(*E*)-**3b**, 117918-88-4; (*E*)-**3c**, 117918-91-9; (*E*)-**3d**, 117918-94-2; (*E*)-**3e**, 117918-97-5; *trans*-**4a**, 117918-87-3; *cis*-**4a**, 118013-65-3; *trans*-**4b**, 117918-89-5; *trans*-**4c**, 117918-92-0; *trans*-**4d**, 117918-95-3; *trans*-**4e**, 117918-98-6; **5a**, 117919-00-3; **5b**, 117918-90-8; **5c**, 117918-93-1; **5d**, 117918-96-4; **5e**, 117918-99-7; **5f**, 117919-01-4; **5g**, 117919-02-5; acetophenone hydrazone, 13466-30-3; 2,2-diphenylpropionaldehyde, 22875-82-7; diphenylpropionitrile, 5558-67-8; methyl cyanoacetate, 105-34-0; acetophenonazine, 729-43-1; *p*-chloroacetophenone hydrazone, 5326-15-8; *p*-chloroacetophenonazine, 5326-15-8.

Substituent-Directing Effects in the Homolytic Acylation of Pyrazine Derivatives

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The homolytic acylation of various monosubstituted pyrazines was studied for a wide spectrum of substituents. Methoxy and chloro substituents were found to direct ortho substitution, thus giving the corresponding 2,3-disubstituted pyrazines. Acetyl, carbethoxy, and carboxamide groups were found to direct para substitution, thus leading to the corresponding 2,5-disubstituted pyrazines. These selectivities result from the combination of the inductive and resonance effects of the substituents. The synthetic potential of the acylation reaction is demonstrated in the preparation of some novel pyrazine flavorants.

In a previous study[1] we described a simple method for the homolytic acylation of pyrazines. Thus, a mixture of a pyrazine and an aldehyde in water containing sulfuric acid, *tert*-butyl hydroperoxide, and ferrous sulfate reacted to form the corresponding monoacylpyrazine derivative as the major product.[1] Under these conditions the aldehyde is converted to an acyl radical, which behaves as a nucleophile and undergoes addition to the pyrazine ring followed by rearomatization.

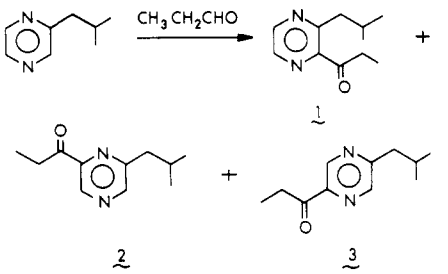
Most of our previous work was carried out on either pyrazine itself or various alkylpyrazines.[1] For example, acylation of isobutylpyrazine with propionaldehyde gave a mixture of all three possible isomers, **1**, **2**, and **3**, in a 3:4:3 ratio (Scheme I).

A study by Caronna et al.[2] describes a similar procedure, which leads to diacylation products. Thus, treatment of pyrazine with the above reagents led to the formation of 2,5-diacylpyrazine (Scheme II). It was suggested that the first acyl group directs the second group into the 5-position.[2]

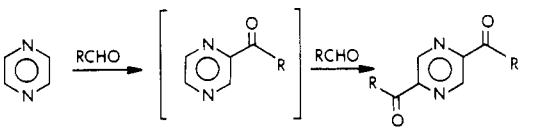
The above observations indicate significant differences in the directing effects of an acyl and an alkyl group in the homolytic acylation process. The aim of the present investigation was to establish the generality of this phenomenon. In particular we were interested to see whether other functional groups show specific directing patterns.

Different substituted pyrazines were selected to cover a wide spectrum of electronic effects. Some substituents, in particular chlorine, were selected because their reaction products can be used as intermediates in the preparation of a variety of new pyrazine derivatives (see below). Aldehydes of different sizes were chosen in order to determine the importance of steric effects in the acylation process. Reactions were carried out as described in our earlier study,[1] and the results are summarized in Table I. Each reaction mixture was analyzed by GC and showed two major peaks, which were identified as the corresponding acyl product and unreacted starting material.

Scheme I



Scheme II



Small amounts of the diacyl product as well as methylated and alkylated products were observed. The latter arise from decomposition of *tert*-butyl hydroperoxide to acetone and a methyl radical and by decarbonylation of the acyl radical to the corresponding alkyl radical, respectively.

Methoxy and chloro substituents were found to direct predominantly ortho substitution, thus giving the 2,3-disubstituted pyrazines, **4–6** and **7–8**, respectively.[3] Acetyl, carbethoxy, and carboxamide groups were found to direct predominantly para substitution, thus giving the 2,5-disubstituted pyrazines, **9**, **10**, and **11**, respectively.[3] Further examination of GC chromatograms of the above reaction mixtures indicated the presence of other minor components. The possibility that these minor components are other structural isomers was investigated in detail in the case of the reaction of chloropyrazine with propionaldehyde. The following reaction mixture composition was obtained (GC yields): unreacted chloropyrazine (26%); **7** (42%); 1-(2-chloro-5-pyrazinyl)-1-propanone (6%), and trace amounts of chloromethylpyrazine, chloroethyl-

(1) Houminer, Y.; Southwick, E. W.; Williams, D. L. *J. Heterocycl. Chem.* **1986**, *23*, 497.

(2) Caronna, T.; Fronza, G.; Minisci, F.; Porta, O. *J. Chem. Soc., Perkin Trans. 2* **1972**, 2035.

(3) In each of the reactions the composition of the crude product was carefully analyzed by GC. The limit of detection was about 2%. Therefore, it is possible that other isomers were formed in amounts smaller than 2%.

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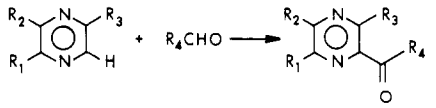
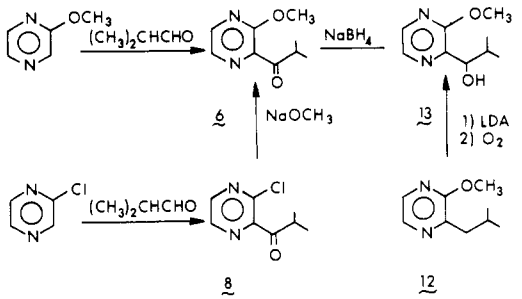
Table I. Homolytic Acylation of Substituted Pyrazines by Aldehydes



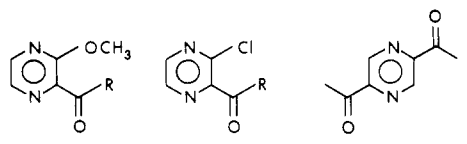
acylpyrazine	R_1	R_2	R_3	R_4	yield, % (isolated)
1–3[a]	H	H	$CH_2CH(CH_3)_2$	CH_2CH_3	29
4	H	H	OCH_3	CH_3	50
5	H	H	OCH_3	CH_2CH_3	47
6	H	H	OCH_3	$CH(CH_3)_2$	46
7	H	H	Cl	CH_2CH_3	15
8	H	H	Cl	$CH(CH_3)_2$	20
9	H	$COCH_3$	H	CH_3	35
10	H	COOEt	H	CH_2CH_3	22
11	H	$CONH_2$	H	CH_2CH_3	25

[a] A mixture of 2,3, 2,6, and 2,5 isomers in a 3:4:3 ratio.

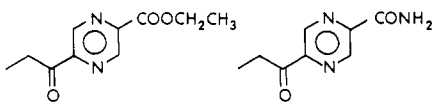
Scheme III



pyrazine, and chlorodipropionylpyrazine. These results indicate that indeed the 2,3-isomer is the predominant one.



4 R = CH_3
5 R = CH_2CH_3
6 R = $CH(CH_3)_2$
7 R = CH_2CH_3
8 R = $CH(CH_3)_2$
9



10 11

The substitution patterns in all products (4–11) were easily determined by measuring the coupling constants of the pyrazine ring protons in the ^1H NMR spectra of these compounds.[4] All 2,3-disubstituted pyrazines have $J \geq 2.5$ Hz, whereas 2,6- and 2,5-disubstituted pyrazines have $J \leq 0.1$ Hz and $J \sim 1.5$ Hz, respectively. Nevertheless, in one case we have also established the substitution pattern by carrying out a number of chemical transformations. Scheme III summarizes these reactions: Chloropyrazine was acylated with isobutyraldehyde to give the chloro ketone 8. The latter was treated with sodium methoxide to give the methoxy ketone 6, which was found to be identical with the acylation product obtained from methoxypyrazine and isobutyraldehyde. Reaction of 6 with $NaBH_4$ afforded the alcohol 13. The same alcohol was obtained from an authentic sample of 2-isobutyl-3-methoxypyrazine (12) treated with LDA followed by oxygen. These transformations established the 2,3-disubstitution pattern in both 6 and 8.

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Table II. Substitution Patterns in the Acylation of Pyrazines

electronic effects of the substituent		main substitution direction
inductive effect	resonance effect	
+I (electron donor)	+M (electron donor)	ortho, meta, and para (see ref 1)
–I	+M	ortho (2,3)
–I	–M	para (2,5)

The results obtained within the series 4–6 and 7–8 (Table I) suggest that steric factors have very little effect on the reaction pathway. This is reflected by the yields, which change only slightly with the bulk of the aldehyde. In addition, we observed the same reaction pathways in all cases without detecting any other disubstituted pyrazines.[3]

The mechanism of the homolytic acylation of heteroaromatic bases has been discussed in detail by Minisci and co-workers.[2,5,6] The nucleophilic character of the acyl radical and its addition to the protonated heteroaromatic bases have been demonstrated in particular for a series of pyridines and quinolines.[2,6,7] It has also been shown that electron-withdrawing groups activate the heteroaromatic ring in these substrates.[2] For example, when 2- and 4-substituted quinolines were acylated with acetaldehyde, the reaction rate increased when the inductive effect of the substituent was larger.[2] On the basis of these results it has been suggested that the course of the homolytic acylation is essentially determined by polar effects in the substrate.[2]

In the case of pyrazines, an attempt to find a correlation between the observed substitution pattern and the substituent's electronic effects is less straightforward. Under strongly acidic conditions the reaction may proceed via protonated species, and the site of protonation, which by itself is affected by the nature of the substituent, can also affect strongly the substitution direction. Nevertheless, we have recently established that acylation of pyrazines can proceed in the absence of any added strong acid.[8] It should, however, be noted that even in the absence of acid the pH of the reaction mixture remains acidic because of partial oxidation of the aldehyde to the corresponding acid.[8] While we cannot totally rule out the involvement of protonated species in the reaction, the above observation and the fact that the pyrazine ring is much more activated

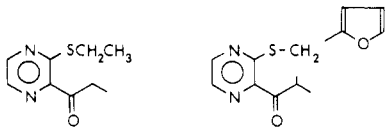
(5) Caronna, T.; Fronza, G.; Minisci, F.; Porta, O. *J. Chem. Soc., Perkin Trans. 2* **1972**, 1477.
(6) Arnoldi, A.; Bellatti, M.; Caronna, T.; Citterio, A.; Minisci, F.; Porta, O.; Sesana, G. *Gazz. Chim. Ital.* **1977**, *107*, 491.
(7) Gardini, G. P.; Minisci, F. *J. Chem. Soc. C* **1970**, 929.
(8) Houminer, Y.; Southwick, E. W.; Williams, D. L., unpublished results.

to nucleophilic attack than the pyridine ring, strongly suggest that the substitution pattern is mainly determined by the polar effect of the substituent itself.

The results obtained in the present study allow us to make a generalization regarding the relationship between the substitution pattern and the electronic effects of the substituents (Table II).

The above results indicate very high direction selectivity in both the –I, +M group and the –I, –M group. It is very interesting to note that a similar selectivity was observed in a study related to substituent effects on the site of addition of ammonia to quaternized pyrazines.[9] In addition, regioselectivities were observed in the radical methylation of substituted pyridazines[10] and in the radical ethoxycarbonylation of substituted pyridines.[11]

Acylated chloropyrazines such as **7** and **8** are useful intermediates in the preparation of new pyrazine flavorants. For example, treatment of both **7** and **8** with desired thiols resulted in the displacement of the chlorine and the formation of the corresponding thioethers **14** and **15**, respectively. Other nucleophiles such as different alkoxide anions can also be used to prepare new pyrazine ethers.



14 **15**

Experimental Section

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. NMR spectra were recorded with a Brucker WP80 spectrometer, and the chemical shifts are given in δ units downfield from internal Me_4Si. Mass spectra were recorded with a MAT 112S spectrometer. IR spectra were recorded with a Perkin-Elmer Model 621 spectrophotometer. Both analytical and preparative TLC were carried out on silica gel GF plates using methylene chloride as the eluent. GC analyses and preparative separations were done on a $^1/_4$ in. × 15 ft Carbowax 20M-TPA column. Elemental analyses were performed by Galbraith Laboratories Inc. Knoxville, TN.

General Procedure for Monoacylation of Pyrazines: Preparation of 1-(2-Methoxy-3-pyrazinyl)-1-ethanone (4). To a stirred mixture of 2-methoxypyrazine (1.5 g, 13.6 mmol) and acetaldehyde (3.6 g, 82 mmol) in 3.4 M sulfuric acid (6.8 mL) at 3–5 °C were added concurrently 70% *tert*-butyl hydroperoxide (7.4 g, 57 mmol) and a solution of $FeSO_4 \cdot 7H_2O$ (22.8 g, 82 mmol) in water (54 mL) over a 15-min period. The resulting mixture was stirred for 1.5 h, during which time the temperature was raised to 15 °C. Solid Na_2SO_3 was added until a test with starch–iodide paper was negative. The mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with water, saturated $NaHCO_3$ solution, and again with water. The solution was dried ($MgSO_4$) and evaporated under reduced pressure to give 1.05 g (50%) of **4** as an oil. A sample, purified first by GC, was crystallized from hexane as needles: mp 46–48 °C; IR (CCl_4) 1700, 1460, 1438, 1418, 1380, 1355, 1310, 1260, 1220, 1160, 1095, 1060, 1005, 950 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.68 (3 H, s, CH_3), 4.08 (3 H, s, CH_3), 8.26 (2 H, AB q, J = 2.6 Hz, H-5 and H-6 pyrazine); MS, m/e (relative intensity) 152 (M^+, 62), 137 (19), 124 (15), 110 (25), 109 (48), 81 (23), 80 (34), 79 (45), 53 (10), 43 (100), 42 (15), 40 (25), 39 (10). Anal. Calcd for $C_7H_8N_2O_2$: C, 55.25; H, 5.30; N, 18.41. Found: C, 55.48; H, 5.34; N, 18.44.

1-(2-Methoxy-3-pyrazinyl)-1-propanone (5). The reaction of 2-methoxypyrazine (1.5 g, 13.6 mmol) and propionaldehyde (4.75 g, 82 mmol) was carried out as described for the case of **4**. Workup gave 1.07 g (47%) of almost pure **5** as an oil. An analytically pure sample, as a liquid, was obtained by GC: ^1H NMR ($CDCl_3$) δ 1.21 (3 H, t, J = 7 Hz, CH_3), 3.13 (2 H, q, J = 7 Hz, CH_2), 4.08 (3 H, s, OCH_3), 8.24 (2 H, AB q, J = 2.6 Hz, H-5 and H-6 pyrazine); MS, m/e (relative intensity) 166 (M^+, 34), 138 (81), 137 (52), 123 (10), 111 (12), 110 (19), 109 (83), 81 (23), 80 (22), 79 (100), 69 (14), 67 (14), 58 (12), 57 (72), 56 (21), 55 (21), 53 (11), 44 (21), 43 (36), 42 (25), 41 (19), 40 (75), 39 (18). Anal. Calcd for $C_8H_{10}N_2O_2$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.68; H, 6.09; N, 16.76.

1-(3-Methoxy-2-pyrazinyl)-2-methyl-1-propanone (6). The reaction of 2-methoxypyrazine (5.0 g, 45 mmol) and isobutyraldehyde (15.8 g, 219 mmol) was carried out as described for the case of **4**. Distillation gave 3.8 g (47%) of pure **6** as a liquid: bp 65–6 °C (0.2 mmHg); IR (neat) 1702, 1560, 1530, 1465, 1445, 1390, 1305, 1245, 1160, 1085, 1010, 990, 860 cm^{-1}; ^1H NMR (CD_2Cl_2) δ 1.13 (6 H, d, J = 7 Hz, 2 CH_3), 3.75 (1 H, heptet, J = 7 Hz, CH), 4.01 (3 H, s, OCH_3), 8.20 (2 H, AB q, J = 2.6 Hz, H-5 and H-6 pyrazine); MS, m/e (relative intensity) 180 (M^+, 62), 152 (21), 137 (84), 109 (85), 79 (100), 43 (63). An analytically pure sample was obtained by GC. Anal. Calcd for $C_9H_{12}N_2O_2$: C, 59.99; H, 6.71; N, 15.54. Found: C, 59.93; H, 6.88; N, 15.78.

1-(3-Chloro-2-pyrazinyl)-1-propanone (7). The reaction of 2-chloropyrazine (1.14 g, 10 mmol) and propionaldehyde (3.48 g, 60 mmol) was carried out as described in the case of **4**. After the usual workup the crude product (1.5 g) in 15% acetone/hexane was passed through a silica gel column and then was purified by preparative TLC to give 0.26 g (15%) of pure **7** as a liquid: IR (neat) 1705, 1380, 1115, 1080, 955 cm^{-1}; ^1H NMR (CD_2Cl_2) δ 1.22 (3 H, t, J = 7 Hz, CH_3), 3.12 (2 H, q, J = 7 Hz, CH_2), 8.52 (2 H, AB q, J = 2.5 Hz, H-5 and H-6 pyrazine). Anal. Calcd for $C_7H_7ClN_2O$: C, 49.28; H, 4.14; Cl, 20.78; N, 16.42. Found: C, 49.30; H, 4.27; Cl 21.00; N, 16.36.

Also separated were small amounts of 1-(2-chloro-5-pyrazinyl)-1-propanone: ^1H NMR ($CDCl_3$) δ 1.23 (3 H, t, J = 7 Hz, CH_3), 3.19 (2 H, q, J = 7 Hz, CH_2), 8.63 (1 H, d, J = 1.4 Hz, pyrazine), 9.00 (1 H, d, J = 1.4 Hz, pyrazine).

1-(3-Chloro-2-pyrazinyl)-2-methyl-1-propanone (8). The reaction of 2-chloropyrazine (5.0 g, 43.7 mmol) and isobuyraldehyde (15.8 g, 218 mmol) was carried out as described in the case of **4**. The crude mixture was distilled (bulb-to-bulb at 70–145 °C/0.1–0.2 mmHg). The product was purified by column chromatography (silica gel 60, eluted with 3% acetone/hexane) to give 1.6 g (20%) of pure **8** as a liquid: IR (neat) 1702, 1540, 1460, 1370, 1245, 1200, 1095, 980, 870, 790 cm^{-1}; ^1H NMR (CD_2Cl_2) δ 1.19 (6 H, d, J = 7 Hz, 2 CH_3), 3.68 (1 H, heptet, J = 7 Hz, CH), 8.53 (2 H, AB q, J = 2.5 Hz, H-5 and H-6 pyrazine); MS, m/e (relative intensity) 184 (M^+, 23), 149 (12), 141 (20), 114 (19), 113 (23), 71 (30), 52 (14), 43 (100), 41 (23). Anal. Calcd for $C_8H_9ClN_2O$: C, 52.04; H, 4.91; Cl, 19.20; N, 15.17. Found: C, 51.92; H, 4.94; Cl, 19.30; N, 15.06.

(2,5-Pyrazinediyl)-1,1′-bis(1-ethanone) (9). The reaction of 2-acetylpyrazine (3.05 g, 25 mmol) and freshly distilled acetaldehyde (6.6 g, 150 mmol) was carried out as described in the case of **4**. The crude product (3.7 g) was recrystallized twice from 3% ethyl acetate/hexane to give 1.44 g (35%) of pure **9** as a yellow solid: mp 158–159 °C (lit.[2] mp 158 °C); IR (CCl_4) 1700, 1415, 1370, 1110, 955 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.76 (6 H, s, 2 CH_3), 9.26 (2 H, s, pyrazine); MS, m/e (relative intensity) 164 (M^+, 10), 136 (14), 122 (30), 121 (15), 80 (13), 79 (10), 53 (25), 52 (40), 44 (100), 43 (100). The above material was found to be identical with a sample of **9** obtained by a literature procedure.

1-(2-Carbethoxy-5-pyrazinyl)-1-propanone (10). The reaction of 2-carbethoxypyrazine (1.52 g, 10 mmol) with propionaldehyde (3.5 g, 60 mmol) was carried out as described in the case of **4**. Workup afforded 1.5 g of crude product, which was purified by column chromatography (on silica gel using 10% ethyl acetate/hexane) to give 0.46 g (22%) of pure **10** as a solid. Recrystallization from hexane gave flakes: mp 81–82 °C; IR (CCl_4) 2965, 2925, 2895, 1755, 1720, 1702, 1470, 1380, 1342, 1300, 1280, 1145, 1030, 970 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.19 (3 H, t, J = 7.2 Hz, CH_3), 1.42 (3 H, t, J = 7.2 Hz, CH_3), 3.19 (2 H, q, J = 7.2 Hz, CH_2), 4.49 (2 H, q, J = 7.2 Hz, CH_2), 9.25 (1 H, d, J = 1.5 Hz, pyrazine), 9.27 (1 H, d, J = 1.5 Hz, pyrazine); MS, m/e (relative intensity) 208 (M^+, 43), 207 (17), 181 (11), 180 (92), 179 (20), 163 (15), 152 (82), 151 (30), 136 (70), 135 (17), 124 (17), 123 (48), 108

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(11) Heinisch, G.; Lötsch, G. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 692.

(50), 106 (15), 95 (13), 80 (10), 78 (11), 67 (10), 57 (100), 52 (13). Anal. Calcd for $C_{10}H_{12}N_2O_3$: C, 57.68; H, 5.81; N, 13.46. Found: C, 57.96; H, 5.88; N, 13.50.

1-(2-Carbamoyl-5-pyrazinyl)-1-propanone (11). The reaction of 2-carbamoylpyrazine (1.23 g, 10 mmol) and propionaldehyde (3.5 g, 60 mmol) was carried out as described for the case of **4**. Workup gave 1.5 g of the crude product, which was recrystallized from hexane to yield 0.45 g (25%) of pure **11**: mp 217–218 °C dec; ^{1}H NMR ($CDCl_3$) δ 1.26 (3 H, t, J = 7.2 Hz, CH_3), 3.27 (2 H, q, J = 7.2 Hz, CH_3), 5.83 (1 H, br s, NH), 7.69 (1 H, br s, NH), 9.18 (1 H, d, J = 1.5 Hz, pyrazine), 9.43 (1 H, d, J = 1.5 Hz, pyrazine); MS, m/e (relative intensity) 179 (M^+, 16), 178 (7), 152 (9), 151 (79), 150 (14), 123 (44), 122 (21), 94 (12), 67 (17), 57 (100), 53 (20), 52 (27), 44 (30), 40 (11). Anal. Calcd for $C_8H_9N_3O_2$: C, 53.62; H, 5.06; N, 23.45. Found: C, 53.89; H, 4.95; N, 23.60.

Reaction of 8 with Sodium Methoxide. To a stirring solution of **8** (513 mg, 2.78 mmol) in methanol (10 mL) was added, at about 5 °C, under N_2, 0.35 M sodium methoxide solution (8.8 mL, 3.06 mmol). The bright yellow solution was stirred at room temperature for 1 h and then at reflux for 1.5 h. Water was added, and the product was extracted with Et_2O. The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure to give 0.50 g (99%) of pure **6**. The material was found to be identical with a sample of **6** obtained by direct acylation of 2-methoxypyrazine.

Sodium Borohydride Reduction of 6. A solution of the ketone **6** (1.1 g, 6.1 mmol) in absolute EtOH (50 mL) was treated with excess of sodium borohydride, and the mixture was stirred at room temperature for 2 h. Water was added followed by a few drops of acetic acid to destroy remaining reducing agent. The product was extracted with CH_2Cl_2, and the organic layer was dried ($MgSO_4$) and evaporated under reduced pressure to give 1.8 g (99%) of pure 1-(3-methoxy-2-pyrazinyl)-2-methyl-1-propanol (**13**) as a liquid. An analytically pure sample was obtained by GC: IR (neat) 3460, 1590, 1550, 1470, 1390, 1315, 1185, 1115, 1105, 1030 cm^{-1}; ^{1}H NMR (CD_2Cl_2) δ 0.95 (3 H, d, J = 8 Hz, CH_3), 1.04 (3 H, d, J = 8 Hz, CH_3), 2.18 (1 H, m, CH), 3.81 (1 H, d, J = 7.5 Hz, OH), 3.98 (3 H, s, OCH_3), 4.70 (1 H, dd, J = 8 Hz, J = 5 Hz, CH), 8.03 (2 H, AB q, J = 2.8 Hz, pyrazine); MS, m/e (relative intensity) 182 (M^+, 2), 153 (34), 140 (48), 139 (100), 125 (16), 124 (44), 111 (25), 109 (20), 83 (26), 81 (20), 80 (19), 79 (26), 68 (20), 56 (20), 53 (21), 52 (33), 43 (31), 42 (50), 41 (44). Anal. Calcd for $C_9H_{14}N_2O_2$: C, 59.32; H, 7.74; N, 15.37. Found: C, 59.49; H, 7.63; N, 15.58.

1-(3-Methoxy-2-pyrazinyl)-2-methyl-1-propanol (13) from Oxidation of 2-Isobutyl-3-methoxypyrazine (12). To a solution of LDA (12 mmol) in Et_2O (100 mL) and hexane (8 mL) under N_2, at −78 °C, was added with stirring 1.66 g (10 mmol) of **12**. The mixture was warmed to 0 °C and stirred for 1 h and then warmed to room temperature and stirred an additional 1 h. Oxygen was passed through the stirring solution for 5 min during which time the color changed from dark brown to bright yellow. Water was added, and the organic layer was separated, washed with a saturated solution of Na_2SO_3 and then with water, dried ($MgSO_4$), and evaporated under reduced pressure to give a liquid (1.91 g). Purification by column chromatography gave 1.05 g (58%) of pure **13**. The material was found to be identical with that obtained by the sodium borohydride reduction of **6**.

1-(3-(Ethylthio)-2-pyrazinyl)-1-propanone (14). A solution of sodium ethoxide (100 mg, 1.47 mmol) and ethanethiol (110 mg, 1.77 mmol) in absolute EtOH (7 mL) was stirred under N_2 at room temperature for 10 min. A solution of **7** (250 mg, 1.47 mmol) in absolute EtOH (5 mL) was added, and the mixture was stirred for 4 h at room temperature. Water was added, and the product was extracted with CH_2Cl_2. The organic layer was washed with water, dried ($MgSO_4$), and evaporated under reduced pressure to give 0.25 g (87%) of **14** as a solid: mp 45–48 °C; ^{1}H NMR ($CDCl_3$) δ 1.25 (3 H, t, J = 7 Hz, CH_3), 1.40 (3 H, t, J = 7 Hz, CH_3), 3.18 (2 H, q, J = 7 Hz, CH_2), 3.21 (2 H, q, J = 7 Hz, CH_2), 8.29 (1 H, d, J = 2.5 Hz, pyrazine), 8.52 (1 H, d, J = 2.5 Hz, pyrazine); MS, m/e (relative intensity) 196 (M^+, 100), 167 (73), 163 (74), 139 (54), 112 (31), 84 (42), 57 (80), 40 (26). Anal. Calcd for $C_9H_{12}N_2OS$: C, 55.08; H, 6.18; N, 14.09; S, 16.47. Found: C, 54.91; H, 6.16; N, 14.27; S, 16.34.

1-(3-(Furfurylthio)-2-pyrazinyl)-2-methyl-1-propanone (15). A solution of sodium ethoxide (148 mg, 2.18 mmol) and furfuryl mercaptan (285 mg, 2.5 mmol) in absolute EtOH (8 mL) was stirred under N_2 at room temperature for 20 min. A solution of **8** (400 mg, 2.17 mmol) in absolute EtOH (4 mL) was added, and stirring was continued for 2 h. Water was added, and the mixture was extracted with CH_2Cl_2. After drying ($MgSO_4$), the solvent was removed under reduced pressure to give 450 mg of crude product. The product was purified by column chromatography (silica gel, eluted with 10% acetone/hexane). Recrystallization from hexane gave 182 mg (32%) of pure **15** as yellow needles: mp 57–58 °C; ^{1}H NMR (CD_2Cl_2) δ 1.17 (6 H, d, J = 7 Hz, 2 CH_3), 4.01, (1 H, heptet, J = 7 Hz, CH), 4.45 (2 H, s, CH_2), 6.20–6.38 (2 H, m, furan), 7.30–7.38 (1 H, m, furan), 8.34 (1 H, d, J = 2.5 Hz, pyrazine), 8.55 (1 H, d, J = 2.5 Hz, pyrazine). Anal. Calcd for $C_{13}H_{14}N_2O_2S$: C, 59.52; H, 5.38; N, 10.68; S, 12.22. Found: C, 59.77; H, 5.40; N, 10.79; S, 12.37.

Registry No. 1, 86461-71-4; **2**, 86461-73-6; **3**, 86461-72-5; **4**, 56343-40-9; **5**, 118043-58-6; **6**, 98618-81-6; **7**, 98618-78-1; **7** (5-isomer), 118043-63-3; **8**, 98618-80-5; **9**, 39248-49-2; **10**, 118043-59-7; **11**, 118043-60-0; **12**, 24683-00-9; **13**, 118043-61-1; **14**, 98618-79-2; **15**, 118043-62-2; isobutylpyrazine, 29460-92-2; 2-methoxypyrazine, 3149-28-8; acetaldehyde, 75-07-0; propionaldehyde, 123-38-6; isobutyraldehyde, 78-84-2; 2-chloropyrazine, 14508-49-7; 2-acetylpyrazine, 22047-25-2; 2-carbethoxypyrazine, 6924-68-1; 2-carbamoylpyrazine, 98-96-4; ethanethiol, 75-08-1; furfuryl mercaptan, 98-02-2.