mL). The suspension was heated at reflux temperature in the dark for 1 h, at which time it was filtered hot through a bed of Celite and washed with hot 50% ethanol (aq, 100 mL). The solvent was evaporated under reduced pressure until a volume of 5 mL was obtained. After cooling the mixture to 0 °C, the precipitate was collected by filtration and then washed with cold water (5 mL). Drying under reduced pressure at 78 °C for 48 h gave 612 mg (94%) of **15** as a brown-red solid: mp 220 °C; $^1$H NMR (DMSO-$d_6$, 300 MHz) $\delta$ 9.84 (bs, 1H, $CONH_2$, $D_2O$ exchangeable), 7.52 (bs, 1H, $CONH_2$, $D_2O$ exchangeable), 7.3−7.0 (m, 6H, colapses to 5H upon addition of $D_2O$), 7.06 (s, 1H, ArH), 6.40 (bs, 1H, $CONH_2$, $D_2O$ exchangeable), 6.21 (bs, 2H, $D_2O$ exchangeable) 5.00 (s, 2H, $CH_2$); $^{13}$C NMR (DMSO-$d_6$, 75 MHz) $\delta$ 168.1 (2 carbons), 147.4, 137.1, 128.6, 127.5, 127.2, 119.6, 113.5, 93.5, 47.5. Anal. Calcd for $C_{13}H_{14}N_4O_2$: C, 60.45; H, 5.46; N, 21.69. Found: C, 60.23; H, 5.68; N, 21.51.

**7-Benzyl-5-carboxamidopyrrolo[2,3-*d*][1,2,3]triazin-4-one (16).** A stirred solution of 2-amino-1-benzylpyrrole-3,4-dicarboxamide (**15**, 258 mg, 1.0 mmol) in 6 N HCl (10 mL) was cooled to −45 °C in a dry ice/acetonitrile bath. A solution of sodium nitrite (120 mg, 2.0 mmol in 2 mL water) was then added dropwise over a period of 5 min (2 mL of ethanol was added to facilitate stirring). The reaction was allowed to proceed at room temperature for 2 h at which time the precipitate was collected by filtration and washed with cold water (10 mL). Drying the solid under reduced pressure at 78 °C for 24 h gave 249 mg (93%) of **16** which was sufficiently pure for further reactions. An analytical sample was prepared by adding 234 mg of **16** to a 50% aqueous ethanol solution (125 mL) at reflux temperature. Allowing the solution to stand for 12 h at room temperature, collecting the precipitate by filtration, and drying as before, gave 180 mg (77% recovery) of **16**: mp 234−235 °C; $^1$H NMR (DMSO-$d_6$, 300 MHz) $\delta$ 15.24 (bs, 1H, $D_2O$ exchangeable, NH), 9.14 (bs, 1H, $D_2O$ exchangeable, $CONH_2$), 8.24 (s, 1H, ArH), 7.52 (bs, 1H, $D_2O$ exchangeable, $CONH_2$), 7.4−7.3 (m, 5H, ph), 5.63 (s, 2H, $CH_2$); $^{13}$C NMR (DMSO-$d_6$, 75 MHz) $\delta$ 162.5, 156.7, 144.1, 136.4, 133.4, 128.8, 128.1, 127.8, 114.4, 106.0, 49.1. Anal. Calcd for $C_{13}H_{11}N_5O_2$: C, 57.99; H, 4.12; N, 26.01. Found: C, 58.11; H, 4.38; N, 26.33.

**7-Benzyl-4-(1,2,4-triazol-1-yl)pyrrolo[2,3-*d*][1,2,3]-triazine-5-carbonitrile (17).** A stirred suspension of 1,2,4-triazole (18.4 g, 266 mmol) in $CH_3CN$ (150 mL), under argon, was treated with phosphorus oxychloride (5.5 mL, 59 mmol), and then the white suspension was cooled to 0 °C. Triethylamine (37 mL, 266 mmol) was added, and the mixture was allowed to stir at 0 °C for 1 h, at which time 7-benzyl-5-carboxamidopyrrolo[2,3-*d*][1,2,3]triazin-4-one (**16**, 2.0 g, 7.4 mmol) was added in one portion. The reaction mixture was stirred for 4.5 h at room temperature and filtered through Celite, and the filter cake was washed with $CH_3CN$ (100 mL). The filtrate and washing were evaporated under reduced pressure, and the oily residue was dissolved in $CHCl_3$ (250 mL) and washed successively with sodium bicarbonate solution (2 × 100 mL), $H_2O$ (100 mL), and brine (100 mL). The organic layer was dried ($MgSO_4$) and filtered, and the filtrate was evaporated under reduced pressure to give a brown solid, which was purified by flash chromatography ($CHCl_3$, 4 cm × 20 cm). The resultant solid, $R_f$ = 0.39 (50% EtOAc/hexanes), was recrystallized from $CHCl_3$/petroleum ether and dried under reduced pressure at 78 °C for 24 h to give 1.10 g (49%) of **17** as light blue needles: mp 238−240 °C; $^1$H NMR (DMSO-$d_6$, 300 MHz) $\delta$ 9.85 (s, 1H), 9.32 (s, 1H), 8.61 (s, 1H), 7.4−7.3 (m, 5H, ph), 5.81 (s, 2H, $CH_2$); $^{13}$C NMR (DMSO-$d_6$, 75 MHz) $\delta$ 154.3, 149.5, 145.7, 144.6, 144.4, 135.4, 128.9, 128.3, 128.0, 114.2, 103.1, 85.1, 49.5. Anal. Calcd for $C_{15}H_{10}N_8$: C, 59.60; H, 3.33; N, 37.07. Found: C, 59.69; H, 3.49; N, 37.21.

**7-Benzyl-4-methoxypyrrolo[2,3-*d*][1,2,3]triazine-5-carbonitrile (18).** Methanolic ammonia (15 mL, sat. at 0 °C) was added to 7-benzyl-4-(1,2,4-triazol-1-yl)pyrrolo[2,3-*d*][1,2,3]-triazine-5-carbonitrile (**17**, 342 mg, 1.13 mmol) in a pressure tube and the tube was sealed. The reaction was stirred for 1

h at room temperature. The solvent was then removed under reduced pressure and subjected to silica gel chromatography (20% EtOAc/hexanes, 30% EtOAc/hexanes, and then 35% EtOAc/hexanes, 2 cm × 20 cm). The resultant solid, $R_f = 0.76$ (50% EtOAc/hexanes), was recrystallized from EtOAc/hexanes and dried under reduced pressure at 78 °C for 36 h to give 40 mg (13%) of **18** as a white solid *(note: this product decomposes on the column!)*: mp 177−178 °C; $R_f = 0.76$ (50% EtOAc/hexanes); $^1$H NMR (DMSO-$d_6$, 300 MHz) $\delta$ 8.93 (s, 1H, ArH), 7.34 (m, 5H, Ph), 5.72 (s, 2H, $CH_2$), 4.28 (s, 3H, $OCH_3$); $^{13}$C NMR (DMSO-$d_6$, 75 MHz) $\delta$ 158.3, 148.1, 140.6, 135.8, 128.8, 128.2, 127.8, 113.8, 102.8, 82.0, 55.5, 49.4. Anal. Calcd for $C_{14}H_{11}N_5O$: C, 63.39; H, 4.18; N, 26.40. Found: C, 63.22; H, 3.90; N, 26.15.

**4-Amino-7-benzylpyrrolo[2,3-*d*][1,2,3]triazine-5-carbonitrile (19).** Ammonia (15 mL) was condensed into a steel tube containing 7-benzyl-4-(1,2,4-triazol-1-yl)pyrrolo[2,3-*d*][1,2,3]-triazine-5-carbonitrile (**17**, 472 mg, 1.56 mmol). The tube was sealed, and the mixture was stirred for 2 h at room temperature. At that time the ammonia was slowly evaporated, and the resultant solid was subjected to column chromatography ($CHCl_3$ then EtOAc, 2 cm × 20 cm). The resultant solid, $R_f =$ 0.18 (50% EtOAc/hexanes), was recrystallized from $H_2O$/methanol and dried under reduced pressure at 78 °C for 24 h to give 235 mg (60%) of **19** as a white solid: mp 225−226 °C; $R_f = 0.18$ (50% EtOAc/hexanes); $^1$H NMR (DMSO-$d_6$, 300 MHz) $\delta$ 8.68 (s, 1H, ArH), 7.43 (s, 2H, $D_2O$ exchangeable, $NH_2$), 7.33 (m, 5H, Ph), 5.59 (s, 2H, $CH_2$); $^{13}$C NMR (DMSO-$d_6$, 75 MHz) $\delta$ 152.8, 146.1, 138.2, 136.2, 128.8, 128.1, 127.7, 114.3, 98.7, 81.8, 48.8. Anal. Calcd for $C_{13}H_{10}N_6$: C, 62.39; H, 4.03; N, 33.58. Found: C, 62.21; H, 4.08; N, 33.31.

**Methyl 4-Amino-7-benzylpyrrolo[2,3-*d*][1,2,3]triazine-5-imidate (20).** Methanolic ammonia (15 mL, saturated at 0 °C) was added to 7-benzyl-4-(1,2,4-triazol-1-yl)pyrrolo[2,3-*d*]-[1,2,3]triazine-5-carbonitrile (**17**, 206 mg, 0.68 mmol) in a pressure tube, and the tube was sealed. The reaction mixture was stirred for 27 h at room temperature, followed by 35 h at 45 °C. The solvent was then removed under reduced pressure and subjected to silica gel chromatography (20% EtOAc/hexanes, 30% EtOAc/hexanes, and then EtOAc, 2 cm × 20 cm), and the fractions containing the product, $R_f = 0.22$ (EtOAc), were evaporated to dryness, suspended in MeOH (5 mL), collected by filtration, and dried under reduced pressure at 78 °C for 36 h to give 66 mg (34%) of **20** as a white solid. Compound **19** was also isolated (33 mg, 19%). Imidate **20**: mp 207−208 °C; $R_f = 0.22$ (EtOAc); $^1$H NMR (DMSO-$d_6$, 300 MHz) $\delta$ 9.78 (bs, 1H, $D_2O$ exchangeable), 8.29 (bs, 1H, $D_2O$ exchangeable), 8.11 (bs, 1H), 7.77 (bs, 1H, $D_2O$ exchangeable), 7.32 (bs, 5H, Ph), 5.55 (s, 2H, $CH_2$), 3.77 (s, 3H, $CH_3$); $^{13}$C NMR (DMSO-$d_6$, 75 MHz) $\delta$ 159.8, 154.1, 146.6, 137.0, 131.2, 128.7 (2 carbons), 127.8, 127.7, 109.1, 97.2, 52.0. Anal. Calcd for $C_{14}H_{11}N_6O$: C, 59.56; H, 5.00; N, 29.77 Found: C, 59.70; H, 5.12; N, 29.87.

**2-Amino-1-benzylpyrrole-3,4-dicarbonitrile (21) and/or 4-Amino-7-benzylpyrrolo[2,3-*d*][1,2,3]triazine-5-carbonitrile (19). Thermal Method.** A 50 mL Pyrex glass test tube was charged with 4-amino-7-benzylpyrrolo[2,3-*d*][1,2,3]-triazine-5-carbonitrile (**19**, 200 mg, 0.66 mmol) and slowly heated neat at 250 °C for 30 s. During this time a very rapid gas evolution commenced. When the vigorous gas release ceased, the resultant amber liquid was cooled to room temperature. The solidified compound was dissolved in 10% MeOH/chloroform (25 mL) and filtered, and the filtrate was evaporated under reduced pressure to dryness. Chloroform/$Et_2O$ (1:1, 25 mL) was added, and after the filtrate was filtered and evaporated to dryness, 131 mg (89%) of compound **21** was obtained as a tan solid, which was pure by $^1$H NMR and TLC, $R_f = 0.51$ (5% MeOH/chloroform). An analytical sample was prepared by recrystallization from methanol/water and drying under reduced pressure at 78 °C to give 86 mg of a tan solid (66% recovery): mp 199−201 °C; $R_f = 0.51$ (5% MeOH/chloroform); $^1$H NMR (DMSO-$d_6$, 300 MHz) $\delta$ 7.4−7.3 (m, 5H, ArH), 7.17 (m, 1H), 6.63 (s, 2H, $D_2O$ exchangeable, $NH_2$), 5.06 (s, 2H, $CH_2$); $^{13}$C NMR (DMSO-$d_6$, 75 MHz) $\delta$ 148.4, 136.2, 129.1, 128.2, 127.5, 125.8, 115.5, 115.1, 90.6, 70.1, 48.8; ; IR (KBr) 3389−3219, 2217, 1655 cm$^{-1}$. Anal. Calcd for $C_{13}H_{10}N_4$: C, 70.26; H, 4.54; N, 25.21. Found: C, 70.13; H, 4.82; N, 25.31.

**Nucleophilic Displacement Method.** A pressure tube containing 1-benzyl-4-(triazol-1-yl)pyrrolo[2,3-*d*][1,2,3]triazine-5-carbonitrile (**17**, 20 mg, 0.06 mmol) and $NH_3$ (0.4 M in $CH_3$-CN, 3 mL) was sealed and stirred at 45 °C for 7 days. At that time the solvent was evaporated to a yellow oil which was dissolved in EtOAc (5 mL) and washed successively with $H_2O$ (5 mL) and brine (20 mL). The aqueous layers were back extracted with EtOAc (20 mL), and the combined organic layers were dried ($Na_2SO_4$), filtered through a 0.5 in. plug of silica gel, and then evaporated under reduced pressure to give a yellow oil which was identified by $^1$H NMR as a mixture of compounds **19** and **21**.

**4-Amino-7-benzylpyrrolo[2,3-*d*][1,2,3]triazine-5-thiocarboxamide (28).** For 30 min, hydrogen sulfide (g) was passed through a solution of sodium methoxide (97 mg, 1.8 mmol) in methanol maintained at 0 °C in an ice bath. This solution was then transferred to a pressure flask containing 4-amino-7-benzylpyrrolo[2,3-*d*][1,2,3]triazine-5-carbonitrile (**19**, 180 mg, 0.72 mmol), and the flask was sealed and heated at 90 °C for 3 h. The solution was then cooled to room temperature, and the pH was adjusted to 7 with 1 N HCl. The solvent was evaporated under reduced pressure, the resultant solid was dissolved in DMF (40 mL), and $H_2O$ (120 mL) was then added rapidly to give a precipitate which was collected by filtration and dried under reduced pressure at 60 °C for 24 h. The resultant solid was washed with $Et_2O$ (10 mL) and EtOAc (10 mL) and dried as before. After suspending in hot methanol, cooling to room temperature, collecting by filtration, and drying as before, 190 mg (90%) of **28** was obtained as a hemihydrate: mp 241−242 °C; $R_f = 0.66$ (EtOAc); $^1$H NMR (DMSO-$d_6$, 300 MHz) $\delta$ 9.76 (bs, 1H, $D_2O$ exchangeable), 9.60 (bs, 1H, $D_2O$ exchangeable), 8.30 (s, 2H, $D_2O$ exchangeable), 8.23 (s, 1H, H-6), 7.34 (m, 5H, Ph), 5.56 (s, 2H, $CH_2$); $^{13}$C NMR (DMSO-$d_6$, 75 MHz) $\delta$ 191.9, 153.5, 146.9, 136.5, 129.8, 128.8, 127.9, 127.8, 119.9, 97.3, 48.2. Anal. Calcd for $C_{13}H_{12}N_6S\cdot 0.5H_2O$: C, 53.23; H, 4.47; N, 28.65. Found: C, 53.44; H, 4.27; N, 28.32.

**4-Amino-7-benzylpyrrolo[2,3-*d*][1,2,3]triazine-5-carboxamide (29).** A solution of $NH_4OH$ (conc, 5 mL), ethanol (2 mL), 30% hydrogen peroxide (2 mL), and 4-amino-7-benzylpyrrolo[2,3-*d*][1,2,3]triazine-5-carbonitrile (**19**, 300 mg, 1.20 mmol) was allowed to stir at room temperature for 3 h. The precipitate that formed during the course of the reaction was collected by filtration, washed with $H_2O$ (20 mL), and dried at 60 °C under reduced pressure to give 298 mg (93%) of **29** as a yellow solid. This solid was suspended in EtOH/$H_2O$ (1:1, 50 mL), and the suspension was heated on a steam bath for 10 min. The flask was cooled to room temperature, and the precipitate was collected by filtration and dried as before to give 285 mg (96% recovery) of pure **29**: mp 289−290 °C; $R_f = 0.30$ (10% MeOH/chloroform); $^1$H NMR (DMSO-$d_6$, 300 MHz) $\delta$ 8.30 (s, 1H, H-6), 8.5−7.5 (bs, 2H, $D_2O$ exchangeable), 8.09 (bs, 1H, $D_2O$ exchangeable, $CONH_2$), 7.54 (bs, 1H, $D_2O$ exchangeable, $CONH_2$), 7.3 (m, 5H, ph), 5.58 (s, 2H, $CH_2$); $^{13}$C NMR (DMSO-$d_6$, 75 MHz) $\delta$ 165.4, 153.8, 146.7, 136.8, 131.1, 128.9, 128.0, 127.7, 109.9, 97.9, 48.1. Anal. Calcd for $C_{13}H_{12}N_6O$: C, 58.20; H, 4.51; N, 31.33. Found: C, 58.61; H, 4.63; N, 31.08.

**Acknowledgment.** The authors would like to thank Mr. Jack Hinkley for the large-scale preparation of compounds **6**, **7**, and **12**, Professor Rich Lawton for useful discussions, and Ms. Kimberly Barrett for assistance in the preparation of this manuscript. This research was supported by research grants U19-AI31718 and 5-R01-AI-36872 from the National Institute of Allergy and Infectious Diseases, the National Institutes of Health.

JO001499I