# Synthesis of Pyrrolo[2,1-*f*][1,2,4]triazine Congeners of Nucleic Acid Purines *via* the *N*-Amination of 2-Substituted Pyrroles [1]



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The synthesis of several new 4-mono- and 2,4-disubstituted pyrrolo[2,1-*f*][1,2,4]triazines is described. Key 1-aminopyrrole-2-carbonitrile intermediates **3** and **15** were obtained by *N*-amination of the corresponding pyrrole-2-carboxaldehyde followed by CHO → CN conversion with either hydroxylamine-*O*-sulfonic acid for **3** or *O*-mesitylenesulfonylhydroxylamine for **15**. Cyclization of **3** or **15** with a variety of amidine reagents or, after conversion of **3** to its corresponding amide, base-catalyzed annulation completed the synthesis of the title products.

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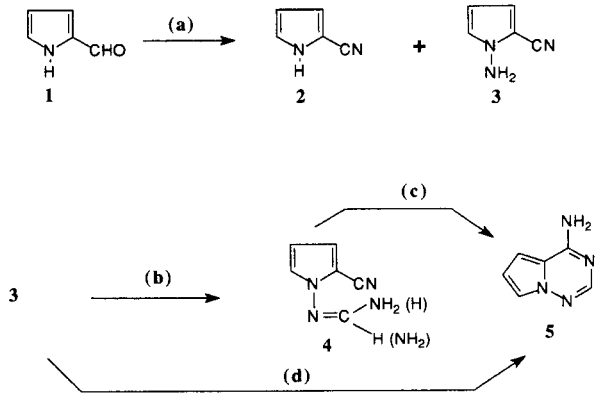
As part of our ongoing synthetic program directed towards the design and evaluation of novel nucleoside analogues of potential biomedical interest we have reported the synthesis of several classes of purine-like *C*-nucleosides [2a-g]. In these, structural modifications to the original purine moiety were restricted to its imidazole ring, while maintaining the integrity of the pyrimidine. One notable exception however has been the case of pyrazolo[1,5-*a*]-*s*-triazine *C*-nucleosides [2a-b] where replacement of the imidazole ring by a pyrazole also results in the replacement of the pyrimidine ring by a 1,3,5-triazine. These analogues, therefore, incorporate a bridgehead nitrogen at the purine-5-position. The fact that such a structural modification does not preclude biological activity [3] suggested that the investigation of new *C*-nucleoside analogues also containing bridgehead-N may be justified and has prompted our interest in the pyrrolo[2,1-*f*][1,2,4]-triazines such as **5** which incorporates a bridgehead-N at the purine-4 position. We should point out that the absence in such a system of a heteroatom at the position corresponding to N-7 in the purines would not necessarily preclude growth inhibitory activity. This has been shown already in the case of the thieno[3,4-*d*]pyrimidine *C*-nucleosides which, although they lack such a heteroatom, *do* possess significant growth inhibitory activity [2f]. Further support for this study was also derived from preliminary computer modeling studies of **5**, adenine and 4-aminopyrazolo[1,5-*a*]-*s*-triazine which indicated considerable similarity between their electrostatic potential maps in the region of their respective six-membered rings when plotted in the plane of the bases [4].

There is only one report of *C*-nucleosides incorporating the pyrrolo[2,1-*f*][1,2,4]triazine system [5a]. In that report, approach to that heterocyclic system was achieved *via* conversion of a C-2-ribosylated furan to a *C*-ribosylpyranulose by oxidation with *m*-chloroperbenzoic acid [5b] followed by further conversion to the appropriately ribosylated N1-ureidopyrrole aldehyde intermediate. The method affords however (and in modest yields at that) purine-like *C*-nucleosides functionalized only at the C-2 position that bear only a remote resemblance to naturally-occurring nucleosides. No biological activity was reported for these derivatives. In searching the literature for a more direct approach to suitably substituted derivatives of this series we identified three general synthetic approaches to heterocycles that incorporate the pyrrolo[2,1-*f*][1,2,4]triazine system. Of these, conversion of 1-aminoindole to *as*-triazino-[1,6-*a*]indole [6a,b] was clearly inapplicable to our purpose. Also structurally and mechanistically inapplicable to our goals was the cycloaddition of 1,2,4-triazines to electron deficient acetylene dicarboxylate [7a,b]. Cyclization of 1-ureido-2-carboalkoxypyrroles [8a,b] akin to the method used in the latter part of Maeba's scheme [5a] was clearly the most useful and was adopted for further exploration. Using approaches amenable to the synthesis of the corresponding *C*-nucleosides, we describe herein the synthetic investigation of several pyrrolo[2,1-*f*][1,2,4]triazines appropriately substituted by amino and/or oxo functions at positions 4 (or 2 and 4). Surprisingly, these pyrrolo[2,1-*f*][1,2,4]-triazine analogues of the common nucleic acid purine bases are not known.

At the onset of this program, we envisaged the key step for the elaboration of the required intermediate to be the *N*-amination of an appropriately 2-substituted pyrrole by utilization of hydroxylamine-*O*-sulfonic acid (HOSA) [9]. HOSA has been used for amination reactions and for the conversion of aldehydes to nitriles *via* elimination of sulfuric acid from an intermediary oxime-*O*-sulfonate [9]. In the case of aromatic aldehydes, such an elimination can be brought about either by simply heating the intermediate or by treating it with a strong base [10a,b]. Since the *N*-amination of various heterocycles with HOSA also requires base catalysis [9], we decided to investigate the possible conversion of pyrrole aldehydes such as the commercially available pyrrole-2-carboxaldehyde (**1**) directly to the desired key intermediate **3**. Our model study on **1** using

HOSA and KOH was reasonably successful and afforded a mixture of the desired *N*-aminopyrrolonitrile **3** and the partially converted non-aminated product **2** in an approximate 1:1 ratio (Scheme 1). Separation by flash column chromatography on silica gel gave **2** and **3** in fair to good yields (37% and 43% respectively).

Scheme 1

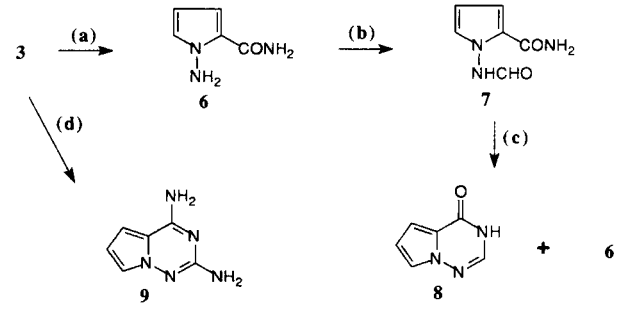


(a) $NH_2OSO_3H$, KOH, Water
(b) $NH_2CH(=)NH$ . AcOH, EtOH, reflux
(c) $K_2CO_3$, $H_2O$, 25 °C
(d) $NH_2CH(=)NH$ . AcOH, $K_2CO_3$, absolute ethanol, reflux.

We investigated next the direct conversion of **3** to the adenine analog **5** by treatment with formamidine acetate in boiling ethanol. This well-known procedure has been used to convert *o*-aminonitrile *C*-nucleoside intermediates directly to the corresponding adenosine analogue [2c,e]. By this procedure carried out in the presence of potassium carbonate as the base, we obtained **5** in crystalline form and in good yield (66%). When the base was omitted, the reaction proceeded only to the stage of the N1-formamidino intermediate **4** which could be isolated by chromatography in 60% yield and characterized by nmr as a mixture of *syn*- and *anti*-isomers. These are not stable and partially convert to **5** during the workup. Evidence of this was obtained by detection of **5** in the nmr spectrum of **4** and by thin layer chromatography of this product where **5** is readily identifiable by its characteristic blue fluorescence under uv illumination. As expected, treatment of **4** with aqueous potassium carbonate cyclizes it rapidly to **5**.

Hypoxanthine analogue **8** was obtained by alkaline hydrolysis of nitrile **3** to amide **6** followed by its *N*-formylation to **7** and final cyclization to **8** in strong base as shown in Scheme 2. Cyclizations of similar 1,2-formamido amides are well documented by us [2f] and others [11]. Partial deformylation to give some of **6** was found to occur simultaneously with the annulation step **7** → **8**. The desired product **8** could be readily purified by chromatography and isolated in 73% yield.

Scheme 2

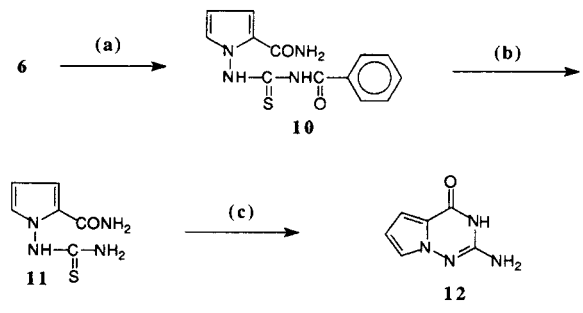


(a) KOH, $H_2O$, 25 °C
(b) HCOOH
(c) $NaOCH_3$/MeOH, reflux
(d) Guanidine carbonate, $NEt_3$, EtOH, 120 °C

Diamino derivative **9** was readily obtained by treatment of the same key intermediate *N*-aminopyrrolonitrile **3** with guanidine carbonate in the presence of triethylamine in ethanol in a pressure vessel. It was isolated by crystallization from water in 62% yield. The bicyclic structure of this product was confirmed by mass spectrometry and by X-ray crystallographic techniques [12].

Guanine analogue **12** was obtained by cyclodesulfurization of 1-(thiocarbamoyl)amino-2-carboxamide **11** according to a procedure developed in Clausen's laboratory [13] for the synthesis of various 9-substituted guanines. Application of that method to the pyrrolo[2,1-*f*]triazine system was equally successful. Thus, reaction of **6** with benzoylisothiocyanate first afforded **10** (obtained crystalline in 89% yield) which, upon alkaline hydrolysis, gave **11** (obtained crystalline in 81% yield). Cyclodesulfurization was finally performed by refluxing **11** in alkaline copper(II) acetate to afford **12** isolated as a crystalline product in 72% yield.

Scheme 3

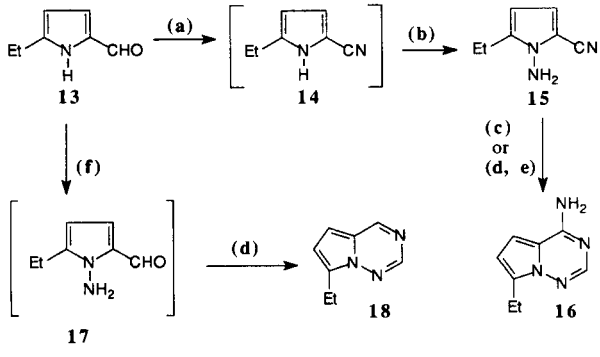


(a) PhCONCS / acetone
(b) $K_2CO_3$, $H_2O$ - acetone - methanol (1:8:8), reflux
(c) 1N NaOH, $Cu(OAc)_2$ , reflux.

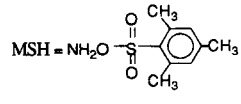
In anticipation of the application of these methods to the corresponding ribosyl 2-substituted pyrrole intermediates, we have also investigated, as a model study, the conversion of 5-ethyl-2-pyrrolaldehyde **13** to the 9-substituted

adenine analog **16** (Scheme 4). Treatment of **13** with HOSA under conditions similar to those which gave **3**, afforded exclusively 5-ethylpyrrole-2-carbonitrile **14** in good yields. It would appear that the ethyl group at C-5 offers, through steric effects, considerable hindrance to the *N*-amination of **14** (or its anion) by HOSA. Utilization of the more reactive *N*-aminating reagent *O*-mesitylenesulfonylhydroxylamine (MSH) [14a-g] was therefore investigated next. We found that, depending on the conditions of the reaction (solvent, temperature and presence or absence of a strong base), this reagent provided a remarkable range of chemical selectivities and could be used to bring about either the *N*-amination of **13** to give **17** (sodium hydride in tetrahydrofuran at 0°) or the conversion of the aldehyde function of **13** to a nitrile to afford **14** (in dichloromethane, without base at room temperature). The latter could be further *N*-aminated with MSH (with sodium hydride in dimethylformamide at 0°) to afford amino nitrile **15**. Finally, the latter could be readily converted to substituted adenine analog **16** upon treatment with formamidine acetate. This same reagent was also used to cyclize **17** to the 4-unsubstituted derivative **18**, the structure of which was further confirmed by mass spectrometry.

Scheme 4




(a) MSH, $CH_2Cl_2$, 25 °C
(b) NaH, MSH, DMF, 0 °C
(c) $NH_2CH{=}NH$ . AcOH, $K_2CO_3$, dimethylacetamide, 100-105 °C
(d) $NH_2CH{=}NH$ . AcOH, EtOH, reflux
(e) $K_2CO_3$, $H_2O$, 25 °C
(f) NaH, MSH, THF, 0 °C




In conclusion, we have developed a simple synthetic approach to obtain 4-mono- and 2,4-difunctionalized derivatives of the pyrrole[2,1-*f*][1,2,4]triazine system which depends on the *N*-amination of 2-pyrrolaldehydes. Its convenience lies in the strategy of utilizing either HOSA or MSH to bring about both *N*-amination and conversion of CHO → CN. Application of the method to the corresponding nucleosides is now in progress and will be described elsewhere.

## EXPERIMENTAL

General Procedures.

Melting points were determined on an electrothermal digital melting point apparatus and are uncorrected. The $^1H$ and $^{13}C$ nmr spectra were run on a Varian XL-200 spectrometer and the chemical shifts were measured relative to tetramethylsilane (TMS). Where possible, signal assignments were confirmed by selective decoupling experiments. Microanalyses were performed by M. H. W. Laboratories, Phoenix, AZ. Thin layer chromatography (tlc) was performed on 250 μm silica gel GHLF plates (Analtech, Inc.), and the substances were visualized by short-wave (254 nm) uv light and/or by spraying with 10% sulfuric acid and charring. Mass spectra were obtained on a Finnigan MAT 90 mass spectrometer using glycerol matrix. The uv spectra were obtained on a Gilford Response II spectrophotometer in 0.05 *M* phosphate buffer, *p*H 7.0 at 25°. Preparative column chromatography was performed by standard flash chromatography techniques on Merck silica gel 60 (230-400 mesh ASTM). Organic extracts and solutions during workup procedures were dried over anhydrous sodium sulfate. Evaporations were performed at the rotary evaporator using either a water aspirator or a vacuum pump as appropriate.

1-Aminopyrrole-2-carbonitrile (**3**).

A mixture of pyrrole-2-carboxaldehyde **1** (25.0 g, 0.26 mole), hydroxylamine-*O*-sulfonic acid (104 g, 0.92 mole) and water (800 ml) was stirred at ambient temperature for 1 hour. The yellow colored solution was cooled to 0° and treated by the dropwise addition of a solution of potassium hydroxide (294.5 g, 5.25 moles) in water (1000 ml) at 0° over a period of 1 hour. The temperature of the reaction mixture was maintained between 0-5° during the addition. After stirring the mixture for 3.5 hours, the insoluble solid was removed by filtration, washed with cold water and the combined filtrate and washings were extracted with dichloromethane (3x). The organic extracts were dried and purified by flash chromatography using hexane-ethyl acetate, 9:1 to give pyrrole-2-carbonitrile **2** (8.94 g, 37%). Further elution with hexane-ethyl acetate, 8:2 gave **3** (12.11 g, 43%); $^1H$-nmr (deuteriochloroform): δ 5.01 (br s, 2H, $NH_2$, exchanged with deuterium oxide), 6.07 (dd, 1H, H-4, $J_{4,3}$ = 4.3 Hz, $J_{4,5}$ = 2.9 Hz), 6.70 (dd, 1H, H-3, $J_{3,5}$ = 1.7 Hz), 6.93 (dd, 1H, H-5); $^{13}C$-nmr (deuteriochloroform): δ 105.8 (C-2), 107.5 (C-4), 113.5 (CN), 118.3 (C-3), 128.4 (C-5).

*Anal.* Calcd. for $C_5H_5N_3$: C, 56.07; H, 4.71; N, 39.23. Found: C, 55.97; H, 4.91; N, 39.12.

4-Aminopyrrolo[2,1-*f*][1,2,4]triazine (**5**).

Method A.

A mixture of **3** (3.0 g, 28 mmoles), formamidine acetate (35.03 g, 0.34 mole), anhydrous potassium carbonate (54.25 g, 0.39 mole) and absolute ethanol (60 ml) was refluxed in an oil bath for 2.5 hours. The brown colored mixture was evaporated to dryness and the residue was triturated with water (150 ml) and cooled in ice. The separated solid was filtered, washed with cold water and dried (2.91 g). Crystallization from hot water afforded **5** as a colorless crystalline solid (2.49 g, 66%), mp 236-239°; $^1H$-nmr (dimethyl sulfoxide-$d_6$ + 2 drops of deuterium oxide): δ 6.60 (dd, 1H, H-6, $J_{6,5}$ = 4.2 Hz, $J_{6,7}$ = 2.6 Hz), 6.85 (dd, 1H, H-5, $J_{5,7}$ = 1.3 Hz), 7.58 (dd, 1H, H-7), 7.77 (s, 1H, H-2); $^{13}C$-nmr (dimethyl sulfoxide-$d_6$ + 2 drops of deuterium oxide): δ 101.3 (C-5), 110.1 (C-6), 114.3 (C-4a), 118.1 (C-7), 147.9 (C-2), 155.5 (C-4); uv: λ max 234,

272 (3.6:1).

*Anal.* Calcd. for $C_6H_6N_4$: C, 53.73; H, 4.51; N, 41.77. Found: C, 53.88; H, 4.55; N, 42.00.

Method B.

A mixture of **4** (0.35 g, 2.61 mmoles, *vide infra*), potassium carbonate (0.72 g, 5.21 mmoles) and water (10.5 ml) was stirred at ambient temperature overnight. The crystallized solid was collected by filtration, washed with water and dried to give (0.25 g, 73%) of **5** identical (tlc, nmr) with the material obtained above.

1-Formamidinopyrrole-2-carbonitrile (**4**).

A mixture of **3** (1.0 g, 9.34 mmoles), formamidine acetate (4.0 g, 38.42 mmoles) and absolute ethanol (20 ml) was refluxed in an oil bath for 2.5 hours. The mixture was cooled in ice and filtered to remove unreacted crystallized formamidine acetate. The filter cake was washed with absolulte ethanol and the combined filtrate and washings were evaporated to dryness. The residue was dissolved in methanol and slurried with silica gel. Upon removal of the solvent, the material was flash chromatographed over silica gel. After elution of unreacted **3** (0.15 g, 15%) with dichloromethane, **4** (0.75 g, 60%) was eluted with dichloromethane-methanol, 99:1 as a ~3:1 mixture of *syn-anti* isomers; $^1$H-nmr (dimethyl sulfoxide-$d_6$ + 2 drops of deuterium oxide): [15] $\delta$ 6.07 (dd, H-4, $J_{4,3}$ = 4.1 Hz, $J_{4,5}$ = 2.7 Hz), 6.74 (dd, H-3, $J_{3,5}$ = 1.4 Hz), 7.19 (dd, H-5), 7.96 (s, -N=CH).

*Anal.* Calcd. for $C_6H_6N_4$: C, 53.73; H, 4.51; N, 41.77. Found: C, 53.47; H, 4.57; N, 41.52.

A small amount of **4** was also eluted which was further purified by trituration of the yellow colored solid first with hexane and then with water to give 0.08 g (6.6%).

1-Aminopyrrole-2-carboxamide (**6**).

A mixture of **3** (12.0 g, 0.11 mole) and potassium hydroxide (151.2 g, 2.70 moles) in water (360 ml) was stirred at ambient temperature for 6.5 hours. Upon cooling in ice, the precipitated solid was collected by filtration and washed with cold water until the washings were neutral and dried to give **6** (3.0 g). The combined washings were neutralized with hydrochloric acid, concentrated to a small volume and kept in the cold overnight. There was obtained an additional 5.44 g (total yield 8.44 g, 60%) of **6**, mp (ethanol) 175-178°; $^1$H-nmr (dimethyl sulfoxide-$d_6$): $\delta$ 5.89 (dd, 1H, H-4, $J_{4,3}$ = 4.2 Hz, $J_{4,5}$ = 2.6 Hz), 6.56 (s, 2H, $NH_2$ exchanged with deuterium oxide), 6.64 (dd, 1H, H-3, $J_{3,5}$ = 2.0 Hz), 6.81 (dd, 1H, H-5), 7.08 (br s, 1H, $NH_2$, exchanged with deuterium oxide), 7.91 (br s, 1H, $NH_2$, exchanged with deuterium oxide); $^{13}$C-nmr (dimethyl sulfoxide-$d_6$ + 2 drops of deuterium oxide): $\delta$ 104.3 (C-4), 110.7 (C-3), 122.8 (C-2), 125.3 (C-5), 163.0 (C=O).

*Anal.* Calcd. for $C_5H_7N_3O$: C, 48.00; H, 5.64; N, 33.58. Found: 48.01; H, 5.60; N, 33.44.

1-Formylaminopyrrole-2-carboxamide (**7**).

A mixture of **6** (4.0 g, 32.97 mmoles), sodium acetate (6.56 g, 80.0 mmoles) and 96% formic acid (45 ml) was stirred overnight. The solvent was removed and the residual oil was triturated with water (20 ml) and cooled in ice. The precipitated solid was collected and washed with cold water to give 3.99 g (81%) of **7**, mp (absolute ethanol) 182-183° dec; $^1$H-mr (dimethyl sulfoxide-$d_6$ + 2 drops of deuterium oxide): [16] $\delta$ 6.05 (m, 1H, H-4), 6.68-7.08 (m, 2H, H-3 and H-5), 8.14 (s, 1H, NHC*H*O); $^{13}$C-nmr (dimethyl sulfoxide-$d_6$): [16] $\delta$ 105.8 (C-4), 111.5 and 112.1 (C-3), 124.3 and 125.6 (C-2), 126.9 and 127.9 (C-5), 160.3 and 165.4 (NHCHO), 161.3 ($CONH_2$).

*Anal.* Calcd. for $C_6H_7N_3O_2$: C, 47.06; H, 4.61; N, 27.44. Found: C, 46.95; H, 4.71; N, 27.33.

Pyrrolo[2,1-*f*][1,2,4]triazin-4(3*H*)-one (**8**).

A mixture of **7** (0.36 g, 2.35 mmoles), 25 wt% of sodium methoxide in methanol (0.17 g, 0.79 mmole) and anhydrous methanol (15 ml) was refluxed in an oil bath for 19 hours. The mixture was neutralized with Amberlite CG-50 ($H^+$) ion exchange resin and evaporated to yield a solid which was dissolved in hot methanol and purified by preparative tlc (1 mm x 7 plates). The plates were developed with dichloromethane-methanol, 9:1 and the two uv absorbing bands were extracted with chloroform-methanol, 1:1. The slower moving compound was identified as **6** (0.056 g, 19%), while the faster moving compound was identified as **8** (0.24 g, 73%), mp (methanol) 227-231°; $^1$H-nmr (dimethyl sulfoxide-$d_6$): $\delta$ 6.52 (dd, 1H, H-6, $J_{6,5}$ = 4.1 Hz, $J_{6,7}$ = 2.9 Hz), 6.87 (dd, 1H, H-5, $J_{5,7}$ = 1.2 Hz), 7.57 (dd, 1H, H-7), 7.81 (ss, 1H, H-2), 11.59 (br s, 1H, NH exchanged with deuterium oxide); $^{13}$C-nmr (dimethyl sulfoxide-$d_6$): $\delta$ 107.3 (C-5), 109.9 (C-6), 119.8 (C-4a), 121.1 (C-7), 138.2 (C-2), 153.9 (C-4); uv: $\lambda$ max 227, 268.5 (4.5:1).

*Anal.* Calcd. for $C_6H_5N_3O$: C, 53.33; H, 3.73; N, 31.10. Found: C, 53.09; H, 4.00; N, 30.87.

2,4-Diaminopyrrolo[2,1-*f*][1,2,4]triazine (**9**).

A mixture of **3** (1.0 g, 9.34 mmoles), guanidine carbonate (5.05 g, 27.8 mmoles), triethylamine (4.73 g, 46.75 mmoles) and absolute ethanol (50 ml) was heated in a stainless steel bomb at 120° for 72 hours. The insoluble guanidine carbonate was removed by filtration and the filtrate was evaporated. The residual solid was purified by flash chromatography eluting unreacted **3** with dichloromethane (0.09 g, 9%). Further elution with dichloromethane-methanol, 95:5 gave **9** (0.86 g, 62%). An analytical sample was obtained by crystallization from hot water, mp 209-213°; $^1$H-nmr (dimethyl sulfoxide-$d_6$): $\delta$ 5.40 (s, 2H, $NH_2$, exchanged with deuterium oxide), 6.30 (dd, 1H, H-6, $J_{6,5}$ = 4.3 Hz, $J_{6,7}$ = 2.5 Hz), 6.66 (dd, 1H, H-5, $J_{5,7}$ = 1.6 Hz), 7.19 (dd, 1H, H-7), 7.27 (br s, 2H, $NH_2$, exchanged with deuterium oxide); $^{13}$C-nmr (dimethyl sulfoxide-$d_6$ + 2 drops of deuterium oxide): $\delta$ 100.5 (C-5); 107.9 (C-6); 111.8 (C-4a); 116.5 (C-7), 155.5 (C-4); 157.2 (C-2); uv: $\lambda$ max 231, 297 (4.3:1); ms: (m/z) 150.1 (M+H).

*Anal.* Calcd. for $C_6H_7N_5$: C, 48.32; H, 4.73; N, 46.96. Found: C, 48.39; H, 4.89; N, 47.01.

1-[[*N*'-Benzoyl(thiocarbamoyl)]amino]pyrrole-2-carboxamide (**10**).

A mixture of **6** (2.0 g, 15.98 mmoles), benzoylisothiocyanate (2.80 g, 17.16 mmoles) and dry acetone (30 ml) was stirred at ambient temperature for 45 minutes. The mixture was cooled in ice and the precipitated solid was collected by filtration, washed with cold acetone and dried (3.83 g). A second crop was similarly obtained by concentration of the filtrate and cooling in ice (0.16 g, for a total yield of 89%), mp (absolute ethanol) 194-196° dec; $^1$H-nmr (dimethyl sulfoxide-$d_6$ + 2 drops of deuterium oxide): $\delta$ 6.09 (dd, 1H, H-4, $J_{4,3}$ = 4.0 Hz, $J_{4,5}$ = 3.0 Hz), 6.80 (dd, 1H, H-3, $J_{3,5}$ = 1.9 Hz), 7.02 (dd, 1H, H-5), 7.53 (t, 2H, H-3' and H-5'), 7.66 (t, 1H, H-4', J = 7.5 Hz), 7.94 (d, 2H, H-2' and H-6', J = 7.2 Hz); $^{13}$C-nmr (dimethyl sulfoxide-$d_6$): $\delta$ 105.7 (C-4), 111.7 (C-3), 124.3 (C-2), 126.7 (C-5), 128.4 and 128.7 (C-2', C-3', C-5', C-6'), 131.8 and 133.2 (C-1' and C-4'), 161.2 ($CONH_2$), 167.4 (C=O), 183.7 (C=S).

*Anal.* Calcd. for $C_{13}H_{12}N_4O_2S$: C, 54.15; H, 4.20; N, 19.43; S, 11.12. Found: C, 54.01; H, 4.20; N, 19.35; S, 11.03.

1-[(Thiocarbamoyl)amino]pyrrole-2-carboxamide (**11**).

A mixture of **10** (4.12 g, 14.29 mmoles), anhydrous potassium carbonate (3.87 g, 28 mmoles), water (17 ml) and acetone-methanol (1:1, 275 ml) was refluxed for 22 hours. Acetic acid (4.01 g) was added and the mixture stirred until the potassium carbonate dissolved. The solution was filtered and concentrated to about a third of its original volume and cooled. There was obtained 2.13 g (81%) of **11** as a crystalline solid in two crops, mp (water) 215-216° dec; $^1$H-nmr (dimethyl sulfoxide-$d_6$ + 2 drops of deuterium oxide): δ 6.03 (dd, 1H, H-4, $J_{4,3}$ = 4.2 Hz, $J_{4,5}$ = 3.0 Hz), 6.74 (dd, 1H, H-3, $J_{3,5}$ = 1.9 Hz), 6.86 (dd, 1H, H-5), 7.0 (br s, slowly exchanged with deuterium oxide), 7.28 (br s, slowly exchanged with deuterium oxide), 8.04 (v br s, exchanged with deuterium oxide), 10.40 (s, 1H, exchanged with deuterium oxide); $^{13}$C-nmr (dimethyl sulfoxide-$d_6$): δ 105.8 (C-4), 112.1 (C-3), 125.1 (C-2), 127.2 (C-5), 161.0 (C=O), 183.9 (C=S).

*Anal.* Calcd. for $C_6H_8N_4OS$: C, 39.12; H, 4.38; N, 30.41; S, 17.40. Found: C, 39.30; H, 4.50; N, 30.62; S, 17.53.

2-Aminopyrrolo[2,1-*f*][1,2,4]triazin-4(3*H*)-one (**12**).

A mixture of **11** (0.2 g, 1.09 mmoles), copper(II) acetate monohydrate (0.24 g, 1.20 mmoles) and 1*N* sodium hydroxide (6.5 ml) was heated in an oil bath at 80° for 1 hour. The mixture was filtered through Celite and the filter cake was washed with 1*N* sodium hydroxide. The filtrate was acidified to *p*H 5.0 with acetic acid and cooled in ice. The resulting product was filtered off, washed with water and dried to give **12** (0.12 g, 72%) as a white crystalline solid, mp (absolute ethanol) >300°; $^1$H-nmr (dimethyl sulfoxide-$d_6$): δ 5.83 (br s, 2H, $NH_2$, exchanged with deuterium oxide), 6.29 (dd, 1H, H-6, $J_{6,5}$ = 4.2 Hz, $J_{6,7}$ = 2.4 Hz), 6.67 (dd, 1H, H-5, $J_{5,7}$ = 1.4 Hz), 7.21 (dd, 1H, H-7), 10.67 (br s, 1H, CONH, exchanged with deuterium oxide); $^{13}$C-nmr (dimethyl sulfoxide-$d_6$): δ 106.2 (C-5), 108.2 (C-6), 116.7 (C-4a), 119.5 (C-7), 148.4 (C-2), 154.6 (C-4); uv: λ max 229, 288 (3.5:1).

*Anal.* Calcd. for $C_6H_6N_4O$: C, 48.00; H, 4.03; N, 37.32. Found: C, 47.90; H, 4.09; N, 37.35.

1-Amino-5-ethylpyrrole-2-carbonitrile (**15**).

A mixture of **13** (2.4 g, 19.5 mmoles), *O*-mesitylenesulfonylhydroxylamine (4.4 g, 20.4 mmoles) and dichloromethane (100 ml) was stirred at ambient temperature for 25 minutes after which the orange-red mixture was washed with aqueous saturated sodium bicarbonate solution and dried. Removal of the solvent gave **14** which was used without further purification in the following step.

A mixture of sodium hydride (60%, 1.56 g, 39 mmoles) and anhydrous dimethylformamide (65 ml) was stirred at 0°. To this was added dropwise a solution of **14** (obtained above) in dimethylformamide (65 ml). After stirring in the cold for 10 minutes, a solution of *O*-mesitylenesulfonylhydroxylamine (5.87 g, 27.3 mmoles) in dimethylformamide (65 ml) was added dropwise over 10 minutes. After stirring at 0° for 30 minutes, the mixture was partitioned between benzene and water and the layers were separated. The aqueous layer was extracted again with benzene. The combined organic extracts were dried and the solvents were removed. The residue was purified by flash chromatography using hexanes-ethyl acetate, 9:1 to give a reddish colored oil from which **15** crystallized upon cooling (1.56 g, 59% based on **13**), mp 41-45°; $^1$H-nmr (deuteriochloroform): δ 1.24 (t, 3H, $CH_3$, J = 7.4 Hz), 2.68 (dq, 2H, $CH_2$), 4.67 (s, 2H, $NH_2$, exchanged with deuterium oxide), 5.84 (dt, 1H, H-4, $J_{4,CH_2}$ = 0.8 Hz, $J_{4,3}$ = 4.4 Hz), 6.65 (d, 1H, H-3).

*Anal.* Calcd. for $C_7H_9N_3$: C, 62.20; H, 6.71; N, 31.09. Found: C, 61.98; H, 6.51; N, 31.03.

7-Ethyl-4-aminopyrrolo[2,1-*f*][1,2,4]triazine (**16**).

Method A.

A mixture of **15** (0.05 g, 0.37 mmoles), formamidine acetate (0.39 g, 3.75 mmoles), potassium carbonate (0.614 g, 4.44 mmoles) and dimethylacetamide (5 ml) was heated in an oil bath at 100-105° for 48 hours. After removal of the solvent the residue was triturated with water, cooled in ice and solid was filtered. The crude product thus obtained was triturated with hexanes and dried. Crystallization from hot water (15 ml) gave pure **16** (0.015 g, 27%).

Method B.

A mixture of **15** (0.05 g, 0.37 mmoles), formamidine acetate (0.39 g, 3.75 mmoles) and absolute ethanol (5 ml) was refluxed for 24 hours. Upon removal of the solvent, the residue was dissolved in water (3 ml) and stirred overnight with potassium carbonate (0.5 g, 3.62 mmoles). The mixture was diluted with water (2 ml) cooled in ice and filtered. The solid which was obtained was triturated with hexanes, dried and crystallized from hot water to give **16** (0.0286 g, 48%), mp 203-208°; $^1$H-nmr (dimethyl sulfoxide-$d_6$): δ 1.23 (t, 3H, $CH_3$, J = 7.6 Hz), 2.82 (q, 2H, $CH_2$), 6.41 (d, 1H, H-6, J = 4.2 Hz), 6.79 (d, 1H, H-5), 7.53 (s, 2H, $NH_2$, exchanged with deuterium oxide), 7.79 (s, 1H, H-2); $^{13}$C-nmr (dimethyl sulfoxide-$d_6$): δ 12.2 ($CH_3$), 18.0 ($CH_2$), 100.4 (C-5), 107.8 (C-6), 113.7 (C-4a), 131.8 (C-7), 147.4 (C-2), 155.4 (C-4).

*Anal.* Calcd. for $C_8H_{10}N_4$: C, 59.24; H, 6.22; N, 34.54. Found: C, 59.20; H, 6.17; N, 34.48.

7-Ethylpyrrolo[2,1-*f*][1,2,4]triazine (**18**).

A solution of **13** (2.0 g, 16.25 mmoles) in dry tetrahydrofuran was added dropwise to a stirred mixture of sodium hydride (60%, 1.35 g, 33.74 mmoles) and dry tetrahydrofuran (50 ml) at 0°. After stirring at 0° for 10 minutes, a solution of *O*-mesitylenesulfonylhydroxylamine [12a] (3.49 g, 16.21 mmoles) in dry tetrahydrofuran (50 ml) was added dropwise over 25 minutes. The mixture was stirred at 0° for 1.25 hours, after which it was partitioned between benzene and water. The layers were separated and the aqueous layer was extracted again with benzene. The combined organic extracts were dried. Filtration followed by removal of the solvent gave **17** which was used without further purification for the preparation of **18** as described below.

A mixture of **17** (obtained above), formamidine acetate (8.46 g, 81.26 mmoles) and absolute ethanol (40 ml) was refluxed in an oil bath for 2 hours. Upon cooling to ambient temperature, the crystallized solid was removed by filtration and washed with ethanol. The combined filtrate and washings were evaporated to dryness. The residue was partitioned between dichloromethane and water and the organic layer was dried and purified by flash chromatography (hexanes-ethyl acetate, 95:5) to give **18** (0.64 g, 27% based on **13**); $^1$H-nmr (deuteriochloroform): δ 1.38 (t, 3H, $CH_3$, J = 7.6 Hz), 3.04 (q, 2H, $CH_2$), 6.79 (d, 1H, H-5 or H-6, J = 4.6 Hz), 6.84 (d, 1H, H-6 or H-5), 8.41 (s, 1H, H-2), 8.84 (s, 1H, H-4); $^{13}$C-nmr (deuteriochloroform): δ 12.0 ($CH_3$), 18.8 ($CH_2$), 104.4 (C-5), 113.4 (C-6), 124.1 (C-4a), 134.5 (C-7), 147.4 (C-2), 151.0 (C-4); ms: (m/z) 148.1 (M+H).

*Anal.* Calcd. for $C_8H_9N_3$: C, 65.29; H, 6.16; N, 28.55. Found: C, 65.12; H, 6.31; N, 28.33.

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[1] This investigation was supported by grants CA-24634 and CA-13330 (Cancer Center Support Grant) from the National Cancer Institute and CH-305 from the American Cancer Society.

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[12] We felt it necessary to dispel any ambiguity concerning the possibility that the product obtained was actually a non-cyclized *N*-guanidino intermediate akin to **4** by further characterization. We thank Dr. Steven E. Ealick (Section of Biochemistry, Molecular and Cell Biology, Cornell University, Ithaca, NY) for confirming its structure by X-ray diffraction studies.

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[15] The $^1$H-nmr spectrum of this compound indicates a mixture of *syn*/*anti* isomers in the approximate ratio of 3:1. The nmr data reported is for the major isomer. The spectrum also shows the presence of small amounts of compound **5** formed as a result of *in situ* cyclization.

[16] The spectrum shows doubling of some of the resonances due to the phenomenon of restricted rotation.