The Mechanism of Thermal Eliminations. Part 18.[1] Relative Rates of Pyrolysis of 2-Ethoxypyrazine, 3-Ethoxypyridazine, 2- and 4-Ethoxypyrimidine, 3-Chloro-6-ethoxypyridazine, and 2-Chloro-4-ethoxypyrimidine: the Effect of the Aza 'Substituent' and π-Bond Order on the Elimination Rate

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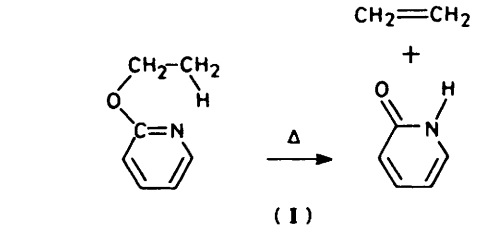
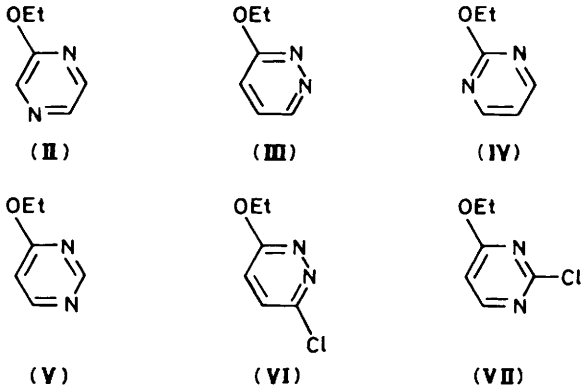
A kinetic study has been made of the first-order thermal decomposition of the title compounds into ethylene and the corresponding aza-substituted pyridines, between 650 and 713 K. The relative elimination rates at 650 K are (2-ethoxypyridine = 1): 0.545, 10.0, 1.03, 1.12, 9.68, and 3.28, respectively. The electronic effects of the aza 'substituent' are small, and a more important factor appears to be the C–N π-bond order; this latter accounts for the high reactivity of the pyridazines. The effects of the chloro substituent and of the aza 'substituent' are explicable in terms of a balance between electron withdrawal from the C–O bond (producing activation) and from the nitrogen involved in the cyclic transition state (producing deactivation). The effects of the chloro substituents confirm that the most important step of the reaction is breaking of the C–O bond. The statistically corrected rate (per ring nitrogen) of 2-ethoxypyrimidine is unexpectedly low. This may reflect difficulty in achieving the coplanar transition state in which the lone pairs in the *s*-orbitals of oxygen and the nitrogen not involved in the elimination are brought into close proximity.

Previously one of us showed that 2-ethoxypyridine undergoes unimolecular first-order thermal decomposition into ethylene and 2-pyridone (**I**) in a reaction which is very similar to the thermal elimination of esters.[2] In a subsequent paper the effects of methyl substituents in the aromatic ring were examined and at 600 K the elimination rates relative to 2-ethoxypyridine were 1.57, 1.02, 0.74, and 1.08 for 3-, 4-, 5-, and 6-methyl, respectively.[3] These were consistent with the dual effect of the substituent, *viz.* electron supply to the C–O bond reducing the rate of elimination (as is true also for esters) and electron supply to the nitrogen increasing its nucleophilicity and hence the rate of elimination, the former effect being the more important one; functions located *ortho* and *para* to methyl are affected more than those *meta* to it. The effect of the 3-methyl substituent also indicated the reaction to be sterically accelerated, though as a result of the present investigation additional factors can be proposed to account for the high reactivity of the 3-methyl compound. Recently Konakahara *et al.*[4] have reported rate data for the elimination corresponding to (**I**), for some alkoxypyrazines, but did not report data for 2-ethoxypyrazine itself, nor rates relative to 2-ethoxypyridine.

In order to learn more about the elimination we felt it would be valuable to have rate data for the ethoxy derivatives of pyrazine (**II**), pyridazine (**III**), and pyrimidine (**IV**), (**V**), and so determine the effect of the aza group on the elimination rate. Arising from our preparative procedure, we also had available 3-chloro-6-ethoxypyridazine (**VI**) and 2-chloro-4-ethoxypyrimidine (**VII**) and have therefore obtained rate data for these, so providing electron-withdrawing substituent effect data to complement those obtained for the methyl substituent.



(**I**)



(**II**) (**III**) (**IV**)

(**V**) (**VI**) (**VII**)

Results and Discussion

Each compound gave excellent and reproducible kinetics, first order to >95% of reaction (greater in the case of the pyrazine and pyridazine compounds since there is no significant secondary decomposition of the vinyl products; the vinylpyrimidines are slightly less stable in this respect). The stoicheiometry of the eliminations in ten half-lives was 1.99 ± 0.03. The rate data (Table 1) gave very good Arrhenius plots (indicated by the correlation coefficients) and the log (A/s^{-1}) values are all of the order expected for the postulated electrocyclic mechanism.

From the rate data obtained previously with 2-ethoxypyridine[3] [which give k(650 K) = 0.255 × 10^{-3}s^{-1}], the rates at 650 K relative to this may be calculated and are given in Table 2.

Table 1. Pyrolysis of compounds ArOEt

Compound	T/K	10^3k/s^{-1}	log(A/s^{-1})	E/kJ mol^{-1}	Correlation coefficient	10^3k/s^{-1} (650 K)
(II)	649.9	0.137	12.851	207.88	0.9989	0.139
	664.5	0.297				
	678.7	0.387				
	698.5	2.14				
	712.9	4.00				
	722.6	6.41				
(III)	649.9	2.47	13.291	197.68	0.9990	2.56
	664.5	5.67				
	678.7	12.3				
	698.5	32.8				
	712.9	62.2				
(IV)	649.9	0.256	13.03	206.35	0.9996	0.262
	664.5	0.581				
	678.7	1.40				
	698.5	3.88				
	712.9	7.54				
	722.6	11.7				
(V)	649.9	0.270	13.201	208.36	0.9990	0.285
	664.5	0.636				
	678.7	1.64				
	698.5	4.29				
	712.9	8.44				
	722.6	13.0				
(VI)	613.9	0.29	13.129	195.78	0.9999	2.47
	649.9	2.46				
	664.5	5.45				
	678.7	12.0				
	698.5	30.1				
	712.9	59.4				
(VII)	651.4	0.900	12.033	188.01	0.9999	0.836
	671.4	2.53				
	698.2	9.08				
	721.6	26.7				

Table 2. Elimination rates at 650 K relative to 2-ethoxypyridine

Compound	k_{rel}[a]
2-Ethoxypyrazine	0.545
3-Ethoxypyridazine	10.0
2-Ethoxypyrimidine	0.513
4-Ethoxypyrimidine	1.12
3-Chloro-6-ethoxypyridazine	9.68
2-Chloro-4-ethoxypyrimidine	3.28

[a] Statistically corrected for the number of ring nitrogens adjacent to ethoxy.

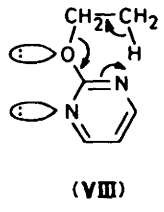
These $k_{rel.}$ values are given in terms of rate per C=N bond adjacent to the ethoxy group, and thus the observed elimination rate for 2-ethoxypyrimidine must be statistically corrected by dividing by two.

2-*Ethoxypyrazine* (**II**).—This is less reactive than 2-ethoxypyridine by a factor of 0.54. This can be readily explained in the manner used for the previously observed methyl substituent effects. Electron withdrawal by the 'substituent' nitrogen will aid C–O bond breakage, but diminish the nucleophilicity of the nitrogen involved in the six-membered transition state. The 'substituent' nitrogen has both $-I$ and $-M$ effects and so electron withdrawal will be greater from the *para* (and *ortho*) than from the *meta* position. Thus in pyrazine the $-I$ effect will aid C–O bond breaking, but this will be outweighed by the greater combined $-I$ and $-M$ effects reducing the nucleophilicity of the other nitrogen; reduced reactivity should be, and is, observed.

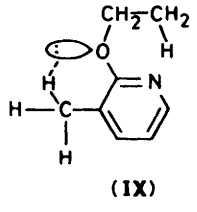
4-*Ethoxypyrimidine* (**V**).—This represents the reverse situation to the above. Now the 'substituent' nitrogen *is para* to the ethoxy group, and *meta* to the nitrogen involved in the elimination. The rate-accelerating effect upon the former should now outweigh the rate-retarding effect upon the latter producing overall activation, as shown by the observed relative rate of 1.12.

2-*Chloro*-4-*ethoxypyrimidine* (**VII**).—The reactivity of this compound can also be accounted for in a straightforward manner. In addition to the effects noted above for 4-ethoxypyrimidine, there is now a chloro substituent *meta* to the ethoxy group (affected therefore by the $-I$ effect) and *ortho* to the nitrogen involved in the elimination (affected by the $-I$ and $+M$ effects). The net electron withdrawal is greater at the former position, so an increase in reactivity should be observed as is the case, the k_{rel} value being 3.28 (and 2.93 relative to 4-ethoxypyrimidine). It should be noted that because of the unique dual function of the substituent, chloro does not produce the opposite effect to methyl in the analogous position (*i.e.* in 6-methyl-2-ethoxypyridine). Both activate the respective molecules, but chloro activates by a greater amount.

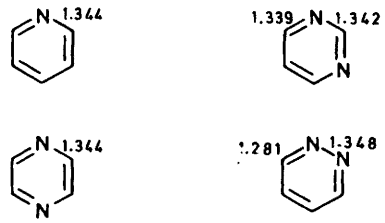
2-*Ethoxypyrimidine* (**IV**).—This compound is abnormally unreactive. The 'substituent' nitrogen *ortho* to the ethoxy group should produce a large rate acceleration ($-I$, $-M$ effect) outweighing the deactivation produced by $-I$ electron withdrawal from the *meta* nitrogen involved in the elimination. This compound should therefore be of similar reactivity to the 4-isomer (after correction for the number of ring nitrogens available for participation in the elimination). It is in fact about half as reactive and we suggest that this may arise because of difficulty in achieving the coplanar transition state (**VIII**) which



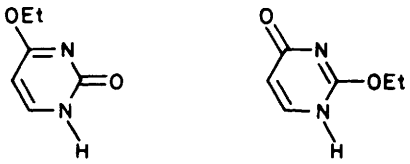
(VIII)



(IX)



Scheme. Calculated bond lengths (Å)



(X)

(XI)

requires juxtaposition of the lone pairs in the oxygen and nitrogen *s*-orbitals. This being so, a factor contributing to the previously observed[3] high reactivity of 2-ethoxy-3-methylpyridine could be favourable hydrogen bonding between the C–H bonds of the methyl group and the lone pair on oxygen (**IX**).

3-*Ethoxypyridazine* (**III**).—The reactivity of this compound cannot be explained solely (or indeed even partially) in terms of the electronic effect of the aza 'substituent'. This is *ortho* to the nitrogen involved in the elimination and so should produce strong deactivation, which should be only partially compensated for by the weaker electron withdrawal from the *meta* ethoxy group. Overall then the molecule should be less reactive than 2-ethoxypyridine whereas it is in fact a very substantial ten times more reactive.

We suggest that the reason for the anomaly lies in the exceptionally high C–N bond order in pyridazine. The higher the bond order the more nucleophilic should be the C–N π-bond giving a faster reaction (iminoether derivatives in which the π-bond is fully localised are extremely reactive[3]). Bond lengths calculated for pyridine and the diazines are shown in the Scheme.[5]

Experimental values have been obtained for each molecule except pyrimidine and the agreement with the calculated values is very good.[6] We therefore employ the calculated values since all the data are available under one 'condition'. These show that for pyridine, pyrazine, and pyrimidine, the C–N bond lengths (and hence the bond orders) are essentially identical. For pyridazine however, the C–N bond is substantially shorter and hence the bond order is significantly higher, which readily accounts for the observed reactivity.

The marked bond fixation in this molecule was also very evident in the n.m.r. data, the coupling constant between 5- and 4-H (13 Hz) being almost double that between 5- and 6-H (7 Hz). Thus the 2,3-, 4,5-, and 1,6-bonds have substantially higher orders than the other three.

We have discounted in the above discussion, any possibility of reaction involving the *N*-alkyl tautomer, since it has been specifically shown that 2-ethoxypyrimidine rearranges to this extremely slowly, even in the presence of a catalysing base.[7]

3-*Chloro*-6-*ethoxypyridazine* (**VI**).—The effect of the chloro substituent here is readily explained. It will have a greater electron withdrawal from the *meta* nitrogen (producing deactivation) than from the *para* ethoxy (producing activation). Overall then deactivation relative to 3-ethoxypyridazine should be, and is, observed. It is noteworthy that the factor (0.97) by which 3-chloro-6-ethoxypyridazine is less reactive than 3-ethoxypyridazine is smaller than the factor (2.93) by which 2-chloro-4-ethoxypyrimidine is more reactive than 4-ethoxypyrimidine. This confirms that the most important step in the reaction is breaking of the C–O bond rather than nucleophilic attack by nitrogen, and these same conclusions were previously reached from our study of the effects of the methyl substituents.

2,4-*Diethoxypyrimidine*.—Preliminary runs with a sample of 2-chloro-4-ethoxypyrimidine (subsequently found to contain 30% of 2,4-diethoxypyrimidine) gave kinetics which accelerated during the initial part of the reaction. We believe this was due to the formation of (**X**) or (**XI**) (probably a mixture of both) either of which would then undergo further and more rapid elimination due to the presence of the localized π-bond. We hope to investigate elimination from compounds of this type at a later time.

Experimental

2-*Ethoxypyrazine*.—2-Chloropyrazine (5.0 g, 0.044 mol; Aldrich) was heated under reflux with sodium (1 g, 0.043 mol) in absolute ethanol (50 ml). Filtration and normal work-up followed by fractional distillation gave 2-ethoxypyrazine (4.6 g, 84%), b.p. 33 °C at 3.0 mmHg (lit.,[8] 72—73 °C at 30 mmHg); n_D^{20} 1.4977; τ($CDCl_3$) 1.82 (1 H, s, ArH), 1.92 (2 H, m, ArH), 4.71 (1 H, sept, CH), and 8.66 (6 H, d, CH_3).

3-*Ethoxypyridazine*.—3,6-*Dihydroxypyridazine*. This compound, m.p. 300—302 °C (lit.,[9] 299.5—300 °C) was prepared in 85% yield from maleic anhydride (34.3 g, 0.35 mol) and hydrazine sulphate (37.5 g, 0.35 mol) by the literature method.[9]

3,6-*Dichloropyridazine*. Reaction of 3,6-dihydroxypyridazine (25 g, 0.22 mol) with phosphonyl chloride (300 ml) by the literature method[9] gave 3,6-dichloropyridazine (28.5 g, 87%), m.p. 60 °C (lit.,[9] 68—69 °C).

3-*Chloro*-6-*ethoxypyridazine*. Reaction of 3,6-dichloropyridazine (20 g, 0.135 mol) with sodium ethoxide in ethanol, by the method given in the literature for preparation of the methoxy compound,[10] gave 3-chloro-6-ethoxypyridazine (19 g, 90%), m.p. 61 °C (lit.,[11] 62 °C). Dehalogenation of 3-chloro-6-ethoxypyridazine (15.0 g, 0.095 mol) using 10% palladium on charcoal as catalyst, by the method used for the 1-propyl homologue,[10,11] gave 3-ethoxypyridazine (7.0 g, 60%), b.p. 75 °C at 4 mmHg; m.p. 34 °C (lit.,[12] b.p. 91—93 °C at 14 mmHg); τ($CDCl_3$) 1.38 (1 H, d, *J* 7 Hz, 6-H), 2.76 (1 H, dd, *J* 7 and 13 Hz, 5-H), 3.20 (1 H, d, *J* 13 Hz, 4-H), 5.51 (2 H, q, CH_2), and 8.60 (3 H, t, CH_3).

2-*Ethoxypyrimidine*.—Reaction of 2-chloropyrimidine (5.0 g, 0.044 mol) with sodium ethoxide by the literature method[7] gave 2-ethoxypyrimidine (4.0 g, 73%), b.p. 40 °C at 4.5 mmHg (lit.,[7] 77—78 °C at 20 mmHg); n_D^{20} 1.4961; τ($CDCl_3$) 1.76 (2 H, d, *J* 7 Hz, 4-, 6-H), 3.26 (1 H, t, 5-H), 5.66 (2 H, q, CH_2), and 8.53 (3 H, t, CH_3).

4-*Ethoxypyrimidine*.—2,4-*Dichloropyrimidine*. This was prepared from uracil and phosphonyl chloride by the literature method.[13]

2-*Chloro*-4-*ethoxypyrimidine*. Reaction of 2,4-dichloropyrimidine (20 g, 0.135 mol) with sodium (3 g) in ethanol (90 ml) (*cf.* ref. 14 for the methoxy homologue) gave impure 2-chloro-4-ethoxypyrimidine (20 g, 95%), b.p. 74 °C at 0.6 mmHg. This was redistilled into two fractions, b.p. 50 and 60 °C at 0.4 mmHg, the latter being the essentially pure compound, m.p. 35 °C; τ($CDCl_3$) 1.71 (1 H, d, *J* 7 Hz, 6-H), 3.37 (1 H, d, *J* 7 Hz, 5-H), 5.54 (2 H, q, CH_2), and 8.60 (3 H, t, CH_3). The former fraction consisted of a *ca.* 1:1 mixture of this compound and 2,4-diethoxypyrimidine, τ($CDCl_3$) 1.84 (1 H, d, *J* 7 Hz, 5-H), 3.68 (1 H, d, *J* 7 Hz, 6-H), 5.59 (2 H, q, CH_2), 5.60 (2 H, q, CH_2), 8.61 (3 H, t, CH_3), and 8.59 (3 H, t, CH_3).

Dechlorination of 2-chloro-4-ethoxypyrimidine (15.0 g, 0.095 mol with hydrogen and 5% palladium on barium sulphate (*cf.* ref. 14) gave 4-*ethoxypyrimidine* (8.6 g, 73%) b.p. 40 °C at 3.6 mmHg; n_D^{20} 1.4897; τ($CDCl_3$) 1.19 (1 H, s, 2-H), 1.55 (1 H, d, *J* 5 Hz, 6-H), 3.26 (1 H, dd, *J* 5 and 1.5 Hz, 3-H), 5.56 (2 H, q, CH_2), and 8.61 (3 H, t, CH_3) (Found: C, 58.0; H, 6.4; N, 22.1. $C_6H_8N_2O$ requires C, 58.1; H, 6.5; N, 22.6%).

Kinetic Studies.—The general method has been described in earlier Parts. Recent improvements to the static stainless steel reactor used, and leading references to the method, are given in ref. 1.

References

1 Part 17, R. Taylor, *J. Chem. Soc., Perkin Trans. 2*, 1983, 1157.
2 R. Taylor, *J. Chem. Soc., Chem. Commun.*, 1978, 732.
3 N. Al-Awadi, J. Ballam, P. R. Hemblade, and R. Taylor, *J. Chem. Soc., Perkin Trans. 2*, 1982, 1175.
4 T. Konakahara, K. Sato, Y. Takagi, and K. Kuwata, *J. Chem. Soc., Perkin Trans. 2*, 1984, 641.
5 F. Török, A. Hegedüs, and P. Pulay, *Theor. Chim. Acta*, 1973, **32**, 145.
6 P. J. Wheatley, *Acta Crystallogr.*, 1957, **10**, 182; P. Cucka and R. W. H. Small, *ibid.*, 1954, **7**, 199; P. Cucka, *ibid.*, 1963, **16**, 318; C. H. Carlisle and M. B. Hossain, *ibid.*, 1966, **21**, 249; B. Bak, L. Hansen-Nygaard, and J. Rastrap-Anderson, *J. Mol. Spectrosc.*, 1958, **2**, 361.
7 D. J. Brown and R. V. Foster, *J. Chem. Soc.*, 1985, 4911.
8 A. E. Erickson and P. E. Spoerri, *J. Am. Chem. Soc.*, 1946, **68**, 400.
9 R. H. Mizzoni and P. E. Spoerri, *J. Am. Chem. Soc.*, 1951, **73**, 1873.
10 J. Druey, K. Meier, and K. Eichenberger, *Helv. Chim. Acta*, 1954, **37**, 121.
11 N. Takahayashi, *J. Pharm. Soc. Jpn.*, 1955, **75**, 778.
12 H. Otomasu, H. Takahashi, and M. Ogata, *Chem. Pharm. Bull.*, 1964, **12**, 714.
13 G. E. Hilbert and J. B. Johnson, *J. Am. Chem. Soc.*, 1930, **52**, 1152.
14 G. W. Kenner, C. B. Reese, and A. R. Todd, *J. Chem. Soc.*, 1955, 855.

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