Studies on the Thermolysis of 2-(2-Hydroxy-2-arylethyl)pyrazines. An Example of a Retro-Ene-Type Reaction

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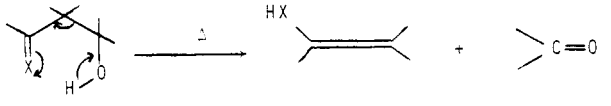
Received October 15, 1979

Several substituted 2-(2-hydroxy-2-arylethyl)pyrazines (1–10) have been prepared and their thermolysis in diglyme and DMF studied. Each of these substrates decomposes to give the parent methylpyrazine and the corresponding aryl aldehyde. Kinetic, isotope effect, and solvent effect studies suggest a mechanism involving a nonpolar concerted six-membered-ring transition state. The degree of proton transfer in the transition state is discussed in detail. Methyl substituents on the pyrazine ring were found to strongly affect the reaction rate. This phenomenon is analyzed in terms of the steric and electronic effects induced by the methyl substituents.

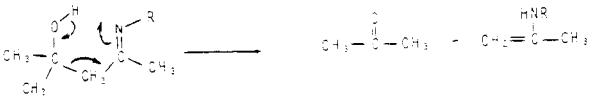
The ene and retro-ene reactions have been investigated extensively and the subject has been reviewed in detail.[1,2] Several hydroxy enes undergo a retro-ene reaction as shown in Scheme I. Examples in which X = CR_2 (where R is alkyl or hydrogen) are common[3-5] and mechanistic studies have shown that these thermal degradations occur via a six-membered cyclic transition state.[4,5] Substrates containing a carbonyl function (X = O) have also been examined and a similar mechanism has been proposed[3] (thermal retro-aldol reactions). Examples in which X = NR (where R is alkyl or hydrogen) are rare and only a limited number of studies are described in the literature. Pollack and Ritterstein[6] investigated in detail the dealdolization of diacetone alcohols catalyzed by primary amines. These authors found that the reaction proceeds via a ketimine intermediate which breaks down to a molecule of acetone plus an enamine and that the transition state does not involve a substantial charge separation (Scheme II). A few other examples in which X = NR are found in systems where the nitrogen atom is part of a heteroaromatic ring. It has been reported that 2-(2-pyridyl)ethanol undergoes a thermal cleavage to produce formaldehyde and 2-methylpyridine[7] (Scheme III). The reaction has been proposed to proceed via a concerted six-membered-ring transition state (Scheme III), but no direct evidence for such a mechanism has been provided.[7] A similar reaction has been observed in the thermal fragmentation of a harmine derivative.[8] Recently, Hansen et al.[9] have studied the thermal cleavage of the two racemic pairs of 1-(3-chlorophenyl)-1-methyl-2-phenyl-2-(2-pyridyl)ethanol, both of which yield 3-chloroacetophenone and 2-benzylpyridine. On the basis of the different reactivities of the two racemic pairs, the authors assigned their stereochemistry and suggested that the reaction proceeds via a six-membered-ring transition state.

To the best of our knowledge, there is only one reported example in the category of X = NR, where the nitrogen atom is part of a pyrazine ring. Thus, 2-(2-pyrazyl)ethanol has been shown to decompose on heating to 2-methylpyrazine and formaldehyde,[7] but the reaction mechanism has not been studied. The present investigation was aimed at establishing the generality of the thermolysis of 2-(2-pyrazyl)ethanol derivatives and particularly at clarifying some aspects related to the mechanism of these reactions.

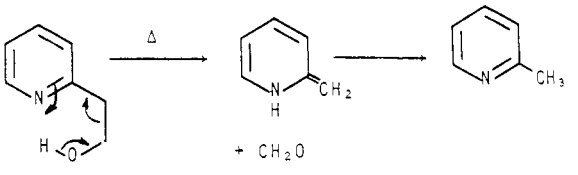
Scheme I



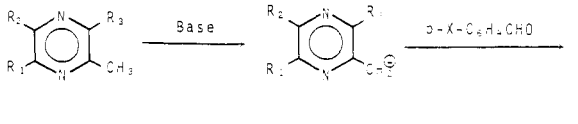
Scheme II

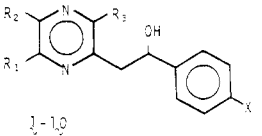


Scheme III



Scheme IV





1-10

1, $R_1 = R_2 = R_3 = CH_3$; X = H
2, $R_1 = R_2 = R_3 = CH_3$; X = CH_3
3, $R_1 = R_2 = R_3 = CH_3$; X = OCH_3
4, $R_1 = R_2 = R_3 = CH_3$; X = $N(CH_3)_2$
5, $R_1 = R_2 = R_3 = CH_3$; X = Cl
6, $R_1 = R_2 = R_3 = CH_3$; X = NO_2
7, $R_1 = CH_3$; $R_2 = R_3 = H$; X = OCH_3
8, $R_2 = CH_3$; $R_1 = R_3 = H$; X = OCH_3
9, $R_3 = CH_3$; $R_1 = R_2 = H$; X = OCH_3
10, $R_1 = R_2 = R_3 = H$; X = H

Results and Discussion

Synthesis. Several substituted 2-(2-hydroxy-2-arylethyl)pyrazines (1–10) have been prepared by using the method shown in Scheme IV. Reactions were carried out in Et_2O with either phenyllithium or lithium diisopropylamide as the base. It should be pointed out that

(1) Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 556.
(2) Oppolzer, W.; Snieckus, V. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 479.
(3) Marvell, E. N.; Whalley, W. "The Chemistry of the Hydroxyl Group"; Patai, S., Ed.; Wiley: London, **1971**, pp 719–54.
(4) Arnold, R. T.; Smolinsky, G. *J. Org. Chem.* **1960**, *25*, 129.
(5) Smith, G. G.; Yates, B. L. *J. Chem. Soc.* **1965**, 7242.
(6) Pollack, R. M.; Ritterstein, S. *J. Am. Chem. Soc.* **1972**, *94*, 5064. Pollack, R. M.; Cooper, J. D. *J. Org. Chem.* **1973**, *38*, 2689.
(7) Goldman, I. M. *J. Org. Chem.* **1963**, *28*, 1921.
(8) Huebner, C. F.; MacPhillamy, H. B.; St. Andre, A. F.; Schlittle, E. *J. Am. Chem. Soc.* **1955**, *77*, 472.
(9) Hansen D. W., Jr.; Sinsheimer, J. E.; Burckhalter, J. H. *J. Org. Chem.* **1976**, *41*, 3556.

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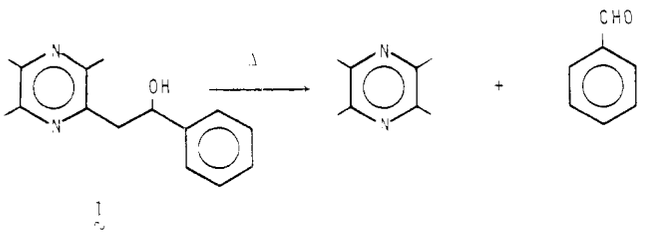
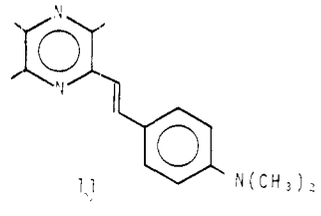
Scheme V



lithium diisopropylamide is preferred in the cases of mono- or disubstituted pyrazines since phenyllithium was also found to add to the pyrazine ring of these substrates.[10,11] The reactions, in general, proceeded smoothly yielding products in moderate yields (25–60%), except for 2,5-dimethylpyrazine which gave a very low yield (ca. 1%). In the latter case, some evidence was found for the formation of self-addition products; i.e., the 2,5-dimethylpyrazine anion adds to the C=N bond of either a 2,5-dimethylpyrazine molecule or anion. The reaction can then proceed resulting in tar formation. While the reason for the different behavior of 2,5-dimethylpyrazine is not well understood, there is some evidence that among the three dimethylpyrazine isomers, the pyrazine ring in the 2,5-dimethyl isomer is more susceptible to nucleophilic attack by organolithium reagents.[11,12]

Thermolysis Products. Each of the substrates (Scheme IV) when heated either in diglyme or in DMF at temperatures above 150 °C underwent cleavage as illustrated in Scheme V for the case of **1**. Except for the thermolysis of **4**, the reactions were found to proceed smoothly, and no side products were observed over the temperature range of 150–180 °C. At these temperatures, the reactions were found to be irreversible: e.g., when an equimolar mixture of both tetramethylpyrazine and benzaldehyde was heated in diglyme at 170 °C, no **1** could be detected, even after prolonged reaction periods (>50 h).

The thermolysis of **4** at 170 °C in diglyme for 4 h gave a mixture in which the presence of a dehydration product



11 (>90%) was clearly indicated by the ^{1}H NMR spectrum. The rest of the mixture was starting material and trace amounts of tetramethylpyrazine and *p*-(dimethylamino)-benzaldehyde. This exceptional behavior could have been a result of either a strong substituent effect favoring dehydration or a base-catalyzed dehydration by the dimethylamino group. These two possibilities were distinguished by carrying out the following experiment: a 0.2 M solution of **3** in diglyme containing either triethylamine or (dimethylamino)benzene (0.2 M) was heated at 170 °C for 10 h. No dehydration product was observed and the reaction proceeded via the pathway shown in Scheme V. We therefore concluded that the dehydration in **4** is due to the substituent, which can stabilize a positive charge on the carbon atom next to the phenyl ring, in an E1-type elimination. The *p*-methoxy-substituted substrates (**3**, **7**–**9**) did not yield any NMR-detectable dehydration products

(10) Houminer, Y., unpublished results.
(11) Cheeseman, G. W. H.; Werstiuk, E. S. G. *Adv. Heterocycl. Chem.* **1972**, *14*, 99.
(12) Rizzi, G. P. *J. Org. Chem.* **1968**, *33*, 1333.

Table I. Thermolysis Rate Data and Activation Parameters for 1-10 in Diglyme-d_{14} and DMF-d_7

	solvent	10^6k,[a] s^{-1} 160 °C	10^6k,[a] s^{-1} 170 °C	$\Delta H^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$, eu
1	diglyme-d_{14}	2.74 ± 0.04	6.28 ± 0.11	30.7	−14
2	diglyme-d_{14}	2.95 ± 0.02	6.43 ± 0.10	28.8	−18
3	diglyme-d_{14}	3.51 ± 0.03	7.28 ± 0.08	26.9	−22
5	diglyme-d_{14}	3.61 ± 0.03	7.00 ± 0.08	24.3	−28
6	diglyme-d_{14}	3.67 ± 0.08	7.05 ± 0.13	24.0	−29
7	diglyme-d_{14}		3.41 ± 0.03		
8	diglyme-d_{14}		1.00 ± 0.01		
9	diglyme-d_{14}		11.81 ± 0.39		
10	diglyme-d_{14}		1.60 ± 0.02		
3	DMF-d_7		7.71 ± 0.16		
5	DMF-d_7		7.47 ± 0.20		

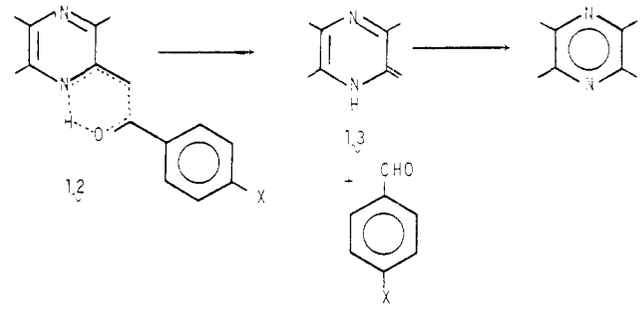
[a] Errors are standard deviations. Repeat kinetic measurements gave reproducibilities of ±2–4%.

Table II. Kinetic Isotope Effect Results for 2, 2-OD, 3, and 3-OD in Diglyme-d_{14} at 171.5 °C

	10^6k,[a] s^{-1}	k_H/k_D[b]
2	7.24 ± 0.06	
2-OD	6.30 ± 0.06	1.15 ± 0.02
3	8.34 ± 0.06	
3-OD	6.96 ± 0.08	1.20 ± 0.02

[a] Errors are standard deviations. [b] Owing to the small amounts of nondeuteriated species in 2-OD and 3-OD, the actual figures should be slightly higher.

Scheme VI



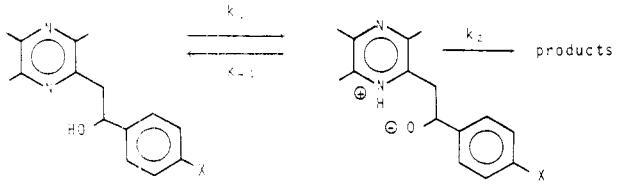
(<3%), thus suggesting again that the dehydration reaction is strongly substituent dependent. On the basis of these data, a $\rho < -3$ was estimated for the dehydration reaction.

Kinetics. The thermolyses of **1**–**10** in solution have been studied by using ^{1}H NMR spectroscopy to follow the reaction progress. Since the reactions are very slow at temperatures <150 °C, only deuterated solvents of relative high boiling point, such as diglyme-d_{14} and DMF-d_7, could be used. All rate measurements covered a wide reaction range (ca. 10–80%). A least-squares computer program was used in calculating the rate constants from the standard first-order rate law. The rate constants were first order over the full range of reactions with correlation coefficients >0.9985. The results are summarized in Table I with the activation parameters calculated for some of the above substrates.

For the determination of the kinetic isotope effect the thermolyses of **2**, **2-OD**, **3**, and **3-OD**, where the OD represents a hydroxy group in which the hydrogen has been replaced by deuterium, were performed simultaneously under identical conditions in order to minimize systematic errors. The rate constants and the isotope effects are given in Table II.

It can be seen from the data in Table I (compare **1**–**6**) that the substituent on the phenyl ring exerts little, if any, influence on the rate of the reaction ($\rho = +0.016 \pm 0.036$). The absence of any observable substituent effect indicates

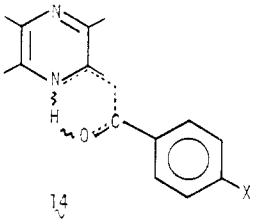
Scheme VII



that there is practically no charge separation in the transition state of the reaction. We therefore propose a reaction mechanism (Scheme VI) which consists of a nonpolar concerted six-membered-ring transition state (**12**). The rearrangement of the intermediate **13** to tetramethylpyrazine which involves a proton transfer is probably very fast since in this step the aromaticity of the pyrazine ring is regained. Indeed this intermediate could not be detected during the course of the reaction.

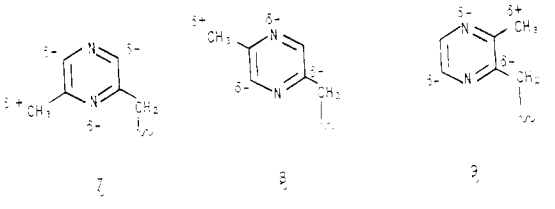
Two alternative mechanisms both of which involve a proton-transfer reaction should also be considered (Scheme VII): (a) a slow, rate-determining proton transfer, followed by rapid cleavage of the carbon–carbon bond, and (b) a preequilibrium proton transfer followed by rate-determining carbon–carbon bond cleavage. The first mechanism which is the case when $k_{obsd} = k_1$ ($k_2 \gg k_{-1}$) is unlikely, since such a reaction is expected to be substituent dependent; i.e., the substituent on the phenyl ring is expected to affect mainly the forward proton-transfer reaction (k_1). Indeed we find that the acidities of the hydroxy groups in **1–6**, as reflected by their NMR chemical shifts, are strongly substituent dependent, both in $CDCl_3$ and in diglyme-d_{14}. The second possibility is more complex. It fits the situation where $k_{obsd} = k_1k_2/k_{-1}$ ($k_2 \ll k_{-1}$) and therefore may result in an observed ρ value being the algebraic sum of the values describing the separate stages. Hence, if the separate stages have opposite substituent effects of similar magnitude, the overall reaction rate may be substituent independent. The mechanism shown in Scheme VII represents a more polar transition state than the concerted mechanism shown in Scheme VI. We therefore expected that a solvent effect study would enable us to further distinguish between the two mechanisms. The results in diglyme-d_{14} and DMF-d_7 (compare **3** and **5** in Table I) indicate only a slight increase in rate in the latter solvent. Data on the polarity of diglyme and DMF at 170 °C are not available. However, at 25 °C DMF has a much higher dielectric constant (ϵ = 36.71)[13] than diglyme (ϵ = 7.23).[14] Any polar transition state should be stabilized in DMF, resulting in an increase in rate in that solvent. The results, however, show very little effect, thus supporting the concerted mechanism proposed in Scheme VI. The entropies of activation obtained for **1–6** at 170 °C are relatively large and negative (Table I), suggesting again a very highly ordered transition state.

The problem related to the degree of proton transfer prior to the carbon–carbon bond cleavage can also be approached by a kinetic isotope effect study, i.e., comparing, for example, the reactivity of **2** and **2**-OD or **3** and **3**-OD. The results obtained for each pair of substrates (Table II) show a very small isotope effect in both cases. This small effect suggests that the proton is not undergoing translation in the rate-determining step.[6] This phenomenon seems to be in contrast with the proposed cyclic transition state in which both proton transfer and carbon–carbon bond cleavage occur simultaneously (Scheme VI). However, a similar situation where a proton is being transferred from an oxygen to a nitrogen atom has been treated by Schowen et al.[15] They suggested that such a proton should lie in an entirely stable potential well at the transition state. Application of this concept[6] to our case suggests that the transition state should involve a proton in a stable potential well between the oxygen and the nitrogen atoms, while the carbon–carbon bond is undergoing cleavage. Therefore, the transition state in Scheme VI can be represented as **14**, with the wavy lines representing a potential well and the dotted lines translation.[6]



14

Effect of Pyrazine-Ring Substitution. The data in Table I demonstrate that the position of the substituent on the pyrazine ring strongly affects the thermolysis rate. Comparison of **8** and **9** (Table I) indicates that the latter is about 1 order of magnitude more reactive. This result is interesting and somewhat unexpected, since inductive and resonance effects in both **8** and **9** should be similar, as demonstrated by the partial charge separation in these molecules.



7 **8** **9**

The difference in reactivity of **8** and **9** can be rationalized in terms of the steric effect of the 3-methyl group in **9** on ground-state energies and on the population of certain conformations, the latter being probably the most important. When the 3-position of the pyrazine ring is occupied by a methyl group, the 2-hydroxy-2-arylethyl moiety will preferentially adopt a conformation with the ArCHOH entity turned toward the nitrogen atom participating in the reaction. It is very interesting to note that a similar phenomenon has been observed in the Claisen rearrangement of allyl 2-alkylphenyl ethers.[16]

The observation that **7** is about 3 times more reactive than **8** can be attributed to electronic effects; i.e., the nitrogen atom participating in the reaction has a higher electron density in **7** than it does in **8**. The results also suggest that the 6-methyl group in **7** may have very little, if any, steric effect on the reaction.

Another noteworthy observation is the slight difference in reactivity between **8** and **10**. Comparison between the two compounds may be meaningless, since **10** contains no *p*-methoxy substituent. However, in view of the results obtained for **1–6**, it is reasonable to assume that the lower reactivity of **8** is mainly due to electronic effects rather than to phenyl-ring substituent effect. Comparison between the rate constant obtained for **3** and the values obtained for **7**, **8**, and **9** (Table I) indicates that the effects

(13) Riddick, J. A.; Bunger, W. B. in "Organic Solvents"; Wiley-Interscience: New York, 1970.
(14) Gol'dshtein, I. P.; Guryanova, E. N.; Alpatova, N. M.; Kessler, Yu. M. *Elektrokhimiya* **1967**, *3*, 1011; *Chem. Abstr.* **1968**, *68*, 99624.
(15) Schowen, R. L. *Prog. Phys. Org. Chem.* **1972**, *9*, 275. Swain, C. G.; Kuhn, D. A.; Schowen, R. L. *J. Am. Chem. Soc.* **1965**, *87*, 1553.
(16) Marvell, E. N.; Burreson, B. J.; Crandall, T. *J. Org. Chem.* **1965**, *30*, 1030. Marvell, E. N.; Richardson, B.; Anderson, R.; Stephenson, J. L.; Crandall T. *Ibid.* **1965**, *30*, 1032.

of methyl substitutions on the pyrazine ring on reactivity are not additive. If additivity existed, we would expect **3** to have a rate constant of 15.73×10^{-6} s^{-1} at 170 °C.

Experimental Section

All reactions involving organometallic reagents were carried out under a N_2 atmosphere. Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. IR spectra were recorded with a Perkin-Elmer 621 spectrophotometer. NMR spectra were recorded with a Varian XL-100 or a Brucker WP80 spectrometer, and the chemical shifts are given in δ downfield from internal Me_4Si. Mass spectra were recorded with a CEC 21-104 spectrometer. UV spectra were taken in 95% EtOH with a Beckman Acta-CV spectrophotometer. Elemental analyses were performed by Galbraith Laboratories Inc. Both qualitative TLC and preparative TLC were carried out on silica gel GF plates with hexane containing 15–40% acetone as the eluent. Column chromatography using hexane containing 5–30% acetone as the eluent was conducted on 60-mesh silica gel.

2-(2-Hydroxy-2-phenylethyl)-3,5,6-trimethylpyrazine (1). The compound was prepared according to the procedure of Levine et al.:[17] mp 126–127 °C (Et_2O) (lit.[17] mp 126–127 °C); IR (Nujol) 3200, 1603, 1584, 1495, 1456, 1053, 765, 700 cm^{-1}; UV λ_{max} 300 (sh) (ϵ 5270), 281 (9550), 215; (11 900) nm; ^1H NMR ($CDCl_3$) δ 2.39 (3 H, s, CH_3), 2.50 (3 H, s, CH_3), 2.52 (3 H, s, CH_3), 3.07 (2 H, d, J = 6 Hz, CH_2), 5.25 (1 H, t, J = 6 Hz., CH), 5.44 (1 H, m, OH), 7.24–7.52 (5 H, m, Ph); MS m/e 242 (1), 224 (14), 223 (11), 136 (100), 106 (29), 105 (34), 77 (38).

Anal. Calcd for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49; N, 11.59. Found: C, 74.16; H, 7.65; N, 11.41.

2-[2-Hydroxy-2-(*p*-methylphenyl)ethyl]-3,5,6-trimethylpyrazine (2). A solution of tetramethylpyrazine (13.6 g, 0.1 mol) was slowly added with stirring to a solution of phenyllithium in 150 mL of 7:3 benzene–ether (0.1 mol) at 0 °C. The mixture was stirred at room temperature for 2 h and then heated under reflux for 1.5 h. The red suspension so obtained was cooled to 0 °C, and a solution of *p*-tolualdehyde (12.0 g, 0.1 mol) in Et_2O (50 mL) was added dropwise. The reaction mixture was stirred at room temperature for 1 h. Water was added, and the Et_2O layer was separated, washed with water, and dried (Na_2SO_4). The solvent was removed under reduced prssure and the residue was recrystallized from Et_2O to give 10.7 g (42%) of **2** as fine needles: mp 99–101 °C; IR (Nujol) 3200, 3040, 3020, 1610, 1510, 1450, 1052, 810 cm^{-1}; UV λ_{max} 300 (sh) (ϵ 5500), 281 (9840), 216 (18 000) nm; ^1H NMR ($CDCl_3$) δ 2.36 (3 H, s, CH_3), 2.38 (3 H, s, CH_3), 2.49 (3 H, s, CH_3), 2.51 (3 H, s, CH_3), 3.06 (2 H, d, J = 6 Hz, CH_2), 5.20 (1 H, t, J = 6 Hz, CH), 5.37 (1 H, m, OH), 7.17 and 7.33 (4 H, AB q, J = 8 Hz, aromatic); MS m/e 256 (2), 238 (5), 237 (5), 223 (4), 137 (10), 136 (100), 135 (9), 123 (20), 120 (21), 119 (28), 91 (31), 54 (31).

Anal. Calcd for $C_{16}H_{20}N_2O$: C, 74.96; H, 7.86; N, 10.93. Found: C, 75.19; H, 7.96; N, 10.88.

2-[2-Hydroxy-2-(*p*-methoxyphenyl)ethyl]-3,5,6-trimethylpyrazine (3). The reaction of tetramethylpyrazine (13.6 g, 0.1 mol) with *p*-anisaldehyde (13.6 g, 0.1 mol) was carried out as described for **2**. Crystallization of the crude product from Et_2O gave 14.2 g (52%) of pure **3**: mp 97–98 °C; IR (CCl_4) 3210, 1613, 1587, 1516, 1442, 1256, 850–800 cm^{-1}; UV λ_{max} 300 (sh) (ϵ 4800), 281.5 (9700), 214 (12 300) nm; ^1H NMR ($CDCl_3$) δ 2.39 (3 H, s, CH_3), 2.49 (6 H, br s, 2 CH_3), 3.04 (2 H, d, J = 6 Hz, CH_2), 3.81 (3 H, s, OCH_3), 5.17 (1 H, t, J = 6 Hz, CH), 5.33 (1 H, m, OH), 6.88 and 7.25 (4 H, AB q, J = 8.5 Hz, aromatic); MS m/e 272 (<1), 254 (22), 136 (100), 135 (48), 71 (33), 69 (28), 57 (36), 54 (58), 46 (52), 43 (61), 42 (45).

Anal. Calcd for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.40; N, 10.29. Found: C, 70.33; H, 7.60; N, 10.19.

2-[2-Hydroxy-2-[*p*-(dimethylamino)phenyl]ethyl]-3,5,6-trimethylpyrazine (4). *n*-BuLi (50 mmol in about 25 mL of hexane) was added with stirring to a solution of diisopropylamine (5 g 50 mmol) in Et_2O (100 mL) at 0 °C. The mixture was stirred at 0 °C for 15 min. A solution of tetramethylpyrazine (6.8 g, 50 mmol) in Et_2O (100 mL) was slowly added, and the resulting red suspension was stirred at 0 °C for 20 min. *p*-(Dimethylamino)-benzaldehyde (7.4 g, 50 mmol) in Et_2O (140 mL) was added with stirring, and the yellow solution was left stirring at room temperature for 40 min. Water was added, and the Et_2O layer was separated, washed with water, and dried ($MgSO_4$). The Et_2O was evaporated under reduced pressure to give an oil (11.2 g). Purification by column chromatography (225 g of silica gel) afforded **4** (6.7 g, 47%). Crystallization from Et_2O gave pure **4** as needles: mp 105–107 °C; IR (Nujol) 3390, 2810, 1610, 1517, 1450, 1414, 1055, and 810 cm^{-1}; UV λ_{max} 300 (sh) (ϵ 1700), 280 (2700), 256.5 (4100), 211 (5000) nm; ^1H NMR ($CDCl_3$) δ 2.40 (3 H, s, CH_3), 2.50 (6 H, s, 2 CH_3), 2.96 (6 H, s, $N(CH_3)_2$), 3.05 (2 H, d, J = 6 Hz, CH_3), 5.15 (2 H, m, CH and OH), 6.75 and 7.32 (4 H, AB q, J = 9 Hz, aromatic); MS m/e 285 (0.4), 267 (47), 252 (14), 136 (18), 74 (67), 59 (100).

Anal. Calcd for $C_{17}H_{23}N_3O$: C, 71.54; H, 8.12; N, 14.73. Found: C, 71.20; H, 8.30; N, 14.54.

2-[2-Hydroxy-2-(*p*-chlorophenyl)ethyl]-3,5,6-trimethylpyrazine (5). The reaction of tetramethylpyrazine (6.8 g, 50 mmol) with *p*-chlorobenzaldehyde (7.0 g, 50 mmol) was carried out as described in the case of **2**. PTLC gave **5** (5.1 g, 37%). Recrystallization from acetone–water (1:1) gave pure **5** as needles: mp 78–80 °C; IR (neat) 3180, 1595, 1490, 1414, 1054, 823, 800–600 cm^{-1}; UV λ_{max} 300 (sh) (ϵ 6500), 281 (12 000), and 214 (21 000) nm; ^1H NMR ($CDCl_3$) δ 2.38 (3 H, s, CH_3), 2.49 (6 H, br s, 2 CH_3), 3.01 (2 H, d, J = 6 Hz, CH_2), 5.18 (1 H, t, J = 6 Hz, CH), 5.55 (1 H, m, OH), 7.35 (4 H, br s, aromatic); MS m/e 260, 258 (4, 12, M – H_2O), 140 (39), 139 (19), 136 (100), 97 (14), 70 (13), 57 (16), 56 (16), 54 (15), 42 (21).

Anal. Calcd for $C_{15}H_{17}ClN_2O$: C, 65.09; H, 6.19; N, 10.12; Cl, 12.81. Found: C, 64.78; H, 6.31; N, 9.95; Cl, 12.75.

2-[2-Hydroxy-2-(*p*-nitrophenyl)ethyl]-3,5,6-trimethylpyrazine (6). The reaction of tetramethylpyrazine (6.8 g, 50 mmol) with *p*-nitrobenzaldehyde (6.0 g, 40 mmol) was carried out as described in the case of **4** with one variation: a benzene solution of *p*-nitrobenzaldehyde was used. Workup afforded an oil which was purified by column chromatography (400 g of silica gel) to give 6.9 g of **6** (60%). Recrystallization from Et_2O–hexane gave yellow needles: mp 131–132 °C; IR (Nujol) 3350, 1610, 1600, 1520, 1495, 1454, 1345, 1070, 853 cm^{-1}; UV λ_{max} 300 (ϵ 9200), 281 (13 500), 213 (11 900) nm; ^1H NMR ($CDCl_3$) δ 2.43 (3 H, s, CH_3), 2.51 (6 H, s, 2 CH_3), 2.95–3.18 (2 H, m, CH_2), 5.39 (1 H, m, CH), 5.85 (1 H, m, OH), 7.64 and 8.25 (4 H, AB q, J = 8.5 Hz, aromatic); MS m/e 287 (18), 269 (7), 151 (26), 150 (29), 136 (100), 123 (27), 54 (46), 53 (38).

Anal. Calcd for $C_{15}H_{17}N_3O_3$: C, 62.70; H, 5.96; N, 14.63. Found: C, 62.84; H, 6.05; N, 14.78.

2-[2-Hydroxy-2-(*p*-methoxyphenyl)ethyl]-6-methylpyrazine (7). A solution of diisopropylamine (5.05 g, 50 mmol) in Et_2O (40 mL) was added to 47.1 mmol of *n*-BuLi in hexane (20 mL) at 0 °C. After the resulting solution was stirred for 15 min, a solution of 2,6-dimethylpyrazine (5.4 g, 50 mmol) in Et_2O (50 mL) was added slowly and the reaction mixture stirred at 0 °C for 30 min. A solution of *p*-methoxybenzaldehyde (5.4 g, 40 mmol) in Et_2O (40 mL) was added, and stirring at 0 °C was continued for an additional 30 min. Water was added, and the organic layer was separated, washed with water, and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure gave an amorphous solid (9.5 g). Two recrystallizations from Et_2O gave 1.0 g of needles: mp 90–92 °C. The remaining material was purified by column chromatography to yield an additional 5.2 g of pure **7** (total 6.2 g, 63%): mp 90–92 °C from Et_2O; IR (Nujol) 3240, 3020, 1617, 1590, 1516, 1259, 1040, 1035, 822 cm^{-1}; UV λ_{max} 306 (sh) (ϵ 2200), 275 (15 600), 224 (17 300), 210 (18 500) nm; ^1H NMR ($CDCl_3$) δ 2.55 (3 H, s, CH_3), 3.10 (2 H, d, J = 6 Hz, CH_2), 3.81 (3 H, s, OCH_3), 4.58 (1 H, OH), 5.11 (1 H, m, CH), 6.82 and 7.34 (4 H, AB q, J = 9 Hz, C_6H_4), 8.20 (1 H, s, pyrazine proton), 8.31 (1 H, s, pyrazine proton); MS m/e 244 (1.6), 226 (100), 225 (79), 211 (18), 183 (16), 135 (76), 108 (72), 77 (33).

Anal. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.84; H, 6.70; N, 11.54.

2-[2-Hydroxy-2-(*p*-methoxyphenyl)ethyl]-5-methylpyrazine (8). The reaction of 2,5-dimethylpyrazine (10.8 g, 0.1 mol) with *p*-methoxybenzaldehyde (13.6 g, 0.1 mol) was carried out as described in the case of **7**. PTLC and recrystallization from Et_2O gave pure **8** (260 mg, 1%) as plates: mp 110–113 °C; IR (Nujol) 3250, 1610, 1585, 1510, 1454, 1248, 1050, 834 cm^{-1}; UV

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Table III. Thermolysis of 3 in Diglyme-d_{14} at 170 ± 0.8 °C

	% reacn calcd from integration[a]		
t, h	arom peaks	OCH_3 peaks	CHO and CH peaks
4	10.1	11.6	9.6
8	19.3	23.7	19.1
12	25.9	29.2	23.1
17	34.0	38.1	34.5
22	42.2	45.9	41.9
28	50.8	53.9	53.8
34	57.3	60.4	59.7
43	64.0	68.6	62.2
48	70.8	72.6	69.6

[a] The accuracy of these determinations is ±3%.

λ_{max} 300 (sh) (ε 1700), 276 (8900), 224 (11 200), 210 (10 800) nm; ^1H NMR ($CDCl_3$) δ 2.54 (3 H, s, CH_3), 3.13 (2 H, d, J = 7 Hz, CH_2), 3.79 (3 H, s, OCH_3), 4.16 (1 H, m, OH), 5.08 (1 H, m, CH), 6.87 and 7.32 (4 H, AB q, J =9 Hz, C_6H_4), 8.28 (1 H, d, J = 1.5 Hz, pyrazine proton), 8.37 (1 H, d, J = 1.5 Hz, pyrazine proton); MS m/e 244 (1), 226 (31), 225 (56), 136 (39), 135 (59), 108 (53), 59 (100).

Anal. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 69.01; H, 6.71; N, 11.37.

This reaction was repeated several times and in each case the yield was low (ca. 1%). Large amounts of tar were isolated and there was some NMR evidence for the formation of condensation products.

2-[2-Hydroxy-2-(*p*-methoxyphenyl)ethyl]-3-methylpyrazine (9). 2,3-Dimethylpyrazine (5.4 g, 50 mmol) was reacted with *p*-methoxybenzaldehyde (6.8 g; 50 mmol) as described in the case of **7**. Workup afforded an oil (10.8 g) which was separated by column chromatography to yield pure **9** (5.9 g, 48%). Recrystallization from Et_2O gave plates: mp 89–91 °C; IR (Nujol) 3325, 1610, 1582, 1504, 1455, 1247, 1050, 837 cm^{-1}; UV λ_{max} 300 (sh) (ε 1400), 275 (9000), 224 (10600), 211 (9300) nm; ^1H NMR ($CDCl_3$) δ 2.45 (3 H, s, CH_3), 3.13 (2 H, m, CH_2), 3.78 (3 H, s, OCH_3), 4.78 (1 H, m, OH), 5.22 (1 H, m, CH), 6.87 and 7.33 (4 H, AB q, J = 9 Hz, aromatic), 8.29 (2 H, s, pyrazine protons); MS m/e 244 (1.5), 226 (37), 225 (71), 211 (13), 136 (59), 135 (88), 108 (82), 92 (20), 77 (37), 67 (100).

Anal. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 69.00; H, 6.71; N, 11.58.

2-[2-Hydroxy-2-phenylethyl)pyrazine (10). The reaction of methylpyrazine (9.4 g, 0.1 mol) with benzaldehyde (10.6 g 0.1 mol) was carried out as described in the case of **7**. Workup gave an oil (7.9 g) which was purified by PTLC to give 5.1 g (25%) of pure **10**. Recrystallization from Et_2O–hexane (3:1) gave needles: mp 87–88 °C (lit.[18] mp 88–89 °C); IR (Nujol) 3280, 1605, 1586, 1497, 1455, 1052 cm^{-1}; UV λ_{max} 305 (ε 850), 273 (6300), 267 (7050), 256 (5450), 208 (12 300) nm; ^1H NMR ($CDCl_3$) δ 3.20 (2 H, d, J = 6 Hz, CH_2), 4.13 (1 H, d, OH), 5.22 (1 H, m, CH), 7.24–7.52 (5 H, m, Ph), 8.38–8.56 (3 H, m, pyrazine protons); MS m/e 200 (1), 182 (23), 181 (87), 167 (25), 149 (81), 106 (28), 105 (36), 104 (19), 94 (36), 77 (40), 70 (57), 67 (57), 65 (76), 41 (100), 39 (64).

Anal. Calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 72.06; H, 6.01; N, 14.92.

2-[2-Deuterioxy-2-(*p*-methylphenyl)ethyl]-3,5,6-trimethylpyrazine (2-OD). The pyrazine **2** (150 mg) in anhydrous Et_2O (10 mL) was washed with D_2O (3 mL). The layers were separated and the process was repeated twice. The Et_2O solution was dried ($MgSO_4$) and evaporated under reduced pressure. The remaining solid was dried (60 °C, 0.05 mmHg) for 1 h. The NMR spectrum of **2**-OD indicated 75% OD.

2-[2-Deuterioxy-2-(*p*-methoxyphenyl)ethyl]-3,5,6-trimethylpyrazine (3-OD). A sample of **3**-OD was prepared as described in the case of **2**-OD. The NMR spectrum indicated 72% OD. Control samples were also made by treating both **2** and **3** with H_2O instead of D_2O.

Kinetic Experiments. Reactions were carried out in either diglyme-d_{14} or in DMF-d_7 (both from Merck Sharp and Dohme, Canada, Ltd.). Both solvents were dried over molecular sieves. A 0.2 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 of all the samples at a given temperature were carried out simultaneously. The tubes were placed in a constant-temperature oil bath preheated to the desired temperature (±0.8 °C at 160–170 °C). At different time intervals the tubes were removed from the bath and cooled to room temperature, and the progress of the reaction in each case was followed by NMR spectroscopy. The method is illustrated for the case of **3**, in diglyme-d_{14} at 170 ± 0.8 °C. The chemical shifts of both reactant and products are presented below in δ upfield or downfield from the diglyme-d_{14} quintet at δ 3.22 [the other diglyme-d_{14} peaks are at δ 3.40 (m) and 3.49 (m)]. **3**: δ 2.20 (3 H, s, CH_3), 2.29 (3 H, s, CH_3), 2.33 (3 H, s, CH_3), 2.92 (2 H, ABX m, CH_2), 3.77 (3 H, s, OCH_3), 4.59 (1 H, m, OH), 5.26 (1 H, m, CH), 7.22 and 7.74 (4 H, AB q, aromatic). **Tetramethylpyrazine**: δ 2.26 (12 H, s, 4 CH_3). ***p*-Methoxybenzaldehyde**: δ 3.92 (3 H, s, OCH_3), 7.48 and 8.36 (4 H, AB q, aromatic), 10.59 (1 H, s, CHO).

The reaction percentage was calculated from the measured integration ratio of peaks of both reactants and products in the aromatic region, OCH_3 region, and CHO and CH regions. In cases where no OCH_3 group was present, only the aromatic peaks and the CHO and CH peaks were analyzed.

A typical kinetic run is illustrated in Table III. In each case the average percent reaction was taken for calculating the rate constants.

Thermolysis of 4. A solution of **4** (0.2 M) in diglyme-d_{14} was heated at 170 °C for 4 h. TLC indicated that all of the starting material had reacted but only trace amounts of tetramethylpyrazine and (dimethylamino)benzene could be detected. ^1H NMR spectroscopy of the mixture indicated the presence of **11** (>90%): δ 2.40 (3 H, s, CH_3), 2.43 (3 H, s, CH_3), 2.50 (3 H, s, CH_3), 2.94 (6 H, s, $N(CH_3)_2$), 6.68 and 7.44 (4 H, AB q, J = 9 Hz, aromatic), 7.02 and 7.69 (2 H, AB q, J = 16 Hz, vinylic). GC/MS gave one major peak: m/e 267 (100), 266 (59), 252 (59), 250 (17), 236 (17), 223 (19), 211 (14), 172 (14), 171 (38), 158 (40), 156 (14), 155 (16), 147 (21), 141 (16), 134 (29), 128 (19), 121 (17), 115 (18), 109 (19), 92 (20).

Acknowledgment. The author gratefully acknowledges the encouragement of Dr. E. B. Sanders during the course of this research. The author is also indebted to Dr. J. F. Whidby, Dr. T. Phil Pitner, and Ronald Bassfield for NMR spectral analyses and for helpful discussion. The help of Dr. Gary Forrest, Gunars Vilcins, and E. Thomas for spectral analyses is fully acknowledged.

Registry No. **1**, 10130-14-0; **2**, 72725-72-5; **2**-OD, 72725-73-6; **3**, 72725-74-7; **3**-OD, 72725-75-8; **4**, 72725-76-9; **5**, 72725-77-0; **6**, 72725-78-1; **7**, 72725-79-2; **8**, 72725-80-5; **9**, 72725-81-6; **10**, 36914-69-9; **11**, 72725-82-7; tetramethylpyrazine, 1124-11-4; *p*-tolualdehyde, 104-87-0; *p*-anisaldehyde, 123-11-5; *p*-(dimethylamino)benzaldehyde, 100-10-7; *p*-chlorobenzaldehyde, 104-88-1; *p*-nitrobenzaldehyde, 555-16-8; 2,6-dimethylpyrazine, 108-50-9; 2,5-dimethylpyrazine, 123-32-0; 2,3-dimethylpyrazine, 5910-89-4; methylpyrazine, 109-08-0; benzaldehyde, 100-52-7.

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