hexane–ethyl acetate (1:2) to afford the following components:

Fraction A gave a pale brown solid, which was recrystallized from boiling ethanol to furnish the macrocycle **29** as brown needles: mp 146–147 °C; 65 mg (3%); R_f 0.27; ^{1}H NMR δ 2.55 (s, γ-CH_2O, 4 H), 2.65 (m, β-CH_2O, 4 H), 3.17 (m, α-CH_2O, 4 H), 4.08 (s, OCH_2CH_2O, 8 H), 7.0 (dd, 5,5′-Pyr-H, J = 7, 2 Hz, 2 H), 7.35 (m, Pyr-H, 7 H); IR (KBr) 2975, 1580, 1530, 1380, 1250, 1200, 1130, 1100 cm^{-1}; mol wt (MS) m/e 587 (M^+). Anal. for $C_{27}H_{29}N_3S_4O_4$: C, H, N.

Fraction B was recrystallized from boiling ethanol to give macrocycle **28** as shiny crystalline plates: mp 183–186 °C; 500 mg (38%); R_f 0.11; ^{1}H NMR (100 MHz, 20% C_6D_6 in $CDCl_3$), Table I; IR (KBr) 2850, 1570, 1430, 1305, 1265, 1210, 1150 cm^{-1}; UV λ_{max} (ϵ) 215 (64 950), 260 (106 100), 306 (40 460); mol wt (MS) m/e 527 (M^+). Anal. for $C_{25}H_{25}N_3S_3O_4$: C, H, N.

Hydrolysis of Macrocycle 28. C,S-Macrocycle 30. A solution of **28** (265 mg, 0.5 mmol) in 80% acetic acid (20 mL) was hydrolyzed according to the above general procedure A. The residue was chromatographed (ThLC), eluting with cyclohexane–ethyl acetate (1:1) to give **30**. Recrystallization from ethanol afforded pale brown needles: mp 158–160 °C; 90 mg (40%); R_f 0.3; ^{1}H NMR (100 MHz, 20% C_6D_6 in $CDCl_3$), Table I; IR (KBr) 3100, 1680 (C=O), 1575, 1240, 1150, 1000 cm^{-1}; UV λ_{max} (ϵ) 237 (29 290), 275 (15 260), 362 (4520); mol wt (MS) 439 (M^+). Anal. for $C_{21}H_{17}N_3S_3O_2$: C, H, N.

Hydrolysis of Macrocycle 29. C,S-Macrocycle 31. Hydrolysis of **29** (298 mg, 0.5 mmol) was carried out as described in procedure A. The residue was chromatographed (ThLC), eluting with cyclohexane–ethyl acetate (1:1) to afford the diketonic macrocycle **31**: mp 129–130 °C; 100 mg (40%); R_f 0.4; ^{1}H NMR δ 2.62 (s, γ-CH_2O, 4 H), 2.80 (m, β-CH_2O, 4 H), 3.20 (m, α-C_2O, 4 H), 7.20 (dd, 5,5′-Pyr-H, J = 7, 2 Hz, 2 H), 7.50 (t, 4,4′-Pyr-H, J = 7 Hz, 2 H), 7.75 (dd, 3,3′-Pyr-H, J = 7, 2 Hz, 2 H), 8.10 (m, 1,2,2′-Pyr-H, 3 H); IR (KBr) 2930, 1685 (C=O), 1580, 1310, 1240, 1160, 1150, 1020 cm^{-1}; mol wt (MS) m/e 499 (M^+). Anal. for $C_{23}H_{21}N_3S_4O_2$: C, H, N.

Reaction of Diketal 4 with Ethanedithiol. C,S-Macrocycle 32. The general macrocycle procedure (2.5-mmol scale) was followed, except for the substitution of ethanedithiol (230 mg, 2.5 mmol). After the standard workup procedure, the residue was chromatographed (ThLC), eluting three times with cyclohexane–ethyl acetate (1:1) to afford the following fractions:

Fraction A gave 15 mg of a crystalline compound: mp 151–152 °C. Insufficient material was available to establish the structure.

Fraction B gave 60 mg (2%) of shining crystalline plates corresponding to **28**: mp 183–186 °C; R_f 0.11.

Fraction C gave a small amount of starting diketal **4**: mp 189–190 °C.

Fraction D was recrystallized from ethanol to give **32** as pale brown needles: mp 236–237 °C; 100 mg (9%); R_f 0.08; ^{1}H NMR (100 MHz, 20% C_6D_6 in $CDCl_3$), Table I; IR (KBr) 2900, 1575, 1560, 1215, 1155, 1110 cm^{-1}; UV λ_{max} (ϵ) 223 (47 740), 261 (112 880), 305 (131 820); mol wt (MS) m/e 467 (M^+). Anal. for $C_{23}H_{21}N_3S_2O_4$: C, H, N.

Hydrolysis of 32. C,S-Macrocycle 33. Macrocycle **32** (233 mg, 0.5 mmol) in 80% acetic acid was hydrolyzed by the standard procedure A. The residue was chromatographed (ThLC), eluting with cyclohexane–ethyl acetate (1:1) to give the diketonic macrocycle **33**, which was recrystallized from ethanol to furnish pale brownish crystalline plates: mp 199–201 °C; 70 mg (40%); R_f 0.12; ^{1}H NMR (100 MHz, 20% C_6D_6 in $CDCl_3$), Table I; IR (KBr) 2960, 1675 (C=O), 1560, 1330, 1310, 1275, 1155 cm^{-1}; UV λ_{max} (ϵ) 235 (102 670), 277 (52 470), 360 (4330); mol wt (MS) m/e 379 (M^+). Anal. for $C_{19}H_{13}N_3S_2O_2$: C, H, N.

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Registry No. **3**, 68871-28-3; **4**, 68871-29-4; **5**, 68871-30-7; **8**, 71435-64-8; **9**, 71435-65-9; **10**, 71435-66-0; **11**, 68871-31-8; **12a**, 68871-32-9; **12b**, 71435-67-1; **12c**, 71435-68-2; **13**, 71435-69-3; **14**, 71435-70-6; **15**, 71435-71-7; **16**, 71435-72-8; **17**, 71435-73-9; **18**, 71435-74-0; **19**, 71435-75-1; **20**, 71435-76-2; **21**, 71435-77-3; **22**, 71435-78-4; **23**, 71435-79-5; **24**, 71435-80-8; **25**, 71435-81-9; **26**, 71435-82-0; **27**, 71435-83-1; **28**, 71435-84-2; **29**, 71435-85-3; **30**, 71435-86-4; **31**, 71435-87-5; **32**, 71435-88-6; **33**, 71435-89-7; 2-bromo-6-lithiopyridine, 37709-60-7; dimethyl 2,6-pyridinedicarboxylate, 5453-67-8; 2,6-dicyanopyridine, 2893-33-6; 2,6-dipicolinoyl dichloride, 3739-94-4; 2-bromoethanol, 540-51-2; ethylene glycol, 107-21-1; acetic acid, 64-19-7; diethylene glycol, 111-46-6; triethylene glycol, 112-27-6; tetraethylene glycol, 112-60-7; pentaethylene glycol, 4792-15-8; hexaethylene glycol, 2615-15-8; bis(2-mercaptoethyl) ether, 2150-02-9; bis(2-mercaptoethyl) sulfide, 3570-55-6; ethanedithiol, 540-63-6.

Supplementary Material Available: Experimental data for **19–25**, analytical data for all new compounds (Table A1) (7 pages). Ordering information is given on any current masthead page.

A New Synthesis of Pyrrolo[3,2-*d*]pyrimidines ("9-Deazapurines") via 3-Amino-2-carboalkoxypyrroles[1]

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Several 3-amino-2-carboalkoxypyrroles have been obtained by the base-catalyzed cyclization of *N*-(2-cyanovinyl)glycine esters. These substituted pyrroles are readily converted in two steps to 5*H*-pyrrole[3,2-*d*]pyrimidines ("9-deazapurines").

As part of an ongoing program directed toward the synthesis of new C-nucleosides of potential biomedical interest, we have recently described a new synthesis of 5*H*-pyrrolo[3,2-*d*]pyrimidines (9-deazapurines) by the hydrogenolytic ring contraction of various pyrimido-[5,4-*c*]pyridazines.[2] As an extension of these studies, we wish to report here an alternate synthetic route to the 9-deazapurine system.

(1) This investigation was supported by funds from the National Cancer Institute, Department of Health, Education and Welfare (Grants CA-08748, 18856 and 24634).

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The most generally used approach to pyrrolo[3,2-*d*]-pyrimidines has so far involved elaboration of the pyrrole ring onto a preformed pyrimidine bearing reactive functionalities at C-4 and C-5. The methods employed have been reviewed,[3] and we have briefly commented on the potential applicability of these to the synthesis of the corresponding C-nucleosides.[2]

A different strategy utilized more recently has involved building of the pyrimidine ring onto a preformed 3-aminopyrrole intermediate, and only a few examples of this general approach have been reported. These include (a) the synthesis of 2-carboalkoxy-3-ureidopyrroles derived from 2,3-dicarboxypyrroles via Curtius rearrangement of the 3-acyl azide intermediate[4,5] (this method has served to synthesize the first reported pyrrolo[3,2-*d*]pyrimidine C-ribonucleoside)[4], and (b) the condensation of α-amino-α-cyanoacetamides with ethyl acetoacetate, followed by cyclization to 3-amino-2-carboxamido-4-ethoxycarbonyl-5-methylpyrroles suitable for further elaboration of a fused pyrimidine ring.[6]

The method we describe herein also involves initial formation of a pyrrole ring but was designed to provide directly the 3-amino-2-carboalkoxypyrrole derivative, thus avoiding selective and/or lengthy conversion of a carboxy to an amino function as in method a. Furthermore, our method can accommodate a variety of substituents at position C-4, instead of the mandatory carboalkoxy group of method b. Such factors, we feel, should make the method particularly suitable for the synthesis of 9-deazapurine C-nucleoside derivatives.

Reaction of α-cyanopropionaldehyde[7] 1 with glycine ethyl ester in aqueous methanol at room temperature readily afforded enaminonitrile **3** isolated as a syrup in 54% yield. Its ^{1}H NMR spectrum exhibited two sets of doublets in roughly 4:1 ratio (δ 6.62, J = 13.1 Hz, and δ 6.45, J = 12.2 Hz, respectively), which collapsed to two singlets after addition of D_2O. This change also coincided with the disappearance of the NH signal at δ 4.94. Two singlets (4:1 ratio) for the methyl groups could also be detected at δ 1.71 and 1.75. No signals which might have been attributed to the alternate iminic structure were detected. These results indicate that the product exists exclusively as an isomeric syn and anti mixture[8] of the enamine structures **3** depicted in Scheme I and are also consistent with earlier observations that similar enamines incorporating electronegative functionalities such as CO, CN, or NO_2 in the β position exist almost entirely as the enamine rather than the imine form.[9,10]

Treatment of **3** with ethanolic sodium ethoxide at 70 °C for 6 h afforded the cyclized 3-amino-2-carboethoxy-4-methylpyrrole (**7**), which was isolated in 30% yield after purification by silica gel column chromatography. Similar results were obtained by using potassium *tert*-butoxide in tetrahydrofuran. The generally low yields obtained for this conversion might be best explained by preferential formation of a highly stabilized anion derived from proton abstraction of N-H, thereby inhibiting generation of the carbanion necessary for cyclization.

Elaboration of the pyrimidine ring was accomplished by the following methods. Compound **7** was first converted to the corresponding (dimethylamino)methylenimine intermediate **10** in 87% yield by treatment with the formylating agent dimethylformamide dimethyl acetal. Cyclization to 7-methyl-4-oxo-3*H*-5*H*-pyrrolo[3,2-*d*]pyrimidine (**12**) was carried out in 92% yield by treatment of **10** with saturated methanolic ammonia at 20 °C for 3 days. The identity of pyrrolopyrimidine **12** was confirmed by ^{1}H NMR, elemental analysis, and comparison of its ultraviolet spectrum with that of the known unmethylated compound[11] (**12**; R = R′ = H). Aminopyrrole **7** also reacted with methyl isocyanate in dichloromethane at 20 °C for 2 h or with methyl isothiocyanate in triethylamine at 70 °C for 3 h to afford the corresponding ureido (**15**) and thioureido (**16**) derivatives in 93 and 76% yields, respectively. Cyclization of these intermediates by treatment with potassium carbonate in methanol afforded 3,7-dimethyl-2,4-dioxo-1*H*,5*H*-pyrrolo[3,2-*d*]pyrimidine[5] (**17**) (95%) and 3,7-dimethyl-4-oxo-2-thioxo-1*H*,5*H*-pyrrolo-[3,2-*d*]pyrimidine (**18**) (87%), respectively.

In order to determine the scope of this synthetic approach to pyrrolo[3,2-*d*]pyrimidines, investigation of a phenyl-substituted pyrrole was also undertaken. While condensation of glycine ethyl ester with 2-formylphenylacetonitrile[12] afforded the desired enamine **5** in good yield, attempts to cyclize **5** to the corresponding 3-amino-4-phenylpyrrole under a variety of conditions in base were unsuccessful. These results were not altogether unanticipated since the anion formed from **5** in base by the abstraction of the NH proton would be even more stable than its methyl analogue as a result of the added conjugation to the aromatic ring. On this basis, blocking of the free secondary amino group was expected to enhance formation of the carbanion intermediate in the cyclization to the desired pyrrole. Ethyl *N*-benzyl-*N*-(2-phenyl-2-cyanovinyl)glycinate derivative **6**, obtained by reaction of ethyl *N*-benzylglycinate with **2**, could thus be converted in 93% yield to 3-amino-1-benzyl-2-carboethoxy-4-phenylpyrrole (**9**) in the presence of ethanolic sodium ethoxide at 20 °C. It was found, furthermore, that cyclization of **4** (the *N*-benzylated derivative of **3**) afforded the pyrrole derivative **8** in 93% yield. These results strongly suggest that competitive ionization of the NH group is a determining factor in the inhibition of cyclization of compounds **3** and **5** to the corresponding pyrroles. The phenyl derivative **9** was converted to the pyrrolo[3,2-*d*]-pyrimidine **13** in two steps. The (dimethylamino)-methylenimine intermediate **11** was first obtained (89%) by treatment of **9** with a dimethylformamide acetal, followed by cyclization in methanolic ammonia to afford **13** in 74% yield. Debenzylation of **13** by hydrogenolysis over Pd/C catalyst was attempted without success but could be achieved by the utilization of sodium naphthylide in tetrahydrofuran[13] to afford **14** in 67% yield.

It is apparent from these preliminary studies that cyclization of enaminonitriles with activated methylene groups of the type described above offer a new and convenient access to 5*H*-pyrrolo[3,2-*d*]pyrimidine systems.

Further investigations of the scope of these transformations and of their application to the synthesis of 9-

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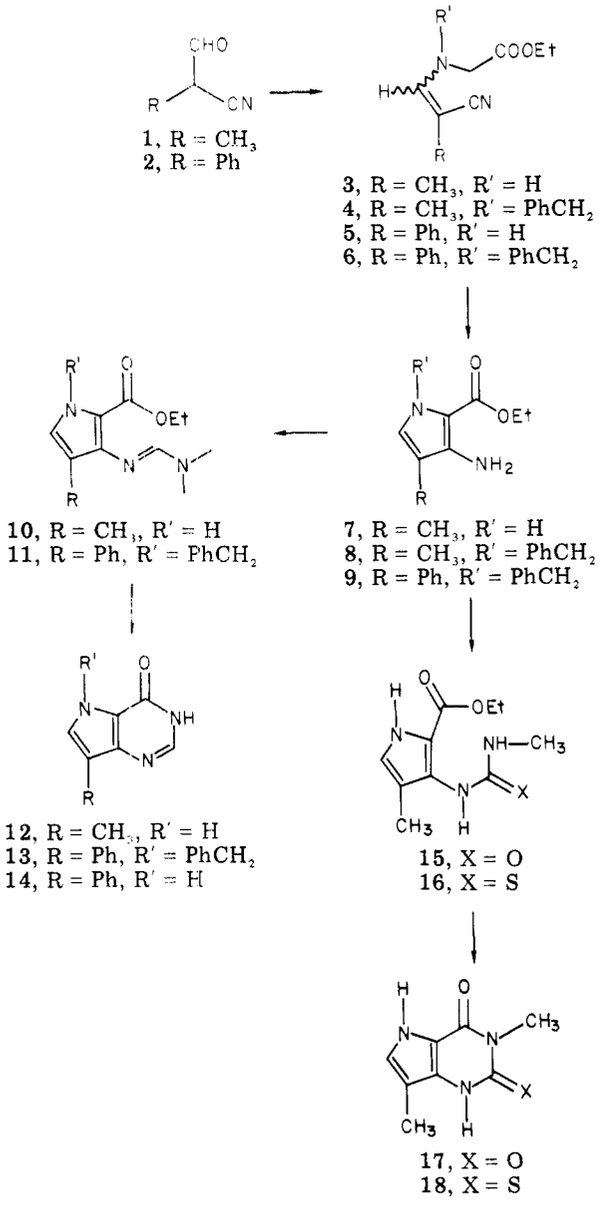
Scheme I



deazapurine C-nucleosides are underway and will be the subject of a separate report.

Experimental Section

Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. The ^{1}H NMR spectra were obtained with a Jeol PFT-100 spectrometer with Me_4Si as internal standard. Ultraviolet absorption spectra were obtained with a Cary recording spectrophotometer, Model 15. Microanalyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, MI. Column chromatography was performed on Woelm silica gel (70–230 mesh). Thin-layer chromatography was performed on 250-μm silica gel plates (Analtech Inc.) using ultraviolet light and iodine vapor for visualization.

***N*-(2-Methyl-2-cyanovinyl)glycine Ethyl Ester (3).** A mixture of α-cyanopropionaldehyde[7] (1) (7.00 g, 84 mmol), glycine ethyl ester hydrochloride (17.6 g, 126 mmol), and sodium acetate (10.3 g, 126 mmol) in 100 mL of methanol–water (8:2) was stirred overnight at 20 °C. After evaporation of methanol, the residue was partitioned between water and ethyl acetate. The organic layer was washed with water, dried over sodium sulfate, and evaporated to dryness. The oily residue was chromatographed on a silica gel column by eluting with CH_2Cl_2–MeOH (30:1) to afford a syn–anti mixture of the enamine **3** (5.38 g, 54%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.29 (t, 3 H, CH_3CH_2, J = 7.2 Hz), 1.71 and 1.75 (2s (4:1), 3 H, CH_3C), 3.89 and 3.91 (2d, 2 H, CH_2NH, J = 5.8 and 6.1 Hz), 4.21 (q, 2 H, CH_2CH_3, J = 7.2 Hz), 4.94 (m, 1 H, NH exchange with D_2O), 6.45, 6.62 (2d (1:4), 1 H, CHNH, J = 12.2 and 13.1 Hz). Careful inspection of the expanded spectrum showed a small allylic coupling of 0.9 Hz for signals δ 1.71, 1.75, 6.45, and 6.62. Anal. Calcd for $C_8H_{12}N_2O_2$: C, 57.13; H, 7.19; N, 16.66. Found: C, 57.12; H, 7.24; N, 16.58.

3-Amino-2-ethoxycarbonyl-4-methyl-1*H*-pyrrole (7). A solution of the enamine **3** (2.73 g, 16 mmol) in ethanolic sodium ethoxide (20 mL of a 0.91 M solution) was heated at 70 °C for 6 h. The reaction mixture was cooled to room temperature and evaporated to dryness in vacuo. The residue was partitioned between water and ethyl acetate. After separation of the organic phase, the water layer was neutralized with acetic acid and extracted twice with ethyl acetate. The organic layer and washings were combined, dried over sodium sulfate, and evaporated to dryness. The residue was chromatographed on a column of silica gel (80 g) by eluting with CH_2Cl_2–MeOH (30:1) to afford **7** (810 mg, 30%) as an oil which was crystallized from dichloromethane–petroleum ether (30–60 °C): mp 98–99 °C; ^{1}H NMR ($CDCl_3$) δ 1.35 (t, 3 H, CH_3CH_2, J = 7.1 Hz), 1.94 (d, 3 H, CH_3C, J = 0.6 Hz), 4.31 (q and br s, 4 H, CH_2 and NH_2), 6.53 (d, 1 H, H-5, J = 2.7 Hz), 8.02 (br s, 1 H, NH exchange with D_2O); UV (pH 1) λ_{max} 270 nm (ϵ 16 960), (pH 7, 13) λ_{max} 270 (19 940). Anal. Calcd for $C_8H_{12}N_2O_2$: C, 57.13; H, 7.19; H, 16.66. Found: C, 57.20; H, 7.26; N, 16.56.

3-[*N*-(Dimethylamino)methylene]amino-2-ethoxycarbonyl-4-methyl-1*H*-pyrrole (10). A mixture of the 3-aminopyrrole **7** (200 mg, 1.2 mmol) and dimethylformamide dimethyl acetal (1 mL) was stored at room temperature for 7 days and evaporated to dryness in vacuo. Crystallization of the residue from dichloromethane–petroleum ether (30–60 °C) afforded analytically pure *N*-(dimethylamino)methylene derivative **10** (230 mg, 87%): mp 101 °C; ^{1}H NMR ($CDCl_3$) δ 1.28 (t, 3 H, CH_3CH_2, J = 7.0 Hz), 1.96 (d, 3 H, CH_3C), 3.01 (s, 6 H, $N(CH_3)_2$), 4.22 (q, 2 H, CH_2CH_3, J = 7.0 Hz), 6.60 (d, 1 H, H-5, J = 2.5 Hz), 7.56 (s, 1 H, N=CH), 8.58 (br s, 1 H, NH); UV (pH 7) λ_{max} 275 nm (ϵ 16 460). Anal. Calcd for $C_{11}H_{17}N_3O_2$: C, 59.17; H, 7.67; N, 18.82. Found: C, 59.24; H, 7.59; N, 18.93.

7-Methyl-4-oxo-3*H*,5*H*-pyrrolo[3,2-*d*]pyrimidine (12). A solution of the *N*-(dimethylamino)methylene derivative **10** (100 mg, 0.45 mmol) in methanol (15 mL) was saturated with ammonia at 0 °C and left at room temperature for 3 days. The reaction mixture which had already precipitated some of the product was cooled in an ice bath. The white solid was collected by filtration and washed with ethyl ether to afford **12** (60 mg, 92%) as an analytically pure crystalline material: mp >310 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.15 (s, 3 H, CH_3), 7.17 (s, 1 H, H-6), 7.76 (s, 1 H, H-2), 11.70 (br s, 2 H, 2NH exchange with D_2O); UV (pH 1) λ_{max} 266 nm (sh) (ϵ 7250), 242 (26 670), (pH 7) λ_{max} 263 (ϵ 25 360), λ_{min} 251 (ϵ 6520), (pH 13) λ_{max} 270 (ϵ 7190), λ_{min} 248 (ϵ 4930). Anal. Calcd for $C_7H_7N_3O$: C, 56.37; H, 4.73; N, 28.17. Found: C, 56.32; H, 4.75; N, 28.20.

2-Ethoxycarbonyl-4-methyl-3-(*N'*-methylureido)-1*H*-pyrrole (15). To a solution of the 3-aminopyrrole **7** (240 mg, 1.43 mmol) in dichloromethane (2.5 mL) was added methyl isocyanate (483 mg, 8.48 mmol). The reaction mixture was stirred at room temperature for 2 h and evaporated to dryness in vacuo, and the residue was crystallized from methanol to afford **5** (300 mg, 93.5%) in analytically pure form: mp 222–223 °C; ^{1}H NMR (Me_2SO-d_6) δ 1.26 (t, 3 H, CH_3CH_2, J = 7.0 Hz), 1.88 (s, 3 H, CH_3C), 2.59 (d, 3 H, CH_3NH, J = 4.6 Hz), 4.19 (q, 2 H, CH_2CH_3, J = 7.0 Hz), 6.35 (q, 1 H, NH exchange with D_2O, J = 4.9 Hz), 6.67 (d, 1 H, H-5, J = 3.1 Hz), 7.43 (s, 1 H, NH exchange with D_2O), 11.15 (broad s, 1 H, NH exchange with D_2O); UV (pH 7) λ_{max} 275 nm (ϵ 12 660). Anal. Calcd for $C_{10}H_{15}N_3O_3$: C, 53.32; H, 6.71; N, 18.65. Found: C, 53.43; H, 6.68; N, 18.63.

2-Ethoxycarbonyl-4-methyl-3-(*N'*-methylthioureido)-1*H*-pyrrole (16). A mixture of the 3-aminopyrrole **7** (148 mg, 0.88 mmol) and methyl isothiocyanate (80 mg, 1.1 mmol) in triethylamine (3 mL) was stirred at 70 °C for 3 h and cooled to 20 °C. The formed precipitate was collected and washed with ethyl ether to afford the thioureido derivative **16** (163 mg, 76%) as an analytically pure crystalline solid: mp 190–191 °C; ^{1}H NMR (Me_2SO-d_6) δ 1.23 (t, 3 H, CH_3CH_2, J = 7.0 Hz), 1.85 (s, 3 H, CH_3C), 2.84 (d, 3 H, CH_3NH, J = 4.6 Hz), 4.14 (q, 2 H, CH_2CH_3, J = 7.0 Hz), 6.77 (d, 1 H, H-5, J = 3.1 Hz), 7.14 (br s, 1 H, NH

exchange with D_2O), 8.64 (s, 1 H, NH exchange with D_2O), 11.52 (broad s, 1 H, NH, exchange with D_2O); UV (pH 7) λ_{max} 275 nm (ϵ 20870), 236 (19970), λ_{min} 253 (14810). Anal. Calcd for $C_{10}H_{15}N_3O_2S$: C, 49.78; H, 6.27; N, 17.42; S, 13.29. Found: C, 49.69; H, 6.27; N, 17.39; S, 13.26.

3,7-Dimethyl-2,4-dioxo-1*H*,5*H*-pyrrolo[3,2*d*]pyrimidine (17). A mixture of the ureido derivative **15** (60 mg, 0.27 mmol) and potassium carbonate (46 mg, 0.33 mmol) in methanol (10 mL) was stirred at 70 °C for 24 h. A precipitate was formed while the reaction proceeded. The mixture was cooled to room temperature, and the precipitate was filtered and washed with cold water and methanol to afford **17** (49 mg, 95%) as an analytically pure solid: mp >310 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.20 (s, 3 H, CH_3), 3.19 (s, 3 H, NCH_3), 6.97 (d, 1 H, H-6, J = 3.0 Hz), 11.11, 11.57 (2 br s, 1 H each, NH exchange with D_2O); UV (pH 1,7), λ_{max} 272 nm (ϵ 14060), λ_{min} 244 (ϵ 3130), (pH 13) λ_{max} 301 (ϵ 5940), 268 (ϵ 9060), λ_{min} 284 (ϵ 4840), 247 (ϵ 4610). Anal. Calcd for $C_8H_9N_3O_2$: C, 53.63; H, 5.06; N, 23.45. Found: C, 53.57; H, 5.01; N, 23.21.

3,7-Dimethyl-4-oxo-2-thioxo-1*H*,5*H*-pyrrolo[3,2-*d*]pyrimidine (18). A mixture of the thioureido derivative **16** (108 mg, 0.45 mmol) and potassium carbonate (68 mg, 0.49 mmol) in methanol (5 mL) was stirred at 80 °C for 16 h. After evaporation of methanol, the residue was dissolved in water and neutralized with 1 N HCl to precipitate **18** (82 mg, 87%) which was collected by filtration and washed with water: mp >310 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.10 (s, 3 H, CH_3), 3.63 (s, 3 H, NCH_3), 7.13 (d, 1 H, H-5, J = 2.1 Hz), 11.94, 12.85 (2 br s, 1 H each, NH exchange with D_2O); UV (pH 1,7) λ_{max} 268 nm (ϵ 28190), λ_{min} 244 (ϵ 8880), (pH 13) 285 (sh) (ϵ 11970) 256 (ϵ 35710), λ_{min} 235 (ϵ 13510). Anal. Calcd for $C_8H_9N_3OS$: C, 49.21; H, 4.65; N, 21.52; S, 16.42. Found: C, 49.05; H, 4.66; N, 21.46; S, 16.42.

***N*-(2-Phenyl-2-cyanovinyl)glycine Ethyl Ester (5).** A mixture of α-formylphenylacetonitrile[12] **2** (7.25 g, 50 mmol), ethyl glycine ester hydrochloride (9.07 g, 65 mmol), and sodium acetate (6.8 g) was dissolved in 50 mL of MeOH and 1 mL of H_2O and stirred at 20 °C for 48 h. After solvent evaporation, the residue was partitioned between water and ethyl acetate. The organic layer was washed with 5% aqueous sodium bicarbonate, dried over sodium sulfate, and evaporated to dryness. Addition of ethyl ether and filtration afforded **5** (8.5 g, 74%) as a chromatographically homogeneous white solid: ^{1}H NMR ($CDCl_3$) δ 1.30 (t, 3 H, CH_3CH_2, J = 7.2 Hz), 4.05 (d, 2 H, NCH_2, J = 5.8 Hz), 4.25 (q, 2 H, CH_2CH_3, J = 7.2 Hz), 5.51 (m, 1 H, NH exchange with D_2O), 7.04–7.32 (m, 6 H, C_6H_5 and olefinic H). This compound was not characterized further.

***N*-Benzyl-*N*-(2-phenyl-2-cyanovinyl)glycine Ethyl Ester (6).** A solution of 2-formylphenylacetonitrile (**2**) (1.0 g, 6.9 mmol) and *N*-benzylglycine ethyl ester (1.6 g, 8.3 mmol) in benzene (25 mL) was heated to reflux under a water separator for 10 h and then evaporated in vacuo. Trituration of the residue with ethyl ether afforded a white crystalline solid (912 mg) identified as a single geometrical isomer of **6**. After filtration, the ethereal mother liquor was chromatographed on a silica gel column (CH_2Cl_2–MeOH, 30:1) to afford an additional 379 mg of this same product: mp 77 °C; ^{1}H NMR ($CDCl_3$) δ 1.29 (t, 3 H, CH_3CH_2, J = 7.2 Hz), 4.26 (m, 4 H, CH_2CH_3 and CH_2CO), 4.62 (s, 2 H, CH_2Ph), 7.09 (s, 1 H, olefinic H), 7.33 (m, 10 H, $2C_6H_5$). Anal. Calcd for $C_{20}H_{20}N_2O_2$: C, 74.98; H, 6.29; N, 8.74. Found: C, 75.13; H, 6.27; N, 8.86.

Collection of a slower moving fraction afforded 227 mg of a syrup identified as the other geometrical isomer: ^{1}H NMR ($CDCl_3$) δ 1.18 (t, 3 H, CH_3CH_2, J = 7.2 Hz), 3.57 (s, 2 H, NCH_2), 4.07 (q, 2 H, CH_2CH_3, J = 7.2 Hz), 4.28 (s, 2 H, CH_2Ph), 6.95 (s, 1 H, olefinic H), 7.25 (m, 10 H, $2C_6H_5$). The overall yield of both isomers was 69%.

3-Amino-1-benzyl-2-ethoxycarbonyl-4-phenyl-1*H*-pyrrole (9). A solution of crystalline *N*-benzyl glycinate **6** (major isomer) (770 mg, 2.4 mmol) in 0.28 M ethanolic sodium ethoxide (10 mL) was stirred at room temperature for 1.5 h. After usual workup and column chromatography (see preparation of **7**), **9** (716 mg, 93%) was obtained as a colorless oil which solidified on standing. Recrystallization from ethyl ether–petroleum ether afforded an analytical sample: mp 67 °C; ^{1}H NMR ($CDCl_3$) δ 1.22 (t, 3 H, CH_3CH_2, J = 7.0 Hz), 4.21 (q, 2 H, CH_2CH_3, J = 7.0 Hz), 4.72 (br s, 2 H, NH_2), 5.36 (s, 2 H, CH_2Ph), 6.77 (s, 1 H, H-5), 7.25 (m, 10 H, $2C_6H_5$). Anal. Calcd for $C_{20}H_{20}N_2O_2$: C, 74.98; H, 6.29; N, 8.74. Found: C, 75.06; H, 6.27; N, 8.75.

***N*-Benzyl-*N*-(2-methyl-2-cyanovinyl)glycine Ethyl Ester (4).** To a solution of 2-cyanopropionaldehyde[7] (**1**) (0.83 g, 10 mmol) in methanol (5 mL) was added *N*-benzylglycine ethyl ester (3.86 g, 20 mmol), trifluoroacetic acid (114 mg, 1 mmol), and enough powdered sodium bicarbonate to neutralize the mixture. After stirring overnight, the solution was evaporated to dryness, and the residue was partitioned between dichloromethane and water. The organic layer was dried over sodium sulfate and evaporated to dryness, and the residue was chromatographed on a silica gel column (200 g) with CH_2Cl_2–MeOH (40:1). Collection of the appropriate fractions and evaporation afforded **4** (850 mg, 33%) as an analytically pure oil: ^{1}H NMR ($CDCl_3$) δ 1.27 (t, 3 H, CH_3CH_2, J = 7.2 Hz), 1.84 (s, 3 H, CH_3C), 4.07 (s, 2 H, CH_2CO), 4.22 (q, 2 H, CH_2CH_3, J = 7.2 Hz), 4.45 (s, 2 H, CH_2Ph), 6.42 (s, 1 H, olefinic H), 7.29 (m, 5 H, C_6H_5). Anal. Calcd for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.84. Found: C, 69.63; H, 7.02; N, 10.84.

3-Amino-1-benzyl-2-ethoxycarbonyl-4-methyl-1*H*-pyrrole (8). The enaminonitrile **4** (258 mg, 1 mmol) was dissolved in 0.1 M ethanolic sodium ethoxide (5 mL) and allowed to react at 20 °C for 16 h. The basic solution was neutralized with an excess of Amberlite IRC-50 (H^+) resin and evaporated to dryness, and the residue was extracted twice with ethyl ether. Filtration and evaporation of the ethereal solution afforded **8** (240 mg, 93%) as an analytically pure and colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.23 (t, 3 H, CH_3CH_2, J = 7.2 Hz), 1.94 (s, 3 H, CH_3C), 4.21 (q, 2 H, CH_2CH_3, J = 7.0 Hz), 4.49 (br s, 2 H, NH_2 exchange with D_2O), 5.31 (s, 2 H, CH_2Ph), 6.49 (s, 1 H, H-5), 7.39 (m, 5 H, C_6H_5). Anal. Calcd for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.84. Found: C, 69.75; H, 7.13; N, 10.83.

1-Benzyl-3-[*N*-(dimethylamino)methylene]amino-2-ethoxycarbonyl-4-phenyl-1*H*-pyrrole (11). A mixture of **9** (925 mg, 2.88 mmol) and dimethylformamide dineopentyl acetal (2.5 mL) in chloroform (3 mL) was heated to reflux with stirring at 80 °C for 5 days. The reaction mixture was evaporated to dryness in vacuo at 50 °C, and the solid residue was washed with cold ethyl ether to afford **11** (942 mg, 86.9%). Recrystallization from ethyl ether gave an analytical sample: mp 108 °C; ^{1}H NMR ($CDCl_3$) δ 1.20 (t, 3 H, CH_3CH_2, J = 7.2 Hz), 3.01 (br s, 6 H, $N(CH_3)_2$), 4.15 (q, 2 H, CH_2CH_3, J = 7.2 Hz), 5.51 (s, 2 H, CH_2Ph), 6.70 (s, 1 H, H-5), 7.07–7.80 (m, 11 H, $2C_6H_5$ and N=CH). Anal. Calcd for $C_{23}H_{25}N_3O_2$: C, 73.58; H, 6.71; N, 11.19. Found: C, 73.53; H, 6.64; N, 11.23.

5-*N*-Benzyl-4-oxo-7-phenyl-3*H*,5*H*-pyrrolo[3,2-*d*]pyrimidine (13). A solution of the *N*-(dimethylamino)methylene derivative **11** (300 mg, 1 mmol) in methanol (10 mL) was saturated with ammonia and stored at room temperature for 3 days. Evaporation of methanol left a white solid which was washed with ethyl ether to give **13** (178 mg, 74%) as an analytically pure crystalline solid: mp 261–262 °C; ^{1}H NMR (Me_2SO-d_6) δ 5.67 (s, 2 H, CH_2Ph), 7.12–8.09 (m, 12 H, $2C_6H_5$, H-2 and H-6), 12.08 (s, 1 H, NH exchange with D_2O). Anal. Calcd for $C_{19}H_{15}N_3O$: C, 75.73; H, 5.02; N, 13.94. Found: C, 75.85; H, 4.95; N, 14.00.

7-Phenyl-4-oxo-3*H*,5*H*-pyrrolo[3,2-*d*]pyrimidine (14). A solution of sodium naphthalene in tetrahydrofuran (12 mL of 0.35 M solution)[13] was added to a suspension of **13** (100 mg, 0.33 mmol) in tetrahydrofuran (50 mL) under nitrogen, and the mixture was stirred at room temperature for 5 h. It was opened to the atmosphere while stirring until the green color had disappeared and then evaporated to dryness in vacuo. The solid residue was washed with ethyl ether (3 × 10 mL), dissolved in water, and carefully neutralized with 1 N HCl. The resulting white precipitate was collected by filtration and washed with ethyl ether to give **14** (47 mg, 67%). Recrystallization from DMF–MeOH afforded an analytically pure sample: mp >300 °C; ^{1}H NMR (Me_2SO-d_6) δ 7.30–8.12 (m, 7 H, C_6H_5, H-2 and H-6), 10.01 and 10.36 (2 br s, 1 H each exchange with D_2O). Anal. Calcd for $C_{12}H_9N_3O$: C, 68.24; H, 4.29; N, 19.89. Found: C, 68.23; H, 4.22; N, 19.97.

Registry No. **1**, 26692-50-2; **2**, 5841-70-3; **3** isomer 1, 71435-26-2; **3** isomer 2, 71435-27-3; **4**, 71435-28-4; **5**, 71435-29-5; **6** isomer 1, 71435-30-8; **6** isomer 2, 71435-31-9; **7**, 71435-32-0; **8**, 71435-33-1; **9**, 71435-34-2; **10**, 71435-35-3; **11**, 71435-36-4; **12**, 71435-37-5; **13**, 71435-38-6; **14**, 71435-39-7; **15**, 71435-40-0; **16**, 71435-41-1; **17**, 67855-91-8; **18**, 71435-42-2; glycine ethyl ester hydrochloride, 623-33-6; *N*-benzylglycine ethyl ester, 6436-90-4.