universal crystallographic computation program system UNICS II.[17]

Registry No. 1b, 12193-69-0; **2**, 36343-88-1; **3**, 33614-96-9; **4**, 79814-94-1; **5**, 2166-14-5; **6**, 79792-50-0; **7**, 79770-04-0; **8**, 79770-05-1; **9**, 79802-89-4; **10**, 79770-06-2; **11**, 79792-51-1; **12**, 79792-52-2; **13**, 79770-07-3; **14**, 72448-17-0; **15**, 6018-41-3; **16**, 79792-53-3; **17**, 79792-54-4; **18**, 79792-55-5; **19**, 79802-90-7.

(17) (a) Sakurai, T.; Iwasaki, J.; Watanabe, Y.; Kobayashi, K.; Bando, Y.; Nakamichi, Y. *Rikagaku Kenkyusho Hookoku* **1974**, *50*, 75–91. (b) Kawano, S. *Koho, Computer Center of Kyushu University*, **1980**, *13*, 39–50.

Supplementary Material Available: Bond angles and their estimated standard deviations (Table VII), ^{13}C NMR spectral data of products **16–19** (Table VIII), atomic parameters (Table IX), and coordinates for hydrogen atoms (Table X) (4 pages). Ordering information is given on any current masthead page.

Pteridines. 49. Synthesis of 2,4-Diamino-6,8-dihydro-7-aryl-8-oxopyrrolo[3,4-*g*]pteridines[1a,b]

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Reaction of ethyl 4-chloro-2-oximino-3-oxobutyrate (**14**) with aminomalononitrile tosylate followed by deoxygenation of the resulting pyrazine 1-oxide provides 2-amino-6-carbethoxy-5-(chloromethyl)-3-cyanopyrazine (**11**). Treatment of **11** with arylamines gives 2-amino-5-[(arylamino)methyl]-6-carbethoxy-3-cyanopyrazines (**12**) which are readily cyclized to 1,3-dihydro-1-oxopyrrolo[3,4-*b*]pyrazines (**13**). Condensation of **13** with guanidine acetate in dimethylformamide then provides the title compounds.

We have recently described the synthesis of a series of 2,4-diaminocycloalka[*g*]pteridines (**1**), many of which exhibited inhibitory activity against dihydrofolate reductase.[2] As a consequence, we have initiated a program directed toward the preparation of analogues of these compounds possessing additional structural features present in the potent antineoplastic agent methotrexate (**2**).[3] In particular, we have sought methods for the synthesis of analogues of **1** which incorporate an arylamino group in the fused aliphatic ring. We report here on a synthesis of the title compounds, 2,4-diamino-6,8-dihydro-7-aryl-8-oxopyrrolo[3,4-*g*]pteridines (**3a,b**), which bear an intriguing structural resemblance to rhizopterin (**4**)[4] and to the coenzyme N^{10}-formyltetrahydrofolic acid (**5**; Chart I).[3b]

In connection with other studies we had in hand both 2-amino-6-(carbomethoxy)-3-cyano-5-(dimethoxymethyl)pyrazine (**6**) and its corresponding *N*-oxide **7**,[5] which appeared to be well suited for further elaboration to pyrrolo[3,4-*g*]pteridines (see Scheme I). Both **6** and **7** were readily converted to the corresponding aldehydes **8** and **9** by treatment with 1 N HCl. Condensation of **9** with ethyl *p*-aminobenzoate in refluxing toluene containing a catalytic amount of *p*-TsOH gave the Schiff base **10**, but surprisingly, no imine could be prepared from **8**. Attempted reduction of **10** (sodium borohydride or sodium cyanoborohydride) led to complex mixtures of products as did attempted deoxygenation (phosphorus trichloride, sodium dithionite, or trimethyl phosphite), while reduction of **10** with Raney nickel gave an unstable compound of undetermined structure which rapidly decomposed on attempted isolation.

Since we had previously shown that 2-amino-3-cyano-5-(halomethyl)pyrazines readily alkylated aromatic amines to give 5-[(arylamino)methyl]pyrazines,[6] we investigated an alternate route to **3** utilizing pyrazine **12**, potentially available from **11** under similar conditions, as a precursor to 1,3-dihydro-1-oxopyrrolo[3,4-*b*]pyrazines (**13**). The required starting material for the synthesis of **11**, ethyl 4-chloro-2-oximino-3-oxobutyrate (**14**), has been prepared by monochlorination of ethyl 2-oximino-3-oxobutyrate and described as a pale yellow oil used without further purification.[7] Since we anticipated difficulties in controlling the degree of chlorination in this reaction, an alternate synthesis was developed which involved oximation of ethyl 4-chloroacetoacetate (**15**) with nitrosyl chloride in dry THF; this procedure provided **14** in 53% yield as a colorless, low-melting solid. Although reaction of **14** with aminomalononitrile tosylate in 2-propanol[8] gave a complex mixture of products, condensation in the presence of a catalytic amount of HCl gave the pyrazine *N*-oxide **16** in 53% yield. Deoxygenation with trimethyl phosphite[9] then provided **11** in 77% yield.

As anticipated, reaction of **11** with methyl *p*-aminobenzoate in acetonitrile solution in the presence of potassium carbonate readily gave the desired [(arylamino)methyl]pyrazine **12a** (76%), which was quantitatively converted to the 1,3-dihydro-1-oxopyrrolo[3,4-*b*]pyrazine

(1) (a) For the previous paper in this series, see Taylor, E. C.; Dumas, D. J. *J. Org. Chem.* **1981**, *46*, 1394–1402. (b) We are indebted to F. Hoffmann-La Roche & Co., Ltd., and to the National Cancer Institute, National Institutes of Health (Grant 1 ROC CA28351), for support of this work. (c) Recipient of an American Can Co. Predoctoral Fellowship.

(2) Taylor, E. C.; Berrier, J. V.; Cocuzza, A. J.; Kobylecki, R.; McCormack, J. J. *J. Med. Chem.* **1977**, *20*, 1215–1218.

(3) For reviews of the medicinal chemistry of methotrexate and its analogues, see (a) Jaffe, N.; Howell, S. In "Advances in Cancer Chemotherapy"; Rosowsky, A., Ed.; Marcel Dekker: New York, 1979; pp 111–142. (b) Pratt, W. B.; Ruddon, R. W. "The Anticancer Drugs"; Oxford University Press: Oxford, 1979; pp 98–113.

(4) Wolf, D. E.; Anderson, R. C.; Kaczka, E. A.; Harris, S. A.; Arth, G. E.; Southwick, P. L.; Mozingo, R.; Folkers, K. *J. Am. Chem. Soc.* **1947**, *69*, 2753–2759.

(5) Taylor, E. C.; Dumas, D. J. *J. Org. Chem.* **1980**, *45*, 2485–2489.

(6) Taylor, E. C.; Portnoy, R. C.; Hochstetler, D. C.; Kobayashi, T. *J. Org. Chem.* **1975**, *40*, 2347–2351.

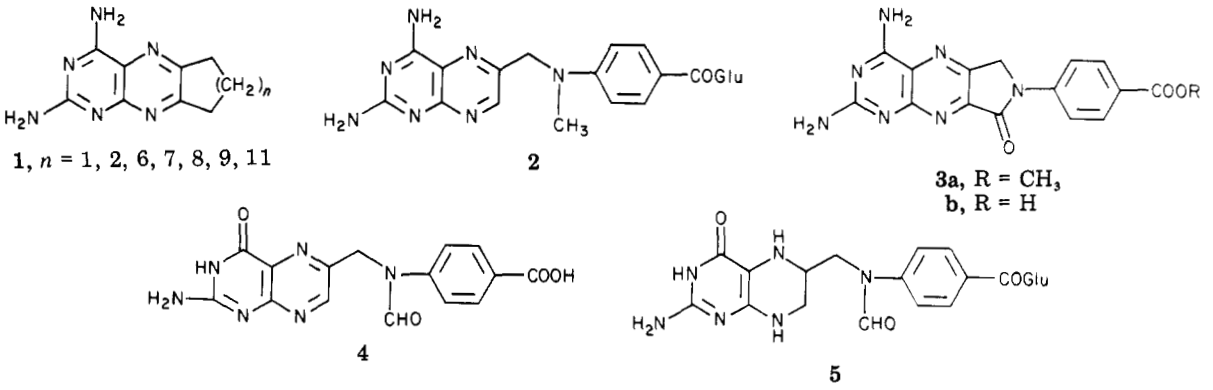
(7) Hatanaka, M.; Ishimaru, T. *J. Med. Chem.* **1973**, *16*, 978–984.

(8) Under the same conditions, β-chloropyruvaldoxime readily provides 2-amino-3-cyano-5-(chloromethyl)pyrazine 1-oxide: Taylor, E. C.; Kobayashi, T. *J. Org. Chem.* **1973**, *38*, 2817–2821.

(9) Dirlam, J. P.; McFarland, J. W. *J. Org. Chem.* **1977**, *42*, 1360–1364.

0022-3263/82/1947-0116$01.25/0

Chart I



1, n = 1, 2, 6, 7, 8, 9, 11

2

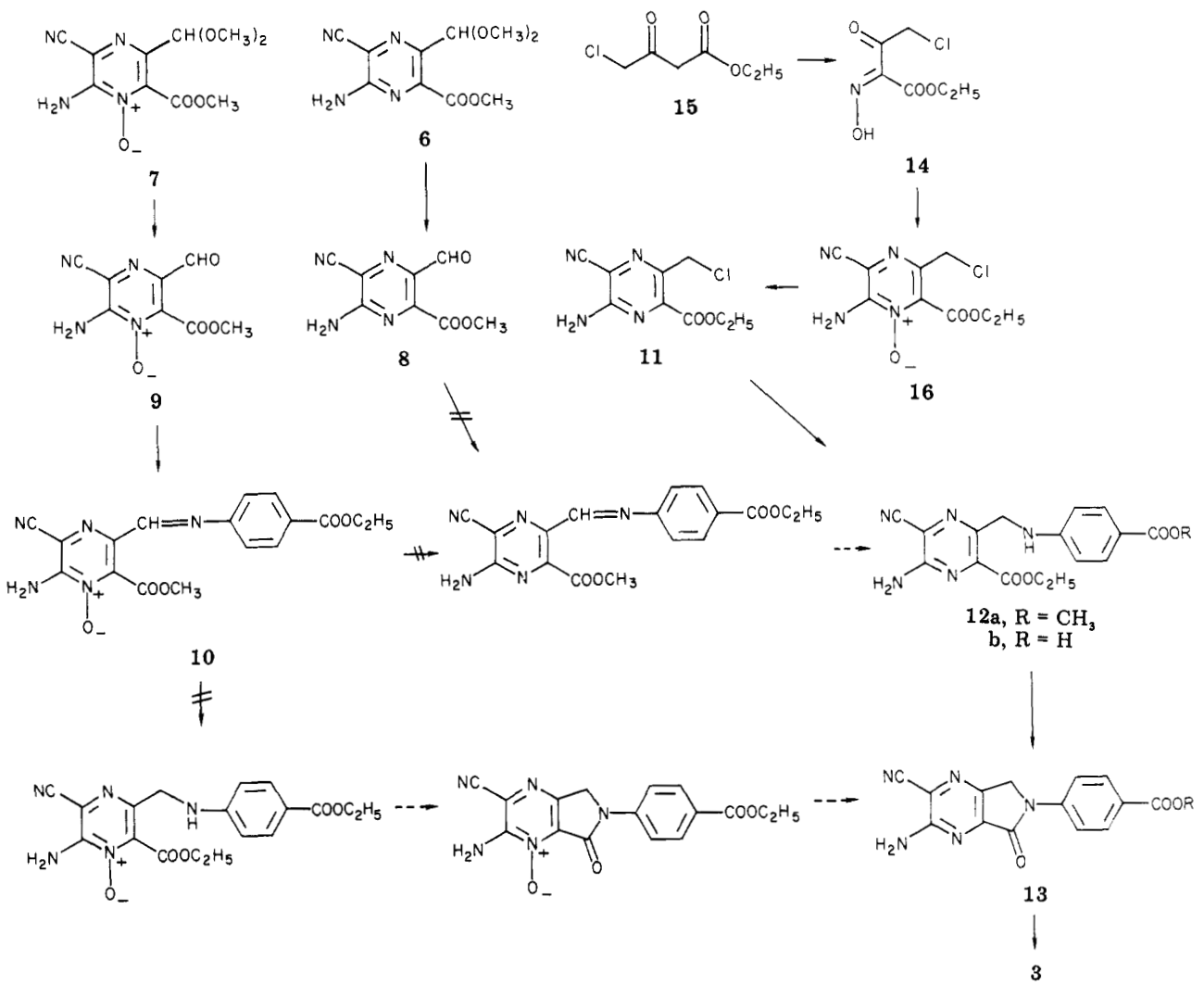
3a, R = CH_3
b, R = H

4

5

Glu = L-NHC(COOH)HCH_2CH_2COOH

Scheme I



13a by heating in methanol. Alternatively, **13a** could be obtained directly from 11 in 94% yield by overnight reaction with methyl *p*-aminobenzoate and potassium carbonate, followed by brief heating with additional potassium carbonate. 2,4-Diamino-6,8-dihydro-7-[4-(carbomethoxy)phenyl]-8-oxopyrrolo[3,4-*g*]pteridine (**3a**) was then prepared in 91% yield by reaction of **13a** with guanidine acetate in dimethylformamide (DMF) at 145 °C.

Our other target compound, the free acid **3b**, was prepared as its trifluoroacetate salt by condensation of pyrazine **11** with *p*-aminobenzoic acid and potassium carbonate, followed by heating of the resulting [(arylamino)methyl]pyrazine **12b** in dry DMF at 160–170 °C with an excess of guanidine acetate, and treatment of the crude product with trifluoroacetic acid.

We have thus developed a flexible route to 2,4-diamino-6,8-dihydro-7-aryl-8-oxopyrrolo[3,4-*g*]pteridines capable of eventual peptide coupling to provide structural analogues of methotrexate.

Experimental Section

Melting points are uncorrected and were determined on a Thomas-Hoover apparatus. Infrared spectra were recorded on a Perkin-Elmer 467 grating infrared spectrometer. ^1H NMR data

were obtained on a Varian A-60A or Perkin-Elmer R32 instrument, using Me_4Si as internal standard except where indicated, and ^{13}C NMR spectra were recorded on a Varian XL 100 Fourier transform spectrophotometer.

2-Amino-6-(carbomethoxy)-3-cyano-5-formylpyrazine (8). A slurry of 0.42 g (1.66 mmol) of **6**[5] in 10 mL of 1 N HCl was stirred at room temperature for 3 h. The mixture was then extracted with ethyl acetate (3 × 20 mL), the combined extracts were dried over sodium sulfate, and the solvent was removed in vacuo to leave 0.32 g of a yellow solid which was recrystallized from chloroform to give 0.22 g of compact, yellow crystals, mp 160–162 °C. Concentration of the mother liquors provided a second crop of 0.03 g (73% total yield). Recrystallization from toluene (carbon) provided the analytical sample: mp 164–165 °C; NMR (Me_2SO-d_6) δ 3.92 (s, 3 H), 8.60 (br s, 2 H), 9.75 (s, 1 H); IR (KBr) 3365, 3290, 3205, 2225, 1740, 1685, 1630 cm^{-1}.

Anal. Calcd for $C_8H_6N_4O_3$: C, 46.60; H, 2.93; N, 27.18. Found: C, 46.50; H, 2.91; N, 27.31.

2-Amino-6-(carbomethoxy)-3-cyano-5-formylpyrazine 1-Oxide (9). A slurry of 1.0 g (3.7 mmol) of **7**[5] in 20 mL of 1 N HCl was stirred at room temperature for 16 h. The mixture was then extracted with ethyl acetate (4 × 25 mL) and dried over sodium sulfate, and the solvent was removed in vacuo to leave 0.78 g (94%) of a yellow solid. Recrystallization from toluene provided 0.71 g (85%) of yellow crystals: mp 202–204 °C dec; NMR (Me_2SO-d_6) δ 3.96 (s, 3 H), 9.97 (br s, 2 H), 10.53 (s, 1 H); IR (KBr) 3340, 3260, 3190, 3140, 2235, 1735, 1690, 1620 cm^{-1}.

Anal. Calcd for $C_8H_6H_4O_4$: C, 43.25; H, 2.72; N, 25.22. Found: C, 43.24; H, 2.51; N, 25.05.

2-Amino-6-(carbomethoxy)-3-cyano-5-[[*N*-(*p*-carbethoxyphenyl)imino]methyl]pyrazine 1-Oxide (10). A slurry of 0.33 g (1.5 mmol) of **9**, 0.25 g (1.5 mmol) of ethyl *p*-aminobenzoate, and a few crystals of *p*-toluenesulfonic acid in 15 mL of toluene was heated to reflux for 1 h. The product, which crystallized on cooling, was collected by filtration, washed with toluene, and dried in vacuo to give 0.52 g (95%) of an orange solid: mp 212–213.5 °C; NMR (Me_2SO-d_6) δ 1.31 (t, J = 7 Hz, 3 H), 3.91 (s, 3 H), 4.29 (q, J = 7 Hz, 2 H), 7.34, 7.98 (A_2B_2 q, J = 8 Hz, 4 H), 8.46 (s, 1 H), 8.76 (br s, 2 H); IR (KBr) 3360, 3270, 3215, 2230, 1750, 1702, 1620, 1590 cm^{-1}.

Anal. Calcd for $C_{17}H_{15}N_5O_5$: C, 55.28; H, 4.09; N, 18.96. Found: C, 55.45; H, 4.08; N, 19.20.

Ethyl 4-Chloro-2-oximino-3-oxobutyrate (14). A solution of 16.46 g (0.1 mol) of ethyl 4-chloroacetoacetate (**15**) in 100 mL of dry THF was cooled to −50 °C and 7.15 mL (0.11 mol) of condensed nitrosyl chloride added dropwise. The solution was allowed to warm slowly to 0 °C and then refrigerated for 16 h. The solvent was removed in vacuo (no external heating) and the residue triturated with hexane to give an oily solid which was collected by filtration, washed with hexane, and dried on a clay plate to give 10.15 g (53%) of a colorless solid: mp 67–71 °C; NMR ($CDCl_3$) δ 1.37 (t, J = 7 Hz, 3 H), 4.43 (q, J = 7 Hz, 2 H), 4.60 (s, 2 H); IR (KBr) 3390 (br), 2995, 2950, 1730–1750, 1704, 1615 cm^{-1}.

Anal. Calcd for $C_6H_8NO_4Cl$: C, 37.22; H, 4.16; N, 7.24; Cl, 18.32. Found: C, 37.23; H, 4.13; N, 7.43; Cl, 18.42.

2-Amino-6-carbethoxy-5-(chloromethyl)-3-cyanopyrazine 1-Oxide (16). To a mixture of 11.5 g (45 mmol) of aminomalononitrile tosylate,[10] 5.8 g (30 mmol) of **14**, and 90 mL of 2-propanol was added 4 mL of concentrated HCl. The reaction mixture was allowed to stir at room temperature for 16 h, the solvent was removed in vacuo, the residue was partitioned between 25 mL of water and 50 mL of CH_2Cl_2, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (4 × 25 mL). The combined organic extracts were then stirred for 3 h with sodium sulfate and activated carbon, filtered, and concentrated in vacuo. The residue was dissolved in 25 mL of warm 1-propanol and refrigerated overnight. The product was collected, washed with cold 1-propanol, and dried in vacuo to give 4.08 g (53%) of yellow crystals, mp 118–120 °C. Recrystallization from CCl_4 provided the analytical sample as shiny yellow plates: mp 120–121 °C; NMR ($CDCl_3$) δ 1.45 (t, J = 7.5 Hz, 3 H), 4.60 (q, J = 7.5 Hz, 2 H), 4.60 (s, 2 H), 6.78 (br s, 2 H); IR (KBr) 3365, 3285, 3220, 2228, 1733, 1635 cm^{-1}.

Anal. Calcd for $C_9H_9N_4O_3Cl$: C, 42.16; H, 3.53; N, 21.83; Cl, 13.82. Found: C, 42.40; H, 3.38; N, 22.54; Cl, 13.69.

2-Amino-6-carbethoxy-5-(chloromethyl)-3-cyanopyrazine (11). To a slurry of 4.80 g (18.7 mmol) of **16** in 18 mL of 1-propanol was added with stirring 2.50 mL (21 mmol) of trimethyl phosphite (exothermic). Once all of the starting material had passed into solution, the reaction mixture was cooled in an ice bath and then refrigerated overnight. The product was collected by filtration, washed with a small amount of cold 1-propanol, and dried in vacuo to give 3.40 g (77%) of yellow crystals, mp 128–129 °C. Recrystallization from toluene/cyclohexane provided the analytical sample as thick yellow needles: mp 129–130 °C; NMR ($CDCl_3$) δ 1.45 (t, J = 7.5 Hz, 3 H), 4.50 (q, J = 7.5 Hz, 2 H), 4.88 (s, 2 H), 5.73 (br s, 2 H); IR (KBr) 3460, 3380, 3285, 3200, 3160, 2220, 1732, 1620 cm^{-1}.

Anal. Calcd for $C_9H_9N_4O_2Cl$: C, 44.92; H, 3.77; N, 23.28; Cl, 14.73. Found: C, 45.11; H, 3.80; N, 23.48; Cl, 14.63.

2-Amino-6-carbethoxy-3-cyano-5-[[4-(carbomethoxy)anilino]methyl]pyrazine (12a). A solution of 0.10 g (0.4 mmol) of **11** and 0.30 g (2.0 mmol) of methyl *p*-aminobenzoate in 5 mL of acetonitrile was slurried with 0.06 g (0.4 mmol) of potassium carbonate and the mixture stirred at room temperature for 16 h. The product was then collected by filtration and washed successively with acetonitrile, water, and ethanol and dried in vacuo to give 0.11 g (76%) of an orange solid, mp 222–223 °C, which analyzed correctly without further purification: NMR (Me_2SO-d_6) δ 1.27 (t, J = 7.5 Hz, 3 H), 3.75 (s, 3 H), 4.35 (q, J = 7.5 Hz, 2 H), 4.49 (t, $J \simeq$ 6 Hz, 2 H), 6.68, 7.73 (A_2B_2 q, J = 9 Hz, 4 H), 6.87 (br, 1 H), 7.61 (br s, 2 H); IR (KBr) 3480, 3365, 3270, 3200, 3160, 2218, 1728, 1700, 1615, 1598 cm^{-1}.

Anal. Calcd for $C_{17}H_{17}N_5O_4$: C, 57.46; H, 4.82; N, 19.71. Found: C, 57.42; H, 4.80; N, 19.91.

2-Amino-6-carbethoxy-3-cyano-5-[(4-carboxyanilino)methyl]pyrazine (12b). A slurry of 0.24 g (1 mmol) of **11**, 0.68 g (5 mmol) of *p*-aminobenzoic acid, and 0.28 g (2 mmol) of potassium carbonate in 10 mL of acetonitrile was stirred at room temperature for 25 h. The product was collected by filtration, washed successively with acetonitrile, water, and acetonitrile, and dried in vacuo to give 0.32 g (94%) of an orange powder, mp > 350 °C with slow discoloration above 270 °C, which analyzed correctly without further purification: NMR (Me_2SO-d_6) δ 1.23 (t, J = 7 Hz, 3 H), 4.36 (q, J = 7 Hz, 2 H), 4.49 (br d, $J \simeq$ 5 Hz, 2 H), 6.63, 7.70 (A_2B_2 q, J = 9 Hz, 4 H), 6.70 (br, 1 H), 7.60 (br s, 2 H); IR (KBr) 3480, 3360, 3270, 3200, 3170, 2228, 1730, 1668, 1625, 1600 cm^{-1}.

Anal. Calcd for $C_{16}H_{15}N_5O_4$: C, 56.30; H, 4.43; N, 20.52. Found: C, 56.05; H, 4.46; N, 20.31.

6-Amino-2-[4-(carbomethoxy)phenyl]-5-cyano-1,3-dihydro-1-oxopyrrolo[3,4-*b*]pyrazine (13a). Method A. To a solution of 1.20 g (5 mmol) of **11** and 3.80 g (25 mmol) of methyl *p*-aminobenzoate in 60 mL of acetonitrile was added 1.40 g (10 mmol) of powdered anhydrous potassium carbonate and the mixture stirred at room temperature for 3 h to give a voluminous precipitate. The mixture was then heated to 50 °C (oil bath temperature) and an additional 0.70 g of potassium carbonate added. After 0.5 h a further 0.70 g of potassium carbonate was added and heating continued until the orange color dissipated (0.5 h). The mixture was allowed to cool, and the yellow solid was collected by filtration, washed successively with acetonitrile, water, and acetonitrile, and dried in vacuo to give 1.46 g (94%) of a yellow powder, mp > 300 °C.

Method B. A slurry of 0.69 g (1.95 mmol) of **12a** in 50 mL of methanol was heated to reflux for 1 h, the mixture was allowed to cool, and the product was collected by filtration, washed with methanol, and dried in vacuo to give 0.60 g (99%) of a yellow powder, mp > 300 °C, which analyzed correctly without further purification: NMR (Me_2SO-d_6) δ 3.88 (s, 3 H), 4.96 (s, 2 H), 7.69 (br s, 2 H), 8.09 (s, 4 H); IR (KBr) 3480, 3320, 3215, 2225, 1718, 1627, 1607 cm^{-1}.

Anal. Calcd for $C_{15}H_{11}N_5O_3$: C, 58.25; H, 3.59; N, 22.65. Found: C, 57.95; H, 3.74; N, 22.51.

6-Amino-2-(4-carboxyphenyl)-5-cyano-1,3-dihydro-1-oxopyrrolo[3,4-*b*]pyrazine (13b). A solution of 0.34 g (1 mmol) of **12b** in 15 mL of dry DMF contained in a 25-mL round-bottom

(10) Ferris, J. P.; Sanchez, R. A.; Mancuso, R. W. "Organic Syntheses", Collect. Vol. 5; Wiley: New York, 1973; pp 32–35.

flask was heated under nitrogen for 2 h at 160–170 °C (oil bath temperature), allowed to cool, and refrigerated overnight. The product was collected by filtration, washed successively with DMF, ethanol, and ether, and dried in vacuo to give 0.14 g (47%) of a yellow powder, mp > 300 °C. The analytical sample was prepared by recrystallization from DMF: IR (KBr) 3440, 3385, 3340, 2220, 1700 (br), 1665, 1635, 1600 cm^{-1}. The compound was too insoluble in Me_2SO or TFA for determination of its NMR spectrum.

Anal. Calcd for $C_{14}H_9N_5O_3$: C, 56.95; H, 3.17; N, 23.72. Found: C, 56.76; H, 3.38; N, 23.42.

2,4-Diamino-6,8-dihydro-7-[4-(carbomethoxy)phenyl]-8-oxopyrrolo[3,4-*g*]pteridine (3a). A slurry of 0.31 g (1 mmol) of **13a** and 0.48 g (4 mmol) of guanidine acetate in 20 mL of dry DMF was heated under nitrogen at 140–145 °C (oil bath temperature) for 2 h. The solution was then allowed to cool, and the precipitate was collected by filtration, washed thoroughly with DMF, and dried in vacuo to give 0.32 g (91%) of a light orange solid, mp > 330 °C, which analyzed correctly without further purification: NMR (TFA, external Me_4Si) δ 4.15 (s, 3 H), 5.38 (s, 2 H), 7.58 (br s, 2 H), 8.05, 8.35 (A_2B_2 q, J = 9 Hz, 4 H), 8.58 (br s, 2 H); ^{13}C NMR (TFA-*d*) δ 171.7, 166.0, 164.8, 158.0, 155.0, 150.9, 149.1, 143.2, 133.4, 130.5, 127.0, 123.2, 55.0, 53.1; IR (KBr) 3430, 3300, 3130, 1715, 1695, 1660, 1620, 1600 cm^{-1}.

Anal. Calcd for $C_{16}H_{13}N_7O_3$: C, 54.73; H, 3.73; N, 27.91. Found: C, 54.45; H, 3.77; N, 28.18.

2,4-Diamino-6,8-dihydro-7-(4-carboxyphenyl)-8-oxopyrrolo[3,4-*g*]pteridine (3b). Method A. A solution of 0.61 g (1.8 mmol) of **12b** in 30 mL of dry DMF contained in a 100-mL round-bottom flask was slowly heated under nitrogen to 150 °C (oil bath temperature) for 1.5 h. The resulting mixture was allowed to cool to room temperature and 1.07 g (9.0 mmol) of guanidine acetate was added along with 30 mL of DMF. The mixture was then heated slowly to 155 °C, kept at 155–165 °C for 2 h, and allowed to cool, and the product was collected by filtration, washed successively with DMF, ethanol, and ether, and dried in vacuo to give 0.58 g (77%) of the guanidinium salt of **3b**: mp > 330 °C; ^{13}C NMR (TFA-*d*) δ 173.7, 166.0, 164.9, 158.0, 155.0, 151.0, 149.1, 143.1, 134.1, 129.5, 127.0, 123.2, 53.0. A slurry of 0.29 g of this material in 5 mL of TFA was warmed to a gentle boil, allowed to cool, and then placed in the freezer overnight. The product was collected by filtration, washed with a small amount of TFA, rinsed with ether, and dried in vacuo to give 0.24 g (58%, based on **12b**) of **3b** as its trifluoroacetate monohydrate: mp > 330 °C; NMR (TFA, external Me_4Si) δ 5.38 (s, 2 H), 7.60 (br, 2 H), 8.09, 8.40 (A_2B_2 q, J = 9 Hz, 4 H), 8.55 (br, 2 H); IR (KBr) 3340 (br), 3100 (br), 1635 with shoulders at 1650, 1675, 1690, 1710, and 1720, 1605, 1510 cm^{-1}.

Anal. Calcd for $C_{17}H_{12}N_7O_5F_3 \cdot H_2O$: C, 43.50; H, 3.01; N, 20.89; F, 12.14. Found: C, 43.68; H, 2.80; N, 20.82; F, 12.01.

Method B. A slurry of 0.12 g (0.4 mmol) of **13b**, 0.24 g (2.0 mmol) of guanidine acetate, and 12 mL of dry DMF was heated at reflux under nitrogen for 2 h. The mixture was cooled to room temperature, and the product was collected by filtration, washed successively with DMF, ethanol, and ether, and dried in vacuo to yield 0.11 g (66%) of a yellow powder, mp > 330 °C, which was converted to its trifluoroacetate monohydrate as described in method A.

Registry No. 3a, 79722-41-1; **3b** quanidinium salt, 79722-43-3; **3b** trifluoroacetate salt, 79722-44-4; **6**, 73198-30-8; **7**, 73198-25-1; **8**, 79722-45-5; **9**, 79722-46-6; **10**, 79722-47-7; **11**, 79722-48-8; **12a**, 79722-49-9; **12b**, 79722-50-2; **13a**, 79722-51-3; **13b**, 79722-52-4; **14**, 50382-11-1; **15**, 638-07-3; **16**, 79722-53-5; ethyl *p*-aminobenzoate, 94-09-7; aminomalononitrile tosylate, 5098-14-6; methyl *p*-aminobenzoate, 619-45-4; *p*-aminobenzoic acid, 150-13-0; quanidine acetate, 34771-62-5.

Lewis Acid Mediated Reactions of Organocopper Reagents. Entrainment in the Conjugate Addition to α,β-Unsaturated Ketones, Esters, and Acids via the $RCu \cdot BF_3$ System[1]

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Lewis acid mediated reactions of organocopper reagents with various kinds of α,β-unsaturated carbonyl derivatives are described. $RCu \cdot BF_3$, as well as RCu–other Lewis acid systems, is useful for the conjugate addition to the α,β-unsaturated ketones and esters, whose double bonds are sterically crowded. Certain α,β-unsaturated carboxylic acids also undergo a 1,4-addition through this reagent. Methyl sorbate undergoes a 1,4-addition via $BuCu \cdot BF_3$, while undergoing a 1,6-α,δ-addition via Bu_2CuLi. $BuCu \cdot BF_3$ reacts more readily with an aldehyde than with a ketone; the degree of chemoselectivity is greater than that of Bu_2CuLi, BuLi, or BuMgBr. The R_2CuLi–BF_3 system is useful for the double alkylation of α,β-unsaturated esters at the β-position and the carbonyl center. Stereochemical aspects of these new copper reagents are also reported.

The conjugate addition of organometallic reagents (R–M) to α,β-unsaturated carbonyl compounds is a highly useful reaction as a basic strategy for organic synthesis. Although organometallic compounds such as M = Li,[2] B,[3] Al,[4] Al–Ni,[5] Si–Ti,[6] Zr–Ni,[7] or Zn[8] have provided convenient methods to the conjugate addition, organocopper derivatives are definitely the most widely used reagents and possess the most universal applicability.[9] Unfortunately, however, the introduction of alkyl substituents at

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