Imidazo[1,5-a]pyrazines. VI. 3-Thio Derivatives[1,2]

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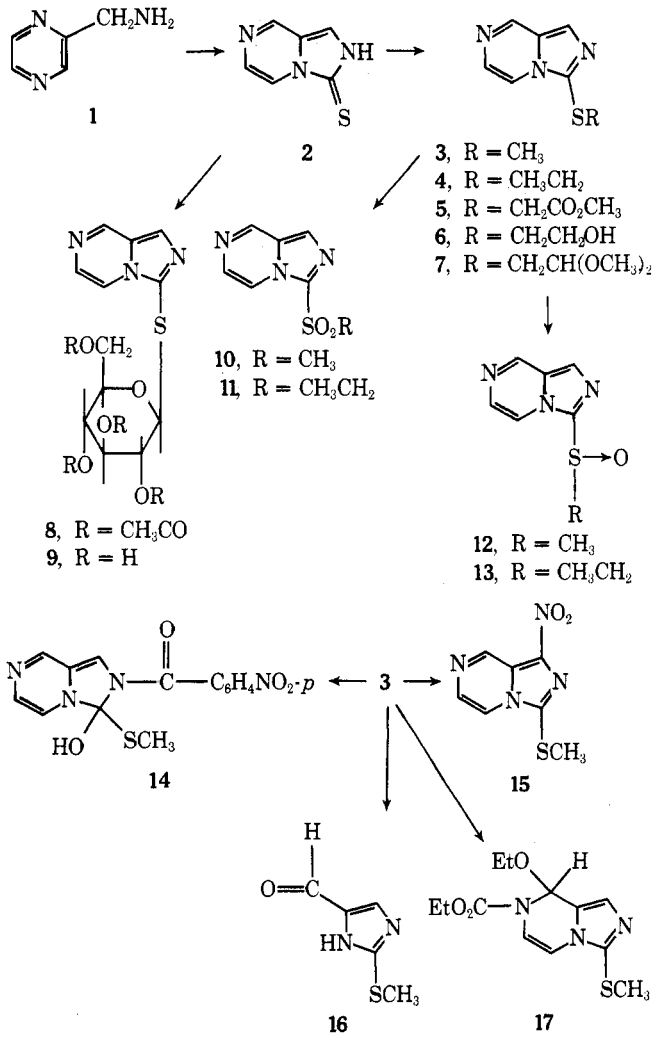
The imidazo[1,5-a]pyrazinthione **2** is prepared from pyrazinemethanamine and CS_2. A number of alkylthioimidazopyrazines and derivatives are described.

Previous papers in this series have described our efforts to prepare functionalized derivatives of the imidazo[1,5-a]pyrazine system. In a continuation of these studies a number of 3-thioimidazo[1,5-a]pyrazines were prepared both for their intrinsic interest as possible antitumor agents and for study as substrates in nucleophilic displacements reactions for further modification of the heterocyclic system.

The parent compound **2** was prepared in excellent yield by reaction of the amine **1**[3] with carbon disulfide. This reaction was patterned after the work of Albert and Ohta,[4] who reported that the reaction of carbon disulfide with 2-amino-3-aminomethylpyrazine yielded 8-aminoimidazo-[1,5]pyrazine-3-thiol. Alkylation of **2** proceeded smoothly to give high yields of **3–7**. Efforts to form a tricyclic compound from **7**, after acid hydrolysis, did not lead to a characterizable product. The alkylated derivatives (**3** and **4**) did not react with *n*-butylamine, cyanide ion, or azide ion in attempted displacement reactions and the oxidized derivatives (**10–13**), prepared with *m*-chloroperbenzoic acid, were also unreactive to these reagents. That oxidation had taken place at sulfur rather than nitrogen in **10–13** was evident both from NMR and mass spectral data. Thus there was the expected downfield shift of the methyl groups in the sulfoxide **12** and the sulfone **10** accompanied by a large deshielding effect on the H-5 proton. The mass spectra of **12** showed the typical M − 15 peak characteristic of methyl sulfoxides[8] while lacking the characteristic peak due to loss of oxygen in *N*-oxides;[9] the mass spectrum of **10** showed a major loss of the CH_3SO_2 moiety. Alkylation of **2** with acetobromoglucose gave a reasonable yield of the nucleoside-like compound **8** whose structure is written on the basis of the "trans rule".[10] Deacetylation with methanolic sodium methoxide afforded **9**.



A brief study was made of the reaction of the methyl sulfide (**3**) with electrophilic reagents. Reaction with nitrosonium tetrafluoroborate in acetonitrile gave a low yield of the 1-nitro derivative (**15**) apparently as the result of further oxidation of an initially formed 1-nitroso compound. There is literature precedent for such a reaction.[11] The reaction of **3** with aqueous nitrous acid resulted in pyrazine ring cleavage to give a low yield of the aldehyde **16**. Apparently the initial attack of the electrophilic agent occurred by reaction at the N-7–C-8 double bond. Indeed, when **3** was treated with ethyl chloroformate and the reaction mixture quenched with ethanol the product was the addition product **17**, completely analogous to the addition products noted with similar reactions of imidazo[1,5-a]pyrazine and 3-methylimidazo[1,5-a]pyrazine.[2] Curiously, when **3** was treated with *p*-nitrobenzoyl chloride and the reaction mixture was quenched with water the product resulted from addition across the N-2–C-3 double bond to give **14** whose aromatic protons did not experience the usual upfield shift when addition takes place at N-7–C-8[2]. Rather, their chemical shifts and coupling constants were very similar to those of the methyl sulfide **3**.

Experimental Section

Melting points (uncorrected) were determined with a Thomas-Hoover capillary apparatus. Ultraviolet data were obtained on a Cary 15 spectrophotometer in ethanol. NMR spectra were determined on a Varian A-60 or a JEOLCO C-60-HL instrument using deuteriochloroform, unless otherwise noted, and tetramethylsilane as the internal standard. Mass spectral data were obtained from a CEC 24-104 spectrometer. Microanalyses were performed by MicroAnalysis, Inc., Marshallton, Del. All evaporations were carried out in vacuo using a water aspirator or a vacuum pump and solutions were dried over anhydrous potassium carbonate unless otherwise noted. Only pertinent spectral data for key compounds are included in the experimental details.

Imidazo[1,5-a]pyrazine-3(2*H*)-thione (2). To the amine **1** [freshly generated from its hydrochloride (5 g, 34.4 mmol) and triethylamine (5.2 ml, 36 mmol)] in 100 ml of methanol was added 15

ml of carbon disulfide and the reaction mixture was heated at reflux for 12 hr. Evaporation of the solvent furnished a residue which was dissolved in 0.5 *N* aqueous sodium hydroxide (100 ml) and the solution was filtered. The filtrate was adjusted to pH 7 with 6 *N* hydrochloric acid and the precipitate (4.1 g, 80%) after washing with water and acetone, was collected by filtration: mp 209° dec; uv (95% EtOH) 245 nm (ε 9400), 298 (9870), 308 (s), 400 (1350); ^{1}H NMR (Me_2SO-d_6) δ 7.88 (H-6, 1 H, d, $J_{5,6}$ = 5 Hz), 7.87 (H-1, 1 H, s), 7.95 (H-5, 1 H, m), 8.91 (H-8, 1 H, d, $J_{5,8}$ = 2 Hz).

Anal. Calcd for $C_6H_5N_3S$: C, 47.66; H, 3.31; N, 27.81; S, 21.19. Found: C, 47.72; H, 3.42; N, 27.49; S, 21.04.

3-Methylthioimidazo[1,5-*a*]pyrazine (3). A solution of the sodium salt of **2** was prepared by mixing 12.08 g (80 mmol) of **2** and 6.0 g (80 mmol) of 85% potassium hydroxide in 300 ml of methanol with stirring to dissolve the solids. Methyl iodide (12.0 g, 84 mmol) was added and the solution was stirred at room temperature for 12 hr, then evaporated. The residue was extracted with four 100-ml portions of ether, the extracts dried and evaporated, and the residue distilled in vacuo to give 11 g (85%) of distillate as a yellow oil that turned reddish on standing, bp 102–105° (0.05 mm). The oil solidified on cooling: mp 34–35°; uv (95% EtOH) 275 nm (s), 285 (ε 7590), 295 (6435), 345 (1690); ^{1}H NMR δ 2.68 (CH_3, 3 H, s), 7.71 (H-6, 1 H, d, $J_{5,6}$ = 5 Hz), 7.93 (H-5, 1 H, m), 8.0 (H-1, 1 H, s), 9.10 (H-8, 1 H, d, $J_{5,8}$ = 2 Hz); MS *m/e* (rel intensity) M^+ 165 (82), 150 ($M^+ - CH_3$, 87), 106 ($M^+ - C_2H_3S$, 100).

Anal. Calcd for $C_7H_7N_3S$: C, 50.89; H, 4.27; N, 25.43; S, 19.41. Found: 50.64; H, 4.15; N, 25.32; S, 19.47.

3-Ethylthioimidazo[1,5-*a*]pyrazine (4). The preparation was conducted as above using 3.02 g (20 mmol) of **2** and giving 4.3 g (90%) of **4** as a yellow oil, bp 97–98° (0.01 mm), that solidified on standing, mp 35–36°.

Anal. Calcd for $C_8H_9N_3S$: C, 53.61; H, 5.06; N, 23.44; S, 17.89. Found: C, 53.82; H, 5.03; N, 23.29; S, 17.62.

3-(Carbomethoxymethyl)thioimidazo[1,5-*a*]pyrazine (5). The preparation was conducted as for **3** using 2.27 g (15 mmol) of **2** and 2.30 g (15 mmol) of methyl bromoacetate to give, after crystallization from hexane, 1.99 g (59%) of **5**, mp 81–82°.

Anal. Calcd for $C_9H_9N_3O_2S$: C, 48.42; H, 4.06; N, 18.82; S, 14.37. Found: C, 48.82; H, 4.08; N, 18.43; S, 13.93.

3-(2-Hydroxyethyl)thioimidazo[1,5-*a*]pyrazine (6). Reaction, as above, of 1.51 g (10 mmol) of **2** and 1.38 g (11 mmol) of bromoethanol gave, after crystallization from acetone–hexane, 1.5 g (77%) of **6**, mp 99–100°.

Anal. Calcd for $C_8H_9N_3OS$: C, 49.23; H, 4.61; N, 21.54; S, 16.41. Found: C, 49.38; H, 4.82; N, 21.23; S, 16.15.

3-(2,2′-Dimethoxyethyl)thioimidazo[1,5-*a*]pyrazine (7). Reaction, as above, of 3.02 g (20 mmol) of **2** and 3.72 g (22 mmol) of bromoacetaldehyde dimethyl acetal gave 3.95 g (83%) of **7** as a yellow oil, bp 130° (0.01 mm).

Anal. Calcd for $C_{10}H_{13}N_3O_2S$: C, 50.23; H, 5.44; N, 17.58; S, 13.41. Found: C, 50.01; H, 5.69; N, 17.49; S, 13.16.

Imidazo[1,5-*a*]pyrazin-3-yl 1-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)sulfide (8). To a filtered solution of 0.66 g (10 mmol) of 85% potassium hydroxide in 50 ml of methanol was added 1.7 g (11.3 mmol) of **2**, and the solution was stirred at room temperature for 6 hr, then evaporated. The residue was suspended in 15 ml of water and the aqueous mixture extracted with five 100-ml portions of chloroform. The combined extracts were washed with 50 ml of water, dried, and evaporated to give 2.5 g (52%) of yellow needles, mp 144–146°. Three recrystallizations from acetone–hexane gave the analytical sample, mp 153–154°.

Anal. Calcd for $C_{20}H_{23}N_3O_9S$: C, 49.89; H, 4.82; N, 8.73; S, 6.66. Found: C, 50.12; H, 4.69; N, 8.64; S, 6.41.

Imidazo[1,5-*a*]pyrazin-3-yl 1-(β-D-Glucopyranosyl)sulfide (9). To a solution of 0.48 g (1 mmol) of **8** in 30 ml of methanol was added 2 mg of sodium and the mixture was stirred at room temperature for 12 hr. Ammonium chloride (2 mg) was added, the solvent was evaporated, and the residue was triturated with 2 ml of cold (0°) water, filtered, and dried to give 0.32 g (100%) of **9**, mp 112–116°.

Anal. Calcd for $C_{12}H_{15}N_3O_5S$: C, 46.00; H, 4.83; N, 13.41; S, 10.23. Found: C, 46.29; H, 4.91; N, 13.21; S, 10.00.

3-Methylsulfonylimidazo[1,5-*a*]pyrazine (10). A solution of *m*-chloroperbenzoic acid (15.0 g, 75 mmol) in 150 ml of chloroform was added to a stirred solution of **3** (4.13 g, 25 mmol) in 100 ml of chloroform. The mixture was stirred at room temperature for 1.5 hr, washed with two 50-ml portions of saturated aqueous sodium bicarbonate, dried, and evaporated. The residue was crystallized from acetone–hexane to give 2.5 g (50%) of **10**: mp 138–139°; ^{1}H NMR (Me_2SO-d_6) δ 3.63 (CH_3, 3 H, s), 8.30 (H-1, 1 H, d, $J_{1,5}$ = 1 Hz), 8.10 (H-6, 1 H, d, $J_{5,6}$ = 5 Hz), 8.90 (H-5, 1 H, m), 9.53 (H-8, 1 H, d, $J_{5,8}$ = 2 Hz); MS *m/e* (rel intensity) M^+ 197 (100), 118 ($M^+ - CH_3SO_2$, 100, confirmed by m* 70.6).

Anal. Calcd for $C_7H_7N_3O_2S$: C, 42.63; H, 3.58; N, 21.31. Found: C, 42.68; H, 3.63; N, 21.32.

3-Ethylsulfonylimidazo[1,5-*a*]pyrazine (11). Using essentially the same procedure as above and purifying the residue by dry column chromatography (Woelm alumina, 18 × 1 in. column) with 2% methanol in chloroform as eluent, there was obtained 4.7 g (74%) of **11**, mp 63–64° after recrystallization from acetone–hexane.

Anal. Calcd for $C_8H_9N_3O_2S$: C, 45.50; H, 4.26; N, 19.90; S, 15.17. Found: C, 45.50; H, 4.40; N, 19.79; S, 15.20.

3-Methysulfinylimidazo[1,5-*a*]pyrazine (12). A solution of *m*-chloroperbenzoic acid (4.67 g, 23 mmol) in 150 ml of chloroform was added dropwise to a stirred, chilled (0°) solution of **3** (3.3 g, 20 mmol) in 50 ml of chloroform over a period of 5 min. The reaction mixture was allowed to stir for 1 hr in the ice bath, washed with three 20-ml portions of saturated aqueous sodium bicarbonate solution, dried, and evaporated. The residue, after crystallization from acetone–hexane, furnished 2.1 g (59%) of **12**: mp 76–77°; ^{1}H NMR δ 3.31 (CH_3, 3 H, s), 8.03 (H-1, 1 H, d, $J_{1,5}$ = 1 Hz), 7.87 (H-6, 1 H, d, $J_{5,6}$ = 5 Hz), 8.78 (H-5, 1 H, m), 9.27 (H-8, 1 H, d, $J_{5,8}$ = 2 Hz); MS *m/e* (rel intensity) M^+ 181 (35), 166 ($M^+ - CH_3$, 100), 118 ($M^+ - CH_3SO$, 35).

Anal. Calcd for $C_7H_7N_3OS$: C, 46.40: H, 3.89; N, 23.19. Found: C, 46.30; H, 3.69; N, 23.24.

3-Ethylsulfinylimidazo[1,5-*a*]pyrazine (13). Using the same procedure and proportions of reagents as above, there was obtained a 97% yield of **13**, mp 81–82° after recrystallization from chloroform–hexane.

Anal. Calcd for $C_8H_9N_3OS$: C, 49.23; H, 4.62; N, 21.54; S, 16.41. Found: C, 49.00; H, 4.64; N, 21.41; S, 16.11.

3-Hydroxy-3-methylthio-2-*p*-nitrobenzoyl-2,3-dihydroimidazo[1,5-*a*]pyrazine (14). Potassium cyanide (0.39 g, 6 mmol) was added to a solution of **3** (0.33 g, 2 mmol) in 25 ml of dichloromethane which contained 0.5 ml of water. A solution of *p*-nitrobenzoyl chloride (0.74 g, 4 mmol) in 10 ml of dichloromethane was added dropwise to the stirred reaction mixture over a period of 10 min and stirring was continued for 2 hr. The mixture was filtered, and the precipitate was washed with water and crystallized from dimethyl sulfoxide–water to give 0.28 g (41%) of **14**: mp 163°; ^{1}H NMR (Me_2SO-d_6) δ 2.7 (CH_3, 3 H, s), 7.8 (H-6, 1 H, d, $J_{5,6}$ = 5 Hz), 8.16 (H-1, 1 H, s), 8.0–8.5 (5 H, m), 9.25 (H-8, 1 H, d, $J_{5,8}$ = 2 Hz)

Anal. Calcd for $C_{14}H_{12}N_4O_4S$: C, 50.60; H, 3.64; N, 16.86; S, 9.65. Found: C, 50.33; H, 3.66; N, 16.68; S, 9.86.

3-Methylthio-1-nitroimidazo[1,5-*a*]pyrazine (15). To a stirred solution of nitrosonium fluoroborate (2.9 g, 25 mmol) in 20 ml of anhydrous acetonitrile, under nitrogen, was added a solution of 1.4 g (8.5 mmol) of **3** in 20 ml of dry acetonitrile. The mixture was stirred at room temperature for 3 hr, the excess nitrosonium salt was decomposed with 1 ml of methanol, and the solvent was evaporated. The residue was chromatographed over alumina (Woelm dry column 12 × 1 in.) using acetonitrile as eluent. The first 100 ml eluted yielded 0.45 g (32% based on recovered **3**) of **15** and 0.35 g of **3**. Recrystallization from acetonitrile–ether gave yellow needles: mp 180–181°; ^{1}H NMR (Me_2SO-d_6) δ 2.76 (CH_3, 3 H, s), 8.23 (H-6, 1 H, d, $J_{5,6}$ = 5 Hz), 8.6 (H-5, 1 H, q, $J_{5,6}$ = 5, $J_{5,8}$ = 2 Hz), 9.76 (H-8, 1 H, d, $J_{5,8}$ = 2 Hz).

Anal. Calcd for $C_7H_6N_4O_2S$: C, 39.99; H, 2.88; N, 26.65; S, 15.35. Found: C, 40.24; H, 2.92; N, 26.34; S, 15.35.

2-Methylthio-4(5)-formylimidazole (16). To a stirred, chilled (0°) solution of **3** (2.0 g, 12 mmol) in concentrated hydrochloric acid (5 ml) and water (10 ml) was added a solution of sodium nitrite (2.0 g, 29 mmol) in 5 ml of water over a period of 10 min. The mixture was stirred in the cold for 15 min and at room temperature for 1 hr. It was evaporated to a volume of about 5 ml, brought to pH 10 with dilute aqueous sodium hydroxide, and extracted with three 50-ml portions of chloroform. The combined extracts were dried and evaporated and the residue sublimed (120°, 0.15 mm) to furnish 0.12 g (7%) of **16** as a colorless solid: mp 125°; ^{1}H NMR (Me_2SO-d_6) δ 2.72 (CH_3, 3 H, s), 8.13 (H-5, 1 H, s), 9.83 (HC=O, 1 H, s), 13.3 (NH, 1 H, broad, D_2O exchangeable).

Anal. Calcd for $C_5H_6N_2OS$: C, 42.24; H, 4.25; N, 19.70; S, 22.55. Found: C, 42.08; H, 4.46; N, 19.55; S, 22.50.

7-Carboethoxy-8-ethoxy-3-methylthio-7,8-dihydroimidazo-[1,5-*a*]pyrazine (17). To a solution of **3** (0.495 g, 3.0 mmol) in

methylene chloride (5 ml) was added a solution of ethyl chloroformate (0.325 g, 3.0 mmol) in methylene chloride (10 ml). After 10 min the reaction mixture was quenched with ethanol (2 ml). The product (0.4 g, 48%) was obtained as an oil by dry column chromatography of the residue, obtained after evaporation, on alumina eluting with chloroform: ^{1}H NMR δ 1.15 (CH_3, 3 H, t), 1.35 (CH_3, 3 H, t), 2.56 (CH_3, 3 H, s), 3.55 (CH_2, 2 H, q), 4.33 (CH_2, 2 H, q), 6.5–6.8 (H-5, H-6, and H-8, m), 7.13 (H-1, 1 H, s); significantly, there was no characteristically low-field absorption for an aromatic-type H-8.

Anal. Calcd for $C_{12}H_{17}N_3O_3S$: C, 50.87; H, 6.05; N, 14.83; S, 11.31. Found: C, 50.60; H, 6.07; N, 14.71; S, 11.57.

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Registry No.—**1**, 20010-99-5; **2**, 56488-16-5; **3**, 56488-17-6; **4**, 56488-18-7; **5**, 56488-19-8; **6**, 56488-20-1; **7**, 56488-21-2; **8**, 56488-22-3; **9**, 56488-23-4; **10**, 56488-24-5; **11**, 56488-25-6; **12**, 56488-26-7; **13**, 56488-27-8; **14**, 56488-28-9; **15**, 56488-29-0; **16**, 56488-30-3; **17**, 56488-31-4; carbon disulfide, 75-15-0; methyl iodide, 74-88-4; methyl bromoacetate 96-32-2; 2-bromoethanol, 540-51-2; bromoacetaldehyde dimethyl acetal, 7252-83-7; *p*-nitrobenzoyl chloride, 122-04-3.

References and Notes

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Solvolysis of Isothiazole Analogs of Cumyl Chloride. Determination of the Brown Electrophilic Substituent Constants for Isothiazole Derivatives

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Rates of solvolysis in 80% ethanol have been determined for 2-(3-isothiazolyl)-2-chloropropane, 2-(4-isothiazolyl)-2-chloropropane, and 2-(5-isothiazolyl)-2-chloropropane. From these rates and the rates of solvolysis of cumyl chlorides bearing electron-withdrawing substituents σ^+ values appropriate for the replacement of the benzene ring by an isothiazolyl moiety have been determined.

The chemistry of isothiazole, which was first prepared in 1956,[2] has recently been reviewed.[3] Electrophilic substitution occurs preferentially in the 4 position, including nitration and halogenation, but relatively few quantitative indices of the reactivity of the system are available. Nitration of phenylisothiazoles leads to substitution in the phenyl moiety.[4,5] The latter authors observed that the phenyl ring is strongly deactivated by the isothiazole ring, which is, of course, protonated by the concentrated acid of the nitration mixture.

In competitive nitrations, Dou and Metzger et al.[6] observed the following relative reactivities for the 4 position of various isothiazoles: 3-methylisothiazole, 1.0; 5-methylisothiazole, 1.7; isothiazole, 0.43. The isothiazoles were substantially less reactive than 2,4-dimethylthiazole.

The most quantitative studies are by Katritzky and his coworkers and include examination of nitration and hydrogen exchange.[7] The acid-catalyzed hydrogen–deuterium exchange of 3,4-dimethylisothiazole showed a change in the slope of the rate–acidity profile at $D_0 = -6.0$.[7] The authors concluded that the reaction at low acidities occurs on the free base and at high acidities on the conjugate acid; they estimated that the free base was 10^8 times more reactive than the conjugate acid. Hydrogen–deuterium exchange in D_2SO_4 of isothiazole and isoxazole and their 3- and 5-methyl derivatives was also studied.[8] Exchange was observed only in the 4 position. Heating with D_2SO_4 of various concentrations did not lead to any observable exchange in the 3 and 5 positions for any conditions under which the compounds were stable. Standard k_0 values for exchange at pH 0 at 100° were calculated as before,[9] with the assumption that pK_a values for isothiazoles follow the same relationship for temperature variation as pyridine. For isothiazole the calculated log k_0 value was −7.5. The authors calculated a log partial rate factor of 3.6 which, with their ρ value of −7.5, corresponds to a replacement σ_{Ar}^+ value[11] for the 4-isothiazolyl group of −0.48. In contrast to their earlier estimation,[7] the order of reactivity for the 4 positions of the 1,2-azoles is found to be pyrazole ≫ isoxazole > isothiazole (> phenyl).

Obviously, the question of the relative electrophilic reactivity of the isothiazoles is far from closed. The available quantitative data show that isothiazole's 4 position is more reactive than a phenyl position and less reactive than the 4-pyrazolyl position[8] or the 5-thiazolyl position.[6] Direct indications of the relative electrophilic reactivity of the 3 and 4 positions are absent, although it is clear that they are both significantly less reactive than the 4 position. Extrapolation from the substitution patterns of 4-substituted isothiazoles would suggest a greater reactivity for the 5 posi-