The Mechanism of Thermal Eliminations. Part 20.[1] The Relative Rates of Pyrolysis of the 2-Ethoxy, 2-Isopropoxy, and 2-t-Butoxy Derivatives of Pyrazine and Pyrimidine to Pyrazin-2-one and Pyrimidin-2-one, respectively: Polarity of the Transition States and the Importance of Nucleophilic Attack

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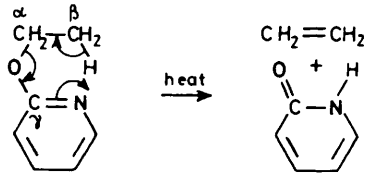
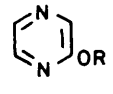
We have measured rates of thermal elimination of the title compounds to give the corresponding cyclic amides, between 587.0 and 698.5 K. The relative rates (primary:secondary:tertiary) at 600 K are 1:27.0:3720 for the pyrazines, and 1:26.4:4150 for the pyrimidines. These ratios are somewhat larger than for the corresponding 2-alkoxypyridines and suggest that C–O bond breaking is kinetically more significant in the pyrazines and pyrimidines, leading to a transition state with greater carbocationic character. This is consistent with electron withdrawal provided by the aza 'substituent' facilitating C–O bond cleavage. It does not however lead to a general increase in reactivity (as would be the case for pyrolysis of comparable esters) because this electron withdrawal reduces the nucleophilicity of the nitrogen involved in the elimination. This latter is particularly important for the primary and secondary compounds (which have more E_i-like transition states) than for the tertiary compounds, which therefore show a normal reactivity *vs.* rate spread pattern. The importance of the nucleophilicity of the nitrogen in the alkoxy-heterocycles, and its ability to be modified, may stem in part from the dual pathway available for transmission of substituent effects in the aromatic ring.

Previously one of us showed that 2-ethoxypyridine undergoes unimolecular first-order thermal elimination to give ethylene and 2-pyridone according to the mechanism shown in the Scheme.[2] Additional mechanistic information was derived from the effects of substituents,[3] and of nitrogen atoms replacing a CH group within the ring,[4] as follows. (i) Electron supply to the C=N bond raises its nucleophilicity, and that of the nitrogen in particular, thereby increasing the reaction rate. (ii) Electron withdrawal from the C–O bond aids its cleavage and so increases the reaction rate; this effect is more important than (i). (iii) If a molecule possesses a substantially higher C=N bond order, then this becomes the factor of overriding kinetic significance; a high bond order gives rise to a substantially increased rate. (iv) The polarity of the transition state, as indicated by the rate ratio (primary:secondary:tertiary) for alkoxypyridines of 1:18.0:1675 at 600 K, is less than that for the pyrolysis of the corresponding acetates, which give relative rates 1:28.8:3315.

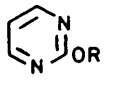
In order to learn more about the reaction transition state, we have measured the relative rates at 600 K of elimination of 2-ethoxy, 2-isoproproxy, and 2-t-butoxy derivatives of pyrazine (**1**) and pyrimidine (**2**). Very recently, while this work was in progress, Konakahara *et al.* reported Arrhenius parameters (but no rate data) for 2-isopropoxy- and 2-t-butoxypyrazine, obtained between 798 and 738 K for the former, and 660 and 630 K for the latter.[5] However, no data were reported for 2-ethoxypyrazine, and the differences in the temperature ranges used for the secondary and tertiary compounds means that large extrapolations are needed to determine the relative rates. At 600 K the tertiary:secondary rate ratio is predicted by their data to be 190:1 but this is, as we shall show, much too high.



Scheme.



(**1**) R = Et, Pr^i, or Bu^t



(**2**) R = Et, Pr^i, or Bu^t

Results and Discussion

Each compound gave excellent first-order kinetic results, linear to >98% of reaction. Rate coefficients were reproducible, there were no deviations on the Arrhenius plots, as indicated by the high correlation coefficients, and the stoicheiometry was 1.99 (±0.02):1. The rate data are given in Table 1; for comparison it should be noted that the corresponding primary, secondary, and tertiary rate coefficients for the alkoxypyridines at 600 K were 12.3, 222, and 20 100 s^{-1}, respectively.[4] The rate ratios for each series of compounds are set out in Table 2, Main features of the results are as follows.

(i) The spread of rates for pyrolysis of both pyrazines and pyrimidines is greater than for the pyridines. This suggests that the transition state for elimination from the former two compounds has more carbocationic character. This is to be expected since the additional electron withdrawal by the extra nitrogen in the ring should facilitate C–O bond cleavage, this being the most rate-controlling step of the reaction. Moreover we would expect that since electron withdrawal by two *ortho*-nitrogen atoms will be greater than by an *ortho*- and a *meta*-nitrogen atom, the polarity of the transition state should be greater for pyrimidine, as appears to be the case.

(ii) In all previous work we have found that increased electron withdrawal from the C_γ (as for example in the corresponding

Table 1. Pyrolysis of 2-alkoxypyrazines and 2-alkoxypyrimidines (ROAr)

R	Heterocycle	T/K	10^3k/s^{-1}	log(A/s^{-1})	E/kJ mol^{-1}	Corr. coefft.	10^6k/s^{-1} at 600 K
Et	Pyrazine	*a*	*a*	12.581	207.88	*a*	5.60
Pr^i	Pyrazine	634.4	1.28	13.197[b]	195.41[b]	0.9999	151
		649.9	3.04				
		664.5	6.82				
		678.7	14.8				
		698.5	37.5				
Bu^t	Pyrazine	587.0	9.66	13.533[c]	174.74[c]	0.9999	20 820
		600.5	21.1				
		613.9	46.3				
		635.7	149				
Et	Pyrimidine	*a*	*a*	13.003	206.35	*a*	10.8
Pr^i	Pyrimidine	613.9	0.688	13.167	191.90	0.9999	285
		637.7	2.79				
		649.9	5.36				
		664.5	12.5				
		678.7	25.2				
		698.5	64.1				
Bu^t	Pyrimidine	587.0	21.1	13.432	169.76	0.9999	44 830
		600.5	46.1				
		613.9	97.1				
		615.6	106				

[a] Data given in ref. 4. [b] Ref 5. gives 13.2 s^{-1} and 197.07 kJ mol^{-1}. [c] Ref 5. gives 12.65 s^{-1} and 164.01 kJ mol^{-1}.

Table 2. Primary:secondary:tertiary (P:S:T) rate ratios for 2-alkoxyheterocycles

	(P: S : T)	T/S	k_{rel} P	k_{rel} T
Pyridines	1 : 18.0 : 1675	91.4	1	1
Pyrazines	1 : 27.0 : 3720	138	0.455	1.035
Pyrimidines	1 : 26.4 : 4160	158	0.878	2.23

elimination in esters) gives rise to an increased reaction rate (*e.g.* ref. 6). The last two columns of Table 2 show that while this is just about qualitatively true for the tertiary compounds, it is not true for the primary ones (the values for the secondary compounds fall in between). We suggest the reason is that the aza 'substituent' retards the elimination by reducing the nucleophilicity of the nitrogen involved in the six-membered ring (Scheme). Thus although on the one hand C–O cleavage is facilitated, this is offset by the reduced nucleophilicity of the nitrogen. A comparable dual substituent effect must also apply in, for example, the pyrolysis of esters where electron withdrawal reduces the nucleophilicity of the carbonyl oxygen, but for esters this appears to be less important than in the present case. The unique aspect of these heterocycles seems to be that the ring provides an additional pathway for modification of the nucleophilicity of the nitrogen, and this, combined with the greater inherent nucleophilicity of nitrogen than of oxygen, gives this feature more importance than in esters. Because of the spectrum of transition states that applies to thermal elimination, the importance of nucleophilic attack lies in the order primary > secondary > tertiary.[7] Consequently the tertiary compounds (with the most *E*1-like transition-state structure) show the rate spread *vs.* reactivity pattern nearest to that expected.

(iii) Since nucleophilic attack should be more important for the primary compounds, one might expect that for these a qualitative correlation of reactivity with basicity of the heterocycle could apply.* This is indeed the case, the reactivity order being pyridine > pyrimidine > pyrazine. However, the correlation of k_{rel} with pK_a is far from quantitative because of the dual effect of the heteroatom noted under (ii). For the tertiary compounds where C–O bond breakage is kinetically more significant, no correlation exists at all.

(iv) The results for pyrazine and pyrimidine do not fit into the previously observed pattern for esters in one further way. Variations in the primary:secondary:tertiary rate ratio have been shown hitherto to be derived mainly from changes in the secondary:primary values,[8] but the present results do not show this. For example between pyridine and pyrimidine the secondary:primary ratio increases by 50% whereas the tertiary:secondary ratio increases by 72%; this may again reflect the two opposing effects of the substituents on the rate-contributing steps.

(v) Our results show a measure of internal consistency in that the log(A/s^{-1}) values for the secondary and tertiary compounds are greater than those for the corresponding primary compounds, as expected on statistical grounds. Although the Arrhenius parameters reported by Konakahara *et al.* for 2-t-butoxypyrazine (see footnote to their Table 2) differ somewhat from ours, their data were obtained in a similar temperature region. If one calculates from their parameters rate coefficients at the temperatures we employed, the values agree (with only one exception) to within ± 1% of ours, which is remarkable in view of the difficulty of measuring absolute (as opposed to relative) temperature at high values. Their parameters for 2-isopropoxypyrazine (see footnote to their Table 2) are very close to those that we have obtained, but because they were determined at very high temperatures, any small errors in them lead to large errors if large extrapolations are made. Thus extrapolation of their data to 600 K leads to a calculated tertiary:secondary ratio which is too large by 50%.

Experimental

2-Isopropoxypyrazine.—2-Chloropyrazine (5.0 g, 0.044 mol; Aldrich) was heated under reflux with sodium (2 g, 0.086 mol) in propan-2-ol (150 ml) during 2 h. Filtration and normal work-up gave 2-isopropoxypyrazine (3.4 g, 59%), b.p. 42 °C at 3.0 mmHg (lit.,[9] 74.5 °C at 22 mmHg); n_D^{20} 1.4885; τ($CDCl_3$) 1.82 (1 H, s, H-3), 1.92 (2 H, m, H-5, -6), 4.71 (1 H, sept, CH), and 8.66 (6 H, d, CH_3).

2-Chloropyrazine.—Further commercial supplies of this compound were unobtainable and it was therefore prepared by each of the following routes:

(i) *From pyrazine* N-*oxide.* Pyrazine (10 g, 0.125 mol) in acetic acid (125 ml) was heated with 30% hydrogen peroxide (14.2 g) in acetic acid (100 ml) at 70—80 °C (ref. 10) to give pyrazine *N*-oxide (8.6 g, 72%). This was heated with phosphoryl chloride according to the literature method[11] except that liquid–liquid extraction (ether) was used during work-up. This route was rather unsatisfactory because of the difficulty of adding the oxide directly into the hot phosphoryl chloride. Interaction of the vapour from the latter with the oxide produced a black intractable solid which tended to block the inlet tube. Work-up[11] gave *ca.* 3.5 g (35%) of crude 2-chloropyrazine, which was added to that produced by the following method.

(ii) *From 2-aminopyrazine.* Sodium nitrite (16.4 g) in conc. sulphuric acid (89 ml) was heated until the solution was clear, then cooled and added to 2-aminopyrazine (20 g, 0.21 mol).[12] After 20 min, the mixture was warmed to 40 °C, poured onto crushed ice, adjusted to pH 6 with 40% sodium hydroxide, then continuously extracted with ether to give crude 2-hydroxy-

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pyrazine, which was purified by vacuum sublimation; yield 5 g (25%), m.p. 188 °C (lit.,[13] 188—190 °C).

(iii) *From glycineamide hydrochloride.* The literature method[14] on a 0.4 mol scale gave, after purification by sublimation, 2-hydroxypyrazine (21 g, 56%), m.p. 188 °C.

The hydroxy product from (ii) was warmed for a few minutes with freshly distilled phosphoryl chloride (30 ml) in a flask equipped with a stirrer and drying tube, then heated under reflux during 40 min. The cooled mixture was poured onto crushed ice (300 g) and continously extracted (ether), and the dried product, together with that from (i), was fractionally distilled to give 2-chloropyrazine (8.5 g, 84%), b.p. 93 °C at 120 mmHg; $\tau(CDCl_3)$ 1.35 (1 H, s, H-3), 1.46 (1 H, d, H-6), and 1.57 (1 H, d, H-5). Similar treatment of the hydroxy compound from batch (iii) gave 2-chloropyrazine (16 g, 64%).

2-*t-Butoxypyrazine.*—Potassium t-butoxide was prepared from t-butyl alcohol [dried by distilling from sodium and collecting the fraction of b.p. 82 °C (traces of moisture caused the subsequent reaction to fail)]. 2-Chloropyrazine (6 g, 0.054 mol) in dry dimethylformamide (DMF) (70 ml) was cooled to 0 °C and treated with potassium t-butoxide (12.5 g, 0.011 mol), and the mixture was allowed to warm to room temperature. The product was poured into water, and the organic layer washed *thoroughly* with water (otherwise t-butoxypyrazine azeotropes with residual DMF during distillation). The dried extract was fractionally distilled to give 2-t-butoxypyrazine (5 g, 80%), b.p. 125 °C at 150 mmHg (lit.,[5] 76.5 °C at 19 mmHg); n_D^{20} 1.4876; $\tau(CDCl_3)$ 1.87 (1 H, d, ArH), 1.95 (2 H, m, ArH), and 8.43 (9 H, s, CH_3); the product crystallised on refrigeration.

2-*Isopropoxypyrimidine.*—Reaction of 2-chloropyrimidine with sodium and propan-2-ol according to the literature method[14] gave 2-isopropoxypyrimidine (70%), b.p. 33 °C at 0.4 mmHg (lit.,[14] 90—91 °C at 18 mmHg); $\tau(CDCl_3)$ 1.54 (2 H, d, H-4, -6), 3.18 (1 H, t, H-5), 4.76 (1 H, sept, CH), and 8.63 (6 H, d, CH_3).

2-*t-Butoxypyrimidine.*—2-Chloropyrimidine (9.0 g, 0.54 mol) was heated under reflux with potassium (4.5 g) in dry t-butyl alcohol (150 ml) during 2 h. Filtration and normal work-up gave 2-*t-butoxypyrimidine* (70%), b.p. 40 °C at 0.4 mmHg; n_D^{20} 1.4930 (Found: C, 63.0; H, 8.1; N, 18.3. $C_8H_{12}N_2O$ requires C, 63.1; H, 7.95; N, 18.4%); $\tau(CDCl_3)$ 1.60 (2 H, d, H-4, -6), 3.20 (1 H, t, H-5), and 8.43 (9 H, s, CH_3).

Kinetic Studies.—The general static method using a stainless steel reactor has been described in earlier papers. Leading references and improvements to the apparatus have recently been described.[1] Each compound gave excellent first-order kinetics with linearity to >97% of reaction. Rates were reproducible to ±1% and there were no deviations in the Arrhenius plots, as indicated by the correlation coefficients. The stoicheiometry of the reactions was 1.99 (±0.02):1.

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