from absolute ethanol; IR 1710 cm^{-1} (amide C=O); ^1H NMR ($CDCl_3$) δ 1.22 (t, J = 7 Hz, 3 H, CH_2CH_3), 1.72 (s, 3 H, $ArCH_3$), 2.58 (s, 3 H, $ArCH_3$), 4.0–4.3 (symmetrical 12-peak multiplet centered at δ 4.15, 2 H, CH_2CH_3), 7–7.6 (m, 4 H, ArH), 8.0–8.2 (m, 1 H, ArH); ^{13}C NMR ($CDCl_3$) δ 12.67 ($ArCH_3$), 19.03 ($ArCH_3$), 21.28 (CH_3CH_2), 45.22 (N–CH_2), 88.18 (C-4), 123.28 (C-3), 126.54, 128.03, 129.31, 129.53, 130.16, 130.66, 130.95, 133.64, 134.56, 137.06, 137.43, 161.57 (C=O); mass spectrum, m/e 449 (5 Cl, M^+), 414 (4 Cl, M – 35), 386 (4 Cl, 414 – 28), 379 (3 Cl, M – 70), 351 (3 Cl, 379 – 28), 344 (2 Cl, 379 – 35), 316 (2 Cl, 351 – 35).

Anal. Calcd for $C_{19}H_{16}Cl_5NO$: C, 50.53; H, 3.57; Cl, 39.25; N, 3.10; m/e 448.9674 (M^+). Found: C, 50.55; H, 3.79; Cl, 39.28; N, 2.88; m/e 448.9728 (M^+).

The 1-benzyl analogue **7b** was similarly derived from difluorooxyborane **6b** (0.30 g) and sulfuryl chloride (1.5 mL); after extraction of the contaminants with warm ethanol, the residual **7b** (0.15 g, 40%) was crystallized from absolute ethanol: colorless crystals; mp 217–220 °C; IR 1720 cm^{-1} (amide C=O); ^1H NMR ($CDCl_3$) δ 1.65 (s, 3 H, $ArCH_3$), 2.52 (s, 3 H, $ArCH_3$), 5.12 (d, J = 15 Hz, 1 H, benzylic H), 5.47 (d, J = 15 Hz, 1 H, benzylic H), 7.0–7.6 (broad 4-phenyl multiplet superimposed on N-benzyl singlet, 9 H, ArH), 8.0 (m, 1 H, ArH); mass spectrum, m/e 511 (5 Cl, M^+), 476 (4 Cl, M – 35), 441 (3 Cl, M – 70).

Anal. Calcd for $C_{24}H_{18}Cl_5NO$: C, 56.12; H, 3.53; Cl, 34.51; N, 2.73; m/e 510.9831 (M^+). Found: C, 56.25; H, 3.68; Cl, 34.91; N, 2.53; 510.9869 (M^+).

Compounds **7a** and **7b** each gave a purple solution in concentrated sulfuric acid.

1-Phenyl-1-[(3′,5′-dichloro-4′,6′-dimethyl-2′-(ethylamino))phenyl]-2,2-dichloroethene(8). Concentrated sulfuric acid (1.6 mL) was added to a mixture of **7a** (0.80 g, 1.8 mmol) and silver sulfate (0.31 g, 1 mmol) after which the permanganate-colored mass was kept at 95 °C (oil bath) for 3 min with intermittent stirring; negligible hydrogen chloride was evolved in contrast to the reaction without silver sulfate. The orange mixture was diluted with ice and water and extracted with chloroform, and the organic phase was washed with water, dried (anhydrous sodium sulfate), and evaporated to leave an orange gum (0.8 g); TLC (benzene) showed several constituents, with **8** (highest R_f value) predominating and a minor amount of (suspected) **2b** (yellow spot). Separation of the gum on a column (Merck, Kieselgel 60; benzene) afforded **8** as an oil (0.30 g, 43%) which solidified on standing: colorless, shining plates (from acetone–ethanol); mp 112–113 °C; IR 3330 cm^{-1} (NH); ^1H NMR ($CDCl_3$) δ 1.11 (t, J = 7 Hz, 3 H, CH_2CH_3), 2.34 (s, 3 H, $ArCH_3$), 2.46 (s, 3 H, $ArCH_3$), ~3.1 (complex m, 2 H, CH_2CH_3), 3.4 (br s, NH, D_2O exchangeable), 7.1–7.5 (m, 5 H, ArH); ^{13}C NMR ($CDCl_3$) δ 16.08 ($ArCH_3$), 17.89 ($ArCH_3$), 19.13 (CH_2CH_3), 42.51 (CH_2CH_3), 122.17 (C-2), 125.16, 127.77, 128.08, 128.50, 128.94, 129.66, 130.60, 133.46, 135.03, 136.62, 137.06, 142.01 (C-1); mass spectrum, m/e 387 (4 Cl, M^+), 352 (3 Cl, M – 35), 351 (3 Cl, M – 36), 336 (3 Cl, 351 – 15), 323 (3 Cl, 351 – C_2H_4), 317 (2 Cl, M – 70).

Anal. Calcd for $C_{18}H_{17}Cl_4N$: C, 55.56; H, 4.40; Cl, 36.44; N, 3.60. Found: C, 55.61; H, 4.52; Cl, 36.16; N, 3.37.

Compound **8** dissolved easily in chloroform, acetone, and benzene but was sparingly soluble in ethanol and in hot 2 M HCl.

Continued elution of the Kieselgel column with benzene–acetone (10:1 to 5:1) and evaporation of the appropriate combined fractions yielded ~50 mg of suspected indenoquinolinone **2b**: yellow crystals (from acetone–methanol); mp 145–155 °C; IR 1650 (amide C=O), 760 cm^{-1} (four adjacent protons); mass spectrum, m/e 377 (3 Cl, M^+), 349 (3 Cl, M – C_2H_4), 342 (2 Cl, M – 35), 314 (2 Cl, 349 – 35).

Registry No. 1f, 73396-48-2; **1l**, 52827-58-4; **2b**, 73396-49-3; **6a**, 73396-50-6; **6b**, 73396-51-7; **6c**, 73396-52-8; **7a**, 73396-53-9; **7b**, 73396-54-0; **8**, 73396-55-1.

Pteridines. 47. Preparation and Chemistry of 2-Amino-6-carbalkoxy-3-cyano-5-substituted Pyrazine 1-Oxides: Synthesis of Pterin-6-carboxaldehyde[1,2]

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A new procedure for the synthesis of 2-amino-3-cyano-5-substituted pyrazines **9**, useful intermediates for the synthesis of pteridines, is described. Oximation of β-keto esters **2** followed by reaction with aminomalononitrile provides 2-amino-6-carbalkoxy-3-cyano-5-substituted pyrazine 1-oxides **5**. Protection of the amino group as its ((dimethylamino)methylene)amino derivative **9** followed by S_N2 decarbalkoxylation provides pyrazines **10** which on removal of the protecting group and deoxygenation give pyrazines **8**. This method is designed to be of use in cases where the β-keto ester cannot be converted directly to the corresponding α-keto aldoxime **3**. The procedure is applied to the synthesis of 2-amino-3-cyano-5-(dimethoxymethyl)pyrazine (**8a**), an intermediate in the synthesis of pterin-6-carboxaldehyde (**1**).

Over the past few years we have developed a versatile new synthetic approach to pteridines which utilizes as its key first (and unequivocal) step the cyclization of an α-oximinocarbonyl compound with an α-aminonitrile to give a 2-amino-3-cyano- (or carbalkoxy-) pyrazine 1-oxide which can then be converted to pteridines and pterins by a series of simple deoxygenation and cyclization steps.[3] We describe in this paper a further extension of this procedure to the preparation of 2-amino-3-cyano-5-(dimethoxymethyl)pyrazine (**8a**) (see Scheme I), which has been shown previously to be an effective intermediate for the synthesis of pterin-6-carboxaldehyde (**1**),[4] a naturally-occurring pterin of particular interest as an intermediate for the synthesis of pteroic acid,[5–8] folic acid,[5–7] and various analogues of these two natural products.[6,9–12]

(1) For the previous paper in this series see E. C. Taylor and A. J. Cocuzza, *J. Org. Chem.*, **44**, 302 (1979).

(2) We are indebted to F. Hoffmann-La Roche & Co., Ltd., for support of this work.

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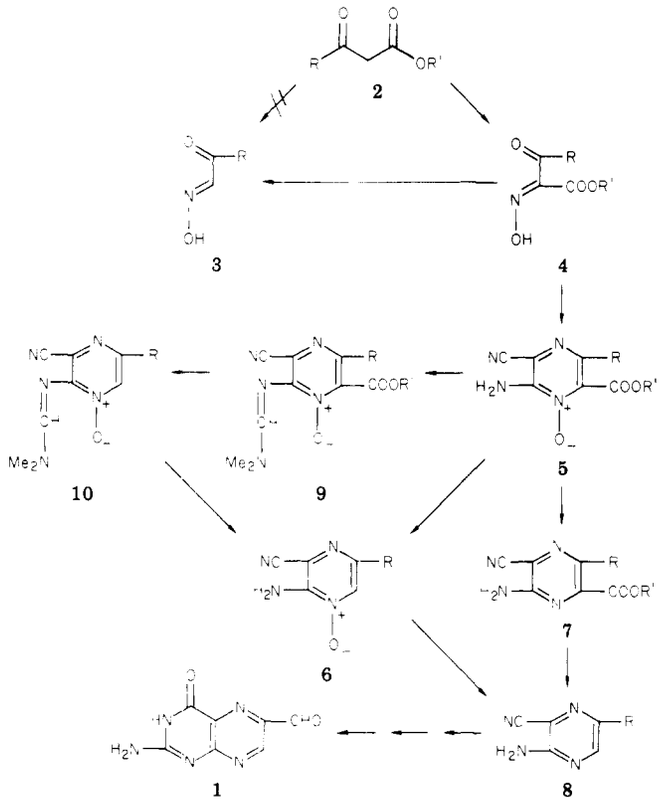
Scheme I



a, R = $CH(OCH_3)_2$, R' = CH_3; b, R = $CH(OCH_3)_2$, R' = $C(CH_3)_3$; c, R = R' = CH_3; d, R = CH_3, R' = C_2H_5

The most effective general approach to α-keto aldoximes (**3**), required intermediates for the preparation of 5-substituted pyrazine 1-oxides by the above route, involves oximation of β-keto esters (**2**) under conditions which effect hydrolysis of the ester to an intermediate α-oximino β-keto acid which decarboxylates in situ.[13] An ideal intermediate for the preparation of 2-amino-3-cyano-5-(dimethoxymethyl)pyrazine (**8a**) would be 1,1-dimethoxy-3-oximino-2-propanone (**3a**). However, treatment of the requisite β-keto ester, methyl 4,4-dimethoxy-3-oxobutyrate (**2a**),[14] under the usual nitrosation/hydrolysis conditions (aqueous potassium hydroxide and sodium nitrite overnight at room temperature followed by acidification) led to a complex mixture of unidentified products. The inverse sequence of reactions involving initial nitrosation to give methyl 4,4-dimethoxy-2-oximino-3-oxobutyrate (**4a**) followed by hydrolysis and decarboxylation proved to be equally disappointing. The nitrosation step to give **4a** could be carried out successfully in 69% yield by utilizing nitrosyl chloride in dry THF, but attempted saponification of **4a** once again led to extensive decomposition. Attempted S_N2 decarbalkoxylation[15] of **4a** using the procedure of Crabbé[16] (basic alumina, aqueous dioxane, room temperature) resulted in complete absorption of the starting material and/or product on the alumina. Treatment of **4a** according to the procedure of Krapcho[17-19] (sodium chloride, wet dimethyl sulfoxide, 130 °C) unexpectedly gave methyl dimethoxyacetate as the only isolable product.

tert-Butyl 4,4-dimethoxy-3-oxobutyrate (**2b**) was prepared in 55% yield by treatment of the lithium salt of *tert*-butyl acetate[20] with methyl dimethoxyacetate, and nitrosation proceeded smoothly either with nitrosyl chloride in dry THF or with sodium nitrite in aqueous acetic acid to give *tert*-butyl 4,4-dimethoxy-2-oximino-3-oxobutyrate (**4b**). However, refluxing **4b** either in chloroform or toluene gave no reaction, while heating in toluene in the presence of *p*-toluenesulfonic acid[21] resulted in extensive decomposition. Heating **4b** under nitrogen without solvent or catalyst at 120 °C led to vigorous gas evolution, but despite the fact that the NMR spectrum of the crude product showed it to be a mixture of compounds containing approximately 30% of the desired α-keto aldoxime **3a**, all attempts to isolate this intermediate from the reaction mixture were unsuccessful.

We therefore resorted to direct cyclization of the alkyl 4,4-dimethoxy-2-oximino-3-oxobutyrates **4** to the pyrazine 1-oxides **5**, which appeared to be ideally suited for subsequent decarbalkoxylation. As models for both the cyclization and decarbalkoxylation reactions, the 5-methylpyrazines **5c** and **5d** were prepared by cyclization of methyl and ethyl α-oximinoacetoacetate[22] (**4c** and **4d**, respectively) with aminomalononitrile tosylate in 4% aqueous hydrochloric acid as solvent. Pyrazines **5a** and **5b** were prepared in moderate yield from **4a** and **4b**, respectively, by condensation with aminomalononitrile tosylate in methanol at 0 °C.

Both **5a** and **5b** decomposed upon attempted saponification; heating the *tert*-butyl ester **5b** in toluene in the presence of *p*-toluenesulfonic acid also led to extensive decomposition. Treatment of **5a** with sodium chloride in wet dimethyl sulfoxide at 170–180 °C resulted in carbon dioxide evolution, but examination of the crude product by NMR failed to give any evidence for the presence of the expected pyrazine **6a** (C-6 proton at δ 8–9). Heating **5a** and **5c** with lithium iodide in wet pyridine[23-25] under reflux for 1.5 h, however, did give the desired pyrazines **6a** and **6c** in crude yields of up to 21%, but these conversions were not reproducible.

These erratic results suggested that the acidity of the 2-amino group in the pyrazine 1-oxides **5** might be responsible for side reactions leading to decomposition. We therefore prepared the deoxygenated pyrazines **7a**, **7c**, and **7d** by reduction of the corresponding *N*-oxides with triethyl phosphite or phosphorus trichloride. Decarbalkoxylation of **7c** by heating for 22 h with 4 equiv of lithium iodide in wet dimethylformamide gave **8c** in 84% yield; as expected,[15] the more sterically hindered ethyl ester **7d**

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required more strenuous conditions and gave **8a** in much lower yield (15%). Unfortunately, attempted decarbalkoxylation of **7a** by this procedure led only to decomposition, presumably because of competing attack by lithium iodide on the dimethyl acetal functionality.

As an alternative procedure for avoiding potential problems caused by the acidity of the 2-amino group in the *N*-oxides **5**, the amino group protected pyrazines **9a** and **9c** were prepared by treatment of **5a** and **5c**, respectively, with dimethylformamide dimethyl acetal.[27] Reaction of **9a** with lithium iodide in refluxing wet pyridine then resulted in smooth decarbalkoxylation to give **10a** (77%); analogous treatment of **9c** with lithium iodide in refluxing wet dimethylformamide gave **10c** (82%).

All that remained to complete our alternate route to 2-amino-3-cyano-5-(dimethoxymethyl)pyrazine (**8a**) was removal of the (dimethylamino)methylene protecting group from **10a** and final deoxygenation. Although the (dimethylamino)methylene protecting group is most often removed with ammonia, this procedure cannot be used on 2-[((dimethylamino)methylene)amino]-3-cyanopyrazines, since these latter compounds have been shown to give 4-aminopteridines upon treatment with ammonia.[28] The protecting group can also be removed by treatment with aqueous acid,[29] but the presence of the acid-sensitive dimethyl acetal group in **10a** posed potential problems. **10a** was, however, successfully deprotected to give 2-amino-3-cyano-5-(dimethoxymethyl)pyrazine 1-oxide (**6a**) in 55% yield after standing for 1 week at room temperature in a 1:1 mixture of methanol/trimethyl orthoformate containing 1 equiv of *p*-toluenesulfonic acid. Deoxygenation of **6a** with trimethyl phosphite then gave the desired **8a** in 68% yield. This material was identical in every respect with an authentic sample.[4]

In summary, we have developed a new procedure for the synthesis of 2-amino-3-cyano-5-substituted pyrazines (**8**), key intermediates for the preparation of 6-substituted pteridines and pterins. This procedure involves cyclization of α-oximino β-keto esters (**4**) with aminomalononitrile tosylate to give the pyrazine 1-oxides **5**. Protection of the 2-amino group by conversion to the 2-((dimethylamino)-methylene)amino derivatives **9** with dimethylformamide dimethyl acetal, decarbalkoxylation of **10** with lithium iodide in wet pyridine or dimethylformamide, deprotection to **6**, and final deoxygenation to **8** completes the reaction sequence. This alternate preparation of 2-amino-3-cyano-5-substituted pyrazines (**8**) may be of particular value in those cases where direct synthesis of α-keto aldoximes (**3**) from β-keto esters is not possible. Since 2-amino-3-cyano-5-(dimethoxymethyl)pyrazine (**8a**) can be prepared in this manner, the above reaction sequence represents still another synthetic approach to pterin-6-carboxaldehyde (**1**).

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. NMR data were obtained on a Varian A-60A instrument, using Me_4Si as internal standard.

***tert*-Butyl 4,4-Dimethoxy-3-oxobutyrate (2b).** A 500-mL round-bottom flask was fitted with a thermometer, a serum stopple (through which both N_2 and *n*-butyllithium could be added), and a drying tube. The flask was charged with 75 mL of dry THF and cooled in an ice bath, 42 mL of 2.4 M *n*-butyllithium (0.1 mol) in hexane was added, and 14 mL of diisopropylamine (0.1 mol) was added dropwise and rinsed in with 25 mL of THF. The solution was stirred at ice temperature for another 5 min and then cooled in an acetone–dry ice bath to an internal temperature of −65 to −70 °C. To this was then added dropwise 6.75 mL (0.05 mol) of *tert*-butyl acetate, which was rinsed in with 25 mL of THF. After 0.5 h at dry ice temperature, 6.7 g (0.05 mol) of methyl dimethoxyacetate was added dropwise and rinsed in with 25 mL of THF. The solution was kept in the dry ice bath for another 0.5 h and then allowed to warm to 0 °C. The solution was acidified with 10% HCl, the layers were separated, the aqueous layer was extracted with 50 mL of ether, the combined organic extracts were dried over Na_2SO_4, the solvent was removed in vacuo, and the residue was distilled under vacuum to give 6.0 g (55%) of a faintly yellow oil, bp 80–95 °C (1.0–1.5 mm). The NMR ($CDCl_3$) spectrum was consistent with an 80:20 mixture of the β-keto ester, δ 1.45 (s, 9), 3.42 (s, 6), 3.49 (s, 2), 4.58 (s, 1), and the enol ester, δ 1.48 (s, 9), 3.39 (s, 6), 4.78 (s, 1), 5.32 (s, 1). IR (neat) 1740 (ester), 1720 (ketone) cm^{-1}.

Methyl 4,4-Dimethoxy-2-oximino-3-oxobutyrate (4a). A solution of 15 g (85 mmol) of methyl 4,4-dimethoxy-3-oxobutyrate[14] in 150 mL of dry THF was cooled to −50 °C and 4.8 mL (94 mmol) of freshly condensed nitrosyl chloride added dropwise. The solution was allowed to warm slowly to 0 °C and then refrigerated overnight. The solvent was then removed in vacuo (no external heating) to leave 23 g of a green oil. This was slurried with 30 mL of toluene and refrigerated to give 7.91 g of chunky white crystals, mp 96–98 °C. Concentration of the mother liquors provided a second crop of 4.18 g, mp 92–97 °C. The total yield was 69%. The analytical sample, mp 96–98 °C, was prepared by recrystallization from toluene: NMR ($CDCl_3$) δ 3.44 (s, 6), 3.89 (s, 3), 5.33 (s, 1); IR (KBr) 3300 (OH), 1750 (ester), 1710 (ketone), 1635 (C=N) cm^{-1}.

Anal. Calcd for $C_7H_{11}NO_6$: C, 40.98; H, 5.40; N, 6.83. Found: C, 40.63; H, 5.12; N, 6.59.

***tert*-Butyl 4,4-Dimethoxy-2-oximino-3-oxobutyrate (4b).** A solution of 1.32 g (6 mmol) of β-keto ester **2b** in 0.9 mL of acetic acid was cooled in an ice bath, and a solution of 0.44 g (6.4 mmol) of sodium nitrite in 1 mL of water was added dropwise. The mixture was stirred at room temperature for 2 h, extracted with ethyl ether (3 × 10 mL), and dried over Na_2SO_4, and the solvent was removed in vacuo to leave 1.6 g of yellow oil which was crystallized from hexane/ether to give 0.55 g (37%) of colorless cubes, mp 107–108 °C. Recrystallization from hexane/ether provided the analytical sample: mp 108–109 °C; NMR ($CDCl_3$) δ 1.55 (s, 9), 3.45 (s, 6), 5.34 (s, 1), 10.35 (br, 1); IR (KBr) 3200 (OH), 1730 (ester), 1705 (ketone), 1620 (C=N) cm^{-1}.

Anal. Calcd for $C_{10}H_{17}NO_6$: C, 48.58; H, 6.93; N, 5.67. Found: C, 48.63; H, 6.82; N, 5.48.

2-Amino-6-(carbomethoxy)-3-cyano-5-(dimethoxymethyl)pyrazine 1-Oxide (5a). A solution of 2.05 g (10 mmol) of α-oximino ketone **4a** in 15 mL of dry methanol was cooled in an ice bath and 3.3 g (13 mmol) of aminomalononitrile tosylate added. The mixture was stirred at ice-bath temperature for 2.5 h, and the magenta precipitate was filtered off, rinsed with a small amount of cold methanol, and recrystallized from toluene (carbon) to give 1.44 g (53%) of pale yellow plates, mp 162.5–163.5 °C. A second recrystallization from toluene provided the analytical sample without any change in the melting point: NMR (Me_2SO-d_6) δ 3.33 (s, 6), 3.91 (s, 3), 5.30 (s, 1), 8.22 (br, 2); IR (KBr) 3380, 3280, 3230 (NH_2), 2230 (CN), 1748, 1720 (ester), 1637 (pyrazine) cm^{-1}.

Anal. Calcd for $C_{10}H_{12}N_4O_5$: C, 44.78; H, 4.51; N, 20.89. Found: C, 44.65; H, 4.42; N, 20.63.

2-Amino-6-(carbo-*tert*-butoxy)-3-cyano-5-(dimethoxymethyl)pyrazine 1-Oxide (5b). A solution of 0.30 g (1.2 mmol) of the α-oximino ester (**4b**), 0.45 g (1.8 mmol) of aminomalononitrile tosylate, and 6 mL of dry methanol was kept at ambient temperature for 24 h. The solvent was then removed in vacuo, the residue was slurried with 6 mL of saturated sodium bicarbonate and extracted with methylene chloride (4 × 10 mL), the combined extracts were stirred with Na_2SO_4 and decolorizing carbon for 20 min, and the solvent was removed in vacuo to leave 0.14 g (40%) of yellow foam. Three recrystallizations from hexane/ether provided the analytical sample: mp 107–108 °C; NMR ($CDCl_3$) δ 1.62 (s, 9), 3.40 (s, 6), 5.34 (s, 1), 6.60 (br, 2); IR

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(KBr) 3385, 3265, 3200, 3120 (NH_2), 2230 (CN), 1738 (ester), 1620 (pyrazine) cm^{-1}.

Anal. Calcd for $C_{13}H_{18}N_4O_5$: C, 50.31; H, 5.85; N, 18.06. Found: C, 50.11; H, 5.86; N, 18.34.

2-Amino-6-(carbomethoxy)-3-cyano-5-methylpyrazine 1-Oxide (5c). A solution of 14.5 g (0.10 mol) of crude methyl α-oximinoacetoacetate[22] in 200 mL of water and 10 mL of concentrated HCl was cooled in an ice bath, and 36 g (0.14 mol) of aminomalononitrile tosylate was added. The mixture was left at ambient temperature for 3 h and then refrigerated overnight. The brown crystalline product was collected and recrystallized from 2-propanol (carbon). Two crops were collected totaling 4.35 g (21%), mp 163–166 °C. Another recrystallization from 2-propanol provided the analytical sample without any change in the melting point:[30] NMR ($CDCl_3$) δ 2.42 (s, 3), 4.05 (s, 3), 6.20 (br, 2); IR (KBr) 3375, 3270, 3205, 3140 (NH_2), 2225 (CN), 1735, 1740 (sh) (ester), 1635 (pyrazine) cm^{-1}.

Anal. Calcd for $C_8H_8N_4O_3$: C, 46.15; H, 3.87; N, 26.92. Found: C, 46.13; H, 3.99; N, 27.02.

2-Amino-6-(carbethoxy)-3-cyano-5-methylpyrazine 1-Oxide (5d). A solution of 4.9 g (31 mmol) of ethyl α-oximinoacetoacetate,[22] 11.67 g (46 mmol) of aminomalononitrile tosylate, 60 mL of water, and 3 mL of concentrated HCl was allowed to stand at ambient temperature for 2 h. The product was filtered off and washed with cold water to leave 1.7 g of yellow crystals, mp 129–131 °C. The mother liquors yielded a second crop of 0.46 g on standing overnight. The total yield was 2.16 g (31%). The analytical sample was prepared by recrystallization from 2-propanol without any change in the melting point: NMR ($CDCl_3$) δ 1.47 (t, 3), 2.45 (s, 3), 4.60 (q, 2), 6.47 (br, 2); IR (KBr) 3395, 3280 (NH_2), 2220 (CN), 1725 (ester) cm^{-1}.

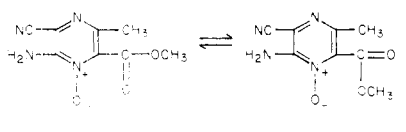
Anal. Calcd for $C_9H_{10}N_4O_3$: C, 48.65; H, 4.54; N, 25.22. Found: C, 48.65; H, 4.41; N, 25.45.

2-Amino-3-cyano-5-(dimethoxymethyl)pyrazine 1-Oxide (6a). Method A. A solution of 0.10 g (0.37 mmol) of methyl ester **5a**, 0.20 g (1.5 mmol) of lithium iodide, and 6.7 μL (0.37 mmol) of water in 7 mL of pyridine was heated to reflux for 1.25 h under nitrogen. The solution was allowed to cool, the solvent was removed in vacuo, the residue was dissolved in 10 mL of water and extracted with ethyl acetate (5 × 10 mL), the combined organic extracts were washed with 10 mL of 10% HCl followed by 10 mL of saturated sodium bicarbonate and dried over Na_2SO_4, and the solvent was removed in vacuo to leave 0.05 g of a brown glassy solid. The product was crystallized from toluene (carbon) to give 0.01 g (13%) of yellow needles, mp 74.5–78 °C. The analytical sample was prepared by column chromatography (silica gel, ether) followed by recrystallization from toluene to give a pale yellow powder, mp 93.5–94.5 °C, after drying in vacuo at 65 °C: NMR ($CDCl_3$) δ 3.43 (s, 6), 5.30 (s, 1), 6.90 (br, 2), 8.50 (s, 1); IR (KBr) 3300, 3100 (NH_2), 2220 (CN), 1640, 1610 (pyrazine) cm^{-1}.

Anal. Calcd for $C_8H_{10}N_4O_3$: C, 45.71; H, 4.80; N, 26.66. Found: C, 45.44; H, 4.64; N, 26.55.

Method B. A solution of 0.265 g (10 mmol) of [((dimethylamino)methylene)amino]pyrazine **10a** and 0.19 g (10 mmol) of *p*-toluenesulfonic acid monohydrate in 2.5 mL of methanol and 2.5 mL of trimethyl orthoformate was left at room temperature for 1 week. The solution was then diluted with 25 mL of ethyl acetate, washed with saturated sodium bicarbonate (2 × 25 mL), and dried over Na_2SO_4, and the solvent was removed in vacuo to leave a golden oil which was crystallized from methanol to give 0.115 g (55%) of pale yellow plates, mp 90–93 °C.

(30) Although this material analyzed correctly, it displayed two spots on TLC (10% CH_3OH, 90% $CHCl_3$) even after five recrystallizations. When the two components were isolated from the TLC plate, they reeluted as single components, but each returned to the original mixture when warmed prior to elution. This observation can be explained by assuming the presence of both conformers of the ester. This hypothesis is supported by the presence of two carbonyl stretching bands in the IR spectrum. Two carbonyl stretching bands were also observed in the IR spectrum of **5a**, although this material was homogeneous by TLC. This phenomenon was not observed with the ethyl ester **5d**.



2-Amino-3-cyano-5-methylpyrazine 1-Oxide (6c). A solution of 0.1 g (0.48 mmol) of methyl ester **5c**, 0.27 g (2.0 mmol) of lithium iodide, and 8.7 μL (0.48 mmol) of water in 10 mL of pyridine was heated to reflux under nitrogen for 2 h. The solution was cooled and concentrated in vacuo, the residue was dissolved in 10 mL of water and extracted with ethyl acetate (5 × 10 mL), the combined organic extracts were washed with 10 mL of 10% HCl followed by 10 mL of saturated sodium bicarbonate and dried over Na_2SO_4, and the solvent was removed in vacuo to leave 0.05 g (7%) of a yellow solid, mp 177–180 °C (lit.[31] mp 187–188 °C). The IR (KBr) spectrum of this material compared well with that of an authentic sample.[31]

2-Amino-3-cyano-5-(dimethoxymethyl)pyrazine (8a). A solution of 0.20 g (0.95 mmol) of *N*-oxide **6a** in 2 mL of trimethyl phosphite was heated to reflux under nitrogen for 4 h. The brown solution was then concentrated in vacuo, the residue was dissolved in 4 mL of water and extracted with ether (4 × 10 mL), the combined extracts were dried over $MgSO_4$, and the solvent was removed in vacuo to leave a yellow oil which crystallized on standing. Recrystallization from toluene/cyclohexane (carbon) gave 0.125 g (68%) of a faintly orange powder, mp 92–93 °C (lit.[4] mp 91–93 °C). The NMR and IR spectra of this material compared well with those of an authentic sample.[4]

2-Amino-3-cyano-5-methylpyrazine (8c). A solution of 0.10 g (0.52 mmol) of methyl ester **7c**, 0.28 g (2.1 mmol) of lithium iodide, and 9.4 μL (0.52 mmol) of water in 10 mL of DMF was heated to reflux under nitrogen for 22 h. The solution was allowed to cool, the solvent was removed in vacuo, the residue was dissolved in 10 mL of water and extracted with ethyl ether (4 × 10 mL), the combined extracts were washed with water (10 mL then 5 mL) and dried over $MgSO_4$, and the solvent was removed in vacuo to leave 0.058 g (84%) of a pale yellow solid, mp 167–171 °C (lit.[31] mp 172–173 °C).

2-Amino-6-(carbomethoxy)-3-cyano-5-(dimethoxymethyl)pyrazine (7a). A solution of 0.10 g (0.37 mmol) of pyrazine 1-oxide **5a**, 0.28 mL (1.35 mmol) of triethyl phosphite, and 2 mL of 1-propanol was left overnight at room temperature. The reaction mixture was then diluted with hexane to give 0.07 g (74%) of a cream colored solid, mp 142–143 °C. The analytical sample was prepared by recrystallization from toluene with no change in melting point: NMR ($CDCl_3$) δ 3.43 (s, 6), 3.97 (s, 3), 5.63 (s, 1), 5.73 (br, 2); IR (KBr) 3468, 3285, 3160 (NH_2), 2215 (CN), 1730 (ester), 1620 (pyrazine) cm^{-1}.

Anal. Calcd for $C_{10}H_{12}N_4O_4$: C, 47.62; H, 4.80; N, 22.22. Found: C, 47.73; H, 4.92; N, 22.43.

2-Amino-6-(carbomethoxy)-3-cyano-5-methylpyrazine (7c). Method A. To an ice-cooled solution of 1.04 g (5 mmol) of pyrazine *N*-oxide **5c** in 50 mL of THF was added 4.4 mL (50 mmol) of phosphorus trichloride. The solution was then kept at room temperature for 15 h, concentrated in vacuo to approximately 10 mL, and poured on 50 mL of ice water, and the precipitate was collected and recrystallized twice from 2-propanol to give 0.50 g (52%) of fluffy yellow crystals: mp 145–146 °C; NMR ($CDCl_3$) δ 2.65 (s, 3), 4.00 (s, 3), 5.50 (br, 2); IR (KBr) 3415, 3320, 3215 (NH_2), 2200 (CN), 1717 (ester), 1625 (pyrazine) cm^{-1}.

Anal. Calcd for $C_8H_8N_4O_2$: C, 49.99; H, 4.20; N, 29.16. Found: C, 49.83; H, 4.05; N, 29.01.

Method B. By using the same procedure as outlined above for the preparation of **7a**, 0.10 g (0.48 mmol) of pyrazine *N*-oxide **5c** gave 0.60 g (65%) of **7c** as a yellow solid, mp 146–148 °C.

2-Amino-6-(carbethoxy)-3-cyano-5-methylpyrazine (7d). By using the same procedure as outlined above for the preparation of **7c** (method A), 2.22 g (10 mmol) of pyrazine *N*-oxide **5d** was deoxygenated to give 1.23 g (60%) of fluffy yellow needles: mp 115.5–117.5 °C after recrystallization from water; NMR ($CDCl_3$) δ 1.42 (t, 3), 2.68 (s, 3), 4.44 (q, 2), 5.34 (br, 2); IR (KBr) 3430, 3340, 3225 (NH_2), 2215 (CN), 1712 (ester), 1635 (pyrazine) cm^{-1}.

Anal. Calcd for $C_9H_{10}N_4O_2$: C, 52.42; H, 4.89; N, 27.27. Found: C, 52.10; H, 4.88; N, 26.98.

6-(Carbomethoxy-3-cyano-5-(dimethoxymethyl)-2-[((dimethylamino)methylene)amino]pyrazine 1-Oxide (9a). A mixture of 1.42 g (5.3 mmol) of aminopyrazine **5a** and 40 mL of DMF dimethyl acetal was warmed on a steam bath until all of

(31) E. C. Taylor, K. L. Perlman, Y.-H. Kim, I. P. Sword, and P. A. Jacobi, *J. Am. Chem. Soc.*, **95**, 6413 (1973).

the pyrazine went into solution. The solution was allowed to cool and concentrated in vacuo. The residue was triturated with hexane to give 1.7 g (99%) of a yellow powder, mp 124–125 °C. The analytical sample was prepared by recrystallization from cyclohexane with no change in melting point: NMR ($CDCl_3$) δ 3.20 (d, J = 2 Hz, 6), 3.43 (s, 6), 4.17 (s, 3), 5.35 (s, 1), 10.1 (s, 1); IR (KBr) 2225 (CN), 1743 (ester), 1608 (sh, pyrazine and C=N) cm^{-1}.

Anal. Calcd for $C_{13}H_{17}N_5O_5$: C, 48.29; H, 5.30; N, 21.66. Found: C, 48.39; H, 5.48; N, 21.41.

6-(Carbomethoxy)-3-cyano-2-[((dimethylamino)methylene)amino]-5-methylpyrazine 1-Oxide (9c). A solution of 0.20 g (0.96 mmol) of aminopyrazine **5c** in 5 mL of DMF dimethyl acetal was stirred at room temperature for 2 h and then worked up in the same manner as **9a** to give 0.24 g (96%) of a yellow powder, mp 114–115.5 °C. Two recrystallizations from cyclohexane provided the analytical sample: mp 115–117 °C; NMR ($CDCl_3$) δ 2.40 (s, 3), 3.19 (d, J < 1 Hz, 6), 4.05 (s, 3), 9.80 (s, 1); IR (KBr) 2215 (CN), 1738 (ester), 1605 (sh, pyrazine and C=N) cm^{-1}.

Anal. Calcd for $C_{11}H_{13}N_5O_3$: C, 50.18; H, 4.98; N, 26.61. Found: C, 50.39; H, 4.90; N, 26.59.

3-Cyano-5-(dimethoxymethyl)-2-[((dimethylamino)methylene)amino]pyrazine 1-Oxide (10a). A solution of 1.62 g (5 mmol) of methyl ester **9a**, 2.68 g (20 mmol) of lithium iodide, and 0.72 mL (40 mmol) of water in 100 mL of pyridine was heated to reflux under nitrogen for 1.5 h. The solution was allowed to cool, the solvent was removed in vacuo, the residue was dissolved in 50 mL of water, neutralized with 6 N HCl, and extracted with ethyl acetate (50 mL then 3 × 25 mL), the combined extracts were dried over Na_2SO_4, and the solvent was removed in vacuo to leave a brown oil which slowly crystallized. Recrystallization from toluene/cyclohexane with hot filtration from some insoluble gum gave 1.02 g (77%) of yellow needles: mp 106–107 °C; NMR ($CDCl_3$) δ 3.22 (s, 6), 3.44 (s, 6), 5.30 (s, 1), 8.33 (s, 1), 9.95 (s, 1); IR (KBr) 2225 (CN), 1608 (sh, pyrazine and C=N) cm^{-1}.

Anal. Calcd for $C_{11}H_{15}N_5O_3$: C, 49.80; H, 5.70; N, 26.40. Found: C, 49.95; H, 5.71; N, 26.59.

3-Cyano-2-[((dimethylamino)methylene)amino]-5-methylpyrazine 1-Oxide (10c). A solution of 0.10 g (0.38 mmol) of methyl ester **9c**, 0.20 g (1.5 mmol) of lithium iodide, and 0.054 mL (3.0 mmol) of water in 10 mL of DMF was heated to reflux for 1 h. The solution was allowed to cool, the solvent was removed in vacuo, the residue was dissolved in 10 mL of water, extracted with ethyl acetate (5 × 10 mL), and dried over Na_2SO_4, the solvent was removed in vacuo, and the yellow solid product was recrystallized from toluene/cyclohexane to give 0.064 g (82%) of yellow microcrystals, mp 172–174 °C. This material was spectrally identical with material prepared by the reaction of authentic **6c**[31] with DMF dimethyl acetal;[27] NMR (Me_2SO-d_6) δ 2.32 (s, 3), 3.10 (d, J = 4.5 Hz, 6), 8.35 (s, 1), 9.49 (s, 1); IR (KBr) 2225 (CN), 1600 (sh, pyrazine and C=N) cm^{-1}.

Anal. Calcd for $C_9H_{11}N_5O$: C, 52.67; H, 5.40; N, 34.13. Found: C, 52.59; H, 5.51; N, 34.10.

Registry No. 2a, 60705-25-1; **2b**, 73198-22-8; **4a**, 73198-23-9; **4b**, 73198-24-0; **4c**, 6743-49-3; **5a**, 73198-25-1; **5b**, 73198-26-2; **5c**, 73198-27-3; **5d**, 73198-28-4; **6a**, 73198-29-5; **6c**, 19994-56-0; **7a**, 73198-30-8; **7c**, 73198-31-9; **7d**, 73198-32-0; **8a**, 64440-77-3; **8c**, 17890-82-3; **9a**, 73198-33-1; **9c**, 73198-34-2; **10a**, 73198-35-3; **10c**, 73198-36-4; *tert*-butyl acetate, 540-88-5; methyl dimethoxyacetate, 89-91-8; aminomalononitrile tosylate, 5098-14-6.

Azetidines. 5. Reaction of 1,1,3,3-Tetramethyl- and 1-Benzyl-1,3,3-trimethylazetidinium Ions with Butyllithium and Phenyllithium. Deuterium Labeling as a Mechanistic Probe[1-3]

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The reactions of 1,1,3,3-tetramethylazetidinium iodide (**1**) and 1-benzyl-1,3,3-trimethylazetidinium bromide (**7**) with butyllithium and with phenyllithium were studied in ether. The products from the reaction of **1** with butyllithium were 1,3,3-trimethylpyrrolidine (**2**), 3,3-dimethyl-4-(methylamino)-1-butene (**3**), 1-(dimethylamino)-2,2-dimethylheptane (**4**), neopentylpyrrolidine (**5**), and 1-(dimethylamino)-2,2-dimethylcyclopropane (**6**). With phenyllithium, **1** gave **2** and 1-(dimethylamino)-2,2-dimethyl-3-phenylpropane (**11**). With butyllithium, **7** gave 2-phenyl-1,4,4-trimethylpyrrolidine (**8**), 1-benzyl-3,3-dimethylpyrrolidine (**9**), and 1-neopentyl-2-phenylpyrrolidine (**10**). The reaction of phenyllithium with **7** gave only **8** and **9**. Mechanistic information was obtained by labeling **1** with deuterium in three different ways: *N*-methyl-d_3, 2,2-d_2, and *N*-methyl-d_3-2,2-d_2. A primary kinetic isotope effect of 9.4 was found for the formation of **2** from 1-*N*-methyl-d_3. When **2** was formed from 1-2,2-d_2, a secondary kinetic isotope effect of 1.17 was measured. The formation of **4** from 1-2,2-d_2 was accompanied by a primary kinetic isotope effect of 4.7, suggesting a carbene intermediate. Ylide carbanions involving decomposition to a carbene carbanion in the formation of **3** and an azomethine ylide in the formation of **5** and **9** are probable intermediates. It is postulated that the azomethine ylides react with ethylene formed from the reaction of butyllithium with the solvent ether by means of a concerted (4 + 2) cycloaddition reaction. A primary kinetic isotope effect of 20 was found for the formation of pentylbenzene from dibenzyldimethylammonium bromide and butyllithium.

Previous papers in this series have reported the results of reactions of certain azetidinium salts with phenyllithium and alkali metal amides.[6] The findings provided evidence for the nature (e.g., carbene or ion pair) of the interme-

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