>300 °C dec (changes crystalline form at 180 °C).

Anal. Calcd for $C_5H_4N_6O_2{\cdot}3H_3O$: C, 25.64; H, 4.30; N, 35.89. Found: C, 25.38; H, 4.59; N, 35.63.

2-Amino-4-(1,2-dimethylhydrazino)-6(1*H*)-pyrimidone (12). To a solution of 10 g (179 mmol) of potassium hydroxide in 175 mL of water was added 11.3 g (85 mmol) of *sym*-dimethylhydrazine dihydrochloride. To this solution was then added 5.75 g (39.5 mmol) of 2-amino-4-chloro-6(1*H*)-pyrimidone,[12] and the resulting mixture was heated to reflux. After 30 min, a clear solution was obtained, and shortly thereafter white crystals started to separate. Refluxing was continued for an additional 1.5 h, the reaction mixture was cooled, and the precipitate was collected by filtration: yield 5.65 g (85%); mp 300–303 °C; NMR (CF_3COOH) (Me_4Si as an external reference) δ 2.56 (s, 3 H, CH_3), 2.96 (s, 3 H, CH_3); IR (KBr) ν_{max} 3350, 3275 cm^{-1}.

Anal. Calcd for $C_6H_{11}N_5O$: C, 42.59; H, 6.55; N, 41.40. Found: C, 42.44; H, 6.75; N, 41.53.

2-Amino-4-(1,2-dimethylhydrazino)-5-(1,2-dicarbethoxyhydrazino)-6(1*H*)-pyrimidone (13). A suspension of 680 mg (4.02 mmol) of 2-amino-4-(1,2-dimethylhydrazino)-6(1*H*)-pyrimidone in 50 mL of dimethylformamide was heated to 100 °C, 775 mg (4.45 mmol) of diethyl azodicarboxylate was added, and the mixture was stirred at 100 °C for 15 min. The resulting orange solution was cooled to room temperature and filtered to remove a small amount of dark solid, and the filtrate was concentrated to dryness under reduced pressure. The gummy orange residue was dissolved in a small amount of ethyl acetate, and ether was added to induce crystallization. Filtration gave a cream-colored solid which was washed with ether, yield 1.12 g (81%). Recrystallization from ethyl acetate/ether gave colorless crystals, mp 192–194 °C dec; although microanalytical data for nitrogen were not satisfactory, the product was assigned structure **13** with confidence on the basis of its NMR spectrum in Me_2SO-d_6: δ 1.12 (t, 3 H), 1.16 (t, 3 H), 2.41 (s, 3 H, $-NHCH_3$), 3.21 (s, 3 H, C-4 NCH_3), 4.05 (2 superimposed quartets, 4 H); IR (KBr) ν_{max} 1750, 1705, 1635, 1595 cm^{-1}.

Anal. Calcd for $C_{12}H_{21}N_7O_5$: C, 41.98; H, 6.17; N, 28.56. Found: C, 41.65; H, 6.24; N, 27.50.

Registry No.—**2**, 68629-77-6; **4**, 6298-85-7; **5**, 6829-78-7; **6**, 68629-79-8; **7**, 67873-21-6; **8a**, 68629-80-1; **8b**, 68629-81-2; **12**, 68629-82-3; **13**, 68629-83-4; 2-amino-4-chloro-6(1*H*)-pyrimidone, 1194-21-4; hydrazine, 302-01-2; methylhydrazine, 60-34-4; *sym*-dimethylhydrazine dihydrochloride, 306-37-6; diethyl azodicarboxylate, 1972-28-7.

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New Synthesis of 2-Amino-6-alkoxypyrazines from *N*-Nitrosobis(cyanomethyl)amine and Alkoxides

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Reaction of *N*-nitrosobis(cyanomethyl)amine with sodium alkoxides gives good yields of 2-amino-6-alkoxypyrazines in one step. Products were tentatively identified initially by spectral (IR, ^1H and ^{13}C NMR, UV, MS), polarographic, and elemental analytical methods. 2-Amino-6-methoxypyrazine was unequivocally identified by single-crystal X-ray examination.

During systematic studies on the analysis and anchimeric properties of *N*-nitrosamines by differential pulse polarography (DPP),[2-4] we examined *N*-nitrosobis(cyanomethyl)amine (**1**), $NCCH_2N(N{=}O)CH_2CN$, in neutral alcohol solutions and also in the presence of the corresponding sodium alkoxides. In neutral alcohols, **1** yields only a single 2e current–potential curve (E_p −1.20 V), but when sodium alkoxide was present as many as four curves were observed. The peak heights of these curves varied with time but finally one curve was obtained (E_p −1.94 V) whose height remained constant.

Since the final electroreducible product is stable, its preparation and identification were undertaken. Compound **1** was dissolved in methanol containing sodium methoxide and the solution was allowed to remain overnight at room temperature. Workup yielded a white, crystalline sublimate, mp 110–112 °C (**2**), in approximately 50% yield. The E_p of **2** was identical with that originally observed for the final stable product derived from **1**.

The product **2** was homogeneous on TLC in several systems. IR (KBr pellet) no longer showed C≡N absorption but a strong band was observed at 1650 cm^{-1}. UV (CH_3OH) showed two absorption bands at 324 nm (ϵ = 6420) and 242 nm (ϵ = 8360). The ^1H-NMR spectrum ($CDCl_3$) showed two sharp singlets at δ 7.41 (1 H) and 7.53 (1 H), a broad singlet centered at 4.3 (2 H), and sharp singlet at 3.8 (3 H). The two-proton signal at δ 4.3 disappeared immediately upon addition of D_2O. A ^{13}C-NMR proton-decoupled spectrum ($CDCl_3$–Me_2SO-d_6) showed five sharp signals. Mass spectral fragmentation of **2** gave a molecular ion peak at *m/e* 125. A chemical ionization mass spectrum of **2** in ammonia–methane showed only two peaks at *m/e* 126 and 58.[5] These values, coupled with elemental analyses and a value of 126 for the osmometric molecular weight, correspond to a molecular formula of $C_5H_7N_3O$ (**2**).

When **1** was similarly treated with ethanol–sodium ethoxide, a white, crystalline product (**3**), mp 77–79 °C, was obtained in about the same yield as **2**. The IR and UV spectra

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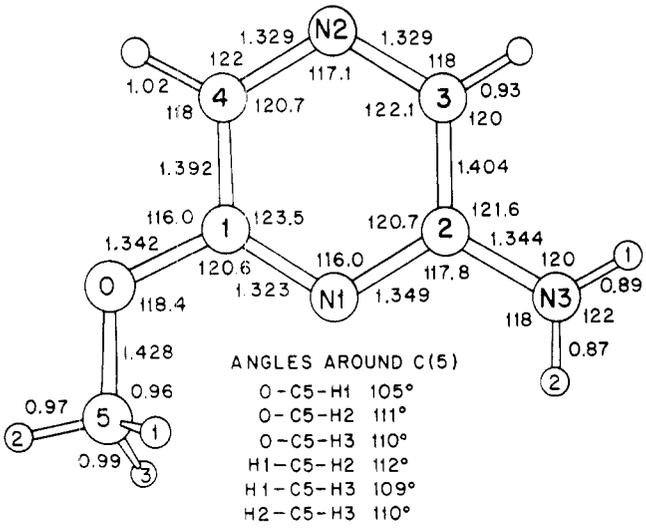


Figure 1.

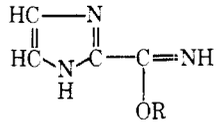
were virtually identical with those of **2**. The ^{1}H-NMR spectrum of **3** was similar to that of **2** except for the typical triplet–quartet of the ethyl group (5 H) and absence of a singlet due to methyl. Two protons were readily exchanged by D_2O. Elemental analysis corresponded to $C_6H_9N_3O$. Similar but slower transformations of **1** occur with *n*-propanol–propoxide and *n*-butanol–butoxide. These experiments were studied only by NMR.

On reaction with hydrogen chloride gas in methanol, **2** instantly forms a hydrochloride, mp 163–165 °C (**4**). Elemental analysis corresponds to $C_5H_8N_3ClO$.

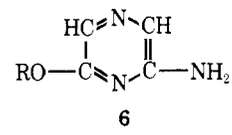
In contrast, the parent unnitrosated amine, bis(cyanomethyl)amine, from which **1** had been prepared, is electrochemically *inactive* and stable under the conditions, which convert **1** → **2** or **3**. This marked difference in reactivity was an important mechanistic clue as it suggested that the acidity of the protons α to the nitrile group in **1** was enhanced by the combined effects of the electron-withdrawing *N*-nitroso and nitrile groups thereby permitting the formation of an anion in the initial step.

A review of the literature revealed that Daeniker[6] had studied the reaction of several *N*-nitrosamines structurally related to **1** with sodium methoxide. Two interesting reactions were reported, isomerization and denitrosation. The reaction that predominated was dependent on the structure of the *N*-nitrosamine starting material.

Reaction schemes based on deprotonation as the initial step, followed by subsequent transformations (see Scheme I), suggested that **2** and **3** were most probably either imidazoles or pyrazines, namely, alkyl 1*H*-imidazole-2-carboximidates (**5**) or 2-amino-6-alkoxypyrazines (**6**). An unequivocal choice



5



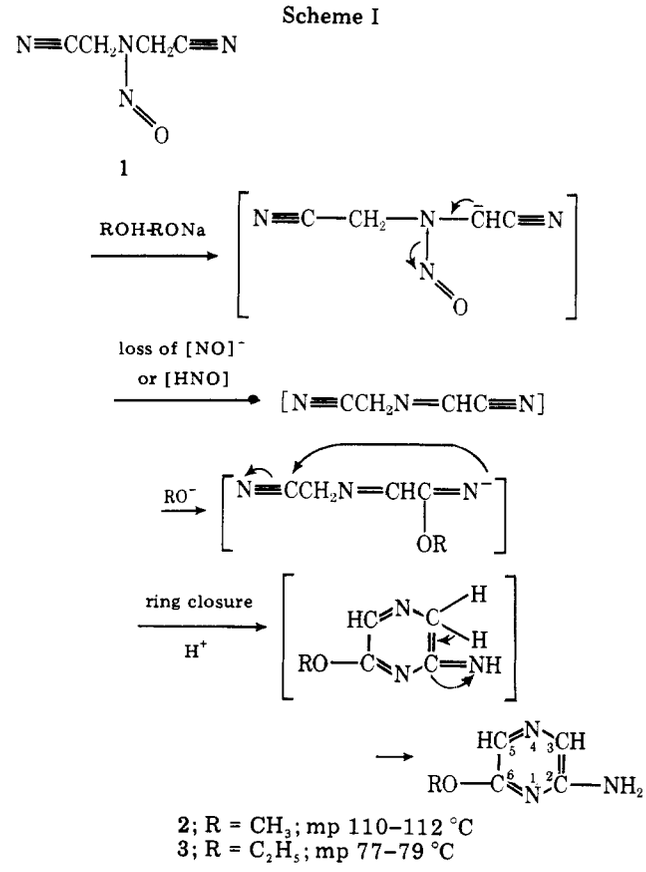
6

R = CH_3 or C_2H_5

could not be made from the IR and NMR spectra and hydrochloride formation, although the rapid exchange of two protons by deuterium favored **6** (pyrazines). UV spectra disqualified **5** and strongly suggested **6**[7] but alternate structures are also possible.

In aqueous solution at pH 1.0, **2** displays polarographic behavior characteristic of a pyrazine;[8] i.e., three peaks are obtained the most anodic of which appears to be a catalytic hydrogen wave. An authentic sample of aminopyrazine was

Scheme I



2; R = CH_3; mp 110–112 °C
3; R = C_2H_5; mp 77–79 °C

obtained. It also displays three polarographic peaks under identical aqueous solution conditions; the peak potentials of aminopyrazine are only slightly different from those of **2**. In strongly basic solution, however, only a single peak is obtained.

X-Ray Structure Determination. A single crystal structure determination on **2** showed it to be 2-amino-6-methoxypyrazine, a compound prepared earlier by Palamidessi and Bernardi;[9] they reported a melting point of 112 °C. The crystal data for **2** are given in Table I. (See Supplementary Material available; ref 10–14 will be found there.)

Reaction Pathways. A possible reaction pathway for the formation of 2,6-disubstituted pyrazines from **1** and alkoxides is given in Scheme I. The loss of a proton is immediately followed by elimination of $[NO]^-$. Addition of ROH to the designated nitrile group followed by ring closure yields an intermediate that readily aromatizes by loss of a proton to yield the 2,6-disubstituted pyrazines. We tentatively assign the ^{13}C NMR signals as follows: C-6 159.4; C-2 154.2; C-5 122.4; C-3 119.4 ppm (Me_4Si = 0, $CDCl_3$–Me_2SO-d_6).

Pyrazines are present in a number of naturally occurring compounds and have useful and interesting biological properties. Synthetic routes to them are limited.[15,16] Although the current sequence requires a specially constructed nitrosamine, 2,6-disubstituted products are obtained in a single operation,

Table I. Crystal Data for 2-Amino-6-methoxypyrazine

molecular formula: $C_5H_7N_3O$	$F_{(000)}$ = 264
formula weight: 125.13	space group = $P2_1/a$
crystal system: monoclinic	systematic absences:
a = 14.510 (3) Å	$h0l$ h odd
b = 10.146 (2) Å	$0k0$ k odd
c = 3.968 (1) Å	$h00$ h odd
β = 94.86 (1)°	crystal shape and size:
V = 582.1 (2) Å^3	prism, 0.2 × 0.2 × 0.3 mm
D_{calcd} = 1.43 g cm^{-3}	
Z = 4	

and a reactive functional group is present for further synthetic manipulations. The 2,6-disubstituted pyrazines are stable in the presence of base and acid; with the latter, salts form. Thus, **2** was recovered unchanged after being refluxed overnight in 0.1 N sodium hydroxide and largely unchanged when heated in 0.1–6.0 M hydrochloric acid or 3.3–9.0 M sulfuric acid followed by basification and solvent extraction. In concentrated acidic media considerable darkening occurred.[17,18]

Experimental Section

Differential Pulse Polarography (DPP). Polarograms were obtained as previously reported.[2]

X-Ray Structure Determination. Three-dimensional data were collected on a Syntex $P2_1$ automated diffractometer with Cu Kα radiation (λ = 1.5418 Å) using the θ–2θ scan technique to $\sin\theta/\lambda = 0.61$ Å^{-1}. Values for $\sigma(I)$ were derived from counting statistics and measured instrumental uncertainties (δ). Values for $\sigma(F)$ were calculated from the expression $(F/2)\{\sigma^2(I)/I^2 + \delta^2\}^{1/2}$ with $\delta = 0.025$ for this experiment. The intensity data were converted to structure amplitudes by application of Lorentz and polarization corrections. A correction for loss of intensity during the data collection as determined from periodic monitoring of four standard reflections (5%) was also made. The data were placed on an absolute scale with a Wilson plot. A total of 1014 data above the observational threshold ($I \geq 2\sigma(I)$) were used in the structure determination and refinement.

Spectra. UV, IR, and ^{1}H-NMR spectra were obtained as previously described.[2] ^{13}C-NMR spectra (Me_4Si = 0) with proton noise decoupling were obtained with a modified XL-100 spectrometer.

***N*-Nitrosobis(cyanomethyl)amine (1).** Bis(cyanomethyl)amine (10.0 g, 0.105 mol) (Aldrich Chemical Co.) was dissolved in 1 N sulfuric acid (90 mL) in a 500-mL round-bottom flask. To the stirred solution sodium nitrite (8.0 g, 0.115 mol) was slowly added. The solution was then cooled and after 2 h a second portion (8.0 g) of sodium nitrite was added. The yellow-brown precipitate was filtered, dried, and recrystallized twice from ethyl acetate–petroleum ether. Purified **1**, mp 38–40 °C (lit.[19] mp 38–38.5 °C), was obtained as a pale yellow solid in 65–70% yields; it gave a single spot on TLC.

2,6-Disubstituted Pyrazines. Typical Procedure. Dry nitrogen was passed through anhydrous methanol (80 mL) for several minutes followed by the addition of freshly cut sodium (0.15 g, 0.0065 g-atom). After the sodium had reacted, **1** (1.0 g, 8 mmol) was added and the solution was maintained under a nitrogen atmosphere overnight (about 16 h). Methanol was removed by vacuum evaporation and the residue was extracted with chloroform (total, 300 mL). Evaporation of the chloroform extract left a yellow-brown residue from which a white, crystalline product, mp 110–112 °C (lit.[9] mp 112 °C), was obtained by sublimation; yield, 0.5 g (50%). The product, which gave a single TLC spot in ethyl acetate, in ethanol, and in chloroform–ethyl acetate (2:3), was identified as 2-amino-6-methoxypyrazine (**2**).

2-Amino-6-ethoxypyrazine (**3**), mp 77–79 °C, was similarly prepared in about 45% yield using ethanol–sodium ethoxide to effect the conversion of **1**. The chlorform-soluble fraction was purified by column chromatography on silica gel using benzene–ethyl acetate (1:4) for elution. Compound **3** gave a single spot on TLC in methanol, ethyl acetate, and chloroform–ethyl acetate (2:3). Anal. Calcd for $C_6H_9N_3O$: C, 51.8; H, 6.48; N, 30.2. Found: C, 51.7; H, 6.44; N, 30.0.

2-Amino-6-methoxypyrazine Hydrochloride (4). Dry hydrogen chloride gas was passed through a methanol solution of **2**. Evaporation of the methanol yielded a light brown crystalline residue, mp 163–165 °C, which gave a single spot on TLC in methanol, ethyl acetate, and methanol–chloroform (1:1). ^{1}H NMR spectrum (D_2O): δ 3.8 (s, 3 H), 4.05 (s, 3 H), 7.5 (s, 1 H), 7.6 (s, 1 H). Anal. Calcd for $C_5H_8N_3ClO$: C, 37.2; H, 4.95; N, 26.0; Cl, 22.0. Found: C, 37.6; H, 5.04; N, 25.7; Cl, 21.4.

Acknowledgment. This research was supported by Grants CA-12227, CA-18618, CA-10925, CA-06927, CA-22780, and RR-05539 from the National Institutes of Health, DHEW; by Grants BC-242 and IN-88J from the American Cancer Society; by Grant AG370 and Instrument Grant CHE 76-05757 from the National Science Foundation; and by an appropriation from the Commonwealth of Pennsylvania and the Samuel S. Fels Fund.

Registry No.—**1**, 16339-18-7; **2**, 6905-47-1; **3**, 54015-49-5; **4**, 69102-56-3; bis(cyanomethyl)amine, 628-87-5; sodium methoxide, 124-41-4; sodium ethoxide, 141-52-6.

Supplementary Material Available: A table of atomic parameters (Table II) and the procedures and computer programs used in the structure determination (3 pages). Ordering information is given on any current masthead page.

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