Steric Effects on Pyrolysis Reactions. The Thermal Retro-Ene Reaction of Pyrazineethanols

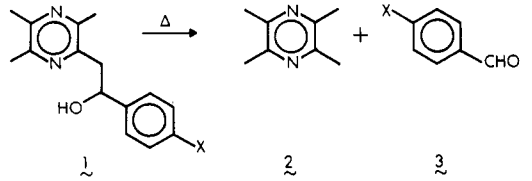
Yoram Houminer,*† Robert A. Fenner, Henry V. Secor, and Jeffrey I. Seeman*‡

Philip Morris USA Research Center, P.O. Box 26583, Richmond, Virginia 23261

Received February 2, 1987

Two series of 2-(2-hydroxy-2-phenylethyl)pyrazines were prepared and subjected to pyrolysis conditions (170 °C/diglyme solution). Series A (**4a–e**) includes substrates in which alkyl groups are placed on the hydroxyalkyl side chain and series B (**5a–f**) includes pyrazineethanols in which alkyl groups are placed at C(3) of the pyrazine ring. In all cases, the retro-ene reaction yields quantitatively the respective alkylpyrazines and acetophenone or benzaldehyde. Increasing substitution, particularly on the ethanol side chain, causes increased thermal reactivity. IR studies were performed on these pyrazineethanols, and the intramolecularly hydrogen-bonded conformations are found to be predominant in all cases.

Systematic studies on the detailed effects of substituents on thermal reactivities of organic molecules are relatively rare. The homolytic cleavage of highly substituted ethanes has been related to ground-state strain energy and to various structural parameters, including the bond length of the weakest C–C bond.[1,2] Thermal chemistry of azo compounds in general and of 1-pyrazolines in particular has been intensively studied.[3,4] The rates of the thermal retroaldol reaction of β-hydroxy esters have been shown to be well correlated with MM2-derived steric energies.[5] Recently, we established that for 2-(2-hydroxy-2-arylethyl)pyrazines (**1**), the rates of retro-ene-type pyrolysis to the corresponding alkylpyrazines **2** and benzaldehydes **3** (eq 1) were insensitive to the X substituent.[6] We now report the rate-accelerating effects of alkyl substituents on this latter reaction as well as the substituent effects on hydrogen bonding in these compounds.



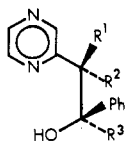
(1)

1 2 3

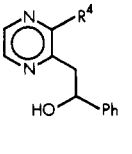
X = CH_3, OCH_3, $N(CH_3)_2$, Cl, NO_2

Results and Discussion

The substrates can be classified into two different groups: group A, those in which additional alkyl groups are placed on the hydroxyalkyl side chain (e.g., **4**); group B, those in which the hydroxyalkyl side chain remains constant but the 3-substituent on the pyrazine ring varies (e.g., **5**).



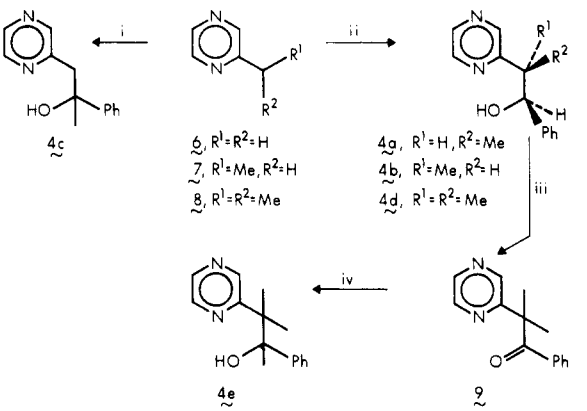
4a, $R^1 = CH_3$, $R^2 = R^3 = H$
b, $R^1 = R^3 = H$, $R^2 = CH_3$
c, $R^1 = R^2 = H$, $R^3 = CH_3$
d, $R^1 = R^2 = CH_3$, $R^3 = H$
e, $R^1 = R^2 = R^3 = CH_3$



5a, $R^4 = H$
b, $R^4 = CH_3$
c, $R^4 = CH_3CH_2$
d, $R^1 = (CH_3)_2CH$
e, $R^1 = (CH_3)_2CHCH_2$
f, $R^4 = (CH_3)_3C$

These compounds were prepared in straightforward manner from either the appropriately monosubstituted pyrazines **6–8** and either benzaldehyde or acetophenone (group A, Scheme I) or from the disubstituted pyrazines **10–14** and benzaldehyde (group B, Scheme II). The trimethyl analogue **4e** was prepared by oxidation of the dimethylethyl analogue **4d** with CrO_3/H_2SO_4 followed by addition of methyllithium. The yields of these condensation reactions were quite reasonable, as discussed in the Experimental Section. It is interesting to note that the condensation between 2-ethyl-3-methylpyrazine (and 2-isopropyl-3-methylpyrazine) and benzaldehyde proceeded

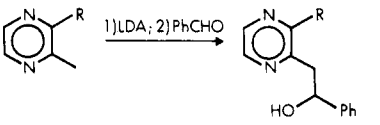
Scheme I[a]



4c
6, $R^1=R^2=H$
7, $R^1=Me, R^2=H$
8, $R^1=R^2=Me$
4g, $R^1=H, R^2=Me$
4b, $R^1=Me, R^2=H$
4d, $R^1=R^2=Me$
4e
9

[a] (i) LDA, then $PhCOCH_3$; (ii) LDA, then PhCHO; (iii) CrO_3–H_2SO_4; (iv) CH_3Li.

Scheme II



10, R = Me
11, R = Et
12, R = *i*-Pr
13, R = *i*-Bu
14, R = *t*-Bu

5a, R = H
b, R = Me
c, R = Et
d, R = *i*-Pr
e, R = *i*-Bu
f, R = *t*-Bu

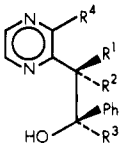
† Current address: Unikoor Company (Industrial Biotechnology), Jerusalem, Israel.

‡ Address correspondence to this author.

(1) Rüchardt, C.; Beckhaus, H.-D. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 429.
(2) Lomas, J. S. *J. Org. Chem.* **1985**, *50*, 4291 and references cited therein.
(3) Crawford, R. J. *J. Am. Chem. Soc.* **1986**, *108*, 1019.
(4) Engel, P. S.; Soltero, L. R.; Baughman, S. A.; Nalepa, C. J.; Cahill, P. A.; Weisman, R. B. *J. Am. Chem. Soc.* **1982**, *104*, 1698.
(5) Houminer, Y.; Kao, J.; Seeman, J. I. *J. Chem. Soc., Chem. Commun.* **1984**, 1608.
(6) Houminer, Y. *J. Org. Chem.* **1980**, *45*, 999.

0022-3263/87/1952-3971$01.50/0

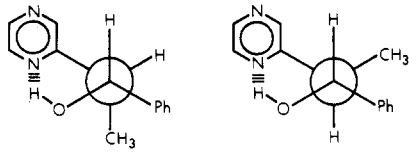
Table I. Pyrolysis Rate Constants for 4a–e and 5a–f



compd	R^1	R^2	R^3	R^4	$10^6 k_{pyr}$, s^{-1}	k_{rel}	k_{add}	k_{rel}/k_{add}
4a	CH_3	H	H	H	5.44	3.01		
4b	H	CH_3	H	H	4.61	2.55		
4c	H	H	CH_3	H	8.91	4.92		
4d	CH_3	CH_3	H	H	53.8	29.7	7.68	3.9
4e	CH_3	CH_3	CH_3	H	427	236	37.8	6.2
5a	H	H	H	H	1.81[a]	1		
5b	H	H	H	CH_3	9.36	5.17		
5c	H	H	H	CH_3CH_2	9.49	5.24		
5d	H	H	H	$(CH_3)_2CH$	8.69	4.80		
5e	H	H	H	$(CH_3)_2CHCH_2$	9.06	5.01		
5f	H	H	H	$C(CH_3)_3$	13.1	7.24		

[a] The pyrolysis of **5a** has previously been reported (ref 6) with $k_{pyr} = 1.60 \times 10^{-6}$ s^{-1}.

exclusively with alkylation on the pyrazyl methyl group rather than on the ethyl (or isopropyl) carbon. The stereostructures of **4a** and **4b** were determined by analysis of the ^1H NMR spectra, where the ^3J for the side chain H–C–C–H fragment are 3 and 7 Hz, respectively[7] (see Newman projections below).



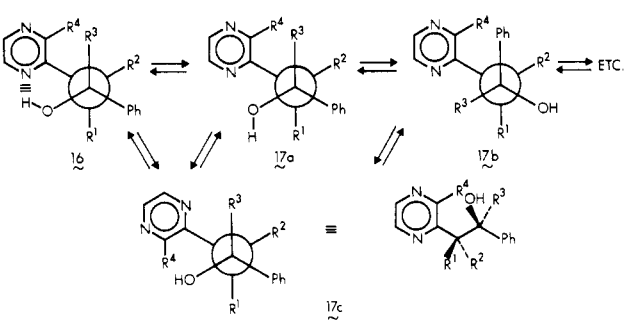
4a **4b**

Table I lists the first order pyrolysis rate constants for the reactions, all performed at 170 °C in diglyme-d_{14}. The course of the reactions was followed by quantitative integration of two or more ^1H NMR resonances of starting material and products. Typically, nine or more data points were obtained, and the linear regressions between log (concentration) and time were always $r \geq 0.997$.

Our previous studies showed that the activation energies of these reactions (eq 1) are essentially independent of the electronic character of the benzene ring.[6] Hence, there is practically no charge separation in the retro-ene transition state. However, there was some indication that steric effects could accelerate the thermolyses. The two series of compounds (**4** and **5**) have now quantified this steric acceleration. Within the series **4a–4e**, the retro-ene acceleration qualitatively parallels an increase in ground-state steric/strain energy which is partially released in the cleavage reaction. Placing a single methyl group on the hydroxyethyl side chain (e.g., **4a–c**) causes a modest (2.5–5.0-fold) increase in the pyrolysis rate constant while two (e.g., **4d**) or three methyl groups (e.g., **4e**) substantially accelerate the reaction. The rate acceleration of the trimethyl analogue **4e** is impressive, being over 225 times more reactive than the parent compound.

Additivity of kinetic effects can be determined by calculating a "additive" rate constant k_{add} based on the rate constants for the singly substituted analogues.[8–10] As shown in Table I, the effect of multisubstitution is nonadditive, with **4d** and **4e** reacting 3.9 and 6.2 times faster than calculated on the basis of substituent kinetic additivity.

Scheme III



The nonadditive kinetics observed for the polymethylated analogues **4d** and **4e** may well be due to nonadditive structural factors. These rate enhancements may be attributed to increased steric/strain energy factors in the ground states of the more highly substituted pyrazines.

Substitution of a methyl group for a hydrogen ortho to the hydroxyethyl side chain (**5a** → **5b**) increases the pyrolysis rate constant by a factor of five. However, placing larger groups at C(3) results in only minor rate modifications. Interestingly, ground-state steric/strain energy apparently does not increase with bulky C(3) substituents, i.e., within the series **5c–e**. The extremely bulky *tert*-butyl group in **5f** causes a rate enhancement of only 40% relative to the methyl-substituted pyrazine **5b**.

We[5] and others[11] have previously presented evidence that the hydrogen-bonded conformations **15** of β-hydroxy esters are the reactive intermediates in the thermal retro-aldol reactions shown in eq 2. The thermal retro-ene reactions (eq 1) discussed herein are analogous, and we propose that the important reactive conformations are the hydrogen-bonded forms **16** as opposed to a multitude of non-hydrogen-bonded forms **17** (Scheme III). The effect of C(3)-substituents (R^4) may be to increase the population of hydrogen-bonded conformations **16** at the expense of less reactive conformations **17c**, thereby increasing the

(7) For configurational assignments on the related pyridines, see: Hamana, H.; Sugasawa, T. *Chem. Lett.* **1984**, 1591.

(8) Note that additivity in free energy of activation implies multiplicativity in reaction rate constants.

(9) See, for example: Seeman, J. I.; Viers, J. W.; Schug, J. C.; Stovall, M. D. *J. Am. Chem. Soc.* **1984**, *106*, 143.

(10) Seeman, J. I. *Pure Appl. Chem.*, in press.

(11) Hajos, Z. G. In *Carbon–Carbon Bond Formation*; Augustine, R. L., Ed.; Marcel Dekker: New York, 1979; Vol. 1, Chapter 1.

overall thermolysis rate constant.[12]

(2)

15

To determine the importance of hydrogen-bonded conformations **16** within the two series of compounds **4a–e** and **5a–f** and to acquire some initial structural ground-state conformational data, we obtained and evaluated the infrared spectrum for each of these compounds (Table II). The IR spectra were obtained at sufficiently low concentrations (<2 mM) to assure that intermolecular hydrogen bonding was not a factor. Spectra were acquired at 4-cm^{-1} resolution and were ratioed against a carbon tetrachloride reference. The resultant spectra, converted to absorbance format, were subjected to a band-fitting analysis within the 3800–3200-cm^{-1} region (cf. Figure 1; available as supplementary material), to establish the relative proportions of the two absorptions observed in each case.

Table II lists the "free" and "intramolecular" hydrogen-bonded hydroxyl stretching frequencies and area percentages/populations of these compounds. All of the compounds exhibit a sharp band at ca. 3615 cm^{-1}, which is indicative of the "free" hydroxyl, and a broad band in the 3400-cm^{-1} region, reflecting an intramolecular (N···H–O) hydrogen-bonded moiety. In all cases, the hydrogen-bonded form predominates. Within the series **5a–f**, as the C(3)-substituent (R^4) becomes larger, the hydrogen-bonded form becomes more predominant, and the strength of its hydrogen bond increases. This is consistent with the pyrolysis results, in that the major population change occurs from the parent **5a** to the methyl-substituted **5b**. A single methyl group at C(1′) on the hydroxyethyl side chain has little effect, but a methyl group at C(2′) significantly increases the strength of the hydrogen bond.

Interestingly, a modest correlation exists between log (k_{pyr}) and $\bar{\nu}_{intramolecular}$ for these pyrazines (eq 3). As $\bar{\nu}$ decreases, the strength of the O–H bond decreases; the strength of the OH···N hydrogen bond therefore increases.

$$\log (k_{pyr}) = 104.8 - 0.032\bar{\nu}_{intramolecular} \quad (3)$$

[$n = 11$, $r = 0.87$, confidence level > 0.999, sdr = 0.324]

The empirical relationship shown in eq 3 indicates that the pyrolysis rate increases as the OH···N hydrogen bond strength increases. The IR spectra were done at room temperature in a nonpolar solvent, while the pyrolyses were performed in diglyme at 170 °C, and additional experimental data are not available at this time to tie together the IR and pyrolysis results. Nonetheless, the correlation in eq 3 does lend further support for the hydrogen-bonded conformation being an important intermediate in the pyrolysis reaction.

Conclusions

Our data suggest that three factors facilitate the retro-ene thermolyses: (a) steric/strain energy relief in the cleavage process; (b) substituent factors which enhance a pseudo-six-membered ring transition state; (c) intramolecular hydrogen bonding. We are in the process of preparing and examining additional substrates which have increased steric bulk, with the goal of enlarging our range in pyrolysis rate. In addition, we are modeling these reactions by using empirical force-field procedures[5] in order to estimate steric energy relief during the retro-ene reaction. The importance of steric effects in the (hydroxyethyl)pyrazines, the putative enamines, and the final products (alkylpyrazines and acetophenone or benzaldehyde) will be evaluated. Further detailed analysis of the energetics of these reactions awaits these theoretical treatments currently in progress.

(12) Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83.

Table II. Free vs. Hydrogen-Bonded Forms of 4a–e and 5a–f

	free hydroxyl		hydrogen-bonded[a]	
compound	freqncy, cm^{-1}	popu-latn,[b] %	freqncy, cm^{-1}	popu-latn,[b] %
series A				
4a	3618	23	3435	77
4b	3620	9	3445	91
4c	3621	18	3409	82
4d	3610	3	3430	97
4e	3612	4	3392	96
series B				
5a	3618	14	3444	86
5b	3618	7	3435	93
5c	3618	6	3433	94
5d	3618	6	3425	94
5e	3618	6	3422	95
5f	3619	3	3404	97

[a] $\bar{\nu}_{intramolecular}$. See eq 3. [b] The molecular populations are approximate, based on the assumption that the extinction coefficient for the conformations are identical.

Experimental Section

All reactions involving organometallic reagents were carried out under a N_2 atmosphere. Melting points were determined with a Buchi 510 capillary melting point apparatus and are uncorrected. IR spectra were recorded with a Digilab Model FTS-20E. NMR spectra were obtained with either a Varian XL-300 or Varian XL-400 NMR spectrometer, and the chemical shifts are given in ppm downfield from internal Me_4Si. TLC was performed on Analtech/Silica gel GF plates, 250 μm. All chromatography was carried out by using a Harrison Chromatotron and 4-mm plates coated with Kieselgel 60 PF_{254} gipshaltig (EM Reagents). Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN.

2-(2-Hydroxy-2-phenylethyl)-3-methylpyrazine (5b). A solution of diisopropylamine (22.2 g, 0.22 mol) in ether (500 mL) was stirred under a N_2 atmosphere and treated with *n*-BuLi (0.20 mol) in hexane (119 mL) at −75 °C. The resulting solution was then warmed to 0 °C, a solution of 2,3-dimethylpyrazine (**10**) (21.6 g, 0.20 mol) in ether (30 mL) was added slowly, and the reaction mixture was stirred at 0 °C for 30 min. A solution of benzaldehyde (21.2 g, 0.20 mol) in ether (30 mL) was added, and stirring at 0 °C was continued for an additional 30 min. The reaction was quenched by the addition of water and the organic layer separated, washed with water, and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure gave an orange-colored oil, which was distilled bulb-to-bulb to give 22.2 g [155–165 °C (oven) (0.02 mmHg)] of a light yellow colored oil, which crystallized. Recrystallization from ether gave 13.84 (32.3%) of **5b**: mp 85–86 °C; ^1H NMR ($CDCl_3$) δ 2.47 (s, 3 H) 3.14 (m, 2 H), 4.83 (d, 1 H, J = 2.9 Hz), 5.30 (m, 1 H), 7.27–7.45 (m, 5 H), 8.35 (q, 2 H, J = 2.7 Hz).

Anal. Calcd for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59, N, 13.08. Found: C, 73.19; H, 6.88; N, 13.09.

2-(1,1-Dimethyl-2-hydroxy-2-phenylethyl)pyrazine (4d). The reaction of isopropylpyrazine (**8**) (439 mg, 3.6 mmol) with benzaldehyde (456 mg, 4.33 mmol) was carried out as described for **5b** with the stirring time extended to 1.5 h. Workup was followed by bulb-to-bulb distillation [105–160 °C (oven) (0.01 mmHg)] to give a semisolid. This material was directly purified by centrifugal chromatography using 100:14:3.6 hexanes/acetone/ethanol to give 177 mg (21%) of **4d**: mp 90–91 °C; ^1H NMR ($CDCl_3$) δ 1.39 (s, 3 H), 1.40 (s, 3 H), 4.50 (d, 1 H, J = 4.5

Hz), 4.95 (d, 1 H, J = 4.5 Hz), 7.10–7.12 (m, 2 H), 7.24–7.28 (m, 3 H), 8.51–8.58 (m, 3 H).

Anal. Calcd for $C_{14}H_{16}N_2O$: C, 73.65; H, 7.06; N, 12.27. Found: C, 73.27; H, 6.96; N, 12.13.

2-Methyl-1-phenyl-2-pyrazinyl-1-propanone (9). A stirred and cooled (0 °C) solution of **4d** (1 g, 4.38 mmol) in acetone (150 mL) was treated with an aqueous solution of CrO_3–H_2SO_4 (1.39 mL, 3.72 mmol). The solution was stirred for 10 min, diluted with water (500 mL), allowed to stand for 1 h, and basified (Na_2CO_3). The solution was extracted with CH_2Cl_2 and the organic extract dried (Na_2SO_4) and concentrated to give 1.2 g of a turbid oil. Purification by centrifugal chromatography using 100:15:3 hexanes/acetone/ethanol gave 710 mg (71%) of **9**: mp 67–68 °C; ^{1}H NMR ($CDCl_3$) δ 1.73 (s, 6 H), 7.23–7.48 (m, 5 H), 8.46–8.59 (m, 3 H).

Anal. Calcd for $C_{14}H_{14}N_2O$: C, 74.31; H, 6.24; N, 12.38. Found: C, 74.22; H, 6.10; N, 12.23.

2-(1,1,2-Trimethyl-2-hydroxy-2-phenylethyl)pyrazine (4e). A solution of **9** (390 mg, 1.73 mmol) in either (100 mL) was stirred, cooled (−70 °C), and treated with 2.23 mL of MeLi (1 M solution, 2.23 mmol) in ether. The reaction was stirred for 2 h at −65 °C and quenched with methanol. The resultant mixture was concentrated, and the residue was taken up in CH_2Cl_2, dried (Na_2SO_4), and filtered. Purification by centrifual chromatography using 95:4:1 hexanes/acetone/ethanol gave 221 mg (53%) of **4e**: mp 99–100 °C; ^{1}H NMR ($CDCl_3$) δ 1.37 (s, 3 H), 1.44 (s, 3 H), 1.47 (s, 3 H), 5.68 (s, 1 H), 7.21–7.34 (m, 5 H), 8.48–8.54 (m, 3 H).

Anal. Calcd for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49; N, 11.56. Found: C, 74.23; H, 7.61; N, 11.48.

2-(2-Hydroxy-2-phenylethyl)-3-isopropylpyrazine (5d). The reaction of 2-isopropyl-3-methylpyrazine (0.62 g, 4.56 mmol) with benzaldehyde (0.48 g, 4.56 mmol) was carried out as described for **5b**. Workup followed by bulb-to-bulb distillation [100–135 °C (oven) (0.01 mmHg)] gave 800 mg of a yellow-orange-colored oil. This material was chromatographed by using 199:1 $CHCl_3$/ethanol to give 386 mg (34.9%) of **5d** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.20, 1.21, 1.24, 1.26 (2 d, 6 H, diastereotopic isopropyl methyl signals), 3.15–3.27 (m, 3 H), 5.02 (d, 1 H, J = 2.6 Hz), 5.3 (m, 1 H), 7.28–7.50 (m, 5 H), 8.35 (d, 1 H, J = 2.4 Hz), 8.47 (d, 1 H, J = 2.4 Hz).

Anal. Calcd for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49; N, 11.56. Found: C, 74.16; H, 7.35; N, 11.33.

2-(2-Hydroxy-2-phenylethyl)-3-isobutylpyrazine (5e). The reaction of 2-isobutyl-3-methylpyrazine (3.0 g, 20 mmol) with benzaldehyde (2.12 g, 20 mmol) was carried out as described for **5b**. Standard workup was followed by bulb-to-bulb distillation [153 °C (oven) (0.01 mmHg)]. The resulting oil crystallized on trituration with hexane to give 2.5 g (48.8%) of **5e**: mp 52–53 °C; ^{1}H NMR ($CDCl_3$) δ 0.92 (d, 6 H, J = 6.7 Hz), 2.0–2.2 (m, 1 H), 2.62–2.64 (m, 2 H), 3.17 (m, 2 H), 5.11 (br s, 1 H), 5.24–5.28 (m, 1 H), 7.25–7.45 (m, 5 H), 8.34 (d, 1 H, J = 2.5 Hz), 8.43 (d, 1 H, J = 2.5 Hz).

Anal. Calcd for $C_{16}H_{20}N_2O$: C, 74.96; H, 7.86; N, 10.93. Found: C, 75.20; H, 7.73, N, 10.87.

2-(2-Hydroxy-2-phenylethyl)-3-*tert*-butylpyrazine (5f). The reaction of 2-*tert*-butyl-3-methylpyrazine (0.89 g, 5.95 mmol) with benzaldehyde (0.63 g, 5.95 mmol) was carried out as described for **5b**. Standard workup was followed by bulb-to-bulb distillation [up to 100 °C (oven) (0.025 mmHg)]. Centrifugal chromatography of the residual fraction using 85:15 hexanes/acetone was followed by bulb-to-bulb distillation [150 °C (oven) (0.01 mmHg)] to give, after recrystallization from hexane, 0.643 g (42%) of **5f**: mp 89–90 °C; ^{1}H NMR ($CDCl_3$) δ 1.44 (s, 9 H), 3.25 (dd, 1 H, J = 16.0, 9.5 Hz), 3.50 (dd, 1 H, J = 16.0, 2.2 Hz), 5.23 (br d, 1 H, J = 9.0 Hz), 5.78 (s, 1 H), 7.30–7.52 (m, 5 H), 8.38 (d, 1 H, J = 2.2 Hz), 8.47 (d, 1 H, J = 2.2 Hz).

Anal. Calcd for $C_{16}H_{20}N_2O$: C, 74.96; H, 7.86; N, 10.93. Found: C, 74.83; H, 7.98; N, 10.88.

2-(2-Hydroxy-2-phenylpropyl)pyrazine (4c). The reaction of 2-methylpyrazine (4.7 g, 0.05 mol) with acetophenone (6.6 g, 0.055 mol) was carried out as described for **5b**. Workup followed by bulb-to-bulb distillation [120–135 °C (oven) (0.01 mmHg)] and centrifugal chromatography using 85:15 hexanes/acetone gave 454 mg (4.2%) of **4c**: mp 53–54 °C (from hexane); ^{1}H NMR ($CDCl_3$) δ 1.61 (s, 3 H), 3.35 (s, 2 H), 5.35 (br s, 1 H), 7.18–7.63 (m, 5 H), 8.38–8.55 (m, 3 H).

Anal. Calcd for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.08. Found: C, 73.03; H, 6.58; N, 13.04.

2-(2-Hydroxy-2-phenylethyl)-3-ethylpyrazine (5c). The reaction of 2-ethyl-3-methylpyrazine (12.2 g, 0.1 mol) with benzaldehyde (10.6 g, 0.1 mol) was carried out as described for **5b**. Workup followed by bulb-to-bulb distillation [155 °C (oven) (0.02 mmHg)] gave 18.2 g of a light yellow colored oil. This material crystallized on trituration with hexane, giving 17.80 g (78%) of **5c**: mp 52–53 °C. An analytical sample was obtained recrystallization from hexane: mp 53–54 °C; ^{1}H NMR ($CDCl_3$) δ 1.25 (t, 3 H, J = 7.4 Hz), 2.77 (q, 2 H, J = 7.4 Hz), 3.16 (d, 2 H, J = 6.2 Hz), 5.01 (d, 1 H, J = 2.5 Hz), 5.28 (m, 1 H), 7.27–7.46 (m, 5 H), 8.33 (d, 1 H, J = 2.8 Hz), 8.40 (d, 1 H, J = 2.8 Hz).

Anal. Calcd for $C_{14}H_{16}N_2O$: C, 73.65; H, 7.06; N, 12.27. Found: C, 73.73; H, 7.01; N, 12.31.

(1*R,2*S**)-2-(1-Methyl-2-hydroxy-2-phenylethyl)pyrazine (4a) and (1*R**,2*R**)-2-(1-Methyl-2-hydroxy-2-phenylethyl)-pyrazine (4b).** The reaction of ethylpyrazine (10.8 g, 0.1 mol) with benzaldehyde (10.6 g, 0.1 mol) was carried out as described for **5b**. Bulb-to-bulb distillation [155 °C (oven) (0.05 mmHg)] afforded 9.07 g (42.4%) of the diastereomeric mixture **4a** (R_f 0.25 on silica, 4:1 hexane/acetone) and **4b** (R_f 0.18). A 1.0-g portion of this mixture was separated by centrifugal chromatography using 100:15 hexanes/acetone to give approximately 650 mg of purified **4a** and **4b**.

4a: mp 79–80 °C; ^{1}H NMR ($CDCl_3$) δ 1.30 (d, 3 H, J = 7.0 Hz), 3.23 (dq, 1 H, J = 7.0, 3.5 Hz), 4.19 (d, 1 H, J = 2.0 Hz), 5.16 (br t, 1 H), 7.38 (br s, 5 H), 8.42 (m, 3 H).

Anal. Calcd for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.08. Found: C, 72.82; H, 6.66; N, 13.05.

4b: mp 58–59 °C; ^{1}H NMR ($CDCl_3$) δ 1.28 (d, 3 H, J = 7.0 Hz), 3.35 (m, 1 H), 3.70 (d, 1 H, J = 5.8 Hz), 5.05 (dd, 1 H, J = 7.0, 5.8 Hz), 7.40 (br s, 5 H), 8.50–8.68 (m, 3 H).

Anal. Calcd for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.08. Found: C, 72.95; H, 6.50; N, 13.13.

Kinetic Experiments. Reactions were carried out in diglyme-d_{14} (Merck Sharp & Dohme, Canada, Ltd.) that was dried over molecular sieves. A 0.4 M solution of each of the substrates (0.5 mL) was placed in a thick-walled NMR tube, and the tubes were sealed. Kinetic runs were carried out in a constant-temperature oil bath preheated to the desired temperature (170 ± 0.8 °C). The progress of each reaction was followed by NMR spectroscopy using a method similar to that described by us in an earlier study.[6] Percentage compositions were calculated from integration of peaks of both reactants and products primarily in the aromatic regions.

Acknowledgment. We thank R. Bassfield and J. Campbell for obtaining the NMR spectra, J. Paine for helpful discussions, and J. Day, A. Donathan, M. Satterfield, and T. Sinkiewicz for assistance in preparing this manuscript.

Registry No. **4a**, 109243-29-0; **4b**, 109243-30-3; **4c**, 108246-76-0; **4d**, 109243-31-4; **4e**, 109243-32-5; **5a**, 36914-69-9; **5b**, 109243-33-6; **5c**, 109243-34-7; **5d**, 109243-35-8; **5e**, 109243-36-9; **5f**, 109243-37-0; **8**, 29460-90-0; **9**, 109243-38-1; **10**, 5910-89-4; **11**, 15707-23-0; **12**, 15986-81-9; **13**, 13925-06-9; **14**, 40790-15-6; benzaldehyde, 100-52-7; methylpyrazine, 109-08-0; acetophenone, 98-86-2; ethylpyrazine, 13925-00-3.

Supplementary Material Available: Original infrared spectrum and infrared spectrum reconstructed from band-fitting analysis for compound **5e** (Figure 1) (1 page). Ordering information is given on any current masthead page.