to a yellow solid, 0.55 g. Flash chromatography of the solid with 50 g of silica gel, eluted with 25% EtOAc/hexanes, yielded, after recrystallization from toluene, light yellow crystals of **11** (.072 g, 13%): mp 189–191 °C. Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 73.28; H, 5.86; N, 10.39.

1-Hydroxy-*N*-(4-methoxyphenyl)-1,2-dihydro-3*H*-3-benzazepine-3-carboxamide (10). Compound **7c** (0.50 g, 1.62 mmol) was dissolved in 4 mL of dry distilled THF and treated with $LiAlH_4$ (0.092 g, 2.43 mmol) dissolved in 10 mL of dry distilled THF by dropwise addition. After 1 h the mixture was quenched by addition of 0.192 mL of H_2O, 0.192 mL of 15% NaOH, and 5.76 mL of H_2O (stirred for 5 min between each addition), filtered, and evaporated in vacuo to a light yellow-white solid, 0.46 g. The solid was recrystallized with 30 mL of anhydrous EtOH, which yielded a white solid, **10** (0.293 g, 58.3%): mp 213–215 °C. Anal. Calcd for $C_{18}H_{18}N_2O_3 \cdot {}^1/_2H_2O$: C, 68.67; H, 5.92; N, 8.90. Found: C, 69.08; H, 5.79; N, 8.88.

Acylation of 1 To Yield 7c. Sodium hydride (60% oil dispersion) (0.075 g, 3.14 mmol), in a 25-mL, three-neck, round-bottom flask fitted with a magnetic stirring bar and a gas inlet connected to a bubbler, was washed free of its oil with 3 × 10 mL of hexanes. To the dry sodium hydride was added 5 mL of dry DMF and **1** (0.499 g, 3.14 mmol). After hydrogen evolution had ceased (20 min), 4-methoxyphenyl isocyanate (0.468 g, 3.14 mmol) was added. The mixture was stirred for 1 h, quenched onto 10 mL of HCl, and extracted with 3 × 100 mL of EtOAc. Pooled organics were washed with 3 × 100 mL of H_2O and brine, dried ($MgSO_4$), filtered, and evaporated in vacuo to a yellow brown oil. Flash chromatography of the oil using 70 g of silica gel eluted with 35% EtOAc/hexanes yielded a yellow solid, **7c** (0.23 g, 23.8%): mp 144–146 °C.

X-ray Crystallographic Analysis of 7c. A large plate crystal of **7c** was obtained by recrystallization from EtOH: $C_{18}H_{16}N_2O_3$; space group $P21/n$; cell constants a = 9.530 (2) Å, b = 27.557 (7) Å, c = 11.924 (2) Å, β = 98.05 (1), z = 8. Lattice constants and intensity data were measured by using graphite-monochromated Cu Kα on a Nicolet R3m/u diffractometer. A total of 3184 unique reflections were observed. The structure was solved by the SHEXTL system and refined to a final R value of 0.065.[8]

Acknowledgment. We wish to thank Dr. B. W. Dominy of Central Research, Pfizer, Inc., for helpful discussions and for carrying out molecular mechanics calculations. We are also indebted to Dr. E. R. Larson and Dr. A. Hoveyda of Pfizer and Professor D. Kemp of Massachusetts Institute of Technology for stimulating intellectual contributions.

Registry No. 1, 117679-10-4; **69**, 35612-81-8; **66**, 15218-07-2; **7a**, 117679-12-6; **7b**, 117679-18-2; **7c**, 117679-11-5; **7d**, 117679-19-3; **7e**, 117679-20-6; **7f**, 117679-21-7; **7g**, 117679-22-8; **7h**, 117679-23-9; **7i**, 117679-17-1; **7j**, 117679-24-0; **7k**, 117679-25-1; **8**, 117679-13-7; **9**, 117679-14-8; **10**, 117679-15-9; **11**, 117679-16-0; **12**, 117679-26-2; **13**, 117679-27-3; phenyl isocyanate, 103-71-9; *p*-methylphenyl isocyanate, 622-58-2; *m*-(trifluoromethyl)phenyl isocyanate, 329-01-1; *o*-ethoxyphenyl isocyanate, 5395-71-1; *o*-isocyanobenzoic acid methyl ester, 1793-07-3; 2,4-dimethylphenyl isocyanate, 51163-29-2; *p*-fluorobenzoic acid chloride, 403-43-0; (dimethylamino)carbonyl chloride, 10270-13-0; *p*-methoxyphenyl isocyanate, 5416-93-3; **14**, 117679-29-5; **15**, 117679-29-5; **16**, 117679-30-8.

Supplementary Material Available: Cartesian coordinates for the initial and optimized geometries of compounds **1** and **12–16**, as well as the atomic coordinate table for the crystallographic structure, **7c** (28 pages). Ordering information is given on any current masthead page.

Chemistry of the Pyrrolo[3,4-*c*]pyrido[2,3-*d*]pyrimidine System. Synthesis of 6,7-Dihydropyrrolo[3,4-*c*]pyrido[2,3-*d*]pyrimidines, a Novel Ring System with Potential Biological Interest

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Two 6,7-dihydropyrrolo[3,4-*c*]pyrido[2,3-*d*]pyrimidines, which contain a novel tricyclic ring system of potential biological interest, were synthesized. 6-(2,5-Dimethoxyphenyl)-6,7-dihydropyrrolo[3,4-*c*]pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**3a**) was prepared from a pyrido[2,3-*d*]pyrimidine. 6-(Acetoxymethyl)-5-methylpyrido-[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**4**) was oxidized with SeO_2 to the corresponding 5-formyl derivative **5**, which was condensed with 2,5-dimethoxyaniline to form the Schiff base. Reduction of the exocyclic azomethine double bond of the Schiff base with $NaBH_3CN$ to **6** followed by thermal cyclization afforded **3a**. 2,4-Diamino-6-(4-methoxyphenyl)-6,7-dihydropyrrolo[3,4-*c*]pyrido[2,3-*d*]pyrimidine (**3b**) was synthesized by addition of a pyrimidine ring to the dihydropyrrolo[3,4-*c*]pyridine system. 1-(4-Methoxyphenyl)pyrrolidin-3-one (**18**) was condensed with malononitrile to give a Knoevenagel adduct **19**. Treatment of **19** with (*N*,*N*-dimethylamino)methylene chloride in the presence of LDA afforded the 4-[(*N*,*N*-dimethylamino)methylene]pyrrolidine derivative **20**, which was converted into 6-amino-7-cyano-2,3-dihydropyrrolo[3,4-*c*]pyridine (**21**) by treatment with NH_3/MeOH. Cyclization of **21** with *N*,*N*-dimethylguanidine afforded the desired **3b** in high yield.

Chemistry of the pteridine system has been studied extensively since this system is found in the vitamin folic acid (**1**, Figure 1). Folic acid is the essential cofactor in the de novo synthesis of thymidylate and hence DNA. During the biosynthesis of thymidylate, folic acid is converted into 5,10-methylenetetrahydrofolic acid (**2**), which donates a one-carbon unit to 2′-deoxyuridylic acid. Synthesis of derivatives of the hitherto unknown 6,7-dihydropyrrolo[3,4-*c*]pyrido[2,3-*d*]pyrimidine ring system (**3**, Figure 1) has been attempted[1-5] since such derivatives are

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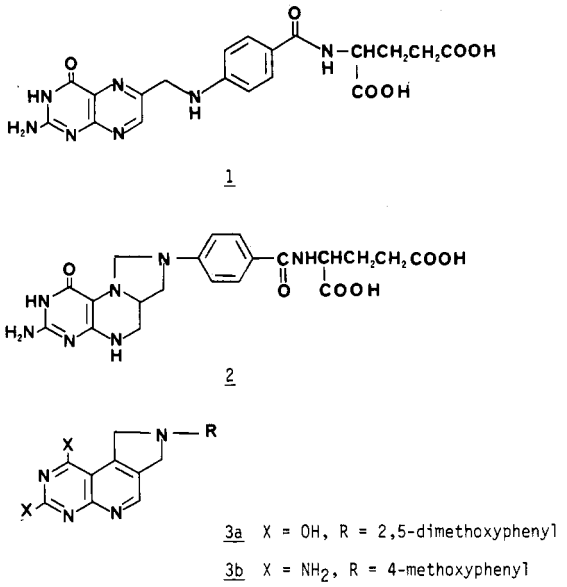
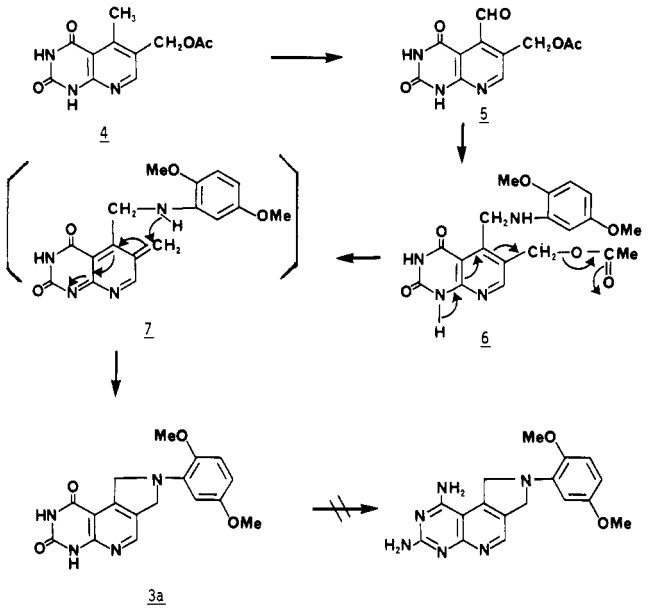


Figure 1.

Scheme I



considered as deaza analogues of **2** and may exhibit potent anticancer activity.

Our recent development of the facile preparation of pyrido[2,3-*d*]pyrimidines from 5-cyano-1,3-dimethyluracil[6] prompted us to challenge the synthesis of **3** from the readily available 6-(acetoxymethyl)-5-methylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**4**)[7] by adding the pyrrolidine ring to the bicyclic system (Scheme I). This paper describes the synthesis of the tricyclic derivatives **3a**, from the pyrido[2,3-*d*]pyrimidine intermediates, and also our successful construction of the 2,4-diamino tricyclic compound **3b**, from 1-substituted pyrrolidin-3-one (**18**).

Oxidation of the methyl group of **4** with SeO_2 afforded the 5-formyl derivative **5**, which was then condensed with 2,5-dimethoxyaniline to form the intermediate Schiff base, which was subsequently reduced with sodium cyanoborohydride to yield 5-[[(2,5-dimethoxyphenyl)amino]-methyl]pyrido[2,3-*d*]pyrimidine **6**. The ^1H NMR spectrum of **6** showed one singlet at δ 0.97 and one broad singlet at δ 4.76 corresponding to $OCOCH_3$ and CH_2NH, respectively. At 212–213 °C, **6** melted to a clear liquid, which resolidified and remelted at 308–309 °C. The ^1H NMR spectrum of the high-melting solid showed the presence of two methylene signals at δ 4.67 and 4.98 and the absence of a $COCH_3$ signal, indicating the tricyclic structure **3a**. This compound was then prepared in larger amounts by heating **6** in diphenyl ether at 210 °C. A possible mechanism for the formation of **3a** from **6** is the formation of the methylene intermediate **7**. Intramolecular nucleophilic attack by the exocyclic nitrogen on the methylene carbon would lead to the formation of **3a** as shown in Scheme I. Our attempts at conversion of **3a** into the 2,4-diamino derivative **3b** by the silylation–amination procedure[7,8] failed.

In an attempt to synthesize the 2,4-diamino analogue **3b**, we used 4-cyano-1-(4-methoxyphenyl)pyrrolidin-3-one (**11**, Scheme II) as the starting material, which was prepared by the procedure developed for the synthesis of similar pyrrolidin-3-ones.[9] β-(4-Methoxyanilino)propionitrile (**9**), obtained by condensation of *p*-anisidine (**8**) and acrylonitrile, was alkylated with ethyl bromoacetate to afford ethyl *N*-(β-cyanoethyl)-*N*-(4-methoxyphenyl)-glycinate (**10**). Compound **10** was subsequently converted into **11** by intramolecular cyclization with base. Treatment of **11** with 1 equiv each of malononitrile and DBU in benzene afforded the Knoevenagel product, 3-cyano-4-(dicyanomethylene)-1-(4-methoxyphenyl)pyrrolidine, which was isolated as the crystalline DBU salt (**12**). The formation of 2,3-dihydropyrrolo[3,4-*c*]pyridine **13** was achieved by heating **12** at 80 °C for 40 min in concentrated HCl. The ^1H NMR spectrum showed the presence of two dissociable protons at δ 7.80 in addition to two methylene signals (δ 4.29 and 4.53) and an AB quartet integrated for four protons (δ 6.54 and 6.86) and a OMe singlet (δ 3.68). Analytical data were consistent with the cyclized structure **13**. After reductive dechlorination of **13**, the product **14** did not undergo pyrimidine ring formation with guanidine, indicating that the amino function was not ortho to the cyano group.

The 2,4-diamino analogue **3b** was synthesized from *p*-anisidine and ethyl acrylate, which gave the addition product ethyl *N*-(4-methoxyphenyl)-β-aminopropionate (**15**, Scheme III). After treatment of **15** with ethyl bromoacetate, the product, ethyl *N*-[β-(ethoxycarbonyl)-ethyl]-*N*-(4-methoxyphenyl)glycinate (**16**), was converted into 1-(4-methoxyphenyl)-4-(ethoxycarbonyl)pyrrolidin-3-one (**17**) by an intramolecular Dieckmann reaction. Hydrolysis of ester **17** and decarboxylation of the product to 1-(4-methoxyphenyl)pyrrolidin-3-one (**18**) were performed in situ with 6 N HCl[10] at 100 °C (bath temperature). The bath had to be removed promptly after evolution of CO_2 ceased because **18** was unstable, undergoing decomposition upon prolonged heating. The conditions required for these reactions were rather strict. At higher temperatures, the product decomposed rapidly. At lower temperatures, the reactions proceeded much more slowly, which led to decomposition of **18**. Knoevenagel conden-

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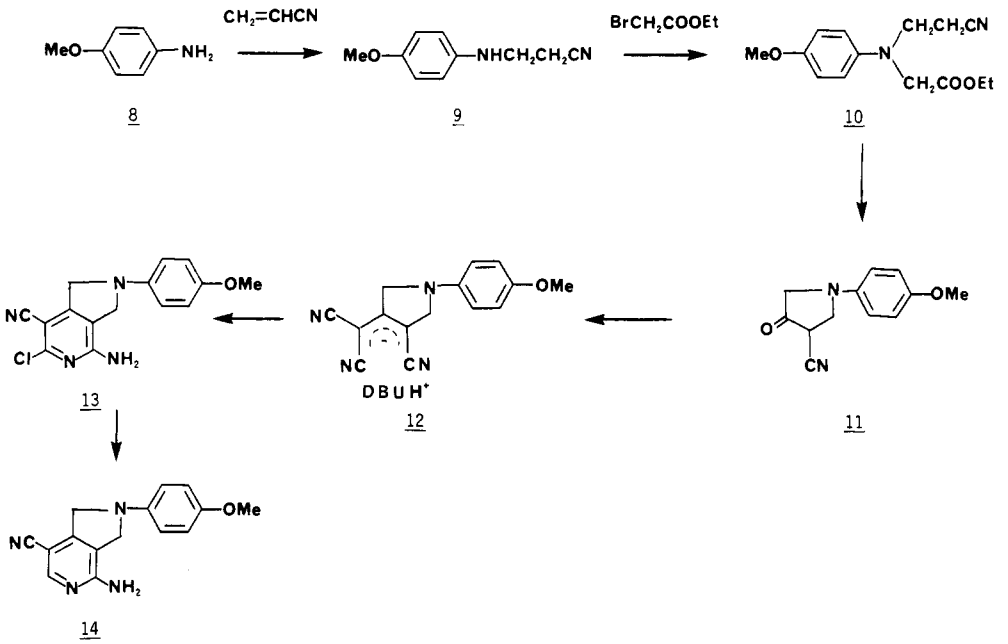
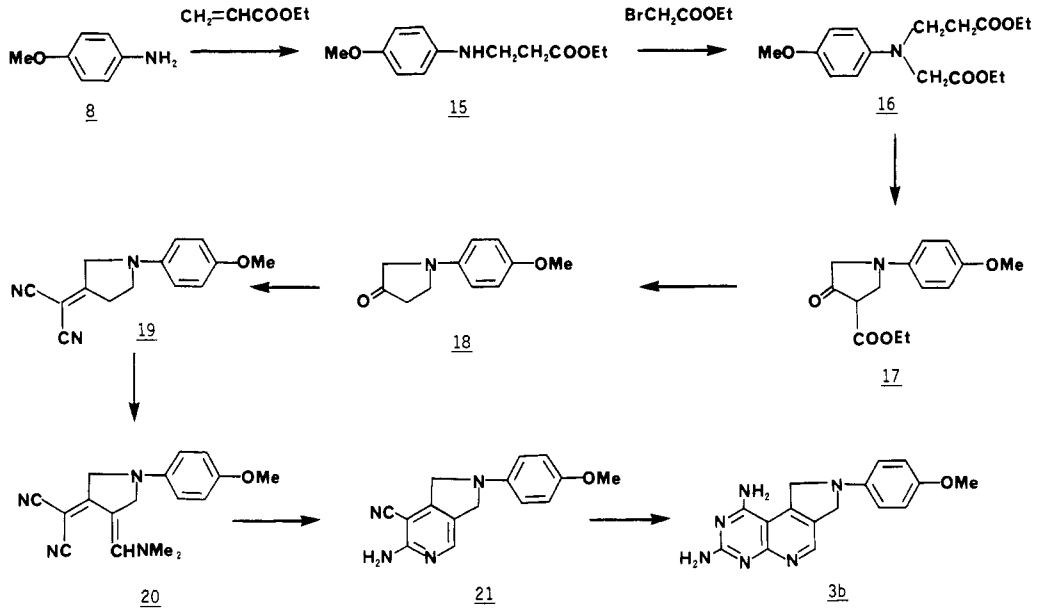
Scheme II



Scheme III



sation of **18** with malononitrile also required caution since the dicyanomethylene product **19** polymerized readily in solution even at room temperature. Among several reactions attempted to convert **19** into a (potential) 4-formyl intermediate such as **20**, the best result was obtained when **19** was lithiated with lithium diisopropylamide in THF at −65 °C followed by treatment with (dimethylamino)-methylene dichloride.[11] The ^{1}H NMR spectrum showed that there were two isolated methylene signals at δ 4.23 and 4.44, indicating that the structure of the product was **20**. When **20** was treated with NH_3/MeOH in a sealed container at 150 °C, 6-amino-7-cyano-2,3-dihydropyrrolo-[3,4-*c*]pyridine (**21**) was obtained. The ^{1}H NMR spectrum of **21** is quite different than that of the isomeric 4-amino congener **14**. The methylene protons on C-3 in **14** (δ 4.34) are shielded by the peri amino function as compared to those in **21** (δ 4.42). The proton on C-6 in **14** (δ 8.31), on the other hand, is more deshielded than H-4 in **21** (δ 8.21). Condensation of **21** with *N*,*N*-dimethylguanidine in DMF at 120 °C[12] for 3 days afforded the desired 2,4-diamino-N^6-(4-methoxyphenyl)-6,7-dihydropyrrolo[3,4-*c*]pyrido-[2,3-*d*]pyrimidine (**3b**) in high yield. The ^{1}H NMR spectrum showed two singlets at δ 4.56 and 4.94 (each integrated for two protons), indicating the presence of two isolated methylene groups in the product.

Although synthesis of the bicyclic 2,3-dihydropyrrolo-[3,4-*c*]pyridine derivatives have been reported,[13-15] the work in this report represents the first synthesis of the tricyclic 6,7-dihydropyrrolo[3,4-*c*]pyrido[2,3-*d*]pyrimidine

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system. Attempts at direct application of the procedure reported herein for the synthesis of the 4-(methoxycarbonyl)phenyl analogue of **3** for eventual preparation of 5,10-methylene-5-deazafolic acid have resulted in little success.

Experimental Section

General Methods. Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Boiling points for fractional distillation were measured under reduced pressure at the indicated millimeters of mercury. ^{1}H NMR spectra were recorded on a JEOL-FT-90Q spectrometer with Me_4Si as the internal standard. Chemical shifts are reported in parts per million (δ). Apparent shapes of signals are described as s (singlet), d (doublet), t (triplet), dd (double doublet), m (multiplet), br s (broad singlet). Values given for coupling constants are first order. Microanalyses were performed by M.H.W. Laboratories. Column chromatography was performed on silica gel G60 (70–230 mesh, ASTM, Merck).

6-(Acetoxymethyl)-5-formylpyrido[2,3-*d*]pyrimidine-2,4-(1*H*,3*H*)-dione (5). A mixture of 6-(acetoxymethyl)-5-methylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione[7] (3.14 g, 12.5 mmol) and SeO_2 (2.09 g, 18.9 mmol) in AcOH (100 mL) was heated at reflux for 20 h and then filtered through a Celite pad while hot. The filtrate was concentrated in vacuo, and the residue recrystallized from MeOH to give **5** (2.94 g, 86.6%): mp 263–264 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 2.02 (3 H, s, Ac), 5.03 (2 H, s, CH_2), 8.75 (1 H, s, H-7), 10.49 (1 H, s, CHO). Anal. Calcd for $C_{11}H_9N_3O_5$: C, 50.19; H, 3.45; N, 15.97. Found: C, 49.94; H, 3.57; N, 15.80.

6-(Acetoxymethyl)-5-[[(2,5-dimethoxyphenyl)amino]-methyl]pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (6). A mixture of **5** (526.4 mg, 2 mmol) and 2,5-dimethoxyaniline (398.3 mg, 2.6 mmol) in AcOH (20 mL) was stirred at room temperature for 5 h under N_2. The mixture was concentrated in vacuo, traces of AcOH were azeotropically removed by several coevaporations with EtOH, and the residue was suspended in absolute EtOH (80 mL). To the suspension was added $NaBH_3CN$ (251 mg, 4 mmol), the mixture was stirred for 4 h at room temperature, and the solid was filtered. The solid was dissolved in $CHCl_3$–MeOH (20 mL, 1:1 v/v). Silica gel (5 g) was added to the solution, the mixture was concentrated in vacuo, and the residue was placed on the top of a silica gel column (3 × 40 cm). The column was washed with $CHCl_3$ containing 0.5% (by volume) of MeOH to elute **6** (616 mg, 77%), which melted at 212–213 °C, resolidified, and remelted at 308–310 °C: ^{1}H NMR (Me_2SO-d_6) δ 0.97 (3 H, s, Ac), 3.64 (3 H, s, OMe), 3.65 (3 H, s, OMe), 4.76 (2 H, br s, CH_2NH), 5.14 (1 H, br, s, CH_2NH), 5.23 (2 H, s, CH_2O), 6.10 (1 H, dd, H-4′, $J_{3',4'}$ = 8.5, $J_{4',6'}$ = 2.7 Hz), 6.34 (1 H, d, H-3′, $J_{3',4'}$ = 8.5 Hz), 6.68 (1 H, d, H-6′, $J_{4',6'}$ = 2.7 Hz), 8.57 (1 H, s, H-7), 11.48 (1 H, br s, NH), 11.72 (1 H, br s, NH). Anal. Calcd for $C_{19}H_{20}N_4O_6$: C, 57.00; H, 5.03; N, 13.99. Found: C, 56.97; H, 5.07; N, 14.10.

6-(2,5-Dimethoxyphenyl)-6,7-dihydropyrrolo[3,4-*c*]-pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (3a). Compound **6** (400 mg, 1 mmol) in Ph_2O (10 mL) was heated at 210 °C for 2 h under N_2. The resulting clear solution was cooled and then diluted with EtOH–Et_2O (1:1, 100 mL). The yellow precipitate was collected by filtration and washed with a boiling mixture of $CHCl_3$–EtOH (1:1 v/v) to give **3a** (311 mg, 91%): mp 308–310 °C; ^{1}H NMR (Me_2SO-d_6) δ 3.70 (3 H, s, OMe), 3.74 (3 H, S, OMe), 4.67 (2 H, br s, CH_2), 4.98 (2 H, br s, CH_2), 6.28 (1 H, s, H-6′), 6.31 (1 H, d, Ph), 6.87 (1 H, d, Ph), 8.53 (1 H, s, H-8), 11.43 (1 H, br s, NH), 11.61 (1 H, br s, NH). Anal. Calcd for $C_{17}H_{16}N_4O_4$: C, 59.99; H, 4.74; N, 16.46. Found: C, 60.14; H, 4.89; N, 16.24.

***N*-(4-Methoxyphenyl)-β-aminopropionitrile (9).** A mixture of *p*-anisidine (61.5 g, 0.5 mol) and acrylonitrile (31.84 g, 0.6 mol) in H_2O (400 mL) was heated at reflux for 5 h. After cooling, the solid was collected by filtration and recrystallized from EtOH to give **9** (79.5 g, 90%): mp 58–60 °C; ^{1}H NMR ($CDCl_3$) δ 2.59 (2 H, t, β-CH_2), 3.45 (2 H, t, α-CH_2), 3.76 (3 H, s, OMe), 6.59 (2 H, d, Ph), 6.81 (2 H, d, Ph). Anal. Calcd for $C_{10}H_{12}N_2O$: C, 68.16; H, 6.86; N, 15.90. Found: C, 68.24; H, 6.80; N, 15.83.

Ethyl *N*-(4-Methoxyphenyl)-β-aminopropionate (15). A mixture of *p*-anisidine (61.6 g, 0.5 mol) and ethyl acrylate (55.1 g, 0.55 mol) in EtOH (400 mL) was heated under reflux for 3 days. After concentration in vacuo, the residue was fractionally distilled and collected the fraction of $bp_{0.5}$ 155–159 °C to give **15** (95.6 g, 86%): ^{1}H NMR ($CDCl_3$) δ 1.26 (3 H, t, $MeCH_2$), 2.58 (2 H, t, β-CH_2), 3.39 (2 H, t, α-CH_2), 3.74 (3 H, s, OMe), 4.15 (2 H, q, CH_2Me), 6.58 (2 H, d, Ph), 6.78 (2 H, d, Ph). Anal. Calcd for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.67; N, 6.27. Found: C, 64.70; H, 7.54; N, 6.22.

Ethyl *N*-[β-(Ethoxycarbonyl)ethyl]-*N*-(4-methoxyphenyl)glycinate (16). To a stirred mixture of **15** (178.4 g, 0.8 mol) and anhydrous K_2CO_3 (150 g, 1.08 mol) in DMF (400 mL) was added ethyl bromoacetate (160.5 g, 0.96 mol) over a period of 2 h at room temperature. The mixture was heated at 60 °C for 10 h with vigorous stirring and then poured into ice-cold NaOH (0.1 N, 300 mL). The stirring continued until the characteristic odor of ethyl bromoacetate disappeared. The mixture was extracted with Et_2O (4 × 400 mL). The combined extracts were washed (H_2O, 4 × 300 mL), dried (Na_2SO_4), and concentrated in vacuo, and the oily product **16** was purified by fractional distillation, $bp_{0.5}$ 185–189 °C (206.2 g, 83%): ^{1}H NMR ($CDCl_3$) δ 1.24 (6 H, t, 2 × $MeCH_2$), 2.63 (2 H, t, CH_2CH_2N), 3.70 (2 H, t, CH_2CH_2N), 3.73 (3 H, s, OMe), 4.04 (2 H, s, NCH_2CO), 4.12 and 4.16 (each 2 H, q, CH_2Me), 6.61 and 6.82 (each 2 H, d, Ph). Anal. Calcd for $C_{16}H_{23}NO_5$: C, 62.12; H, 7.49; N, 4.53. Found: C, 62.38; H, 7.52; N, 4.49.

By following the same procedure but with use of **9** and ethyl bromoacetate, **ethyl *N*-(β-cyanoethyl)-*N*-(4-methoxyphenyl)glycinate (10)** was synthesized in 66% yield after crystallization from EtOH: mp 42–43 °C; ^{1}H NMR ($CDCl_3$) δ 1.26 (3 H, t, CH_2Me), 2.65 (2 H, t, NCH_2CH_2), 3.73 (2 H, t, NCH_2CH_2), 3.75 (3 H, s, OMe), 4.05 (2 H, s, CH_2CO), 4.18 (2 H, q, CH_2Me), 6.63, 6.84 (each 2 H, d, Ph). Anal. Calcd for $C_{14}H_{18}N_2O_3$: C, 64.10; H, 6.92; N, 10.68. Found: C, 64.21; H, 6.85; N, 10.61.

4-(Ethoxycarbonyl)-1-(4-methoxyphenyl)pyrrolidin-3-one (17). A solution of **16** (106.7 g, 0.345 mol) in dry C_6H_6 (400 mL) was added to a mixture of NaOEt/EtOH in C_6H_6 (prepared by dissolving 13.1 g of Na metal in 300 mL of EtOH and then diluted with 500 mL of C_6H_6) at room temperature over a period of 90 min. The mixture was heated at reflux for 30 min, cooled to room temperature, and filtered. The resulting solid was suspended in ice–water (1 L) and neutralized with 1 N HCl, and the mixture was extracted with Et_2O (3 × 500 mL). The combined extracts were washed (H_2O), dried (Na_2SO_4), and concentrated, and the residue was crystallized from *n*-hexane–Et_2O to afford **17** (87.4 g, 64%): mp 58–60 °C; ^{1}H NMR ($CDCl_3$) δ 1.34 (3 H, dt, CH_2Me), 3.76 (3 H, s, OMe), 3.75 (2 H, dq, CH_2Me), 4.14 (2 H, s, 2-CH_2), 4.12–4.39 (3 H, m, H-4 and 5-CH_2), 6.46 and 6.86 (each 2 H, m, Ph). Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.86; H, 6.51; N, 5.32. Found: C, 63.78; H, 6.56; N, 5.41.

In a similar manner **10** was converted into 4-cyano-1-(4-methoxyphenyl)pyrrolidin-3-one (11) in 80% yield: mp 107–108 °C; ^{1}H NMR ($CDCl_3$) δ 3.78 (3 H, s, OMe), 3.45–4.25 (5 H, m, 2 × CH_2 and H-4), 6.66, 6.90 (each 2 H, d, Ph). Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.71; H, 5.65; N, 12.85.

3-Cyano-4-(dicyanomethylene)-1-(4-methoxyphenyl)-pyrrolidine DBU Salt (12). To a suspension of **11** (10.81 g, 50 mmol) and malononitrile (4.95 g, 75 mmol) in dry C_6H_6 (100 mL) was added DBU (7.92 g, 52 mmol). The mixture was vigorously stirred at room temperature for 30 min and at 60 °C for 40 min. After concentration of the mixture in vacuo, the residue was dissolved in $CHCl_3$ (300 mL), and the solution was washed (H_2O), dried (Na_2SO_4), and then concentrated. The residue was crystallized from EtOAc to give **12** (19.1 g, 91%): mp 107–108 °C; IR (KBr) 2165, 2190, 2210 cm^{-1} (CN); ^{1}H NMR ($CDCl_3$) δ 1.79 (6 H, br s), 2.03–2.16 (2 H, m), 2.75 (2 H, br s), 3.40 (6 H, m), 3.75 (3 H, s, OMe), 4.19 (4 H, s, 2 × CH_2), 6.47, 6.85 (each 2 H, d, Ph), 9.09 (1 H, br s, exchangeable). Anal. Calcd for $C_{24}H_{28}N_6O$: C, 69.20; H, 6.78; N, 20.18. Found: C, 69.31; H, 6.53; N, 20.04.

4-Amino-6-chloro-7-cyano-2-(4-methoxyphenyl)-2,3-dihydropyrrolo[3,4-*c*]pyrimidine (13). A mixture of DBU salt **12** (20.82 g, 50 mmol) in concentrated HCl (100 mL) was stirred at room temperature for 1 h and then at 80 °C for 40 min. The mixture was poured into ice (500 g), and the precipitate **13** was collected by filtration, washed successively with H_2O, EtOH, and Et_2O, and air-dried (8.84 g, 59%). This product was sufficiently pure to be used directly in the next step. An analytical sample was prepared by recrystallization from DMF–H_2O: mp 296–297

°C; IR (KBr) 2220 cm^{-1} (CN); ^1H NMR (Me_2SO-d_6) δ 3.68 (3 H, s, OMe), 4.29 (2 H, br s, CH_2), 4.53 (2 H, br s, CH_2), 6.54, 6.86 (each 2 H, d, Ph), 7.80 (2 H, br s, NH_2). Anal. Calcd for $C_{15}H_{13}ClN_4O \cdot {}^1/_2H_2O$: C, 58.16; H, 4.56; Cl, 11.45; N, 18.09. Found: C, 58.03; H, 4.49; Cl, 11.43; N, 18.11.

4-Amino-7-cyano-1-(4-methoxyphenyl)-2,3-dihydropyrrolo[3,4-*c*]pyridine (14). A mixture of **13** (902 mg, 3 mmol), Et_3N (0.8 mL), and 10% Pd/C (500 mg) in a mixture of dioxane (150 mL) and EtOH (200 mL) was hydrogenated in a Parr apparatus with an initial pressure of 50 psi for 5 days. The catalyst was removed by filtration through a Celite pad. The filtrate was concentrated in vacuo, and the residue was recrystallized from $CHCl_3$–EtOH to give **14** (184 mg, 23%): mp 253–254 °C; IR (KBr) 2210 cm^{-1} (CN); ^1H NMR (Me_2SO-d_6) δ 3.69 (3 H, s, OMe), 4.34 (2 H, br s, 3-CH_2), 4.58 (2 H, br s, 1-CH_2), 6.58, 6.90 (each 2 H, d, Ph), 7.12 (2 H, s, NH_2), 8.31 (1 H, s, H-6). Anal. Calcd for $C_{15}H_{14}N_4O$: C, 67.65; H, 5.30; N, 21.04. Found: C, 67.74; H, 5.26; N, 21.10.

1-(4-Methoxyphenyl)pyrrolidin-3-one (18). A mixture of **17** (10.53 g, 0.04 mol) in 6 N HCl (120 mL) was heated at 100 °C (bath temperature) until evolution of CO_2 ceased (about 1 h). The mixture was cooled in an ice bath, neutralized with 10 N NaOH, and extracted with Et_2O (4 × 200 mL). The combined extracts were washed (H_2O), dried (Na_2SO_4), and concentrated, and the residue was crystallized from Et_2O–hexane to give **18** (5.68 g, 67%): mp 104–105 °C; ^1H NMR ($CDCl_3$) δ 2.68 (2 H, t, 5-CH_2), 3.61 (2 H, t, 4-CH_2), 3.63 (2 H, s, 2-CH_2), 3.77 (3 H, s, OMe), 6.63, 6.89 (each 2 H, d, Ph). Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.33. Found: C, 68.95; H, 6.77; N, 7.31.

3-(Dicyanomethylene)-1-(4-methoxyphenyl)pyrrolidine (19). A mixture of **18** (17.41 g, 0.084 mol), malononitrile (6.66 g, 0.1 mol), and DBU (1 mL) in dry C_6H_6 (200 mL) was stirred below 10 °C for 2 h and then concentrated in vacuo below 20 °C. The dark residue was triturated with EtOH (200 mL), and the dark green solid was collected by filtration to give **19** (10.5 g, 48%): mp 144–145 °C; IR (KBr) 2250 cm^{-1} (CN); ^1H NMR ($CDCl_3$) δ 3.22 (2 H, dt, 5-CH_2, J = 7.0 and 1.4 Hz), 3.56 (2 H, dt, 4-CH_2, J = 7.0 and 1.4 Hz), 3.77 (3 H, s, OMe), 4.32 (2 H, t, 2-CH_2, J = 1.4 Hz), 6.64, 6.69 (each 2 H, d, Ph). Anal. Calcd for $C_{14}H_{13}N_3O$: C, 70.27; H, 5.48; N, 17.56. Found: C, 70.37; H, 5.40; N, 17.69.

3-(Dicyanomethylene)-4-[(*N*,*N*-dimethylamino)methylene]-1-(4-methoxyphenyl)pyrrolidine (20). Lithium diisopropylamide mono(tetrahydrofuran) (7.1 mL, 10.5 mmol, 1.5 M in cyclohexane) was added dropwise to a suspension of **19** (2.10 g, 8.8 mmol) in THF (150 mL, freshly distilled over $CaCl_2$) in an dry ice–Me_2CO bath. After the mixture was stirred for 1 h, (dimethylamino)methylene chloride (prepared from 1.64 mL of $POCl_3$ and 1.36 mL of DMF in 10 mL of THF) was added dropwise, and the stirring was continued at −65 °C for 18 h. The solid was collected by filtration and triturated with boiling EtOH (50 mL) to give **20** (1.02 g, 40%): mp 218–219 °C dec; IR (KBr) 2210 cm^{-1} (CN); ^1H NMR (Me_2SO-d_6) δ 3.31 (6 H, s, NMe_2), 3.68 (3 H, s, OMe), 4.23 (2 H, br s, CH_2), 4.44 (2 H, br s, CH_2), 6.60, 6.85 (each 2 H, d, Ph), 8.24 (1 H, s, NCH=). Anal. Calcd for $C_{17}H_{18}N_4O \cdot {}^1/_4H_2O$: C, 68.32; H, 6.24; N, 18.75. Found: C, 68.41; H, 6.31; N, 18.74.

6-Amino-7-cyano-2-(4-methoxyphenyl)-2,3-dihydropyrrolo[3,4-*c*]pyridine (21). A mixture of **20** (2.94 g, 10 mmol) in saturated NH_3/MeOH (60 mL) was heated in a sealed steel vessel at 150 °C for 3 h. After cooling, yellow needles separated and were collected by filtration and washed with MeOH to give **21** (2.17 g, 81%): mp 242–243 °C; IR (KBr) 2210 cm^{-1} (CN); ^1H NMR (Me_2SO-d_6) δ 3.68 (3 H, s, OMe), 4.42 (2 H, br s, 3-CH_2), 4.55 (2 H, br s, 1-CH_2), 6.61, 6.87 (each 2 H, d, Ph), 6.89 (2 H, br s, NH_2), 8.21 (1 H, s, H-4). Anal. Calcd for $C_{15}H_{14}N_4O$: C, 67.65; H, 5.30; N, 21.04. Found: C, 67.60; H, 5.31; N, 21.13.

2,4-Diamino-6-(4-methoxyphenyl)-6,7-dihydropyrrolo-[3,4-*c*]pyrido[2,3-*d*]pyrimidine (3b). To a solution of *t*-BuOK (94 mg, 0.84 mmol) in DMF (8 mL) was added *N*,*N*-dimethylguanidine sulfate (204 mg, 0.75 mmol) with stirring. After 15 min, **21** (133 mg, 0.5 mmol) was added. The mixture was heated at 120 °C (bath temperature) under N_2 for 3 days and then cooled to room temperature. The yellow solid was collected by filtration, washed (DMF), and triturated with boiling water to give **3b** (126 mg, 82%): mp 327–328 °C; ^1H NMR (Me_2SO-d_6) δ 3.70 (3 H, s, OMe), 4.56 (2 H, br s, CH_2), 4.94 (2 H, br s, CH_2), 6.71 (2 H, br s, NH_2), 6.81, 6.86 (each 2 H, d, Ph), 8.65 (1 H, s, H-8). Anal. Calcd for $C_{16}H_{16}N_6O \cdot {}^1/_4H_2O$: C, 61.43; H, 5.32; N, 26.86. Found: C, 61.26; H, 5.28; N, 26.84.

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Preparation of Highly Substituted 2-Pyridones by Reaction of Vinyl Isocyanates and Enamines

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A method for the synthesis of highly substituted 2(1*H*)-pyridones is reported. Vinyl isocyanates, prepared from the corresponding α,β-unsaturated carboxylic acids, undergo cyclization with various enamines to furnish six-membered heterocycles. The methodology is exemplified by numerous examples. Application of this strategy is further illustrated by the synthesis of several aza steroid analogues.

The 2(1*H*)-pyridone moiety is a prominent structural feature in a variety of natural products as well as in other species of medicinal interest.[1] Classical approaches to these systems have generally relied on a variety of condensation reactions to effect the ring closure of appropriate precursors.[2] More recently, Overman has reported the preparation of alkyl-substituted 2-pyridones from propargylic pyrrolidine pseudoureas,[3] and Ghosez has de-

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