

The Chemistry of 1,2,5-Thiadiazoles V. Synthesis of 3,4-Diamino-1,2,5-thiadiazole and [1,2,5]Thiadiazolo[3,4-*b*]pyrazines

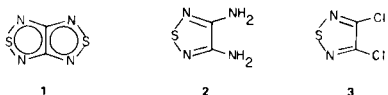
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The *o*-diamine, 3,4-diamino-1,2,5-thiadiazole (**2**), was synthesized from 3,4-dichloro-1,2,5-thiadiazole (**3**) by three methods. Aqueous glyoxal cyclized **2** into [1,2,5]thiadiazolo[3,4-*b*]pyrazine (**14**). 3,4-Dichloro-1,2,5-thiadiazole 1,1-dioxide (**18**) reacted with **2** to give 1,3-dihydrobis[1,2,5]thiadiazolo[3,4-*b*:3',4'-*e*]pyrazine 2,2-dioxide (**19**). The reaction of **2** with selenium oxychloride led to [1,2,5]selenadiazolo[3,4-*c*][1,2,5]thiadiazole (**12**). Ring closure of 2,3-diaminoquinoxaline (**4**) with thionyl chloride or selenium oxychloride gave [1,2,5]thiadiazolo[3,4-*b*]quinoxaline (**21**) and [1,2,5]selenadiazolo[3,4-*b*]quinoxaline (**22**), respectively. Sulfurous acid reduced **21** to the 4,9-dihydro derivative **23**, which was reoxidized to **21** with chloranil. Aqueous base hydrolyzed **21** to **4** via the hydrated intermediate **24**. Aqueous glyoxal cyclized **4** to the covalent hydrate of pyrazino[2,3-*b*]quinoxaline (**26**), **27**, which was dehydrated to **26**. Compound **26** underwent rapid addition of two alcohols in a process analogous to covalent hydration.

In order to synthesize additional heterocyclic compounds analogous to [1,2,5]thiadiazolo[3,4-*c*][1,2,5]thiadiazole (**1**) (**1**), we desired to have 3,4-diamino-1,2,5-thiadiazole (**2**) as a starting material. Three previous



attempts to synthesize **2** were unsuccessful (**2**). Substitution of both chlorine atoms of 3,4-dichloro-1,2,5-thiadiazole (**3**) (**3**) via nucleophilic substitution offered the best alternative route.

Synthesis of **2**.

Method A.

As expected, the strongly electron-withdrawing 1,2,5-thiadiazole nucleus activates the chlorine atoms in **3** toward nucleophilic attack by metal amides. Although the reaction of **3** with lithium or sodium amide in liquid ammonia did produce the desired diamine **2** in 4% yield, the major products were ring-opened materials, possibly containing cyano functions as evidenced by three infrared bands between 4.4 and 4.83 μ . These side reactions are best explained as the consequence of competing attack on the sulfur atom similar to those observed with dialkyl and diaryl 1,2,5-thiadiazoles with lithium alkyls or Grignard reagents (**4a**). Mechanistically, they can be interpreted analogously to the ring opening of 2-chloropyrazine with potassium amide (**5**).

Method B.

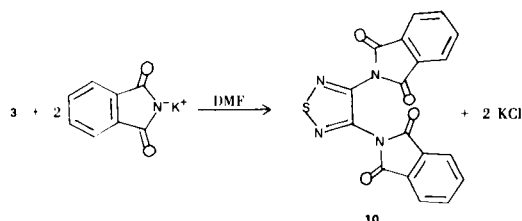
From the above experiment, it was apparent that metal amides are unnecessarily powerful nucleophiles; ammonia alone at moderately elevated temperature was found to be more discriminating. The most convenient synthesis of 2,3-diaminoquinoxaline (**4**) proceeds in excellent yield on heating 2,3-dichloroquinoxaline (**5**) and ammonia at 90° for four hours (**6**). The amination of 2,3-dichloropyrazine (**6**) is more difficult. We found that ammonolysis at 85-90° (3 hours) replaced only one chlorine of **6** to give 3-amino-4-chloropyrazine (**7**) in high yield (**7**). Replacement of the second chlorine atom to give 2,3-diaminopyrazine (**8**) requires one day at 135° in ammonia with copper catalysis (**8**). The synthesis of 3,4-bis-(*N,N*-dimethylamino)-1,2,5-thiadiazole (**9**) in 49% yield from **3** in dimethylamine-DMSO has been reported (**9**).

When **3** was heated with ammonia at 45-55° for 12 hours, an inky-blue liquid ammonia solution resulted, from which **2** was isolated in 24% yield. Ring-opening was still the dominant reaction, since considerable quantities of elemental sulfur were recovered.

Method C.

In view of the poor nucleophilic selectivity in the above methods, we resorted to the milder reagent, potassium phthalimide, in a Gabriel synthesis of **2**. Although ring chlorinated aromatic compounds are generally unreactive in the Gabriel synthesis, electron-deficient compounds (e.g. picryl chloride and cyanuric chloride) react with

reasonable facility (10). 3,4-Dichloro-1,2,5-thiadiazole (**3**) is unusually reactive in this sense, since both chlorines are replaced (without detectable buildup of the mono-substituted intermediate) to give 3,4-di(*N*-phthaloyl)-1,2,5-thiadiazole (**10**), m.p. 276.2-278°. The reaction conditions



show considerable latitude. When **3** was heated with potassium phthalimide at 65° for 5 hours in DMF or at 100° for 20 minutes, **10** was obtained in 66% yield. A reaction conducted at room temperature for 18 hours gave **10** in 19% yield. Both DMF and DMSO gave good results provided they were dry, since the addition of water was found to inhibit the reaction strongly.

Under reaction conditions similar to those which gave **10**, 3-chloro-1,2,5-thiadiazole (**11**) and **7** were unreactive. Under more vigorous conditions, **5** reacted slowly. After 7 hours at reflux in DMF with potassium phthalimide, **5** yielded a mixture of the mono- and diphtalimido products as shown by mass spectral analysis.

For the cleavage of **10** to diamine **2**, we wished to avoid the usual vigorous procedures (10). Therefore, the uncommon aminolysis procedure was used (11,12). When **10** was treated at room temperature with ammonia in DMF or methylamine in chloroform, cleavage to **2** was complete.

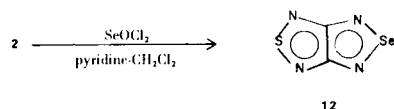
Method D.

We have previously reported the synthesis of **2** by the hydrolysis of **1** in dilute ammonium hydroxide (1a).

Reactions of 2.

[1,2,5]Selenadiazolo[3,4-c][1,2,5]thiadiazole (**12**).

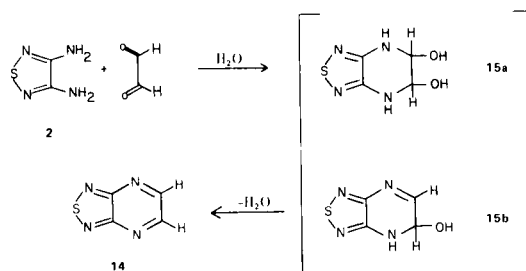
In an earlier publication, we reported the synthesis of **1** from **2** with either sulfur monochloride in DMF or thionyl chloride in pyridine (1a). In an extension of the latter reaction, **2** in pyridine and methylene chloride was treated with selenium oxychloride (*vide infra*). Elution of the reaction mixture through silica gel afforded a pale orange solid (13), identified as [1,2,5]selenadiazolo[3,4-c][1,2,5]thiadiazole (**12**) by its infrared and mass



spectra. Compound **12** appears to be less stable than **1**, possibly due to the greater sensitivity of the 1,2,5-selenadiazole nucleus to reducing and oxidizing agents (4a), as well as hydrolysis (*vide infra*).

[1,2,5]Thiadiazolo[3,4-*b*]pyrazine (**14**).

The reaction of 3,4-diaminopyrazine (**8**) with aqueous glyoxal at reflux gave pyrazino[2,3-*b*]pyrazine (**13**) in 77.3% yield (8). Similarly, diamine **2** reacted with glyoxal to product [1,2,5]thiadiazolo[3,4-*b*]pyrazine (**14**) in 81.5% yield. The two reactions differ, however, in the ability of the fully aromatic products, **13** and **14**, to undergo covalent hydration. Diamine **8** yields the anhydrous species **13** after only 5 minutes at reflux temperature (8), while **2** first gives a precipitate, **15a** or **15b**, on the addition of glyoxal. The solid was found to be insoluble in chloroform, yet displayed nearly the same mass spectrum as **14** (14). Apparently, the initial product **15**, is dehydrated rather slowly to yield the aromatic



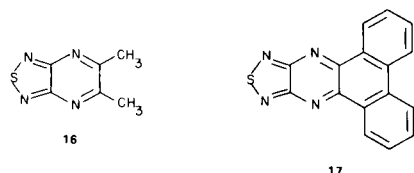
(chloroform soluble) product **14**. Sublimed **14**, m.p. 161-162° dec., shows a singlet at δ 9.06 in its ¹H nmr for the equivalent protons. The mass spectrum of **14** (M^+ m/e 138, 100%) contains fragment ions typical of both pyrazine and 1,2,5-thiadiazole fragmentation pathways.

Synthesis of **14** in 30% yield from **8** with thionyl chloride in xylene has recently been reported (15). In a similar closure of **8** with thionyl chloride in pyridine-chloroform, we found the crude **14** underwent reaction with residual thionyl chloride with the development of a blue color on exposure to the atmosphere. A mass spectral examination of the highly insoluble blue-black product showed a major ion at m/e 274 (fragments at m/e 164 and 128), probably corresponding to a dimer of **14** less two hydrogens (16). The same or similar solid was also isolated from a solution of pure **14** in chloroform exposed to sunlight or ultraviolet light.

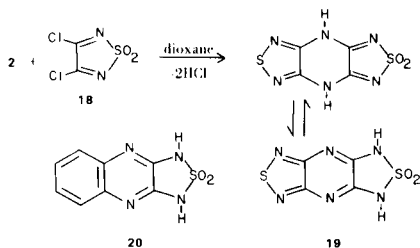
Other [1,2,5]Thiadiazolo[3,4-*b*]pyrazines and Quinoxalines.

The reaction of **2** with diacetyl in water led to the dimethyl analog of **14**, 5,6-dimethyl[1,2,5]thiadiazolo[3,4-*b*]pyrazine (**16**). The ¹H nmr of **16** showed the two equivalent methyl groups as a singlet at δ 2.82 (for comparison, the methyl groups of tetramethylpyrazine appear at δ 2.45 (s)).

Dibenzo[*f,h*][1,2,5]thiadiazolo[3,4-*b*]quinoxaline (**17**) was obtained in 92% yield from **2** and 9,10-phenanthrenequinone in refluxing acetic acid. Recrystallization of **17** from toluene gave either fine orange needles or yellow crystals, m.p. 298-300°, which could be interconverted by recrystallization.



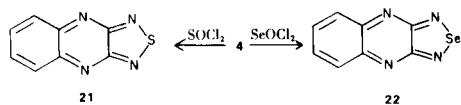
Diamine **2** was cyclized with 3,4-dichloro-1,2,5-thiadiazole 1,1-dioxide (**18**) (**17**) to give 1,3-dihydrobis[1,2,5]-thiadiazolo[3,4-*b*:3',4'-*e*]pyrazine 2,2-dioxide (**19**), m.p. $> 360^\circ$, in 95% yield. The mass spectrum of **19** shows a



molecular ion at m/e 230 ($C_4H_2N_6O_2S_2$, 100%) and fragments at m/e 166 ($M^+ - SO_2$, 34%), 99 (C_2HN_3S , 56%), and 46 (NS, 42%). Previously, we found that the major fragment of **20** resulted from loss of sulfur dioxide (**17**).

Synthesis and Reactions of 2,3-Ring Fused Quinoxalines.

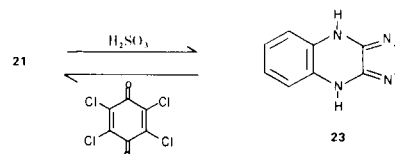
A relative of the [1,2,5]thiadiazolo[3,4-*b*]pyrazine series was synthesized from 2,3-diaminoquinoxaline (**4**). Addition of thionyl chloride (2 moles) to a suspension of **4** in methylene chloride and excess pyridine gave a nearly quantitative yield of [1,2,5]thiadiazolo[3,4-*b*]quinoxaline (**21**) as an orange-yellow solid, m.p. $199.5-200.5^\circ$. The selenium analog of **21**, [1,2,5]selenadiazolo[3,4-*b*]quinoxaline (**22**), a red solid melting at $265-266^\circ$ dec., was synthesized by a similar procedure with selenium oxychloride. We have found that selenium oxychloride is a new and useful reagent for the cyclization of electron-deficient aromatic diamines to the corresponding 1,2,5-selenadiazoles. It is particularly convenient since selenium dioxide fails to close weakly basic diamines (*i.e.*, **2** and **4**).



In one of our first experiments for closing **4** to **21**, an additional compound, 4,9-dihydro[1,2,5]thiadiazolo[3,4-*b*]quinoxaline (**23**), was isolated. Dihydro derivative **23** was cleanly separated from **21** by utilizing its insolubility in chloroform, which readily extracts **21**; the striking difference in solubilities was observed with several other pairs of analogous compounds. An elemental analysis and exact mass determination of **23** gave the molecular formula $C_8H_6N_4S$ (m/e 190, 100%). The dihydro structure of **23** was confirmed by a mass spectrum of a deuterated sample which showed two exchangeable protons (*i.e.*, the 4 and 9 protons), and by rearomatiza-

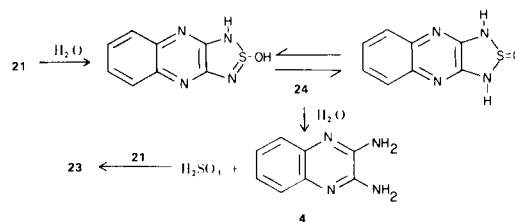
tion to **21**.

After several experiments, we concluded that sulfurous acid, derived from residual thionyl chloride during aqueous work-up, was responsible for the reduction of **21** to **23**. This was verified by the rapid reduction of **21** to **23** by



sulfur dioxide in aqueous alcohol. The reverse reaction, oxidation of **23** to **21**, was readily accomplished in 91% yield by refluxing **23** briefly with chloranil in ethanol.

Hydrolysis of **21** at reflux in water produced two compounds in a *ca.* 1:1 ratio, identified as **4** and **23**. Since dihydro compound **23** was found to be unchanged after 1 hour at reflux in water or aqueous sulfur dioxide, **4** was produced directly from **21**. When **21** was hydrolyzed with hot 3 *M* ammonium hydroxide, only pure white (**18**) **4** was obtained. By analogy to the hydrolysis of **1** (**1a**), **21** may be considered to contain a sulfodiimide linkage which can hydrolyze to diamine **4** *via* the hydrated intermediate **24**, with liberation of sulfurous acid. The sulfurous acid

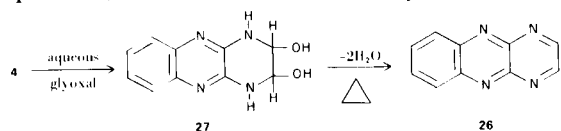


then rapidly reduces a second molecule of **21** to produce **23**. Intermediate **24** is not only a 1,2,5-thiadiazole analog of a pyrazine covalent hydrate, but is also the last intermediate in the reaction mechanism of 1,2,5-thiadiazole formation from aromatic *o*-diamines. Compound **24** was isolated in nearly pure form (contaminated with some **4**) from the hydrolysis of **21** in dilute alkaline solution followed by acidification. The mass spectrum of **24** shows a molecular ion at m/e 206 ($C_8H_6N_4OS$) with the base peak at m/e 188 ($M^+ - H_2O$, $C_8H_4N_4S$) (**14**). A similar hydrolysis of **21** employing deuterium oxide led to di-deuterated **24** which displays a molecular ion at m/e 208 (base peak m/e 188, $M^+ - \text{deuterium oxide}$).

Additional hydrolysis reactions of compounds containing a quinoxaline ring fused to a 1,2,5-thiadiazole or 1,2,5-selenadiazole ring led to the respective diamines. When **22** was warmed with 3 *M* ammonium hydroxide, **4** was obtained in quantitative yield. The hydrolysis of **22** is more rapid than that of **21** and the hydrated intermediate was not isolated. In the case of **17**, DMF and aqueous base were required due to the low solubility of **17** in water. The hydrolysis produced 2,3-diaminodi-

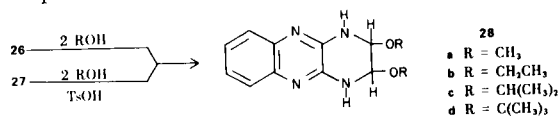
benzo[*f,h*]quinoxaline (**25**), the structure of which was assigned on the basis of its mass spectrum and method of formation. In contrast to the clean hydrolysis of [1,2,5]-thiadiazolo[3,4-*b*]quinoxalines, [1,2,5]thiadiazolo[3,4-*b*]pyrazine (**14**) produced a complex mixture. The dimethyl derivative, **16**, hydrolyzed to 2,3-diamino-5,6-dimethylpyrazine.

Although a number of 2,3-disubstituted pyrazino-[2,3-*b*]quinoxalines have been reported, the unsubstituted parent compound, pyrazino[2,3-*b*]quinoxaline (**26**), was unknown. Reaction of **4** with aqueous glyoxal at reflux (15 minutes) yielded a powder, m.p. > 360°, which was totally insoluble in chloroform (both **21** and **22** are readily soluble). An infrared spectrum of the solid showed no aldehyde carbonyl as would be expected if ring closure were incomplete, yet a mass spectrum showed the correct molecular weight for **26** (*m/e* 182) and the expected fragmentation pattern ($M^+ - \text{HCN}$ and -2HCN) (14). These data suggest that the compound is the exceptionally strong covalent hydrate of **26**, 1,2,3,4-tetrahydro-2,3-dihydroxypyrazino[2,3-*b*]quinoxaline (**27**). When **27** was dehydrated by vacuum sublimation at high temperature, **26** was obtained. Recrystallization from



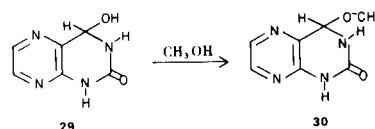
methylene chloride-hexane gave **26** as fluffy orange-yellow needles, m.p. 249° dec. The ^1H nmr of **26** showed the two strongly deshielded pyrazine protons as a singlet at δ 9.23, and an AA'BB' pattern for the aromatic protons centered at δ 8.41 and 8.00. The mass spectrum of **26** showed the expected fragmentation pattern (*vide supra*).

In view of the unusual ability of **26** to form a double covalent hydrate, the reactions of **26** and **27** with alcohols were studied. Compound **26** reacted very rapidly with methanol, ethanol, and 2-propanol, and slowly with *t*-butyl alcohol to give the corresponding di-addition products **28a-d** (19). The covalent hydrate **27** was converted directly into **28a-c** in high yield by refluxing it in the respective alcohol with a trace of *p*-toluenesulfonic acid. The di-*t*-butyl alcohol adduct **28-d** was prepared from **28-c** in *t*-butyl alcohol with *p*-toluenesulfonic acid. The alcohol adducts are highly crystalline white solids which do not melt but decompose on heating above 190°. The mass spectra of **28a-d** all show molecular ions and in each

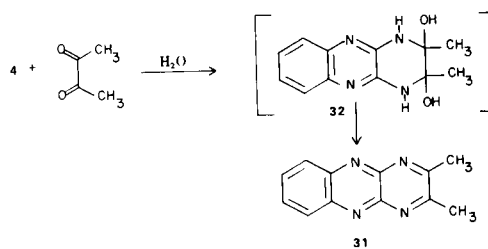


case a major ion appears at *m/e* 182 ($\text{C}_{10}\text{H}_6\text{N}_4$). The ion at *m/e* 182 is probably in part an artifact from **26** forming on the heated probe, since high temperature vacuum

sublimation of **28a** was found to give **26** (14). The 220 MHz ^1H nmr spectrum of **28a** shows a singlet at δ 3.35 for the two methyl groups, a very slightly broadened singlet at δ 4.75 for the 2 and 3 protons, a mildly broadened singlet at δ 6.76 for the N-H protons, which disappears after shaking with deuterium oxide, and an AA'BB' pattern centered at δ 7.31 and 7.53 for the aromatic protons. It has been shown that 2-hydroxypteridine monohydrate (**29**) reacts slowly with methanol at reflux to yield the methanol-incorporated product **30** (20).



The methyl-blocked analog of **26**, 2,3-dimethylpyrazino-[2,3-*b*]quinoxaline (**31**), has been prepared from **4** and diacetyl in non-aqueous media (acetic acid or neat) (21). Methyl substitution on carbons which normally form covalent hydrates reduces the degree of hydration greatly (22). Thus, **4** heated for 4 minutes with aqueous diacetyl yielded the fully aromatic compound **31** directly in 81% yield (*i.e.*, the covalently hydrated intermediate **32**, analogous to **27**, was not isolated).



EXPERIMENTAL

General.

Melting points (open tube) were determined on a Mel-Temp apparatus and are uncorrected. Infrared spectra were taken on a Perkin-Elmer 137 spectrometer. The ^1H nmr spectra were obtained on a Varian HR-220 instrument with internal TMS as reference. The ^{13}C nmr spectra were measured on a Varian XL-100-15 instrument in FT mode (the chemical shifts with respect to chloroform were converted to TMS by adding 77.2 parts per million). Low-resolution mass spectra (70 ev) were obtained on a Varian MAT CH-7 instrument. High-resolution mass spectra were obtained on an AEI MS-9 spectrometer. Analyses were performed by Midwest Microlab, Indianapolis, IN.

N,N-Dimethylformamide (DMF) was distilled successively from phosphorus pentoxide and calcium hydride and stored over 4Å molecular sieves as were pyridine and dioxane. Chloranil was recrystallized from acetone (carbon). Selenium oxychloride was unpurified Baker technical grade. The activated carbon used for decolorizing solutions was Norit A (alkaline). In many cases, other types of activated carbon did not function as well. The autoclave was unstirred and had a volume of 1.8 l.

3,4-Dichloro-1,2,5-thiadiazole (**3**).

Compound **3** was readily prepared from cyanogen and sulfur monochloride in DMF (scaled to 2.5-5.0 moles of cyanogen) (**3a**) and showed: ^{13}C nmr (chloroform): 143.6 ppm; mass spectrum *m/e* (relative intensity [^{35}Cl -containing ions are uncorrected for isotopes], assignment) 154 (53, M^+), 93 (100, $\text{M}^+ - \text{ClCN}$), 61 (5, ClCN), 58 (8, CNS), 46 (8, NS), 35 (7, Cl), and 32 (23, S).

3-Chloro-1,2,5-thiadiazole (**11**).

Compound **11** was prepared from α -aminoacetonitrile bisulfate and sulfur monochloride in DMF (**3a**) and showed: ^{13}C nmr (chloroform): 144.8 and 148.0 ppm; mass spectrum *m/e* (relative intensity [^{35}Cl -containing ions are uncorrected for isotopes], assignment) 120 (86, M^+), 93 (100, $\text{M}^+ - \text{HCN}$), 61 (5, ClCN), 59 (46, $\text{M}^+ - \text{ClCN}$), 58 (17, CNS), 46 (11, NS), 32 (30, S), and 27 (9, HCN).

3,4-Diamino-1,2,5-thiadiazole (**2**).

Method A. From Lithium Amide and **3**.

A lithium amide suspension was prepared from 1.40 g. (200 mmoles), of lithium wire and 300 ml. of liquid ammonia with ferric nitrate nonahydrate as catalyst. Compound **3** (7.75 g., 50.0 mmoles) in 50 ml. of anhydrous ether was added dropwise over 30 minutes to the lithium amide suspension at -33° . After the ammonia had been evaporated, 50 ml. of water was added cautiously to the dark residue. The aqueous layer was extracted with ether (6 x 100 ml.). The combined ether extracts were dried and evaporated to dryness (pumped at 0.05 mm) yielding 253 mg. of crude **2** (4.3%). After recrystallization from water (carbon), the ir and mass spectra of the white product were identical with those of **2** produced by the other methods.

The aqueous layer was extracted with ethyl acetate (3 x 50 ml.). The combined extracts were evaporated to an oil which showed infrared bands at 4.40, 4.63, and 4.83 μ .

Variation of the reaction temperature, solvent, and mole ratio of **3** did not increase the yield of **2**. Similar results were obtained with sodium amide.

Method B. From Ammonia and **3**.

Compound **3** (40 ml., 423 mmoles) was poured slowly into 400 ml. of liquid ammonia contained in a Pyrex autoclave liner. The autoclave was heated at ca. 48° for 14 hours, cooled to -78° , and the inky blue liner contents decanted into a beaker. After the liquid ammonia had evaporated, 100 ml. of warm water was added to the tan-yellow residue and 3 ml. of unreacted **3** was drawn off. The mixture was heated to 90° and filtered to remove elemental sulfur. The filtrate was cooled on ice and the resulting off-white crystals of **2** were collected. Additional product was obtained by ether extraction of the filtrate. The combined diamine (10.9 g., 24.0% based on 37 ml. of **3** reacted) was recrystallized from boiling water (carbon) to give white **2**, m.p. $181.5\text{--}182.5^\circ$; ir (potassium bromide): 6.16, 6.65, 7.10, 7.70, 11.90, and 12.87 μ ; mass spectrum: *m/e* (relative intensity, assignment) 116 (100, M^+), 89 (1, $\text{M}^+ - \text{HCN}$), 88 (1, $\text{M}^+ - \text{H}_2\text{CN}$), 74 (89, $\text{M}^+ - \text{CH}_2\text{N}_2$), 73 (2, $\text{M}^+ - \text{CH}_3\text{N}_2$), 70 (2, $\text{M}^+ - \text{NS}$), 53 (3, HC_2N_2), 47 (20, HNS), 46 (23, NS), 43 (21, CH_3N_2), 42 (8, CH_2N_2), 41 (2, CHN_2), 32 (3, S), 28 (15, H_2CN), and 27 (2, HCN).

A sample of **2** was dissolved in deuterium oxide and lyophilized (three times) to give **2-d₄**: mass spectrum: *m/e* 120, 92, 90, 76, 74 (doublet), 54, 48, 46 (doublet), 44, 42, 32, 30, and 28.

Exact Mass Calcd. for $\text{C}_2\text{H}_4\text{N}_4\text{S}$: 116.0157. Found: 116.0156. Calcd. for $\text{C}_2\text{D}_4\text{N}_4\text{S}$: 120.0408. Found: 120.0405.

Anal. Calcd. for $\text{C}_2\text{H}_4\text{N}_4\text{S}$: C, 20.68; H, 3.47; N, 48.24. Found: C, 20.38; H, 3.45; N, 48.52.

Variation of the reaction conditions (mole ratio of ammonia, maximum temperature achieved, and length of heating) gave yields in the range of 12 to 28%. The use of solvents (ether, toluene, methanol, or DMF) gave less satisfactory results.

Method C. *via* **10**.

3,4-Di-*N*-phthaloyl-1,2,4-thiadiazole (**10**).

Potassium phthalimide (22.2 g., 120 mmoles; powdered and oven dried), **3** (7.75 g., 50.0 mmoles), and DMF (350 ml.) were stirred at 65° for 5 hours (the white suspension changed to reddish-brown). The mixture was cooled to room temperature, poured into 500 ml. of water, and filtered immediately (the filtrate precipitated some phthalimide on standing). The solid filter cake was washed with water and dried to give 12.4 g. (66.0%) of **10**. Recrystallization from chloroform or acetone (carbon) gave transparent crystals of **10** which became opaque white on vacuum drying; m.p. $276.2\text{--}278^\circ$; ir (potassium bromide): 5.59, 5.63, 5.76, 6.73, 6.84, 7.19, 7.36, 7.48, 7.78, 8.97, 9.32, 11.13, 11.23, 11.63, 12.21, 13.97, and 14.09 μ ; ^1H nmr (deuteriochloroform): AA'BB' spectrum δ 7.80 (mult, 4), 7.91 (mult, 4); mass spectrum: *m/e* (relative intensity) 376 (100), 304 (11), 204 (87), 158 (39), 104 (75), 102 (7), 76 (77), 75 (9), and 50 (25).

Exact Mass Calcd. for $\text{C}_{18}\text{H}_8\text{N}_4\text{O}_4\text{S}$: 376.0266. Found: 376.0266.

Anal. Calcd. for $\text{C}_{18}\text{H}_8\text{N}_4\text{O}_4\text{S}$: C, 57.44; H, 2.14. Found: C, 57.44; H, 2.36.

In similar experiments with potassium phthalimide in DMF, **3** heated at 100° for 20 minutes or 25° for 18 hours, gave 66% and 19% of **10**, respectively. The reaction gave similar yields when dry DMSO was used as the solvent. The addition of several drops of water at the onset of a typical reaction was found to inhibit the reaction. In most cases, the odor of **3** was evident in the filtrate, and on steam distillation, a few drops of **3** could be recovered.

Compound **2** from **10**.

Recrystallized **10** (22.6 g., 60.0 mmoles) was stirred in 200 ml. of DMF with ice cooling while ammonia was introduced from a tank for 10 minutes. After the solution had been stirred for 1 hour at room temperature, the excess ammonia was removed under aspirator vacuum and the DMF was vacuum distilled at $<40^\circ$ to give an off-white solid. A mass spectrum of the solid showed only **2** and phthalimide; neither unreacted **10** nor by-products were seen. Fractional crystallization of the solid from water removed the phthalimide and gave **2** identical with **2** synthesized by the other methods.

A reaction similar to the above was carried out on **10** in chloroform with methylamine to give **2** and *N,N'*-dimethylphthalimide (ring closure to *N*-methylphthalimide proceeds on warming with water).

2,3-Dichloropyrazine (**6**).

The literature procedure has been adapted to give a 17% increase in yield (23). Chloropyrazine (29.7 g., 250 mmoles based on 97% Aldrich chloropyrazine) and DMF (21.2 g., 290 mmoles) were heated to 70° . Sulfuryl chloride (73.0 g., 540 mmoles) was added dropwise at $68\text{--}70^\circ$ over 1 hour. After the solution had been heated at 70° for an additional 10 minutes and cooled on ice, 90 ml. of ice water was added. The solution was brought to pH 7 initially with 50% sodium hydroxide and finally with potassium carbonate. The product was steam distilled. After the organic layer of the steam distillate had been separated, the aqueous layer was extracted with 20 ml. of ether. The combined organic layers were dried and fractionated to give 29.9 g. (79.6%) of **6**: ^1H nmr (deuteriochloroform): δ 8.28 (s); ^{13}C nmr

(chloroform): 142.2 and 146.8 ppm; ir (neat): 5.97, 7.42, 8.37, 8.68, 9.53, 11.60, and 12.40 μ ; mass spectrum: m/e (relative intensity, number of ^{35}Cl atoms) 148 (100, 2), 113 (81, 1), 94 (15, 2), 87 (6,1), 86 (23, 1), 62 (12, 1), 52 (20, 0), 51 (20, 0), 47 (6, 1), and 26 (17, 0).

2-Amino-3-chloropyrazine (7).

2,3-Dichloropyrazine (29.9 g., 200 mmoles) was cautiously poured into 400 ml. of liquid ammonia contained in a Pyrex autoclave liner. The autoclave was heated at 85-90° for 3 hours, then cooled on dry ice. The nearly colorless contents of the liner were transferred to a beaker for evaporation of the ammonia. The product was recrystallized from ethanol (carbon), m.p. 168-169° [lit (8) 168-169°]; ^1H nmr (deuteriochloroform): δ 5.03 (broad s, 2), 7.67 (d, J = 2.4 Hz, 1) and 7.89 (d, J = 2.4 Hz, 1).

2,3-Diaminopyrazine (8).

Compound 7 was converted to 8 by heating it with ammonium hydroxide, liquid ammonia, and copper dust at 145-150° for 28 hours (8).

Reaction of 6 with Potassium Phthalimide.

Potassium phthalimide (24 g., 130 mmoles) and 6 (7.45 g., 49.3 mmoles) were heated at 100° in 350 ml. of DMF for 8 hours. The DMF and unreacted 6 were distilled under high vacuum. A mass spectrum of the residual solid indicated only a trace of the mono adduct at m/e 259 with a fragment at m/e 224 ($\text{M}^+ - \text{Cl}$).

Attempted Reaction of 11 with Potassium Phthalimide.

Potassium phthalimide (2.22 g., 12.0 mmoles), 11 (1.205 g., 10.0 mmoles), and DMF (35 ml.) were heated at 65-70° for 24 hours. Work-up as for compound 10 afforded no phthalimide adduct.

Reaction of 5 with Potassium Phthalimide.

Potassium phthalimide (5.00 g., 27.0 mmoles) and 5 (1.99 g., 10.0 mmoles) were refluxed for 7 hours in 150 ml. of DMF. The mixture was cooled to room temperature and diluted with water to give a yellow precipitate. A mass spectral analysis of the solid showed it to be a mixture of the monosubstituted product (m/e 309, fragment at 274 ($\text{M}^+ - \text{Cl}$)); and the disubstituted product (m/e 420).

2,3-Dihydroxyquinoxaline.

The procedure was adapted from that of Phillips (24). A solution of 150 g. (1.19 moles) of technical oxalic acid dihydrate in 400 ml. of water was heated (hot plate) to 95° in a 2 l. beaker. Concentrated hydrochloric acid (200 ml.) was added followed by *o*-phenylenediamine (110.2 g., 1.00 mole based on 98% Aldrich material). The temperature was maintained between 98 and 106° for 15 minutes with continuous stirring. The mixture was cooled by the addition of ice (ca. 600 g.) and the silvery-grey needles were collected by filtration, washed with water, and dried at 75° to give 154 g. (95%) of 2,3-dihydroxyquinoxaline. The crude product was dissolved in ca. 1 N sodium hydroxide at room temperature, treated with carbon, and filtered. The colorless filtrate was acidified with 4-6 N hydrochloric acid and the bulky white precipitate was filtered, washed well with water then methanol, and dried, m.p. > 360°.

If freshly purified *o*-phenylenediamine was used in the synthesis, the initial product was white and did not require further purification.

2,3-Dichloroquinoxaline (5).

2,3-Dihydroxyquinoxaline (81.0 g., 500 mmoles), thionyl chloride (250 ml.), and DMF (5.0 ml.) were refluxed until the

solid had completely dissolved (ca. 2 hours). The excess thionyl chloride was recovered by distillation at atmospheric pressure, then at aspirator vacuum, and finally at high vacuum. The solid was triturated with ice water, filtered, washed with water, and dried to give 5 in 98-100% yield. Recrystallization (carbon) from 110-115° petroleum ether gave 5 identical to an authentic sample.

2,3-Diaminoquinoxaline (4).

The procedure was adapted from the literature (6). 2,3-Dichloroquinoxaline (5) (80.0 g., 402 mmoles) was placed in a Pyrex autoclave liner and liquid ammonia (ca. 300 ml.) was added. The autoclave was heated at 90° for 6-12 hours. After the autoclave had been cooled on dry ice, the liner was emptied into a 2 l. beaker and the ammonia evaporated. The yellow residue was triturated with hot water (500 ml.), filtered, washed with hot water (1 l.), and dried at 75° to give 61.5 g. (95.5%) of 4. Diamine 4 was dissolved in boiling DMF and ice water was stirred in to precipitate fine yellow crystals of 4 which were washed with water and dried. The reverse procedure, addition of 4 in DMF to ice water, gave 4 as a light yellow powder. Pure white (18) 4 was obtained if the DMF solution was treated with a generous amount of carbon. The infrared spectra of yellow and white 4 were identical.

[1,2,5]Selenadiazolo[3,4-c][1,2,5]thiadiazole (12).

Dry 2 (580 mg., 5.00 mmoles) was suspended in 15 ml. of methylene chloride and 10 ml. of pyridine. Selenium oxychloride (2.0 g., 12 mmoles) was added dropwise over 5 minutes. After the mixture had been stirred for 5 hours at 25°, it was eluted with methylene chloride through a 15 x 1.5 cm column of silica gel. The eluent was concentrated under vacuum, treated with carbon, and evaporated to dryness yielding pale orange 12 (13). Infrared and mass spectra were obtained on 12 prior to its decomposition; ir (potassium bromide): 5.80, 6.96, 7.18, 10.94, 12.05, and 13.57 μ ; mass spectrum: m/e (relative intensity, ^{80}Se -containing ions have been corrected to account for the other selenium isotopes) 192 (100, M^+), 152 (6, $\text{C}_2\text{N}_2\text{SSe}$), 146 (2, $\text{C}_2\text{N}_3\text{Se}$), 126 (28, NSSe), 120 (19, CN_2Se), 112 (5, SSe), 106 (1, CNSe), 94 (6, NSe), 80 (13, Se), 72 (10, CN_2S), 58 (0.5, CNS), 46 (28, NS), and 32 (3, S).

[1,2,5]Thiadiazolo[3,4-c]pyrazine (14).

Aqueous glyoxal (4.5 ml. of a 40% solution) was added to a solution) was added to a solution of 2 (2.32 g., 20.0 mmoles) in 35 ml. of boiling water to give a chloroform-insoluble precipitate within seconds. A mass spectrum of the solid (15) showed all of the ions for 14 plus the ions for water (14). The mixture was refluxed for 20 minutes, cooled, and extracted with chloroform (4 x 50 ml.). The combined extracts were washed with water (2 x 10 ml.) and dried. The aqueous layer and the first water wash were refluxed an additional 40 minutes, cooled, and extracted with chloroform (3 x 25 ml.). The combined extracts were washed with water (2 x 15 ml.), dried, and combined with the original chloroform extract. Removal of the chloroform gave 2.25 g (81.5%) of bright yellow 14, which after sublimation at 65° (0.2 mm) showed, m.p. 161-162° dec. (sealed tube); ^1H nmr (deuteriochloroform): δ 9.06 (s); ir (potassium bromide): 6.67, 7.18, 7.48, 7.57, 7.88, 8.36, 9.91, 10.53, 11.21, 11.44, and 12.20 μ ; mass spectrum: m/e (relative intensity) 138 (100), 111 (2), 84 (49), 59 (39), 58 (20), 53 (27), 52 (4), 46 (43), 40 (6), 39 (6), 38 (5), and 32 (19).

Exact Mass Calcd. for $\text{C}_4\text{H}_2\text{N}_4\text{S}$: 138.0000. Found: 137.9997.

Anal. Calcd. for $\text{C}_4\text{H}_2\text{N}_4\text{S}$: C, 34.77; H, 1.46; N, 40.55. Found: C, 34.58; H, 1.56; N, 40.85.

A solution of 14 in chloroform was exposed to sunlight or

ultraviolet light until it had become green. After the solvent had been evaporated, the green solid was vacuum sublimed to remove unreacted **14**. A mass spectrum of the residual fluffy blue solid showed an ion at *m/e* 274 with fragments at *m/e* 228 and 164.

Reaction of 2,3-Diaminopyrazine (**8**) with Thionyl Chloride.

A suspension of **8** (110 mg., 1.00 mmoles) in 2.8 ml. of chloroform and 0.83 ml. of pyridine was treated with 0.83 ml. of thionyl chloride. After the mixture had been refluxed for 15 minutes, it was concentrated under vacuum leaving moist yellow **14**. As soon as the crude product was exposed to air, it began to turn blue. The solid was treated with ice water, filtered, washed with water, and dried. A mass spectrum of the blue-black solid showed a major ion at *m/e* 274 with fragments at *m/e* 228 and 164.

5,6-Dimethyl[1,2,5]thiadiazolo[3,4-*b*]pyrazine (**16**).

Reaction of aqueous diacetyl with **2** as for **14** gave a low yield of light yellow **16** which was vacuum sublimed, recrystallized from acetone, and vacuum sublimed, m.p. 124-125° (sealed tube); ¹H nmr (deuteriochloroform): δ 2.82 (s) (for comparison, the methyl groups of tetramethylpyrazine appear at δ 2.45 (s) (deuteriochloroform)); mass spectrum: *m/e* (relative intensity) 166 (97), 125 (9), 84 (23), 73 (100), 67 (16), 58 (9), 46 (11), 32 (7), and 15 (12).

Exact Mass Calcd. for C₆H₆N₄S: 166.0313. Found: 166.0315.

Dibenzo[*f,h*][1,2,5]thiadiazolo[3,4-*b*]quinoxaline (**17**).

9,10-Phenanthrenequinone (833 mg., 4.00 mmoles) and **2** (465 mg., 4.00 mmoles) were refluxed in 28 ml. of acetic acid for 24 hours. After the mixture had been cooled to 25°, the orange product was filtered, washed with water, and dried to give 1.06 g. (92.1%) of **17**. Recrystallization from benzene or toluene gave bright orange needles, m.p. 298-300°; ¹H nmr (deuteriochloroform): δ 7.73 (t, J = 8 Hz, 2), 7.85 (t, J = 8 Hz, 2), 8.49 (d, J = 8 Hz, 2), and 9.33 (d, J = 8 Hz, 2); ir (potassium bromide): 6.23, 6.90, 7.12, 7.29, 7.51, 11.19, 12.05, 13.20 and 13.81 μ; mass spectrum: *m/e* (relative intensity) 288 (100), 287 (14), 261 (7), 247 (6), 230 (15), 203 (8), 190 (14), 177 (4), 176 (9), 163 (4), and 144 (9, M⁺).

Exact Mass Calcd. for C₁₆H₈N₄S: 288.0470. Found: 288.0468.

Anal. Calcd. for C₁₆H₈N₄S: C, 66.65; H, 2.80. Found: C, 66.43; H, 2.77.

Compound **17** was occasionally obtained as yellow crystals (interconvertible with the orange form), m.p. nmr, and mass spectrum same as above.

Anal. Found: C, 66.42; H, 2.74.

1,3-Dihydrobis[1,2,5]thiadiazolo[3,4-*b*:3',4'-*e*]pyrazine 2,3-Dioxide (**19**).

A solution of **2** (1.34 g., 11.5 mmoles) in 75 ml. of dioxane was treated dropwise with **18** (**17**) (2.15 g., 11.5 mmoles) in 15 ml. of dioxane over 5 minutes. After the mixture had been stirred for 6 hours at 25°, the faint yellow solid was filtered, washed with dioxane, and dried at 0.02 mm to give 2.52 g. (95.3%) of **19**. The product was dissolved in dilute ammonium hydroxide, treated with carbon, and acidified with dilute hydrochloric acid. The white crystalline **19** showed, m.p. > 360°; ir (potassium bromide): 6.10, 6.62, 6.80, 7.15, 7.44, 8.49, 10.36, 11.51, 11.67, 12.40, and 12.79 μ; mass spectrum: *m/e* (relative intensity) 230 (100), 166 (34, M⁺ - SO₂), 99 (56, C₂HN₃S), 74 (9), 73 (7), 72 (12), 68 (19), 64 (8), 53 (12), 48 (10), 46 (42, NS), and 32 (8).

Exact Mass Calcd. for C₄H₂N₆O₂S₂: 229.9681. Found:

229.9679.

Anal. Calcd. for C₄H₂N₆O₂S₂: C, 20.87; H, 0.88. Found: C, 20.64; H, 0.86.

A portion of **19** was dissolved in warm DMF, treated with deuterium oxide, and evaporated to dryness under vacuum yielding dideuterated **19**, mass spectrum: *m/e* 232, 168, 100, 76, 74, 72, 70, 64, 54, 48, 46, and 32.

[1,2,5]Thiadiazolo[3,4-*b*]quinoxaline (**21**).

A suspension of **4** (16.0 g., 100 mmoles) in a mixture of pyridine (40.5 ml., 500 mmoles) and methylene chloride (400 ml.) was stirred vigorously at -20° during the dropwise addition of thionyl chloride (15.0 ml., 206 mmoles in 50 ml. of methylene chloride) over 30 minutes. The orange mixture was warmed to 25° and the solvent removed at aspirator vacuum followed by pumping at 0.02 mm. The dry solid was stirred with 400 ml. of ice water, filtered, washed well with water, and dried at 75° to give **21** in nearly quantitative yield. A mass spectrum of the product showed none of the dihydro compound **23**. Recrystallization from methylene chloride-hexane (carbon) gave **21** as orange-yellow plates, m.p. 199.5-200.5°; ¹H nmr (deuteriochloroform): AA'BB' spectrum δ 8.26 (m, 2) and 7.91 (m, 2); ir (potassium bromide): 6.51, 6.80, 7.04, 7.14, 7.43, 7.50, 7.62, 7.91, 8.66, 8.77, 10.54, 10.92, 11.25, 11.35, 13.08, and 13.38 μ; mass spectrum: *m/e* (relative intensity) 188 (100), 162 (1), 142 (3), 136 (3), 130 (10), 128 (2), 103 (1), 102 (2), 94 (2, M⁺), 90 (19), 78 (2), 77 (2), 76 (2), 75 (1), 64 (4), 63 (5), 62 (1), 58 (1), 52 (3), 51 (5), 50 (3), 46 (17), and 32 (2).

Exact Mass Calcd. for C₈H₄N₄S: 188.0157. Found: 188.0156.

Anal. Calcd. for C₈H₄N₄S: C, 51.05; H, 2.14. Found: C, 50.91; H, 2.04.

[1,2,5]Selenadiazolo[3,4-*b*]quinoxaline (**22**).

A suspension of **4** (4.00 g., 25.0 mmoles) in a mixture of pyridine (10 ml., 125 mmoles) and methylene chloride (100 ml.) was stirred at -20° during the addition of selenium oxychloride (9.14 g., 55.0 mmoles in 20 ml. of methylene chloride) during 15 minutes. The reaction was worked up by the procedure for **21**. Recrystallization from methylene chloride-hexane (carbon) gave red **22**, m.p. 265-266° dec.; ¹H nmr (deuteriochloroform): AA'BB' spectrum δ 8.08 (m, 2) and 7.78 (m, 2); ir (potassium bromide): 6.54, 7.06, 7.14, 7.57, 8.55, 8.70, 11.07, 13.11, 13.21, 13.62, and 13.87 μ; mass spectrum: *m/e* (relative intensity, ⁸⁰Se-containing ions have been corrected to account for the other selenium isotopes) 236 (100), 210 (5), 184 (15), 130 (21), 118 (4, M⁺), 104 (6), 103 (6), 102 (4), 94 (4), 90 (3), 80 (6), 78 (7), 77 (7), 76 (4), 64 (2), 63 (2), 52 (7), 51 (8), and 50 (4).

Exact Mass Calcd. for C₈H₄N₄⁸⁰Se: 235.9601. Found: 235.9603.

Anal. Calcd. for C₈H₄N₄Se: C, 40.87; H, 1.72. Found: C, 40.90; H, 1.83.

4,9-Dihydro[1,2,5]thiadiazolo[3,4-*b*]quinoxaline (**23**).

Compound **4** (16.0 g., 100 mmoles) was suspended in 81 ml. of pyridine and 300 ml. of methylene chloride at -10°. Thionyl chloride (40 ml., 550 mmoles in 100 ml. of methylene chloride) was added dropwise at -10 to -20° over 30 minutes. The suspension was warmed to 30° to give an orange solution. Most of the excess thionyl chloride and solvent was distilled at partial aspirator vacuum. The residual thick orange paste was cooled on ice and cautiously treated with 400 ml. of ice water (vigorous reaction of the remaining thionyl chloride). The exotherm is accompanied by a color change to pale green-yellow. The solid was filtered, washed with 1.5 l. of water, and dried. A mass

spectral analysis of the product showed mostly **23** with a small amount of **21**. The solid was extracted for 2 hours with chloroform in a Soxhlet apparatus to give a chloroform solution containing **21** and analytically pure **23** in the extraction shell. The pale green-yellow **23** showed, m.p. $> 270^\circ$ dec.; ir (potassium bromide): 6.07, 6.15, 6.37, 6.46, 6.61, 6.71, 7.23, 7.71, 8.81, 9.00, 9.59, 12.58, 13.02, and 13.75 μ ; mass spectrum: m/e (relative intensity) 190 (100), 189 (28), 188 (12), 163 (9), 143 (6), 136 (5), 104 (7), 95 (8, M^{++}), 90 (9), 63 (5), 52 (7), 51 (7), 46 (10), 39 (5), and 28 (6).

Exact Mass Calcd. for $C_8H_6N_4S$: 190.0313. Found: 190.0312.

Anal. Calcd. for $C_8H_6N_4S$: C, 50.51; H, 3.18. Found: C, 50.78; H, 3.22.

A dideuterated sample of **23** was prepared by dissolving **23** in DMF and precipitating it with deuterium oxide. The solid was filtered, washed with deuterium oxide, and vacuum dried; mass spectrum: m/e 192, 191, 190, 164, 144, 136, 106, 96 (M^{++}), and 90.

The chloroform extract was evaporated to dryness to give **21**. The ratio of the products **21** and **23** was determined by the thionyl chloride content of the distilled reaction mixture. The combined yield of the two products remained nearly quantitative.

Reaction of **21** with Water.

A 188-mg. sample of **21** was refluxed for 30 minutes in distilled water (10 ml.). The mixture was cooled to room temperature, filtered, washed with water, and dried to give a ca. 1:1 mixture of **4** and **23**.

A similar reaction conducted in deuterium oxide gave **4-d₄** and **23-d₂**.

Hydrolysis of **21** to **4**.

Recrystallized **21** (188 mg., 1.00 mmoles) was refluxed for 5 minutes in 6 ml. of 3 *M* ammonium hydroxide (**21** dissolved with decolorization and shortly white **4** began to crystallize). After an additional 0.5 ml. of ammonium hydroxide had been added, the mixture was refluxed for 5 minutes and cooled to 25° . The solid was filtered, washed with water, and dried to give a nearly quantitative yield of white **4** (18).

1,3-Dihydro[1,2,5]thiadiazolo[3,4-*b*]quinoxaline 2-Oxide (**24**).

Recrystallized **21** was dissolved in a minimum amount of DMF and added in one portion to ice cold water containing two moles of sodium hydroxide (decolorization was immediate). Ice cold hydrochloric acid was added to neutralize the base and the resulting precipitate of **24** was filtered, washed with water, and vacuum dried (contaminated with some **4** by mass spectral analysis); ir (potassium bromide): 6.09, 6.30, 6.72, 7.15, 7.44, 7.60, 8.67, 8.92, 9.25, 9.60, 10.76, 12.2, 13.3, and 13.8 μ ; mass spectrum: m/e (relative intensity) 206 (4), 188 (100), and ions corresponding to the fragmentation of **21** (14).

Exact Mass Calcd. for $C_8H_6N_4OS$: 206.0262. Found: 206.0258. m/e 188 Ion Calcd. for $C_8H_4N_4S$: 188.0157. Found: 188.0155.

In a similar experiment, **21** was hydrolysed in deuterium oxide to give **24-d₂** (contaminated with **4-d₄**); mass spectrum: m/e 208 and base peak 188.

Reduction of **21** to **23**.

A solution of **21** in warm ethanol was treated with excess sulfurous acid or aqueous sodium bisulfite. The mixture was diluted with ice water, and the precipitate was filtered, washed with water and dried to give pure **23** in nearly quantitative yield.

Compound **21** was also reduced to **23** by shaking it with aqueous THF containing excess sodium borohydride.

Chloranil Oxidation of **23** to **21**.

A suspension of **23** (1.90 g., 10.0 mmoles) and chloranil (2.46 g., 10.0 mmoles) in ethanol (150 ml.) was refluxed until all of the **23** had dissolved (ca. 2 minutes). A mass spectrum of a portion of the solution (dried under vacuum) showed no starting material. The orange-yellow solution was allowed to cool slowly to room temperature and 1.51 g. of pure **21** was collected as orange-yellow needles. The mother liquor was concentrated to give a second crop, which after recrystallization from ethanol yielded 0.20 g. of **21** (total 1.71 g., 91.0%).

p-Benzoquinone also oxidized **23** to **21**, using a similar procedure.

Hydrolysis of **22** to **4**.

Compound **22** was warmed with 3 *M* ammonium hydroxide (decolorized as it dissolved). The mixture was cooled to room temperature, filtered, and the filter cake washed with water and dried to yield white **4** (18).

Hydrolysis of **17** to **25**.

Compound **17** was dissolved in hot DMF and boiled with 6 *M* ammonium hydroxide (frequently replenished) until the solution had nearly decolorized. The solution was cooled and diluted with ice water. The precipitate of crude **25** was filtered, washed with water, and dried. The product was recrystallized from ethanol with generous carbon treatment to give **25** in modest yield as pale yellow needles; mass spectrum: m/e (relative intensity) 260 (100), 244 (7), 234 (6), 233 (26), 232 (8), 205 (19), 190 (13), 130 (4, M^{++}), and 116.5 (10, 233^{++}).

Exact Mass Calcd. for $C_{16}H_{12}N_4$: 260.1062. Found: 260.1058.

Reaction of **14** with Ammonium Hydroxide.

Freshly sublimed **14** was warmed with 3 *M* ammonium hydroxide. The solution darkened rapidly and formed a precipitate. The mixture was lyophilized to give a black powder which showed major molecular ions in its mass spectrum at m/e 274, 138, 116, and 110.

Hydrolysis of **16** to 2,3-Diamino-5,6-dimethylpyrazine.

A solution of **16** in dilute sodium hydroxide was refluxed for 15 minutes, cooled to 25° , neutralized with dilute hydrochloric acid, made basic with ammonium hydroxide, and evaporated to dryness. A mass spectral analysis showed 2,3-diamino-5,6-dimethylpyrazine.

1,2,3,4-Tetrahydro-2,3-dihydroxypyrazino[2,3-*b*]quinoxaline (**27**).

Compound **4** (16.0 g., 100 mmoles) was suspended in 350 ml. of boiling water and 40% aqueous glyoxal (35 ml.) was added. The suspension was refluxed gently for 15 minutes, and then cooled and filtered. The filter cake was washed well with water and dried at 75° to give 20.4 g. of crude **27** as a powder, m.p. $> 240^\circ$ (blackens); ir (potassium bromide): 6.30, 6.43, 6.51, 6.70, 6.98, 7.16, 7.49, 7.93, 8.63, 8.81, 9.60, 9.81, and 13.22 μ ; mass spectrum (probe temperature 140°) same spectrum as **26** (*vide infra*) plus the ions of water.

Pyrazino[2,3-*b*]quinoxaline (**26**).

Portions of **27** were sublimed under vacuum with heating by a Bunsen flame. The orange sublimate and black residue were triturated twice with methylene chloride and filtered. The filtrate was treated with carbon, filtered, concentrated, and crystallized from methylene chloride-hexane. A second crystallization from the same solvents gave **26** as fine orange-yellow needles, m.p. 249°

(rapid dec.); ^1H nmr (deuteriochloroform): δ 9.28 (s, 2), AA'BB' pattern centered at 8.41 (m, 2), and 8.00 (m, 2); ir (potassium bromide): 6.63, 6.81, 7.11, 8.51, 8.84, 9.77, 10.43, 11.20, 11.91, 12.96, 13.13, and 13.66 μ ; mass spectrum: *m/e* (relative intensity) 182 (100), 155 (12), 128 (70), 102 (8), 101 (19), 77 (9), 76 (12), 75 (9), 52 (7), 51 (8), and 50 (11), metastable ions for $182 \rightarrow 155$, and $155 \rightarrow 128$.

Exact Mass Calcd. for $\text{C}_{10}\text{H}_6\text{N}_4$: 182.0592. Found: 182.0590.

Anal. Calcd. for $\text{C}_{10}\text{H}_6\text{N}_4$: C, 65.92; H, 3.32. Found: C, 65.92; H, 3.24.

Compound **26** was also prepared by dehydration of **27** in toluene with a catalytic amount of *p*-toluenesulfonic acid and azeotropic removal of water.

Compound **28b** from **26**.

A 91-mg. sample of **26** was refluxed with 15 ml. of ethanol for 1 hour (experiments with more dilute solutions were complete by the time reflux was achieved, possibly due to catalysis by the glass surface). After the solution had cooled to 25° , 119 mg. of **28b** was collected. Concentration of the mother liquor afforded an additional 12 mg. of **28b** (95.6%). Recrystallization from ethanol gave **28b** identical with that prepared from **27**.

Similar experiments with **26** in methanol and isopropanol gave **28a** and **28c**, respectively. The analogous reaction of **26** with *t*-butanol gave a mixture of unreacted starting material and **28d** (19).

Compound **28b** from **26** with Base Catalysis.

A solution of **26** in hot benzene was treated with ethanol containing a trace of sodium ethoxide. Decolorization was immediate. Solvent removal gave **28b**.

1,2,3,4-Tetrahydro-2,3-dimethoxypyrazino[2,3-*b*]quinoxaline (**28a**).

A 2.00-g. sample of **27** was refluxed with 100 ml. of methanol and 50 mg. of *p*-toluenesulfonic acid monohydrate for 30 minutes. The mixture was treated with carbon and filtered hot. The filtrate was concentrated to 60 ml. and allowed to crystallize. A second crop of **28a** was obtained after concentration of the mother liquor. Recrystallization from methanol (carbon) gave 2.16 g. (89.5% overall from **4**) of white **28a**, m.p. $> 195^\circ$ dec.; ^1H nmr (deuteriochloroform): δ 3.35 (s, 6), 4.75 (s, 2), 6.76 (mildly broadened s, 2), and an AA'BB' pattern at 7.31 (m, 2), and 7.53 (m, 2), the singlet at 6.76 disappeared after shaking with deuterium oxide; ir (potassium bromide): 6.30, 6.50, 6.71, 6.92, 7.50, 7.72, 8.43, 8.57, 9.27, 9.52, 10.92, 11.18, 11.89, 13.37, and 13.58 μ ; mass spectrum: *m/e* (relative intensity) 246 (32), 231 (11), 215 (23), 203 (19), 184 (24), 183 (29), 182 (100), 171 (29), 155 (14), 144 (25), 129 (18), 128 (81), 102 (19), 101 (25), 90 (13), 77 (13), 76 (16), 75 (12), 52 (12), 51 (12), 50 (15), 32 (20), 31 (38), 29 (30), and 15 (15).

Exact Mass Calcd. for $\text{C}_{12}\text{H}_{14}\text{N}_4\text{O}_2$: 246.1117. Found: 246.1125.

Anal. Calcd. for $\text{C}_{12}\text{H}_{14}\text{N}_4\text{O}_2$: C, 58.52; H, 5.73. Found: C, 58.45; H, 5.92.

1,2,3,4-Tetrahydro-2,3-diethoxypyrazino[2,3-*b*]quinoxaline (**28a**).

A 2.00-g. sample of **27** was refluxed for 10 minutes with 50 mg. of *p*-toluenesulfonic acid monohydrate in 200 ml. of ethanol. A work-up similar to that for **28a** gave 2.24 g. (83.4% overall from **4**) of white **28b**, m.p. $> 195^\circ$ dec.; ir (potassium bromide): 6.28, 6.47, 6.68, 7.15, 7.48, 7.69, 8.52, 9.30, 9.43, 9.73, 9.90, 11.61, and 13.26 μ ; mass spectrum: *m/e* (relative intensity) 274 (36), 245 (29), 229 (13), 217 (34), 201 (12), 184 (16), 183 (28), 182 (100), 171 (28), 161 (34), 144 (24), 129 (11), 128 (69), 102

(11), 101 (21), 90 (11), 76 (13), 50 (14), 46 (14), 45 (28), 31 (75), 29 (27), and 27 (22).

Exact Mass Calcd. for $\text{C}_{14}\text{H}_{18}\text{N}_4\text{O}_2$: 274.1430. Found: 274.1429.

Anal. Calcd. for $\text{C}_{14}\text{H}_{18}\text{N}_4\text{O}_2$: C, 61.29; H, 6.61. Found: C, 61.22; H, 6.72.

1,2,3,4-Tetrahydro-2,3-diisopropoxypyrazino[2,3-*b*]quinoxaline (**28c**).

Compound **27** (8.00 g.), *p*-toluenesulfonic acid monohydrate (100 mg.), and isopropanol (350 ml.) were refluxed for 20 minutes (40 ml. of 2-propanol was allowed to distil). A work-up similar to that for **28a** gave 10.3 g. (87.0% overall from **4**) of white **28c**, which could also be recrystallized from methylene chloride-hexane as fine white needles, m.p. $> 192^\circ$ dec.; ir (potassium bromide): 6.27, 6.44, 6.67, 6.87, 7.14, 7.24, 7.53, 7.68, 8.91, 9.42, 9.55, 13.17, and 13.34 μ ; mass spectrum: *m/e* (relative intensity) 302 (10), 259 (11), 217 (18), 189 (11), 184 (12), 183 (19), 182 (79), 161 (22), 155 (9), 144 (9), 128 (56), 102 (9), 101 (14), 76 (9), 45 (100), 43 (23), 39 (9), and 27 (12).

Exact Mass Calcd. for $\text{C}_{16}\text{H}_{22}\text{N}_4\text{O}_2$: 302.1743. Found: 302.1746.

Anal. Calcd. for $\text{C}_{16}\text{H}_{22}\text{N}_4\text{O}_2$: C, 63.55; H, 7.33. Found: C, 63.41; H, 7.32.

1,2,3,4-Tetrahydro-2,3-di-*t*-butoxypyrazino[2,3-*b*]quinoxaline (**28d**).

Compound **28c**, *t*-butyl alcohol, and a trace of *p*-toluenesulfonic acid monohydrate were heated and a third of the solvent was distilled. After standing overnight at room temperature, the crystals of **28d** were filtered and vacuum dried. After recrystallization from *t*-butyl alcohol, **28d** showed; m.p. $> 192^\circ$ dec.; ir (potassium bromide): 6.29, 6.51, 6.67, 7.12, 7.17, 7.31, 7.75, 8.39, 8.64, 9.52, 9.79, 13.07, and 13.20 μ ; mass spectrum: *m/e* (relative intensity) 330 (11), 217 (62), 201 (11), 189 (25), 184 (13), 183 (25), 182 (69), 161 (42), 144 (11), 128 (47), 101 (14), 59 (100), 57 (42), 43 (15), 41 (35), 39 (10), 31 (29), and 29 (16).

Exact Mass Calcd. for $\text{C}_{18}\text{H}_{26}\text{N}_4\text{O}_2$: 330.2056. Found: 330.2055.

2,3-Dimethylpyrazino[2,3-*b*]quinoxaline (**31**).

Finely divided **4** (4.00 g., 25.0 mmoles) suspended in 75 ml. of hot water was treated with 4.30 g. (50.0 mmoles) of diacetyl. The suspension was heated (without boiling) for 4 minutes, and then cooled on ice to room temperature and filtered. The yellow filter cake was washed with 100 ml. of water and dried at 75° to give 4.25 g. (81%) of **31**. After recrystallization from methylene chloride-hexane, **31** showed, m.p. $> 190^\circ$ dec., [lit (21) 193° (dec.)]; ^1H nmr (deuteriochloroform): δ 2.88 (s, 6), AA'BB' pattern at 7.84 (m, 2) and 8.25 (m, 2); ir (potassium bromide): 6.44, 6.66, 6.82, 6.95, 7.08, 7.22, 7.87, 8.32, 8.78, 9.87, 10.00, 13.03, 13.32, and 14.33 μ ; mass spectrum: *m/e* (relative intensity) 210 (94), 169 (62), 129 (13), 128 (100), 102 (11), 101 (30), 77 (4), 76 (14), 75 (9), 52 (4), 51 (7), and 50 (10).

Exact Mass Calcd. for $\text{C}_{12}\text{H}_{10}\text{N}_4$: 210.0905. Found: 210.0904.

Anal. Calcd. for $\text{C}_{12}\text{H}_{10}\text{N}_4$: C, 68.55; H, 4.80. Found: C, 68.58; H, 4.86.

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- (13) The orange color of **12** is probably due to elemental selenium (red) as an impurity.
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- (18) The literature reports of 2,3-diaminoquinoxaline (**4**) report it to be bright yellow or gold; however, high purity **4** is white (see Experimental). The yellow color might be due to traces of the yellow dye 6,13-dihydropyrazino[2,3-b:5,6-b']diquinoxaline (fluorubine), which can be derived from **4** (6).
- (19) Even in the reaction of **26** with *t*-butyl alcohol, none of the mono-addition product was observed. Apparently, once one mole of alcohol was added to **26**, further addition of alcohol to the remaining C=N bond is facilitated.
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