The Mechanism of Thermal Eliminations. Part 21.[1] Rate Data for Pyrolysis of 2-Ethoxyquinoline, 1- and 3-Ethoxyisoquinoline, and 1-Ethoxythiazole: Correlation of Reactivities with π-Bond Order of the C=N Bond

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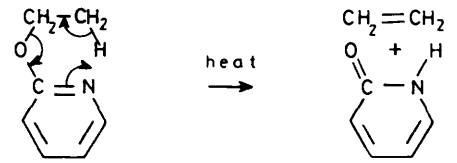
We have measured the rates of thermal elimination of ethylene from the title compounds between 587.3 and 722.9 K. The reactivities relative to 2-ethoxypyridine at 650 K are: 3-ethoxyisoquinoline (0.21), 2-ethoxyquinoline (3.13), 1-ethoxyisoquinoline (6.47), 2-ethoxythiazole (63.1). These reactivities parallel the π-bond order of the C=N bond, though the exceptional reactivity of 2-ethoxythiazole is attributed to additional acceleration through $+M$ electron release from sulphur to nitrogen. This emphasizes the greater relative importance of nucleophilic attack by the nitrogen upon the β-hydrogen atom as compared with the analogous mechanism for pyrolysis of esters. Because of the semi-concerted nature of the reaction, interruption of aromaticity is much less significant than in, for example, electrophilic aromatic substitution. Thus retention of the benzenoid character of the ring not involved in the elimination is not an important rate-determining feature, as shown by the lower reactivity of 3-ethoxyisoquinoline relative to 2-ethoxypyridine. The unimportance of the interruption of aromaticity of the benzenoid ring means that conjugative effects are better relayed to nitrogen in the β-naphthalene-like position (isoquinoline) than in the α-naphthalene-like position (quinoline). This is the reverse of the familiar pattern for reactions of naphthalene-like systems where full charges are involved, and may be an additional factor contributing to the higher reactivity of 1-ethoxyisoquinoline than of 2-ethoxyquinoline, as may also be the $-I$ effect of the benzo substituent. The conclusions are used to predict elimination rates for alkoxyheterocycles not yet studied.

Our investigations of the rates of thermal eliminations involving a six-membered transition state, depicted generally in Scheme 1, have shown that two mechanistic features can be clearly identified.[2] These are cleavage of the C–D bond, and nucleophilic (strictly basic) attack of the group F upon the B–H bond. Most thermal eliminations fall into one of two classes, *viz.* those in which the rate-limiting step is the former, and those in which it is the latter (though of course both steps contribute to the overall rate in each case).

Scheme 1.

The pyrolysis of 2-ethoxypyridine takes place according to Scheme 2,[3] and we have shown that it is a reaction of the first type, *i.e.* C–O bond breaking is of primary significance. Thus the primary:secondary:tertiary rate spreads for pyrolysis of the 2-alkoxy derivatives of pyridine, pyrazine, and pyrimidine are close to those found for the pyrolysis of esters.[1] However, the effects of substituents on the ring,[4] as well as aza 'substituents' within it,[5] whilst confirming these conclusions, have indicated that nucleophilic attack upon the β-hydrogen atom by the C=N bond (or by nitrogen if we use the $C^+–N^-$ resonance form) is more important than the corresponding attack by the C=O bond in ester pyrolysis; this is confirmed by certain anomalies[1] in the primary:secondary:tertiary rate spread pattern between the three classes of compounds noted. We have suggested that the greater importance of nucleophilic attack in the alkoxy-heterocycles may arise because in the aromatic ring there are two pathways for relay of electron release from the substituent to the nitrogen.[1] Added to this of course is the greater inherent nucleophilicity of nitrogen as compared with oxygen.



Scheme 2.

Confirmation of the importance of the nucleophilicity of the C=N bond and hence of its π-bond order was provided by the substantially higher reactivity of 3-ethoxypyridazine, pyridazine having localized π-bonds such that (**1**) is a much more important canonical form than is (**2**).[5]

(1) (2)

In order to investigate further the effect of π-bond order upon the reaction rate we have measured the rates of elimination of 2-ethoxyquinoline (**3**), 1- and 3-ethoxyisoquinoline [(**4**) and (**5**)], and 2-ethoxythiazole (**6**).

Results and Discussion

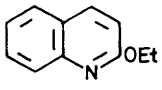
The compounds gave excellent and reproducible first-order kinetic results with linearity to >95% reaction, no deviations in the Arrhenius plots, and stoicheiometry of 2.00 (±0.03):1. The data are summarized in Table 1, which shows that the $\log(A/s^{-1})$ values are all within the range 12.3—13.3 which has been found

Table 1. Pyrolysis of compounds ArOEt

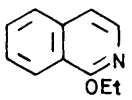
	T/K	10^3k/ s^{-1}	log (A/s^{-1})	E/kJ mol^{-1}	Corr. coefft.	$10^3k/s^{-1}$ (600 K)
2-Ethoxyquinoline	649.9	0.766	12.916	199.25	0.9997	0.798
	664.5	1.84				
	678.7	3.94				
	698.5	10.3				
	712.9	20.3				
1-Ethoxyisoquinoline	649.9	1.60	13.064	197.17	0.9997	1.65
	664.5	3.69				
	678.7	7.92				
	698.5	21.3				
	712.9	39.9				
3-Ethoxyisoquinoline	649.9	0.548	12.269	205.76	0.9999	0.054
	664.5	0.122				
	678.7	0.270				
	698.5	0.745				
	712.9	1.53				
	722.9	2.59				
2-Ethoxythiazole	587.3	0.459	12.513	178.00	0.9997	16.1
	634.4	7.44				
	635.7	8.20				
	649.9	15.9				
	664.5	32.6				
	678.8	62.6				

Table 2. Relationship between relative rates of pyrolysis of ethoxyheterocycles at 650 K, and C–N bond lengths

	k_{rel}	C–N bond length (Å)
3-Ethoxyisoquinoline	0.21	1.366
2-Ethoxypyridine	1.0	1.340
2-Ethoxyquinoline	3.13	1.330
1-Ethoxyisoquinoline	6.47	1.300
2-Ethoxythiazole	63.1	1.304
3-Ethoxypyridazine	9.8	1.281



(3)



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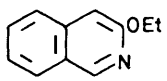

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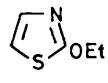


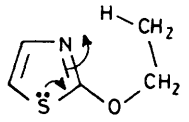
(6)

to apply to this reaction. The rates of pyrolysis at 650 K relative to that of 2-ethoxypyridine[4] are given in Table 2, together with that for 3-ethoxypyridazine.[5]

The main features of the results are as follows.

(i) There is a parallel between the relative rates of elimination and the C=N bond order. The bond orders are of course not directly available, but the bond lengths are.[6–10] In the case of quinoline (where the bond lengths relate to a nickel complex) and isoquinoline (where they relate to the 3-methyl derivative) the values may not be as accurate as the others, but they are probably not in error by more than 0.005 Å. The bond lengths are given in Table 2, and the bond orders will be approximately inversely proportional to these.

(ii) 2-Ethoxythiazole stands out as being substantially more reactive than expected, even allowing for the high C–N bond order. This will be derived in part from the increased ease of C–O cleavage as a result of the $-I$ effect of sulphur, though data for the effect of the aza 'substituent' suggest that this effect is fairly small.[5] Much more important, we feel, is the greatly enhanced nucleophilicity of the C–N bond arising from the $+M$ effect of sulphur, as shown in (7). If, as seems likely, this is the case, then we may predict that 2-ethoxyoxazole will be even



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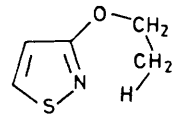


(8)

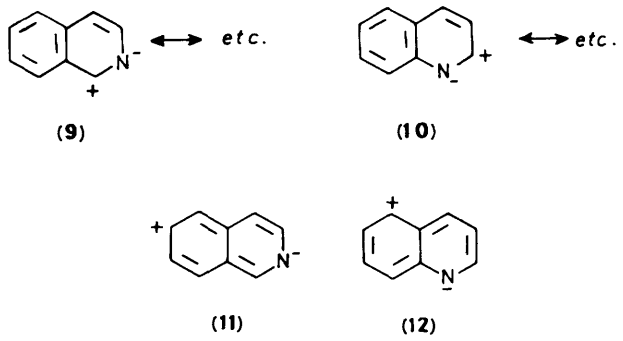
more reactive because both $-I$ and $+M$ effects are greater for oxygen than for sulphur.

In contrast, the nucleophilicity of the C–N bond or the nitrogen cannot be enhanced in such a way in 2-ethoxyisothiazole [see (8)], and moreover the C–O bond is further from the sulphur. Consequently the elimination rate is predicted to be less here, *ca.* 6-fold greater than for 2-ethoxypyridine, with much the same rate being found for 2-ethoxyisoxazole.

In this discussion we have excluded the possibility that the high reactivity of 2-ethoxythiazole arises from reaction of the *N*-ethyl tautomer, formed from the *O*-ethyl compound by isomerization at high temperature. If the latter occurred then some at least of the *N*-alkyl tautomer should be evident in the starting material, especially after heating during fractional distillation. However, no trace was evident from the n.m.r. spectrum, and in any event, the *N*-alkyl tautomer, being an amide, would be expected to be rather unreactive.[11]

(iii) The ability of alkoxyheterocycles to undergo elimination is at first consideration surprising, since the aromaticity of the ring is interrupted. However, because of the concerted nature of the reaction, this interruption is only marginal, and the result is demonstrated most notably by the reactivity of 3-ethoxyisoquinoline. In electrophilic aromatic substitution, naphthalene is more reactive than benzene, because in the transition state for reaction of the former, the benzenoid character of the ring is retained; hence there is a much smaller loss of resonance energy than is the case for benzene. If the same reasoning could be applied to these heterocycles, one would expect the quinoline and isoquinoline compounds to be much more reactive than 2-ethoxypyridine. The result for 3-ethoxyisoquinoline shows that this is not the case, so that interruption of aromaticity is relatively unimportant.

(iv) The relative reactivities of 1-ethoxyisoquinoline and 2-



(9) (10)

(11) (12)

ethoxyquinoline are in the order predicted from the π-bond effect, but other factors may contribute. The benzo substituent is known to have a $-I$ effect, and hence electron withdrawal should be greater at the adjacent α rather than the more remote β-position. Since C–O bond breakage is aided by electron withdrawal, this will also serve to make (**4**) more reactive than (**3**).

A further factor may contribute to the higher reactivity of (**4**) than of (**3**). The ease of reaction will be related to the ease of localization of an electron pair onto nitrogen in (**9**) and (**10**), respectively. In the respective resonance hydrids, the extent to which bond fixation in the ground state is interrupted will be important, *i.e.* the extent to which a bond that is largely double in the ground state becomes single, *etc.* In electrophilic substitution of naphthalene, such considerations are outweighed by the importance of retaining maximum benzenoid character in the transition state, leading to a greater ease of delocalizing a pair of electrons to the α-position as in (**10**). When this factor becomes unimportant, it turns out that it is easier to localize a pair of electrons to the β-position, as in (**9**). It is not necessary to show all five canonical forms for each resonance hybrid because four of these for each hybrid have the same degree of bond fixation, with four, six, eight and ten bonds, respectively, in the correct position relative to the ground state. The key structures are (**11**) and (**12**), having six and two bonds, respectively, in the correct position relative to the ground state. Consequently (**12**) is of considerably higher energy than (**11**), and this incidentally is the factor responsible for the poor transmission of electronic effects between the 1- and 5-position of naphthalene, and for the 5-position of quinoline being the most reactive towards electrophilic substitution.[12] Structure (**11**) is of lower energy (and shown to be so by calculations[13]), and accounts for the good transmission of electronic effects between the 2- and 6-position of naphthalene and the fact that, relative to the corresponding positions in naphthalene, the 6-position of isoquinoline is more deactivated towards electrophilic substitution than is the 8-position.[12]

Given the factors governing elimination rates which we have elucidated in this series of papers, it becomes possible to predict relative stabilities for compounds as yet unstudied (or made), as follows

(*a*) Since nucleophilic attack diminishes in importance along the series of compounds primary > secondary > tertiary, then the importance of the bond order effect should decrease on going to t-butoxyheterocycles. Hence the rate differences noted in Table 2 should be diminished for the t-butoxy homologues and as a consequence the primary > secondary > tertiary rate spread will vary inversely as the $k_{rel.}$ values in Table 2. This will not be exact because the $-I$ effect upon C–O bond breakage will be more important for the tertiary compounds, and may have a secondary effect on the reactivity of 2-t-butoxythiazole. The same argument leads one to expect that 2-t-butoxyoxazole will be substantially more reactive than 2-t-butoxythiazole.

(*b*) 2-(2-Hydroxyethyl)pyridine undergoes elimination *via* a six-centre process but falls within the class of reactions where nucleophilic attack is of primary importance. One can expect therefore that 2-(2-hydroxyethyl) derivatives of the heterocycles studied in this paper will show very wide variations in reactivity, *i.e.* substantially greater than found in Table 2.

Experimental

2-Ethoxythiazole.—2-Bromothiazole (7.4 g, 0.045 mol) was heated under reflux with sodium ethoxide (4 g, 0.06 mol) in ethanol (100 ml) to give, after normal work-up and fractional distillation, 2-ethoxythiazole (5.2 g, 90%), b.p. 35 °C at 3.7 mmHg (lit.,[14] 32 °C at 2 mmHg); τ($CDCl_3$) 3.11 (1 H, d, *J* 6 Hz, H-4). 3.57 (1 H, d, *J* 6 Hz, H-5), 5.69 (2 H, q, CH_2), and 8.63 (3 H, t, CH_3).

2-Ethoxyquinoline.—2-Chloroquinoline (16.4 g, 0.1 mol) was heated under reflux during 3 h with sodium ethoxide (8 g, 0.12 mol) in ethanol (150 ml) to give, after normal work-up and fractional distillation, 2-ethoxyquinoline (13.5 g, 78%), b.p. 78 °C at 0.2 mmHg (lit.,[15] 130 °C at 12 mmHg); τ($CDCl_3$) 1.82—2.54 (5 H, m, ArH), 2.88 (1 H, d, ArH), 5.18 (2 H, q, CH_2), and 8.29 (3 H, t, CH_3).

1-Ethoxyisoquinoline.—Isoquinoline *N*-oxide was prepared in 75% yield from isoquinoline and peroxyacetic acid by the literature method.[16] 1-Chloroisoquinoline, m.p. 65 °C, was prepared in 60% yield by reaction of the *N*-oxide with phosphoryl chloride.[17] Reaction of 1-chloroisoquinoline (10 g, 0.06 mol) with sodium ethoxide (6 g, 0.09 mol) in ethanol (100 ml) gave, after normal work-up, 1-ethoxyisoquinoline (5 g, 48%), b.p. 72 °C at 0.3 mmHg (lit.,[18] 102 °C at 3.5 mmHg); τ($CDCl_3$) 1.78—1.92 (1 H, m, ArH), 2.07 (1 H, d, ArH), 2.32—2.78 (3 H, m, ArH), 2.92 (1 H, dd, ArH), 5.48 (2 H, q, CH_2), and 1.46 (3 H, t, CH_3).

3-Ethoxyisoquinoline.—3-Chloroisoquinoline (10 g, 0.06 mol) (prepared from homophthalic acid by the literature method[19–21]) was heated in a sealed tube at 150 °C during 15 h with sodium ethoxide (6 g, 0.09 mol) and ethanol (100 ml). Normal work-up, involving liquid–liquid extraction (chloroform) and fractional distillation, gave 3-ethoxyisoquinoline (8 g, 77%), b.p. 97 °C at 0.7 mmHg; n_D^{20} 1.5994; τ($CDCl_3$) 1.05 (1 H, s, H-1), 2.12—2.77 (4 H, m, H-5 to -8), 3.05 (1 H, s, H-4), 5.62 (2 H, q, CH_2), and 8.55 (3 H, t, CH_3).

Kinetic Studies.—The general method of the kinetic studies, together with recent improvements to the apparatus, has been recently described.[22]

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