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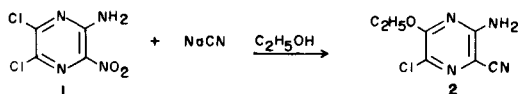
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Treatment of 2-chloro-3-nitropyrazine and 2-chloro-5-nitropyrazine with 3-amino-1,2-propanediol affords products derived from displacement of chloride, while similar reaction of methyl 3-nitropyrazinoate and 2-chloro-3-nitroquinoxaline gives clean nitro group replacement. Analogous reaction of methyl 6-chloro-3-nitropyrazinoate affords a mixture containing products derived from competitive displacement of chloride and nitrite.

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The impressive biological activity [1-3] of numerous nitro heterocycles has fostered continuing interest in the chemistry of this structural class. Recently, there has been particular interest in the nucleophilic displacement of nitrite in nitro heterocycles [4]. This transformation is important both as a synthetic preparative technique [5], as well as a tool in understanding the mechanism of the selective toxicity of these molecules toward anaerobic microorganisms [6].

Nucleophilic displacement of the nitro group has been reported for substituted derivatives of imidazo [5,6] furan [7], dinitrothiophene [8,9], pyridine [10], quinoline [11], thiazole [12], 1,3,4-thiadiazole [13], 1,2,4-triazole [14], and furazan *N*-oxide [15]. In addition, we have recently discovered [16] that treatment of 5,6-dichloro-3-nitropyrazine-amine (**1**) with sodium cyanide in ethanol gave **2** by cyanide displacement of the nitro function. We wish to report herein our continuing work involving the regioselectivity of amine attack on nitroheterocycles, specifically pyrazines and quinoxalines containing additional electron-withdrawing functionality.



The preparation of each of the nitroheterocycles described in this paper is based on the report by Taylor, *et al.* [17] that the sulfilimine derivatives of certain amino heterocycles can be oxidized *via* the corresponding nitroso compound, to the nitro aromatic. We have found that while 2-aminopyridine and aminopyrazine were readily converted to their sulfilimines as reported, the presence of electron-withdrawing functionality in these, as well as in other amino heterocycles, rendered analogous sulfilimine formation problematic. Thus, treatment of 2-amino-3-chloropyrazine (**3a**) with dimethyl sulfide dichloride [17] under the standard conditions gave a 1:1 mixture of starting material and sulfilimine (**3b**). However, treatment of **3a** with dimethyl sulfide ditriflate (DMSD) [18], prepared from dimethyl sulfoxide and trifluoromethanesulfonic an-

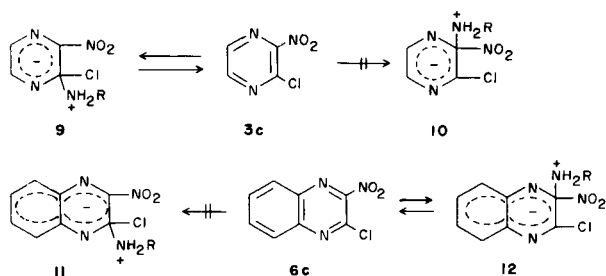
Table  
Products from the Reaction of Nitro Heterocycles with 3-Amino-1,2-propanediol

Nitroheterocycle	Product
<b>3c</b>	
<b>4c</b>	
<b>5c</b>	
<b>6c</b>	
<b>7c</b>	

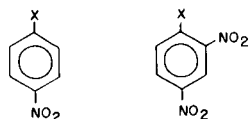
hydride, cleanly afforded **3b** in high purity in 85% yield [19]. In the course of these studies we have found that this synthetic technique employing dimethyl sulfide ditriflate (DMSD) constitutes the method of choice for the conversion of amino heterocycles, possessing either electron-withdrawing functionality or extended conjugation, such as in **6a**, to their sulfilimines.

Oxidation of sulfilimines **3b-7b** to the nitroso stage was carried out with *m*-chloroperbenzoic acid [17], and formation of the nitro compounds **3c-7c** was achieved by ozonolysis without isolation of the intermediate nitroso species. The overall yield of nitro compound from sulfilimine was typically in the range 50-60%.

Treatment of 2-chloro-3-nitropyrazine (**3c**) and 2-chloro-5-nitropyrazine (**4c**) separately with 3-amino-1,2-propanediol (**8**) cleanly afforded in each case the product derived by nucleophilic displacement of chloride. These products were produced in yields of 83% and 79%, respectively, with no evidence for the presence of significant amounts of the nitro-substitution product. However, treatment of methyl 3-nitropyrzinoate (**5c**) and 2-chloro-3-nitroquinoxaline (**6c**) separately with **8** afforded high yields of methyl 3-(2,3-dihydroxypropyl)amino-2-pyrzinoate (**5d**) and 2-(2,3-dihydroxypropyl)amino-3-chloroquinoxaline (**6d**), respectively, from displacement of the nitro group. It is noteworthy that the reaction between **5c** and **8** was the most rapid reaction of the entire group, being complete within 15 minutes at room temperature. Finally, treatment of **7c** and **8** gave a product mixture containing methyl 3-nitro-6-(2,3-dihydroxypropyl)aminopyrazinoate (**7d**) and methyl 6-chloro-3-(2,3-dihydroxypropyl)aminopyrazinoate (**7e**) in yields of 60% and 25%, respectively.



The data indicates that nucleophilic attack by **8** on pyrazines **3c** and **4c** occurs exclusively to give products derived from loss of chloride. However, under similar conditions, **5c** and **6c** give exclusive nitrite displacement, while **7c** affords a mixture of products from competitive displacement of nitrite and chloride. The mechanism of these reactions is probably best understood in terms of the two-step, addition-elimination model for nucleophilic aromatic substitution [4,20,21]. Displacement of chloride in **3c** and **4c** occurs, in analogy with loss of chloride from 4-chloronitrobenzene [20], by rate-limiting addition of the amine (**8**) to afford an intermediate (**9**) which re-aromatizes with loss of chloride. Products derived from chloride loss are exclusive because the activation energy for the transition state leading to **9** is less than that for **10**, due to conjugative stabilization in **9** of the developing negative charge by the nitro group.

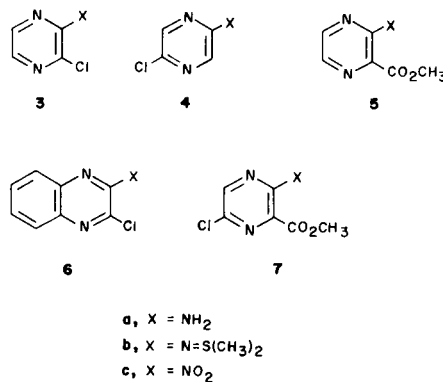


The observation of exclusive nitro group displacement in the case of **6c** indicates that stabilization of the anionic transition state by the nitro function is no longer the pro-

duct determining factor. Conjugative anionic stabilization by the benzo ring, which is available to both **11** and **12**, apparently levels the effect of the nitro function, thereby allowing other factors to become important in determining product ratios.

It is generally accepted that among the factors which determine reactivity patterns in nucleophilic aromatic substitution, two of the more important are charged polarization at the reactive bond and repulsive forces between electron clouds of the entering and leaving groups. Polarization of the carbon-nitrogen bond of **6c** would be expected to be greater than that for the carbon-chlorine bond and therefore nucleophilic attack at the former would be favored. Also, it is likely that for the amine nucleophile, the nitro group, because it is larger and more polarizable than chloro, offers a better opportunity for bond making by the nucleophile by minimizing electron repulsion phenomena. Therefore, both charge polarization and electron repulsion factors reasonably favor formation of the observed nitro substitution product. The finding that competitive displacement of chloride and nitrite occurs for **7c** is taken to signify that the anionic stabilization, charge polarization and electronic repulsion are roughly balanced.

The dramatic reversal of regioselectivity for nucleophilic attack by **8** as one proceeds from **3c** to **6c** is reminiscent of data from studies on the comparative nucleofugicity of groups in nitrobenzenes. For example, the relative rate of displacement of the nitro group was 9-times that of chloride when 1-X-4-nitrobenzenes (**13**) were treated with piperidine in dimethyl sulfoxide [22], and 200-times that of chloride when 1-X-2,4-dinitrobenzenes (**14**) were treated with piperidine in methanol [23]. We are continuing to study the regioselectivity of attack by amines and other nucleophiles on symmetrically-substituted halo nitroheterocycles.



#### EXPERIMENTAL

Melting points were determined in air employing a Thomas-Hoover apparatus using a capillary tube and are uncorrected. Proton nmr spectra were obtained using a Varian T-60A spectrometer. The elemental

analyses were carried out by Dr. H. Ramjit and his staff using an LKB-9000S at 70 eV.

*S,S*-Dimethyl-*N*-(3-chloropyrazin-2-yl)sulfilimine (**3b**).

To a mechanically stirred solution of 3.9 g (0.05 mole) of dimethyl sulfide in 30 ml of dry methylene chloride at  $-78^{\circ}$  under nitrogen was added 13.1 g (0.046 mole) of trifluoromethanesulfonic anhydride dropwise at  $-78^{\circ}$  to afford a white precipitate. To this was added a solution of 5.0 g (0.039 mole) of 2-amino-3-chloropyrazine (**3a**) [24] in 30 ml of methylene chloride/15 ml of dimethyl sulfoxide and the resulting orange solution was stirred at  $-78^{\circ}$  for 2 hours and at  $-55^{\circ}$  for 1 hour. The reaction mixture was diluted with 200 ml of methylene chloride and the phases were separated. The aqueous phase was extracted with 250 ml of methylene chloride and the combined organic phases were washed with three 75 ml portions of water and dried over anhydrous sodium sulfate. The solvent was removed on the rotary evaporator to give 5.8 g (79%) of **3b** as smelly, yellow crystals, mp 106-108 $^{\circ}$ ;  $^1\text{H}$  nmr (deuteriochloroform):  $\delta$  2.85 (6H, singlet), 7.57 (1H, doublet), 7.78 (1H, doublet); ms: *m/e* 189.

*Anal.* Calcd. for  $\text{C}_6\text{H}_8\text{ClN}_3\text{S}$ : C, 38.00; H, 4.25; N, 22.15. Found: C, 37.90; H, 4.33; N, 22.06.

3-Chloro-2-nitropyrazine (**3c**).

To 7.9 (0.46 mole, 80-90%) of *m*-chloroperbenzoic acid in 70 ml of methylene chloride cooled to  $-5^{\circ}$  and stirred mechanically was added a solution of 5.36 g (0.028 mole) of **3b** in 30 ml of methylene chloride dropwise at such a rate that the temperature did not exceed  $0^{\circ}$ . The reaction mixture was stirred at  $0^{\circ}$  for 40 minutes and then 3 ml of dimethyl sulfide was added with stirring for an additional 10 minutes. The cold reaction mixture was filtered quickly to afford a clear, green solution of the nitroso derivative. This solution was cooled to  $0^{\circ}$  and ozone was bubbled through until the solution was nearly colorless. The resulting suspension was extracted with  $2 \times 50$  ml of saturated sodium bicarbonate and the organic phase was dried over anhydrous sodium sulfate. The solvent was removed on the rotary evaporator to give a pungent yellow oil which gave on flash chromatography with silica gel eluted with chloroform 2.5 g (56%) of **3c** as a yellow oil, *R*<sub>f</sub> 0.6 (chloroform);  $^1\text{H}$  nmr (deuteriochloroform):  $\delta$  8.60 (1H, singlet), 8.83 (1H, singlet); ms: *m/e* 159.

*Anal.* Calcd. for  $\text{C}_4\text{H}_2\text{ClN}_3\text{O}_2$ : C, 30.12; H, 1.26; N, 26.34; Cl, 22.22. Found: C, 30.15; H, 1.41; N, 24.33; Cl, 22.44.

*S,S*-Dimethyl-*N*-(5-chloropyrazin-2-yl)sulfilimine (**4b**).

This was prepared from 2-amino-5-chloropyrazine (**4a**) [25] as described above for **3b**, to give **4b** in 88% yield as a tan solid, mp 119-120 $^{\circ}$ ;  $^1\text{H}$  nmr (deuteriochloroform):  $\delta$  2.74 (6H, singlet), 7.76 (2H, singlet); ms: *m/e* 189.

*Anal.* Calcd. for  $\text{C}_6\text{H}_8\text{ClN}_3\text{S}$ : C, 38.00; H, 4.25; N, 22.15. Found: C, 37.98; H, 4.35; N, 22.14.

2-Chloro-5-nitropyrazine (**4c**).

This was prepared from **4b** as described above for **3c**, to give crude **4c** as a yellow solid. This was purified by flash chromatography on silica gel with chloroform elution to give pure **4c** as yellow crystals in 60% yield, mp 88-90 $^{\circ}$ ;  $^1\text{H}$  nmr (deuteriochloroform):  $\delta$  8.68 (1H, doublet), 9.38 (1H, doublet); ms: *m/e* 189.

*Anal.* Calcd. for  $\text{C}_4\text{H}_2\text{ClN}_3\text{O}_2$ : C, 30.12; H, 1.26; N, 26.34. Found: C, 30.38; H, 1.31; N, 26.16.

*S,S*-Dimethyl-*N*-(3-carbomethoxyprazin-2-yl)sulfilimine (**5b**).

This was prepared from methyl 3-aminopyrazinoate (**5a**) [26] as described above for **3b**. Crude **5b** was obtained as a smelly, yellow oil which was purified by flash chromatography on silica gel eluted with 5% methanol/chloroform, *R*<sub>f</sub> 0.5. Pure **5b** was obtained in 85% yield as a yellow semi-solid;  $^1\text{H}$  nmr (DMSO-*d*<sub>6</sub>):  $\delta$  2.80 (6H, singlet); 3.74 (3H, singlet); 7.48 (1H, doublet); 7.91 (1H, doublet); ms: *m/e* 213.

Methyl 3-Nitropyrazinoate (**5c**).

This was prepared from **5b** as described above for **3c**. Crude **5c** was purified by flash chromatography on silica gel with 2% methanol/chloro-

form to give pure **5c**, *R*<sub>f</sub> 0.5, in 55% yield as pungent, yellow crystals, mp 73-74 $^{\circ}$ ;  $^1\text{H}$  nmr (deuteriochloroform):  $\delta$  4.02 (3H, singlet); 8.60 (1H, doublet); 9.0 (1H, doublet); ms: *m/e* 183.

*Anal.* Calcd. for  $\text{C}_6\text{H}_5\text{N}_3\text{O}_4$ : C, 39.35; H, 2.75; N, 22.95. Found: C, 39.34; H, 2.70; N, 22.91.

*S,S*-Dimethyl-*N*-(3-chloroquinoxal-2-yl)sulfilimine (**6b**).

This was prepared from 2-amino-3-chloroquinoxaline [27] as described above for **3b**. Crude **6b** was recrystallized from methylene chloride/hexane to afford an 88% yield of pure **6b** as pale yellow crystals, mp 154-156 $^{\circ}$ ;  $^1\text{H}$  nmr (DMSO-*d*<sub>6</sub>):  $\delta$  2.87 (6H, singlet), 7.45 (4H, multiplet); ms: *m/e* 239.

*Anal.* Calcd. for  $\text{C}_{10}\text{H}_{10}\text{ClN}_3\text{S}$ : C, 50.10; H, 4.20; N, 17.53. Found: C, 49.81; H, 4.14; N, 17.18.

2-Chloro-3-nitroquinoxaline (**6c**).

This was prepared from **6b** as described above for **3c**. Crude **6c** was purified by flash chromatography on silica gel eluted with chloroform to give a 62% yield of **6c** as a tan solid, mp 143-144 $^{\circ}$ ;  $^1\text{H}$  nmr (deuteriochloroform):  $\delta$  8.10 (4H, multiplet); ms: *m/e* 209.

*Anal.* Calcd. for  $\text{C}_8\text{H}_4\text{ClN}_3\text{O}_2$ : C, 45.84; H, 1.92; N, 20.05. Found: C, 45.99; H, 1.91; N, 20.11.

*S,S*-Dimethyl-*N*-(5-chloro-3-carbomethoxyprazin-2-yl)sulfilimine (**7b**).

This was prepared from methyl 6-chloro-5-amino-pyrazinoate (**7a**) [28] as described above for **3b**. Crude **7b** was recrystallized from methylene chloride/hexane to give pure **7b** in 90% yield as yellow crystals, mp 167-169 $^{\circ}$ ;  $^1\text{H}$  nmr (deuteriochloroform):  $\delta$  2.77 (6H, singlet), 3.88 (3H, singlet), 7.86 (1H, singlet); ms: *m/e* 247.

*Anal.* Calcd. for  $\text{C}_8\text{H}_{10}\text{ClN}_3\text{O}_2\text{S}$ : C, 38.79; H, 4.07; N, 16.96. Found: C, 38.36; H, 4.09; N, 16.84.

Methyl 6-Chloro-3-nitropyrazinoate (**7c**).

This was prepared from **7b** as described above for **3c**. Crude **7c** was purified by flash chromatography on silica gel with 2% methanol/chloroform to afford a smelly, yellow oil in 51% yield;  $^1\text{H}$  nmr (deuteriochloroform):  $\delta$  4.08 (3H, singlet); 8.75 (1H, singlet); ms: *m/e* 217.

2-(2,3-Dihydroxypropyl)amino-3-nitropyrazine (**3d**).

To a solution of 1.5 g (0.0094 mole) of **3c** and 1.01 g (0.01 mole) triethylamine in 25 ml of 2-propanol was added 0.91 g (0.01 mole) of 3-amino-1,2-propanediol (**8**). After stirring at room temperature the crude reaction showed a single major yellow spot on tlc (*R*<sub>f</sub> 0.5) with 10% methanol/chloroform. The solvent was removed on the rotary evaporator and the residue purified by flash chromatography on silica gel with 8% methanol/chloroform to afford 1.7 g (83%) of **3d** as a yellow solid, mp 100-102 $^{\circ}$ ;  $^1\text{H}$  nmr (DMSO-*d*<sub>6</sub>):  $\delta$  3.50 (5H, multiplet), 4.65 (1H, triplet), 5.03 (1H, doublet), 7.85 (1H, doublet), 8.33 (1H, triplet), 8.58 (1H, doublet); ms: *m/e* 214.

*Anal.* Calcd. for  $\text{C}_7\text{H}_{10}\text{N}_4\text{O}_4$ : C, 39.25; H, 4.71; N, 26.16. Found: C, 39.31; H, 4.84; N, 25.70.

2-(2,3-Dihydroxypropyl)amino-5-nitropyrazine (**4d**).

To a solution of 0.5 g (0.003 mole) of **4c** and 0.3 g (0.003 mole) of triethylamine in 10 ml of acetonitrile was added 0.32 g (0.0035 mole) **8** in 10 ml of 2-propanol. After stirring for 18 hours at room temperature the tlc (silica gel) of the crude reaction mixture showed only 1 major yellow spot, at *R*<sub>f</sub> 0.3 with 10% methanol/chloroform. The solvent was removed on the rotary evaporator and the residue was purified by flash chromatography on silica gel with 10% methanol/chloroform to give pure **4d** in 79% yield as a pale yellow solid, mp 185-187 $^{\circ}$ ;  $^1\text{H}$  nmr (DMSO-*d*<sub>6</sub>):  $\delta$  3.30 (5H, multiplet), 4.55 (1H, triplet), 4.85 (1H, doublet), 7.87 (1H, doublet), 8.50 (1H, triplet), 8.90 (1H, doublet); ms: *m/e* 214.

*Anal.* Calcd. for  $\text{C}_7\text{H}_{10}\text{N}_4\text{O}_4$ : C, 39.25; H, 4.71; N, 26.16. Found: C, 39.22; H, 4.80; N, 26.33.

Methyl 2-(2,3-Dihydroxypropyl)amino-3-pyrazinoate (**5d**).

To 0.05 g (0.0027 mole) **5c** in 10 ml of acetonitrile was added a solution

of 0.27 g (0.0027 mole) of triethylamine and 0.32 g (0.0036 mole) of **8** in 10 ml of 2-propanol at room temperature. After stirring for 18 hours at room temperature tlc (silica gel) of the reaction mixture showed only one major yellow spot at  $R_f$  0.5 with 10% methanol/chloroform. The solvent was removed on the rotary and the residue was purified by flash chromatography on silica gel eluted with 10% methanol/chloroform to give a yellow oil, which was triturated with methanol/ether to give **5d** as a pale yellow solid in 82% yield; mp 110-112°;  $^1\text{H}$  nmr (DMSO- $d_6$ ):  $\delta$  3.38 (3H, multiplet), 3.68 (2H, multiplets), 3.87 (3H, singlet), 4.72 (1H, triplet), 5.02 (1H, doublet), 7.88 (1H, doublet), 8.16 (1H, triplet), 8.32 (1H, doublet); ms: m/e 227.

*Anal.* Calcd. for  $\text{C}_9\text{H}_{13}\text{N}_5\text{O}_4$ : C, 47.57; H, 5.77; N, 18.49. Found: C, 47.84; H, 5.99; N, 18.37.

#### 3-Chloro-2-(2,3-dihydroxypropyl)aminoquinoxaline (**6d**).

To 0.6 g (0.0028 mole) of **6c** in 15 ml of acetonitrile was added a solution of 0.4 g (0.004 mole) of triethylamine and 0.36 g (0.004 mole) of **8** in 15 ml of 2-propanol at room temperature. After stirring for 16 hours at room temperature tlc (silica gel) showed only one major spot at  $R_f$  0.3 with 5% methanol/chloroform. The solvent was removed on the rotary evaporator and the residue was purified by flash chromatography on silica gel with 8% methanol/chloroform to give a 77% yield of **6d** as a reddish solid, mp 133-135°;  $^1\text{H}$  nmr:  $\delta$  3.38 (3H, singlet), 3.45 (3H, multiplet), 3.62 (1H, multiplet), 3.83 (1H, multiplet), 7.20 (1H, triplet), 7.42 (1H, multiplet), 7.64 (2H, multiplet), 7.78 (1H, doublet); ms: m/e 253.

*Anal.* Calcd. for  $\text{C}_{11}\text{H}_{12}\text{ClN}_5\text{O}_2$ : C, 52.17; H, 4.74; N, 16.60. Found: C, 51.83; H, 4.83; N, 16.40.

#### Reaction of Methyl 6-Chloro-3-nitropyrazinoate (**7c**) with **8**.

To 2.0 g (0.008 mole) of **7c** in 60 ml of 2-propanol at room temperature was added 0.8 g (0.008 mole) of triethylamine and 0.72 g (0.008 mole) of **8**. After stirring for 16 hours at room temperature tlc (silica gel) showed 2 major components were present. The solvent was removed on the rotary evaporator and the residue subjected to flash chromatography on silica gel with 10% methanol/chloroform elution. The first component had  $R_f$  0.6 under these conditions and 0.52 g (25%) of a yellow solid was isolated and shown to be methyl 6-chloro-3-(2,3-dihydroxypropyl)aminopyrazinoate (**7e**), mp 108-110°;  $^1\text{H}$  nmr (DMSO- $d_6$ ):  $\delta$  3.30 (5H, multiplet), 3.85 (3H, singlet), 4.63 (1H, triplet), 4.95 (1H, doublet), 8.22 (1H, triplet), 8.44 (1H, singlet); ms: m/e 261.

*Anal.* Calcd. for  $\text{C}_9\text{H}_{12}\text{ClN}_3\text{O}_4$ : C, 41.31; H, 16.06; N, 4.62. Found: C, 40.99; H, 15.89; N, 4.68.

The second component had  $R_f$  0.4 under these conditions and 1.3 g (60%) of a yellow solid was isolated and known to be methyl 6-(2,3-dihydroxypropyl)amino-3-nitropyrazinoate (**7d**), mp 107-109°;  $^1\text{H}$  nmr (perdeuteriomethanol):  $\delta$  3.57 (5H, multiplet), 3.92 (3H, singlet), 4.70 (2H, broad singlet), 7.87 (1H, singlet); ms: m/e 272.

*Anal.* Calcd. for  $\text{C}_9\text{H}_{12}\text{N}_4\text{O}_6$ : C, 39.71; H, 4.44; N, 20.58. Found: C, 39.32; H, 4.44; N, 20.28.

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