constants were confirmed, when necessary, by reconstruction of the spectra using the LAOCN 3 program modified for an IBM 1130 computer. ^{13}C proton satellites were measured on a Brucker WH-90 Fourier transform pulsed NMR spectrometer using block averaging techniques to overcome dynamic range problems. Only the low-field satellites were accessible for measurement. Infrared spectra were recorded on a Perkin-Elmer Model 457 spectrophotometer.

Samples were analyzed with a Model 810 F & M gas chromatograph using the following columns: (A) SS colum 0.25 in. × 6 ft, saturated $AgNO_3$/ethylene glycol on 60/80 mesh Anakrom ABS; (B) SS column 0.25 in. × 8 ft, 10% DEGS on 60/80 mesh Anakrom ABS; (C) Glass column 0.25 in. × 4 ft, 5% DEGS on 60/80 mesh Anakrom ABS.

Reagents. The olefins (*cis*-3-hexene, *trans*-3-hexene, *cis*-β-methylstyrene, and *trans*-β-methylstyrene) were from Chemical Samples Co. The isomeric purity of each sample was determined by GLC with column A. The lead thiocyanate used to generate thiocyanogen was prepared by a previously described method.[18]

Thiocyanation of Olefins. The α,β-dithiocyanate and α-isothiocyanato-β-thiocyanate adducts were prepared as follows. Lead thiocyanate (125 g, 0.38 mol) and acetic acid (2 L) were added to a three-neck flask equipped with a true-bore stirrer and maintained under nitrogen. The mixture was stirred for 10 min, bromine (31 g, 0.19 mol) was added, and stirring was continued until the solution became colorless. Olefin (0.097 mol) was added, and the mixture stirred overnight to ensure complete reaction, then filtered. The filtrate was shaken with water to destroy excess thiocyanogen, and the aqueous layer extracted with ethyl ether. The extract was water washed, dried over anhydrous $MgSO_4$, and concentrated to a thick, amber liquid. The adducts in the mixture were thereby separated by CCD. Individual components were checked for purity by GLC using column B. Elemental analyses were satisfactory for all compounds described. The following compounds were isolated in this manner.

erythro-3,4-Dithiocyanatohexane (**3**) was isolated as a white, crytalline solid: mp 62–63 °C; IR (KBr) 2150 cm^{-1} (SCN).

threo-3,4-Dithiocyanatohexane (**4**) was isolated as an amber-colored, viscous oil, IR (neat) 2150 cm^{-1} (SCN).

threo-3-Isothiocyanato-4-thiocyanatohexane (**7**) from the addition of thiocyanogen to *cis*-3-hexane was recovered as a brown liquid: IR (neat) sharp –SCN peak at 2150 cm^{-1} and broad –NCS peak at 2080 cm^{-1}.

erythro-3-Isothiocyanato-4-thiocyanatohexane (**9**), from the addition of thiocyanogen to *trans*-3-hexene, was separated as a brown, oily liquid: IR (neat) sharp –SCN peak at 2160 cm^{-1} and broad –NCS peak at 2080 cm^{-1}.

threo-1,2-Dithiocyanato-1-phenylpropane (**11**) was isolated as a viscous oil from the addition of thiocyanogen to *cis*-β-methylstyrene. The purity of this sample was checked by GLC using column C, IR (neat) 2160 cm^{-1} (SCN).

erythro-1,2-Dithiocyanato-1-phenylpropane (**13**) from the addition of thiocyanogen to *trans*-β-methylstyrene was isolated as a white, crystalline solid: mp 110–111 °C; IR (KBr) 2160 cm^{-1} (SCN).

cis- and *trans*-4,5-diethyl-1,3-dithiolane-2-iminium methanesulfonate (**5** and **6**) were obtained by cyclization of **3** and **4** in methanesulfonic acid as described in part 3 of this series.[8]

Registry No.—**3**, 30647-63-3; **4**, 61521-96-8; **5**, 61521-98-0; **6**, 61522-00-7; **7**, 61522-01-8; **9**, 61522-02-9; **11**, 60212-01-3; **13**, 60212-00-2; *cis*-3-hexene, 7642-09-3; *trans*-3-hexene, 13269-52-8; *cis*-β-methylstyrene, 766-90-5; *trans*-β-methylstyrene, 873-66-5; methanesulfonic acid, 75-75-2; lead thiocyanate, 592-87-0; thiocyanogen, 505-14-6.

References and Notes

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Pteridines. 40. Some Reactions of 2-Amino-3-cyano-5-bromomethylpyrazine and 2-Amino-3-cyano-5-methylpyrazine[1]

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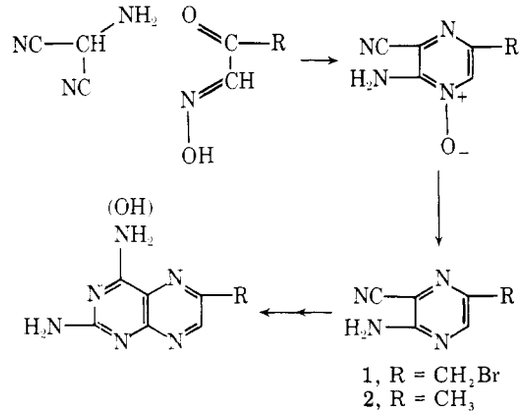
Some chemistry of 2-amino-3-cyano-5-bromomethylpyrazine (**1**) and 2-amino-3-cyano-5-methylpyrazine (**2**) has been explored to determine their usefulness as intermediates for the preparation of C-6 substituted pteridines. In general, new carbon–carbon bonds can be formed at the 5 position of **1** if weakly basic nucleophiles are employed. The synthetic potential of **2** was less than expected, however, owing to the nonacidity of the 5-methyl protons. By contrast, 2-amino-3-cyano-6-methylpyrazine could be alkylated to give 2-amino-3-cyano-6-*n*-propylpyrazine. A general discussion is given of the reactivity of both **1** and **2**.

Previous papers in this series have detailed an unambiguous approach to the synthesis of 6-substituted pteridines (i.e., L-*erythro*-biopterin, xanthopterin, methotrexate, folic acid, Asperopterin B), by guanidine cyclization of a 2-amino-3-cyano- (or carboalkoxy-) pyrazine suitably substituted at position 5. These latter critical intermediates were prepared in turn by an unequivocal cyclization of aminomalononitrile or an ester of α-aminocyanoacetic acid with an α-ketoaldoxime followed by deoxygenation of the resulting pyrazine 1-oxide.[3]

One obvious disadvantage of this procedure for the preparation of pteridines possessing complex side chains at position 6 (pyrazine position 5) was the inaccessibility of the requisite α-ketoaldoxime intermediates. We have therefore investigated the possible utility of two readily accessible pyrazines, 2-amino-3- cyano-5-bromomethylpyrazine (**1**)[4] and 2-amino-



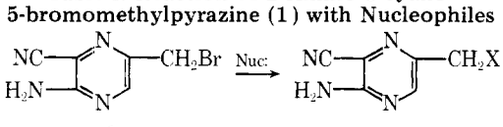
1, R = CH_2Br
2, R = CH_3

3-cyano-5-methylpyrazine (**2**),[5] as possible relay compounds for the construction of complex side chains.

We have already described some reactions of **1** with phosphorus, nitrogen, and sulfur nucleophiles.[4,6,7] Of particular interest would be the utilization in such displacement reactions of carbon nucleophiles for the eventual preparation of pteridines bearing complex carbon side chains at position 6. For example, it was envisioned that the reaction of **1** with an acyl anion equivalent might provide a convenient route to 2,4-diamino-6-acylmethylpteridines, compounds of considerable interest as potential xanthine oxidase inhibitors. Similarly, treatment of **1** with the anion of a β-keto ester should lead eventually to pteridines bearing oxygenated side chains reminiscent of the naturally occurring side chains found in biopterin and neopterin and thus of potential interest as inhibitors of various enzymatic hydroxylation and dehydrogenation reactions. Alternately, the dianion of **2** appeared to be an attractive intermediate for elaboration of more complex side chains at position 5, particularly in view of the reported successful C-alkylation of the dianions of 2-amino-4-methylpyrimidine and 2-methylbenzimidazole.[8]

Because of the susceptibility of the cyano substituent in **1** to attack by strong nucleophiles, our initial attempts to utilize **1** as an intermediate for the formation of new carbon–carbon bonds at position 5 were restricted to investigations with weak nucleophiles. For example, treatment of **1** with a slight excess of sodium cyanide in Me_2SO afforded the cyanomethyl derivative **3** in 65% yield. It is interesting to note that the reaction of cyanide ion with the 1-oxide of **1** was not successful because of a competing reaction involving addition of cyanide ion to position 6 of the pyrazine ring, followed by aromatization by dehydration. Similarly, the sodium salts of diethyl malonate, ethyl acetoacetate, ethyl γ-methoxyacetoacetate, and potassium phthalimide all reacted successfully with **1**; results are summarized in Table I. In a few instances, the desired products were contaminated by some dialkylated product; with the sodium salt of methyl cyanoacetate, only dialkylated material could be obtained.

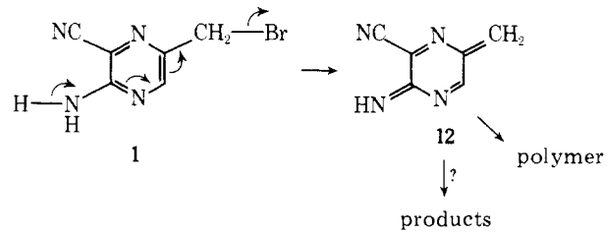
Table I. Reaction of 2-Amino-3-cyano-5-bromomethylpyrazine (1) with Nucleophiles



1

Product	X	Yield, %
3	—CN	65
4	—$CH(COOC_2H_5)_2$	60 + 20% dialkylated product (**5**)
6	—$CHCOCH_3$ with $COOC_2H_5$	65 + 15% dialkylated product (**7**)
8	—$CHCCH_2OC_2H_5$ with O and $COOC_2H_5$	70 + 20% dialkylated product (**9**)
10	—N(C=O)$_2$C$_6$H$_4$	91
11	>C(CN)COOCH$_3$	67 (dialkylated product)

Unfortunately, reactions of **1** with carbanions derived from weaker carbon acids were not successful. For example, addition of **1** to 2-lithio-1,3-dithiane in THF at −25 °C resulted in the formation of an extremely insoluble black solid which did not melt below 300 °C. Inverse addition led to identical results. The IR spectrum of this solid showed that the nitrile function at position 3 was still present, and we surmise that the strongly basic dithiane anion initiated dehydrobromination of **1** by deprotonation of the amino group, and that the resulting quinoidlike pyrazine intermediate **12** subsequently polymerized. An attempt to remove the acidic protons of the 2-amino grouping of **1** by conversion to its 2-dimethylaminomethylenamino derivative (vide infra) by reaction with dimethylformamide dimethyl acetal led only to decomposition, apparently because reaction also took place at the (activated) 5-bromomethyl group.

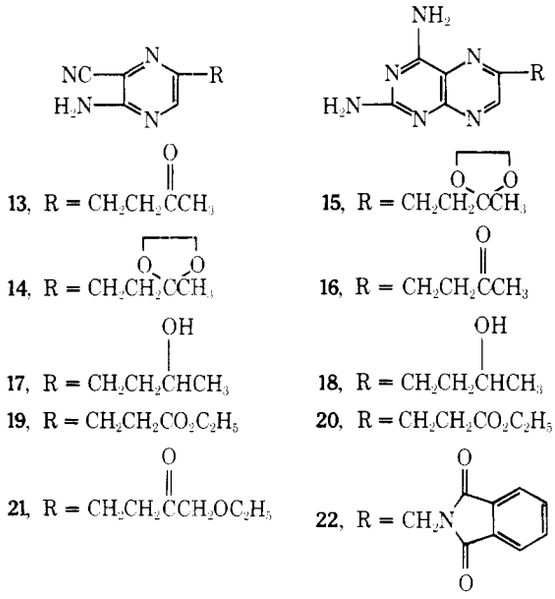


These results with 2-lithio-1,3-dithiane were unfortunately not unique. Thus, treatment of **1** with the anion of methyl methylthiomethyl sulfoxide gave analogous results. Attempts to react **1** with lithium acetonitrile or with the sodium salt of acetophenone also failed.

The above observations do not allow a clear-cut interpretation of the mechanism of the reaction of **1** with nucleophiles. It is clear that anions of compounds with $pK_a > 19$ (acetophenone, acetonitrile, dithiane) do not react successfully with **1**, whereas anions derived from less basic substrates ($pK_a < 13$), such as keto esters and malonates, give excellent yields of displacement products. However, it is not clear whether the unsuccessful results observed in the former cases are due to dehydrohalogenation followed by polymerization of **12**, or to the fact that those anions which bring about polymerization, being very poor Michael donors, fail to capture the intermediate quinoidlike pyrazine intermediate **12**, which could conceivably be formed in all instances where **1** was treated with carbanions. An attempt to prepare a 2,4-diaminopteridine from **3** by reaction with guanidine again gave a black, polymeric solid similar in its general properties to the above black solid isolated from reactions of **1** with highly basic carbanions. Elimination of HCN from **3**, initiated by guanidine acting as a base, would appear to be responsible.

In view of these results, it is clear that synthetic schemes leading from **1** to pteridines carrying complex side chains at position 6 are more limited than originally envisioned. Nevertheless, we have been successful in converting compounds **3, 4, 6,** and **10** to various 2,4-diaminopteridines of potential interest as biopterin inhibitors. Thus, decarboethoxylation of the ethyl acetoacetate displacement product **6** was effected

by the method of Krapcho.[9] The resulting ketone **13** was first converted to its ethylene ketal **14** which was then cyclized with



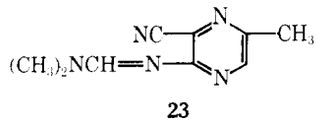
guanidine in the presence of sodium methoxide to the protected 2,4-diaminopteridine **15.** Removal of the protecting group then gave 1-(2,4-diamino-6-pteridinyl)-3-butanone (**16**) in 33.5% overall yield from **6.**

The carbonyl function in the intermediate pyrazine **13** could be reduced in moderate yield with sodium borohydride to give the secondary alcohol **17,** which was then cyclized with guanidine to the 6-hydroxybutylpteridine derivative **18** in 81% yield.

Decarboethoxylation of the malonate displacement product **4** gave 2-amino-3-cyano-5-(2-carboethoxyethyl)pyrazine (**19**) in 77% yield. This was cyclized in moderate yield with guanidine acetate in dimethylformamide to the 2,4-diaminopteridine **20;** a competing reaction was acylation of guanidine either by **19** or by **20.** Curiously, attempts to decarboethoxylate the displacement product **8** (from **1** and ethyl γ-ethoxyacetoacetate) were only moderately successful, and nothing further was done with the derived pyrazine **21.**

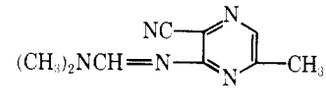
The phthalimidomethylpyrazine **10** was converted to 2,4-diamino-6-phthalimidomethylpteridine **22** in modest yield, but attempts to remove the phthalimido grouping from **22** were unsuccessful, probably because of its insolubility.

We have also briefly investigated the possible intermediacy of 2-amino-3-cyano-5-methylpyrazine (**2**) for the construction of more complex side chains at position 5. Since the above results with **1** appeared to indicate that deprotonation of the amino group at position 2 was possible with strongly basic carbanions, we protected the 2-amino group in **2** by reaction with dimethylformamide dimethyl acetal to give the protected derivative **23.** However, attempts to form a carbanion from **23** were unsuccessful. Thus, treatment of **23** with butyllithium/TMEDA led only to nucleophilic addition to the 3-cyano grouping. Only starting material was recovered after attempted alkylation when a nonnucleophilic base, lithium diisopropylamide, was employed.



23

The failure of **23** to deprotonate under the above conditions might not be surprising in view of the unfortunate positioning of the dimethylformamidylamino substituent para to the (potentially) acidic methyl group. In order to ascertain whether the failure of **2** to deprotonate was indeed due to this structural feature or to some inherent property of the pyrazine ring, we briefly examined 2-(*N,N*-dimethylformamidylamino)-3-cyano-6-methylpyrazine (**24**), a structural isomer of **23**



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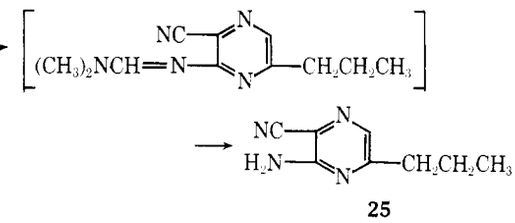

25

in which an electron-withdrawing nitrile group is now situated para to the methyl group. In fact, deprotonation of **24** with lithium diisopropylamide followed by addition of ethyl iodide, and then removal of the protecting group by acid hydrolysis, gave 2-amino-3-cyano-6-*n*-propylpyrazine (**25**) in 52% yield. The inability of either **2** or its amino-protected derivative **23** to undergo carbon alkylation is thus apparently the result of both the nature and positioning of the substituents on the pyrazine ring.

Experimental Section

2-Amino-3-cyano-5-cyanomethylpyrazine (3). A solution of 0.58 g (11 mmol) of sodium cyanide in 25 ml of Me_2SO was stirred at room temperature in a 50-ml round-bottomed flask fitted with a thermometer and condenser. To this solution was added 2.13 g (10 mmol) of 2-amino-3-cyano-5-bromomethylpyrazine (**1**);[4] the temperature of the reaction mixture rose from 22 to 36 °C. The mixture was heated at 40 °C for 2.5 h and then poured into 100 ml of a saturated solution of sodium chloride. Extraction with methylene chloride (4 × 40 ml) followed by drying of the combined methylene chloride extracts (Na_2SO_4), filtering, and evaporation (to remove traces of Me_2SO) gave an oil which solidified upon trituration with 2-propanol. The solid which separated was collected by filtration, dried, and recrystallized from 2-propanol to give 1.03 g (65%) of **3** as light orange needles, mp 169–170 °C.

Anal. Calcd for $C_7H_5N_5$: C, 52.83; H, 3.17; N, 44.00. Found: C, 52.87; H, 3.46; N, 43.92.

2-Amino-3-cyano-5-(2,2-dicarboethoxyethyl)pyrazine (4). A solution of the sodium salt of diethyl malonate was prepared by adding 1.53 g (11 mmol) of a 50% NaH–paraffin oil dispersion to 20 ml of freshly distilled dry THF and then, under nitrogen at 5 °C, slowly adding a solution of 1.68 g (10.5 mmol) of diethyl malonate in 10 ml of dry THF. This mixture was stirred at room temperature for 1 h and then added dropwise to a solution of 2.13 g (10 mmol) of **1** in 15 ml of dry THF at room temperature under nitrogen. This mixture was stirred for 4 h and poured into 50 ml of saturated sodium chloride solution. The mixture was neutralized with 6 N HCl and extracted four times with 20-ml portions of chloroform. The combined chloroform layers were dried (Na_2SO_4), filtered, and evaporated to give a crude solid which was recrystallized from carbon tetrachloride to give 1.75 g (60%) of **4** as a white, crystalline solid, mp 115–116 °C.[10]

Anal. Calcd for $C_{13}H_{16}N_4O_4$: C, 53.42; H, 5.52; N, 19.24. Found: C, 53.62; H, 5.59; N, 19.01.

1-(2-Amino-3-cyano-5-pyrazinyl)-2-carboethoxy-3-butanone (6). A solution of the sodium salt of ethyl acetoacetate was prepared by adding 3.17 g (0.066 mol) of a 50% NaH–paraffin oil dispersion to 40 ml of freshly distilled dry THF and then adding slowly, under nitrogen at 5 °C, a solution of 8.19 g (0.063 mol) of ethyl acetoacetate in 25 ml of dry THF. The mixture was stirred at room temperature for 1 h and then added dropwise to a solution of 12.78 g (0.060 mol) of **1** in 75 ml of dry THF at room temperature under nitrogen. This mixture was stirred for 4 h and then poured into 150 ml of a saturated solution of sodium chloride. This mixture was neutralized with 6 N HCl and extracted four times with 50-ml portions of chloroform, and the combined chloroform layers dried (Na_2SO_4), filtered, and evaporated to give an oil which solidified on trituration with cyclohexane.

Recrystallization from carbon tetrachloride gave 10.2 g (65%) of **6** as a white, crystalline solid, mp 96–97 °C.

Anal. Calcd for $C_{12}H_{14}N_4O_3$: C, 54.96; H, 5.38; N, 21.36. Found: C, 54.88; H, 5.45; N, 21.36.

The material insoluble in carbon tetrachloride was removed by filtration and recrystallized from ethanol/acetonitrile to give 1.0 g of the dialkylated product (**7**), mp 237–238 °C.

Anal. Calcd for $C_{18}H_{18}N_8O_3$: C, 54.82; H, 4.60; N, 28.41. Found: C, 54.84; H, 4.63; N, 28.24.

2-Amino-3-cyano-5-phthalimidomethylpyrazine (10). A mixture of 2.69 g (12.6 mmol) of **1**, 2.6 g (14 mmol) of potassium phthalimide, and 35 ml of DMF was stirred at room temperature for 30 min. There was an initial mild exothermic reaction with the temperature rising from 18 to 33 °C. The mixture was poured into 50 ml of water and the resulting precipitate collected by filtration, dried, and recrystallized from 350 ml of acetonitrile to give 3.2 g (91%) of a white, crystalline solid, mp 275–276 °C dec.

Anal. Calcd for $C_{14}H_9N_5O_2$: C, 60.21; H, 3.25; N, 25.08. Found: C, 60.58; H, 3.36; N, 24.94.

2-Amino-3-cyano-5-(2-carboethoxyethyl)pyrazine (19). A mixture of 0.58 g (2.0 mmol) of **4**, 0.15 g (2.5 mmol) of sodium chloride, 0.15 ml (8.0 mmol) of water, and 15 ml of Me_2SO was placed in a three-necked 50-ml round-bottomed flask fitted with a thermometer, condenser, and magnetic stirrer. Attached to the condenser was a trap containing a solution of saturated barium hydroxide which was used to monitor CO_2 evolution. The mixture was heated at 155–170 °C for 6 h, cooled, and poured into 50 ml of water. The aqueous solution was extracted five times with 15-ml portions of chloroform. The combined chloroform extracts were dried (Na_2SO_4), filtered, and evaporated to give an oil which solidified upon drying in vacuo for 4 h. Recrystallization from carbon tetrachloride (charcoal) gave 0.34 g (77%) of **19** as a white, crystalline solid, mp 85–86 °C.

Anal. Calcd for $C_{10}H_{12}N_4O_2$: C, 54.54; H, 5.49; N, 25.44. Found: C, 53.98; H, 5.29; N, 25.14.

1-(2-Amino-3-cyano-5-pyrazinyl)-3-butanone (13). Using the same procedure as outlined above for the preparation of **19**, 10.2 g (0.039 mol) of the keto ester **6** was decarboethoxylated to give 5.3 g (72%) of **13** as a white, crystalline solid, mp 130–131 °C after recrystallization from benzene.

Anal. Calcd for $C_9H_{10}N_4O$: C, 56.83; H, 5.30; N, 29.46. Found: C, 56.98; H, 5.38; N, 29.02.

1-(2-Amino-3-cyano-5-pyrazinyl)-2-carboethoxy-4-ethoxy-3-butanone (8). A solution of the sodium salt of ethyl γ-ethoxyacetoacetate was prepared by adding 0.48 g (10 mmol) of a 50% NaH–paraffin oil dispersion to 25 ml of freshly distilled dry THF followed by addition, under nitrogen at 5 °C, of a solution of 1.74 g (10 mmol) of ethyl γ-ethoxyacetoacetate in 10 ml of dry THF. The mixture was stirred at room temperature for 1 h and then added dropwise to a solution of 2.13 g (10 mmol) of **1** in 25 ml of dry THF at room temperature under nitrogen. This mixture was stirred for 4 h, poured into 50 ml of saturated sodium chloride solution, neutralized with 6 N HCl, and then extracted three times with 40-ml portions of chloroform. The combined chloroform extracts were dried (Na_2SO_4), filtered, and evaporated to give an oil. Trituration with benzene resulted in a separation of a solid which was collected by filtration, dried, and recrystallized from 2-propanol to give 0.60 g (20%) of a white solid, mp 194–195 °C, which appeared from microanalytical data and spectral analysis to be the dialkylated product **9**.

Anal. Calcd for $C_{20}H_{22}N_8O_4$: C, 54.79; H, 5.06; N, 25.56. Found: C, 54.80; H, 5.28; N, 25.51.

Evaporation of the benzene filtrates then gave 2.1 g (70%) of **8** as an oil: NMR ($CDCl_3$) δ 8.18 (s, 1), 5.65 (b, 2), 4.5–3.2 (m, 9), 1.25 (t, 6); IR (neat) 1750 (ester), 1725 (ketone), 2225 (CN), 3250–3450 cm^{-1} (NH_2).

1-(2-Amino-3-cyano-5-pyrazinyl)-4-ethoxy-3-butanone (21). A mixture of 2.1 g (7 mmol) of the keto ester **8**, 0.58 g (10 mmol) of sodium chloride, 0.5 ml of water, and 20 ml of Me_2SO was placed in a 50-ml three-necked round-bottomed flask fitted with a thermometer, condenser, and magnetic stirring bar. The mixture was heated at 150–160 °C for 5 h, cooled, and poured into 100 ml of water. Some black, polymeric material precipitated which was removed by filtration. The aqueous filtrate was then extracted four times with 50-ml portions of chloroform and the combined chloroform extracts dried (Na_2SO_4), filtered, and evaporated. The residual oil crystallized upon trituration with hexane and cooling. Recrystallization from carbon tetrachloride gave 0.30 g (19%) of **21** as a white, crystalline solid, mp 89–91 °C.

Anal. Calcd for $C_{11}H_{14}N_4O_2$: C, 56.40; H, 6.02; N, 23.92. Found: C, 56.28; H, 5.89; N, 24.18.

1,3-Bis(2-amino-3-cyano-5-pyrazinyl)-2-cyano-2-carbomethoxypropane (11). A solution of the sodium salt of methyl cyanoacetate was prepared by adding 1.62 g (15.7 mmol) of 97% methyl cyanoacetate in 15 ml of dry THF to a stirred mixture of 0.75 g (15.7 mmol) of 50% NaH–paraffin oil dispersion in 15 ml of THF under nitrogen at 0 °C. After stirring at room temperature for 30 min, this mixture was added to a stirred solution of 3.20 g (15 mmol) of **1** in 30 ml of dry THF at room temperature under nitrogen. The mixture was stirred at room temperature for 4 h, poured into 100 ml of saturated sodium chloride solution, neutralized with 10% HCl, and then extracted with 100 ml of chloroform. The chloroform extracts were dried (Na_2SO_4), filtered, and evaporated to give a crude solid which was partially purified by extraction with hot benzene. The benzene-insoluble material was further purified by dissolving in 60 ml of boiling acetonitrile, decolorizing with charcoal, and then concentrating to a small volume followed by cooling. This gave 1.9 g (67%) of **11** as a yellow solid, mp 213–215 °C dec.

Anal. Calcd for $C_{16}H_{13}N_9O_2$: C, 52.89; H, 3.61; N, 34.70. Found: C, 52.54; H, 3.92; N, 34.79.

1-(2-Amino-3-cyano-5-pyrazinyl)-3-ethylenedioxybutane (14). A mixture of 1.90 g (10 mmol) of **13**, 0.93 g (15 mmol) of ethylene glycol, 50 mg of *p*-toluenesulfonic acid, and 40 ml of benzene was placed in a 100-ml round-bottomed flask fitted with a Dean-Stark trap and condenser, and heated under reflux for 8 h. The reaction mixture was decanted while hot to remove some insoluble tarry material and poured into an equal volume of hexane. Cooling resulted in the separation of yellow needles which were collected by filtration, dried in vacuo, and recrystallized from benzene/cyclohexane to give 1.90 g (82%) of **14**, mp 126–127 °C.

Anal. Calcd for $C_{11}H_{14}N_4O_2$: C, 56.40; H, 6.02; N, 23.92. Found: C, 56.59; H, 6.20; N, 24.87.

1-(2,4-Diamino-6-pteridinyl)-3-ethylenedioxybutane (15). To a solution of sodium methoxide [from 0.55 g (24 mmol) of sodium in 30 ml of dry methanol] was added 1.2 g (12 mmol) of guanidine hydrochloride. The mixture was stirred briefly and then filtered into a 100-ml round-bottomed flask containing 1.87 g (8.0 mmol) of **14**. The reaction mixture was heated under reflux for 40 h, cooled, concentrated to 10 ml, and diluted with 40 ml of 2-propanol. Cooling at −20 °C for 1 h resulted in the separation of a solid which was collected by filtration, washed with 2-propanol, dried, and recrystallized (charcoal) from 2:1 acetonitrile/methanol to give 1.53 g (70%) of **15** as a yellow, microcrystalline solid, mp 269–270 °C.

Anal. Calcd for $C_{12}H_{16}N_6O_2$: C, 52.16; H, 5.84; N, 30.42. Found: C, 52.26; H, 5.86; N, 30.28.

1-(2,4-Diamino-6-pteridinyl)-3-butanone (16). To a stirred mixture of 1.9 g (7 mmol) of **15** and 25 ml of trifluoroacetic acid at 0 °C was added 0.5 ml of concentrated H_2SO_4. The resulting solution was stirred for an additional 15 min at 0 °C, poured into 50 ml of ice water, stirred for 15 min, and filtered. The collected solid was stirred with 50 ml of 2 N NaOH for 1 h, collected by filtration, and triturated with hot methanol. Cooling and filtration gave 1.31 g (81%) of analytically pure **16** as a light yellow solid, mp 286–287 °C.

Anal. Calcd for $C_{10}H_{12}N_6O$: C, 51.72; H, 5.21; N, 36.19. Found: C, 51.61; H, 5.25; N, 35.95.

1-(2-Amino-3-cyano-5-pyrazinyl)-3-butanol (17). A mixture of 1.52 g (8 mmol) of **13**, 0.16 g (4.2 mmol) of sodium borohydride, and 50 ml of dry methanol was stirred at 0 °C for 10 min and at room temperature for 1 h, and then evaporated to dryness. The residue was dissolved in 20 ml of water and extracted with four 15-ml portions of chloroform. The combined chloroform extracts were dried (Na_2SO_4), filtered, and evaporated to give 0.98 g of a crude solid which was recrystallized from benzene to give 0.83 g (54%) of **17** as a fluffy, yellow solid, mp 101.5–103 °C.

Anal. Calcd for $C_9H_{12}N_4O$: C, 56.24; H, 6.29; N, 29.15. Found: C, 55.64; H, 6.37; N, 28.42.

1-(2,4-Diamino-6-pteridinyl)-3-butanol (18). To a solution of sodium methoxide [from 0.69 g (20 mmol) of sodium in 40 ml of dry methanol] was added 0.57 g (6.0 mmol) of guanidine hydrochloride. After brief stirring, this mixture was filtered into a 100-ml round-bottomed flask containing 0.77 g (4.0 mmol) of **17**. The resulting mixture was heated under reflux for 40 h, cooled, concentrated to 10 ml by evaporation in vacuo, and diluted with 25 ml of 2-propanol. After thorough cooling, the mixture was filtered and the collected solid washed with cold 2-propanol, dried, and recrystallized from 1-propanol to give 0.76 g (81%) of **18** as a microcrystalline, yellow powder, mp 257–258 °C.

Anal. Calcd for $C_{10}H_{14}N_6O$: C, 51.27; H, 6.02; N, 35.89. Found: C, 51.53; H, 5.99; N, 35.89.

2,4-Diamino-6-(2-carboethoxyethyl)pteridine (20). A mixture of 0.44 g (2 mmol) of **19**, 0.26 g (2.2 mmol) of guanidine acetate, and 20 ml of DMF was heated at 120 °C for 39 h. It was then evaporated

under reduced pressure and the residual solid triturated with 2-propanol. Filtration gave 0.27 g (52%) of a yellow solid which was recrystallized from 2-propanol, mp 266–267 °C dec.

Anal. Calcd for $C_{11}H_{14}N_6O_2$: C, 50.38; H, 5.38; N, 32.04. Found: C, 50.37; H, 5.44; N, 31.91.

2,4-Diamino-6-phthalimidomethylpteridine (22). A mixture of 2.5 g (9 mmol) of **10**, 1.13 g (9.5 mmol) of guanidine acetate, and 50 ml of DMF was heated at 120 °C for 48 h. The reaction mixture was cooled, diluted with an equal volume of methanol, and filtered. The collected solid was washed copiously with methanol and recrystallized from 1:1 DMF/methanol to give 1.5 g of **22** as yellow needles, mp 338 °C dec.

Anal. Calcd for $C_{15}H_{11}N_7O_2$: C, 56.07; H, 3.45; N, 30.52. Found: C, 55.70; H, 3.56; N, 29.55.

2-(*N,N*-Dimethylformamidylamino)-3-cyano-5-methylpyrazine (23). A mixture of 2.68 g (20 mmol) of **2**, 20 ml of dimethylformamide dimethyl acetal, and 30 ml of dry DMF was stirred at room temperature for 12 h. Evaporation in vacuo then gave a residual oil which solidified on trituration with cyclohexane. Recrystallization from cyclohexane then gave 3.48 g (92%) of **23** as white, fluffy needles, mp 102.5–103.5 °C.

Anal. Calcd for $C_9H_{11}N_5$: C, 57.13; H, 5.86; N, 37.01. Found: C, 57.22; H, 5.68; N, 37.01.

2-(*N,N*-Dimethylformamidylamino)-3-cyano-6-methylpyrazine (24) was prepared in 82% yield from 2-amino-3-cyano-6-methylpyrazine[11] as described above for the conversion of **2** to **23**, yellow needles (from benzene), mp 182.5–183 °C.

Anal. Calcd for $C_9H_{11}N_5$: C, 57.13; H, 5.86; N, 37.01. Found: C, 57.24; H, 5.85; N, 36.92.

2-Amino-3-cyano-6-*n*-propylpyrazine (25). A 5.3-mmol solution of lithium diisopropylamide was prepared in a 100-ml round-bottomed flask fitted with a septum, addition funnel, and gas inlet tube, by syringe addition of 2.2 ml of a 2.4 M solution of *n*-butyllithium to 0.54 g (5.3 mmol) of diisopropylamine in 10 ml of dry THF under nitrogen. This was stirred at −78 °C for 30 min and then to it was added a solution of 0.95 g (5 mmol) of **24** in 40 ml of warm THF. After addition was complete, the reaction mixture was stirred for 1 h at −78 °C and a solution of 0.94 g (6 ml) of ethyl iodide in 10 ml of dry THF was added. Stirring was continued as the reaction mixture was allowed to warm to room temperature. After 20 h the solution was quenched with 25 ml of 10% HCl, heated on a steam bath for 15 min, and then extracted with chloroform. The combined chloroform extracts were dried (Na_2SO_4), filtered, and evaporated to give 0.51 g of a crude solid. Sublimation at 100 °C (0.1 Torr) gave 0.42 g (52%) of **25** as a white, crystalline solid, mp 115–116 °C.

Anal. Calcd for $C_8H_{10}N_4$: C, 59.24; H, 6.21; N, 34.54. Found: C, 59.13; H, 6.21; N, 34.25.

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References and Notes

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Highly Stereospecific Dimerization of 5-Formyl-5-methyl-1-pyrazolines. Preparation and Characterization of Stable Carbinolamines (Amino Hemiacetals)

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The unstable 5-methyl-5-formyl-2-pyrazolines **3**, generated in situ by a 1,3-dipolar additon of α-methylpropenal (methacrolein) to α-diazo esters, dimerize in a highly specific way to *meso*-**4**, which are stable carbinolamines. Surprisingly, the latter show no equilibrium with the monomers (pyrazolines) in solution, even at 90 °C in Me_2SO, but they are cleanly transformed into the aminals **5** by a variety of nucleophiles. The conversion of **4** to **5** occurs with retention of configuration at the reacting center, as established by x-ray diffractometry.

It has been clearly recognized for a long time that the formation of hydrazones, imines, oximes, etc., is a two-step reaction, a carbinolamine being an obligatory intermediate.[1] However, the carbinolamine function itself (also called hemiaminal or amino hemiacetal) has attracted much less attention, although several natural compounds have recently been recognized to possess a stable amino hemiacetal function.[2] From a synthetic point of view, with the exceptions of halogen stabilized molecules,[3] or derivatives of strained cyclopropanones,[4] the dimerization of five-membered heterocycles with a formyl group α to an endocyclic NH constitutes to our best knowledge the only systematic attempts to the synthesis of heterocyclic amino hemiacetals;[5] however, in this case, never was the function clearly and fully characterized, because of nonresolved mixtures and of a dimer–monomer equilibrium in solution. We now report the facile synthesis and characterization of stable carbinolamines from the stereospecific dimerization of substituted 5-formyl-2-pyrazolines.