Electrophilic Aromatic Reactivities *via* Pyrolysis of 1-Arylethyl Acetates. Part XII.[1] Total Reactivity of Isoquinoline

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All seven 1-(isoquinolyl)ethyl acetates have been prepared and their rates of elimination of acetic acid determined together with that of 1-phenylethyl acetate at temperatures between 351.8 and 426.3°. The results give the first measure of the quantitative electrophilic reactivity of the neutral isoquinoline molecule and the positional reactivity order is: 4 > (phenyl) > 5 = 7 > 8 > 6 > 3 > 1. Each position is less reactive than the corresponding position in naphthalene and more reactive than the corresponding position in pyridine. The electrophilic substituent constants are: −0.025(4); +0.07(5,7); +0.255(8); +0.31(6); +0.41(3); +0.51(1). The reactivity pattern shows that the formation of mainly 4-derivatives in electrophilic substitutions under neutral conditions is not anomalous as hitherto supposed, and the special mechanism invoked to account for this substitution pattern is no longer necessary. Isoquinoline is more reactive overall than quinoline; the benzenoid ring is much less reactive than in quinoline, but the pyridinoid ring is correspondingly much more reactive than in quinoline. The deactivating effect of the nitrogen in quinoline and isoquinoline is closely paralleled by the effects of substituents in hydrogen exchange of naphthalenes. The weak deactivation of the 5-position in quinoline, and the greater deactivation at the 1- relative to the 3-position in isoquinoline are shown to be due to bond fixation effects. As with pyridine and quinoline, Hückel π-electron densities are found to be the best theoretical indices of reactivity, and with an auxiliary inductive parameter of $\gtrsim$0.018 they predict not only the observed reactivity order, but also the activation at the 4-position. The reactivity order is also predicted almost quantitatively by the difference between the localization energy at position *j* of *i*-methylenenaphthalene and that at position *j* of naphthalene.

In this series we have sought to determine the electrophilic reactivities of aromatic compounds (and heterocycles in particular) by measuring the ability of the compound to stabilise the incipient carbonium ion produced in the gas-phase elimination of acetic acid from 1-arylethyl acetates. The particular advantage of this technique is that the quantitative reactivity of the free base is being measured, something that is sufficiently difficult to achieve under solution conditions for there to be no data at all for the more basic, *e.g.* nitrogen-containing heterocycles. The low ρ factor for the reaction also dispenses with the need to use the overlap technique to determine relative reactivities. Thus far we have measured the reactivity of furan, thiophen, pyridine, quinoline, and pyridine *N*-oxide; for the former two molecules data are now available from other reactions and these are in excellent agreement with the gas-phase results.[2]

[1] Part XI, E. Glyde and R. Taylor, *J.C.S. Perkin II*, 1975, 1463.

[2] E. A. Hill, M. L. Gross, M. Stasiewicz, and M. Manion, *J. Amer. Chem. Soc.*, 1969, **91**, 7381; R. Taylor, *J. Chem. Soc.* (*B*), 1970, 1364; D. S. Noyce, C. A. Lipinski, and G. M. Loudon, *J. Org. Chem.*, 1970, **25**, 1718; S. Clementi, P. Linda, and G. Marino, *Tetrahedron Letters*, 1970, 1389.

In Part VII we described measurement of the total reactivity of quinoline and the reactivity order for the neutral *molecule* was 5 > (phenyl) > 8 = 6 > 3 > 7 > 2 > 4. More recently the quantitative reactivity of the quinolinium ion has been determined in nitration,[3] and the positional reactivity order was: 5 > 8 > 6 > 3 ≈ 7 ⩾ (2 + 4, since no nitration at these positions was detected). The two sets of data are therefore in very good agreement, though this to some extent may be fortuitous because there is no reason to suppose that in general the positional reactivities of protonated basic heterocycles should parallel those of the free bases.

We also found that the simple Hückel MO calculations of π-electron density gave the best indication of reactivity for pyridine, quinoline, and pyridine *N*-oxide; for quinoline the supposedly superior MINDO/2 calculations were in fact worse at predicting the reactivity order than the Hückel method.[4] We found too that the reactivity of quinoline at least at some positions could be represented by a combination of the reactivity of pyridine and naphthalene. To further evaluate this possibility with respect to isoquinoline, to determine the positional reactivity order, and to evaluate the theoretical predictions of reactivity, this work was undertaken.

RESULTS AND DISCUSSION

The rates of pyrolysis of the esters (individual rates could be duplicated to within ±1%) are given in the Table together with the temperature of measurements, the values of log k/k_0 (log k_{Het}/log k_{Ph}), and the energies and entropies of activation calculated at 625 K from the Arrhenius plot (not shown). The data give very good Arrhenius plots as indicated by the correlation coefficients given in the Table; the data for 1-phenylethyl acetate agree well with earlier values given in previous Parts.

Pyrolysis of compounds $CH_3CHROAc$

R	T/°C	10^3k/s^{-1}	log (A/s^{-1})	E / kcal mol^{-1}	ΔS / cal mol^{-1} K^{-1}	log k/k_0 at 625 K	Correlation coefficient
Phenyl	421.2	105	12.7	43.7	−2.6	0	0.99967
	411.7	70.0					
	393.4	29.4					
	372.0	9.53					
	351.8	3.24					
1-Isoquinolyl	421.2	54.8	12.6	44.4	−2.2	−0.32	0.99999
	409.9	32.3					
	393.1	14.1					
	376.9	6.25					
	361.4	2.68					
3-Isoquinolyl	421.2	60.9	12.6	44.2	−2.2	−0.26	0.99984
	409.9	37.7					
	393.1	15.9					
	376.9	7.20					
	361.4	3.05					
4-Isoquinolyl	421.2	106	12.5	43.0	−2.7	+0.015	0.99988
	409.9	64.1					
	393.1	29.8					
	376.9	13.1					
	361.4	5.66					
5-Isoquinolyl	426.3	117	12.5	43.2	−2.6	−0.045	0.99983
	409.9	58.2					
	393.1	26.0					
	376.9	11.6					
	361.4	4.93					
6-Isoquinolyl	421.2	70.5	12.6	44.1	−2.0	−0.195	0.99987
	409.9	43.2					
	393.1	18.7					
	376.9	8.40					
	361.4	3.52					
7-Isoquinolyl	426.3	118	12.5	43.2	−2.8	−0.045	0.99978
	409.9	57.0					
	393.1	26.8					
	376.9	11.7					
	361.4	4.98					
8-Isoquinolyl	426.3	95.5	12.5	43.6	−2.7	−0.16	1.00000
	409.9	44.7					
	393.1	20.1					
	376.4	8.86					
	361.4	3.92					

From the ρ factor for the reaction (−0.63 at 625 K) the σ^+ values can be obtained from the log k_{rel} values and the results are shown in Figure 1 with, for comparison, the values previously obtained for quinoline and pyridine;[5] the log k_{rel} values previously obtained for the 1- and 2-positions of naphthalene were 0.134 and 0.110[6] which correspond to σ^+ values of −0.213 and −0.175.

[3] D. H. G. Grout, J. R. Penton, and K. Schofield, *J. Chem. Soc.* (*B*), 1971, 1254.
[4] J. N. Murrell, W. Schmidt, and R. Taylor, *J.C.S. Perkin II*, 1973, 179.
[5] R. Taylor, *J. Chem. Soc.* (*B*), 1971, 2382.
[6] R. Taylor, G. G. Smith, and W. H. Wetzel, *J. Amer. Chem. Soc.*, 1962, **84**, 4817.

The availability of these reactivity data opens a new area for interpretation of electronic effects in aromatic chemistry. Analysis of the results in terms of theories which are largely successful in describing the reactivities of substituted benzenes may not be appropriate, but are a necessary approximation at this time. The problem is related to the rationalization of the positional reactivities of substituted naphthalenes, and which is not yet fully possible. Some of the conclusions which follow are obvious and predictable; others are the reverse of intuitive expectation.

(i) All positions in isoquinoline are less reactive than the corresponding positions in naphthalene, and this is true also of quinoline; [5] this is the expected result arising from the electronegativity of the nitrogen.

(ii) All positions in isoquinoline (as in quinoline [5]) are more reactive than the corresponding positions in pyridine; this is the expected result arising from the activating effect of the benzo-substituent.

(iii) The sum of the σ^+ values for isoquinoline is $+1.60$ whereas for quinoline it is $+1.73$. It follows therefore

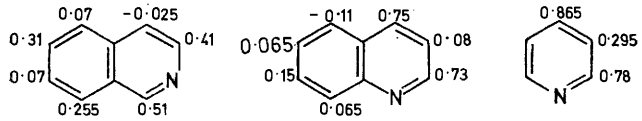
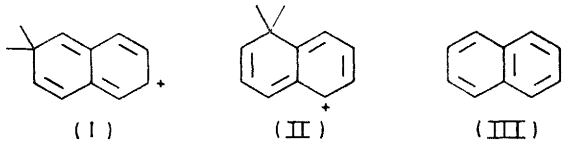


FIGURE 1 σ^+ Values

that isoquinoline is overall more reactive than quinoline. This could be argued to follow logically from the fact that there are four α-naphthalene-like and three β-naphthalene-like positions in the former molecule whereas in quinoline the converse is true. Since the α-position of naphthalene is more reactive than the β-position the result is the expected one. Both π-electron densities and localization energies (calculated with the parameters $\beta_{CN} = \beta_{CC}$, $\alpha_N = \alpha_C + 0.5\beta$, $\alpha_{C'} = \alpha_C + 0.085\beta$, and $\delta = 0.45$) [5] predict that isoquinoline should be the more reactive, but only marginally so, the sum of the π-electron densities being 6.857 (isoquinoline) and 6.832 (quinoline) with the sum of the localization energies being -17.39β (isoquinoline) and -17.40β (quinoline).

(iv) The spread of reactivities for isoquinoline (given by the difference between the extreme σ^+ values of 0.535) is less than for quinoline (which gives a difference of 0.86). Again both π-electron densities and localization energies (see below) predict a lower rate spread for isoquinoline.

(v) The pyridinoid ring in quinoline ($\Sigma\sigma^+ = 1.56$) is much less reactive than the pyridinoid ring in isoquinoline ($\Sigma\sigma^+ = 0.895$) and this follows because the nitrogen occupies an α-naphthalene-like position in the former and a β-like position in the latter. By contrast the benzenoid ring in quinoline ($\Sigma\sigma^+ = 0.17$) is more reactive than the benzenoid ring in isoquinoline ($\Sigma\sigma^+ = 0.705$) and this can be traced to the greater stability of the structure (I) compared to structure (II). Theoretical calculations confirm the particular stability of the *p*-quinonoid structure (I) [7] and substituent effects in hydrogen exchange are relayed particularly effectively between the 2- and 6-positions.[8]



By contrast there is a very poor relay of conjugative effects between the 1- and 5-positions in detritiation of substituted naphthalenes [8] which implies that structure (II) is particularly unstable. Further evidence from the present work to support this is given below, but the reason for the instability is most probably as follows. Structure (III) is the most important contributor to the ground state resonance hybrid for naphthalene, consequently those bonds shown as double and single in (III) have a high double- and single-bond order, respectively. In structure (II) however, all the double and single bonds are in the wrong position relative to the ground state structure (III) and hence formation of (II) will be energetically unfavourable. The same arguments apply to quinoline and isoquinoline which have similar bond orders for bonds analogous to these in naphthalene.[9]

(vi) In pyridine, the positions conjugated with the nitrogen (the 2- and 4-positions) are the most deactivated. This is true also for isoquinoline where the conjugated positions *viz.* 1-, 3-, 6-, and 8- are the least reactive, and approximately so for quinoline. Here the 2-, 4-, 5-, and 7-positions are conjugated with respect to the nitrogen, only the 5-position being more reactive than expected and this follows from the reason given under (v). Data from hydrogen exchange which show a strong measure of consistency with the pyrolysis results are given in Figure 2 which illustrate the deactivating effect of an α- or β-chlorine substituent in naphthalene upon the reactivity of the positions in naphthalene conjugated with it. The strong deactivation from the 5-position in 1-chloronaphthalene is evidently due to the weak $+M$ interaction between the 1- and 5-positions.

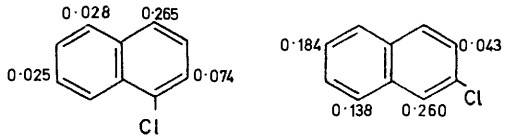


FIGURE 2 Deactivating effects of a chloro-substituent at conjugated sites in hydrogen exchange of naphthalenes [8]

(vii) The 3-position of isoquinoline which is β-naphthalene-like is more reactive than the 1-position (which is α-naphthalene-like). This then is contrary to the expectation based upon the analogy with naphthalene, but is again readily explained in terms of the lower bond order of the 2,3-bond (0.586) relative to that of the 1,2-bond

[7] H. G. Benson and J. N. Murrell, *J.C.S. Faraday II*, 1972, 129.

[8] C. Eaborn, P. Golborn, R. E. Spillett, and R. Taylor, *J. Chem. Soc.* (*B*), 1968, 1112.

[9] A. T. Amos and C. G. Hall, *Mol. Phys.*, 1961, **4**, 25.

(0.742).[9] The electron-withdrawing effect of the nitrogen is therefore more effectively relayed to the 1-position than to the 3-position and this more than compensates for the greater activating effect of a 2,3-benzo- relative to a 3,4-benzo-substituent.

A precedent for this bond-order effect may again be found in data for hydrogen exchange of substituted naphthalenes.[8] The activating effect of a 2-methyl or 2-methoxy substituent upon the 1- and 3-positions is shown in Figure 3. The effects here appear at first sight to be much more dramatic than those we observe in isoquinoline but in fact this arises substantially from the differences in ρ factors. Thus in terms of σ^+ values the differential deactivating effect of the nitrogen upon the 1- and 3-positions in isoquinoline is 0.14 whereas the differential activating effect of the 2-methyl group for example is 0.22.

FIGURE 3 Activating effects of 2-methyl and 2-methoxy-substituents at the adjacent sites in hydrogen exchange of naphthalenes [8]

The greater deactivating effect of the 2-chloro-substituent upon the 1- relative to the 3-position is evident from the data for hydrogen exchange in Figure 2 and the same bond order arguments apply here also.

(viii) Further parallels between hydrogen exchange data and the reactivity of these heterocycles may be drawn by considering the deactivating effect of nitrogen across the 1,2-bond. In terms of σ^+ values and correcting for the intrinsic reactivity of the α- and β-naphthalene-like positions this comes out to be 0.78 (pyridine), 0.723 (isoquinoline), and 0.905 (quinoline). The corresponding activativating effects of an *o*-methoxy-group in hydrogen exchange of [2-^{3}H]anisole, [1-^{3}H]-2-methoxynaphthalene, and [2-^{3}H]-1-methoxynaphthalene are 7.3×10^4, 2.2×10^4, and 3.7×10^5 respectively. This not only parallels the results for the heterocycles qualitatively but *quantitatively* as well because division of the logarithms of these activating effects by the reactivity parameters (above) for the heterocycles gives truly remarkably constant values of 6.01, 6.23, and 6.15 respectively. Moreover, calculations of the effect of a conjugating substituent upon the localization energy for substitution adjacent to it,[8] do predict that for substitution in benzene and at the 1-position of naphthalene (substituent in the 2-position and therefore analogous to isoquinoline) the substituent effect should be similar, with a larger effect for reaction at the 2-position of naphthalene (substituent in the 1-position and therefore analogous to quinoline).

(ix) The deactivating effect of the *meta*-nitrogen in isoquinoline upon the 4-position (0.213 − 0.025 = 0.188) is less than that of a *meta*-nitrogen in quinoline upon the 3-position (0.175 + 0.08 = 0.255). This again finds an exact parallel in the smaller activating effect of a methyl group at the 3-position upon hydrogen exchange at the 1-position of naphthalene (2.75) compared to the effect of this group at the 4-position upon the rate of exchange at the 2-position of naphthalene (3.00).[8] Furthermore the deactivation effect of the *meta*-nitrogen is greatest in pyridine (0.295) and the activating effect of a *meta*-methyl group is greatest in benzene (Figure 4). The

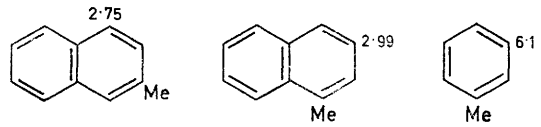


FIGURE 4 Activating effect of a methyl substituent in hydrogen exchange

agreement with theory is here not quite as good for although the effect is predicted to be largest from the 1- to the 3-naphthalene-like position (analogous to quinoline) than from the 3- to the 1-naphthalene-like position (analogous to isoquinoline) both are predicted to be greater than the *meta*-interaction in benzene.[8]

We may develop this argument further. In our previous discussion of the reactivity of quinoline,[5] we showed that the positions ' *meta* ' to the nitrogen could be represented in terms of the reactivity of pyridine and naphthalene. For convenience here we shall discuss reactivities in terms of σ^+ rather than log k_{rel} values. Equations (1)—(6) show the data for quinoline and isoquinoline in these terms. It is evident that the β-naphthalene-like

$$\sigma^+_{6\text{-Q}} = \sigma^+_{\beta\text{-naph}} + 0.240 \quad (1)$$

$$\sigma^+_{3\text{-Q}} = \sigma^+_{\beta\text{-naph}} + 0.255 \quad (2)$$

$$\sigma^+_{8\text{-Q}} = \sigma^+_{\alpha\text{-naph}} + 0.275 \quad (3)$$

$$\sigma^+_{5\text{-iQ}} = \sigma^+_{\alpha\text{-naph}} + 0.280 \quad (4)$$

$$\sigma^+_{7\text{-iQ}} = \sigma^+_{\beta\text{-naph}} + 0.240 \quad (5)$$

$$\sigma^+_{4\text{-iQ}} = \sigma^+_{\alpha\text{-naph}} + 0.190 \quad (6)$$

positions differ in reactivity from that of the β-position in naphthalene by an almost identical amount. Likewise the 8-quinoline and 5-isoquinoline positions differ in reactivity from that of the α-position of naphthalene by the same amount. By contrast the 4-position of isoquinoline does not fit the pattern and it is evident the second-order relay from the conjugatively deactivated positions to the 4-position is very poor. Again data from hydrogen exchange confirm this observation; Figure 5 illustrates the deactivating effect of an α- or

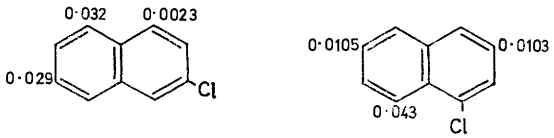
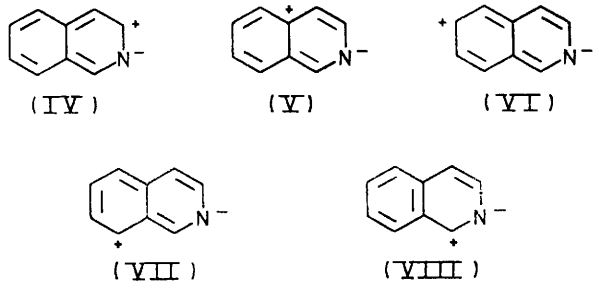


FIGURE 5 Deactivation effects of a chloro-substituent at non-conjugated sites in hydrogen exchange of naphthalenes [8]

β-chlorine substituent in naphthalene upon the reactivity of the positions in naphthalene which are not conjugated with it. The much greater deactivation of the 4-

position by the 2-chloro-substituent demonstrates the low secondary relay of the $+M$ effect to the 4-position. The reason for this poor relay of conjugative effects to the 4-position is evident from consideration of structures (IV)—(VIII). Structure (VIII) is benzenoid and therefore of low energy whilst structures (VI) and (VII) are *p*-quinonoid and therefore also of high stability. By contrast structure (V) does not have any commending feature whilst (IV) is *o*-quinonoid and therefore of high energy. Formation of structures (IV) and (V) is therefore unfavourable and as a consequence the 4-position does not get much positive charge placed upon positions adjacent to it in the transition state.

It is evident that the difference in reactivities given in equations (1)—(5) [equation (6) being the exception as noted above] is approximately equal to the σ^+ value *meta* to the nitrogen in pyridine (0.295), the differences between this value and those observed probably arising from the greater polarisability of the benzo-substituent in the relatively unreactive quinoline or isoquinoline compared to the benzo-substituent in naphthalene.



(IV) (V) (VI) (VII) (VIII)

(x) Although in the above analysis we have distinguished between the reactivities of α- and β-naphthalene-like positions, it is by no means certain that this is valid for it assumes that a 2,3-pyrido-substituent will be more electron-supplying than a 3,4-pyrido-substituent, by analogy with the effect of the benzo-substituent. Our present state of knowledge does not permit proper evaluation of this point. There is a trend in our results which suggests however that this may not be true, because if we look again at the σ^+ values for the non-conjugated positions we find (leaving aside the 4-position of isoquinoline) that they have almost identical values, *viz.* 0.08 (3-Q), 0.07 (5-iQ, 7-iQ), and 0.065 (6-Q, 8-Q). Further evidence to suggest that the effect of the nitrogen is not modified by an intrinsic α- and β-naphthalene-like reactivity comes from theoretical calculations, below.

(xi) One final analogy can be drawn between hydrogen exchange data and the reactivity of these heterocycles. In Figure 6 we show the deactivating effect of the nitrogen at the conjugated positions in the benzenoid ring. These are in terms of σ^+ units corrected for the intrinsic reactivity of the α- and β-naphthalene-like positions. (This as we have noted above may not be valid, but makes no difference to the argument, in fact the point we make is more noticeable if the correction is not made.) In Figure 6 we show also the activating effect of a methyl group at the corresponding position in hydrogen exchange. It is evident from both sets of data that the 2,6- is greater than the 2,8-interaction, and that the 1,7- is greater than the 1,5-interaction.

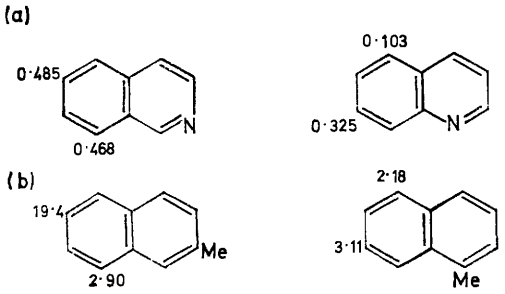


FIGURE 6 (a) Deactivating effect of the ring nitrogens in σ units; (b) activating effect of a methyl group in hydrogen exchange of naphthalene [8]

(xii) *Theoretical Calculations of Reactivity.*—Previously we showed that π-electron densities calculated with the parameters noted in (iii) gave a quantitative prediction of the relative reactivities of the position in pyridine relative to benzene,[10] and were reasonably successful for quinoline giving the order **8** > (phenyl) > **6** > **3** > **5** > **7** ⩾ **4** > **2** compared with the observed order of **5** > (phenyl) > **8** = **6** > **3** > **7** ⩾ **2** > **4**. The main discrepancy is that the 5-position is predicted to be much too deactivated and the reason for this is now explained under (v) above. Variation of the auxilliary inductive parameter from 0.0 to 0.9 produces only one slight variation in the reactivity order, with the 3-position being slightly more reactive than the 6-position below a value of *ca.* 0.06.[11]

Using these parameters for isoquinoline gives the π-electron densities shown in Figure 7. These give the order (phenyl) > **5** > **7** > **8** > **6** > **3** > **4** > **1**, compared to the observed order of **4** > (phenyl) > **5** = **7** > **8** > **6** > **3** > **1**. However, the π-electron densities for isoquinoline (and especially that for the 4-position) [12] are much more sensitive to the value chosen for the auxilliary inductive parameter than is the case for quinoline and if a value <0.018 is used the order becomes **4** > **5** > (phenyl) > **7** > **8** > **6** > **3** > **1**. Not only is this precisely the observed reactivity order, but the intuitively unexpected activation at the 4-position is predicted. Indeed

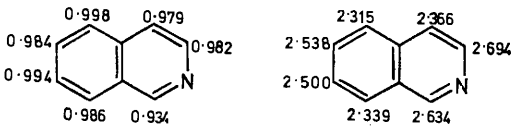


FIGURE 7 π-Electron densities and localization energies (−β) for isoquinoline

the only discrepancy is the slight activation of the 5-position (predicted) compared to the deactivation (observed). The reason for the need to use a smaller auxilliary inductive parameter in order to obtain the correct reactivity order is presently obscure.

[10] R. Taylor, *J. Chem. Soc.*, 1962, 4881.
[11] R. D. Brown and R. D. Harcourt, *J. Chem. Soc.*, 1959, 3451.
[12] R. D. Brown and R. D. Harcourt, *Tetrahedron*, 1960, **8**, 23.

Localization energies (Figure 8) are less satisfactory as indices of reactivity, giving the order 5 > 8 > 4 > 7 > 6 > (*phenyl*) > 1 > 3 and, as in the case of quinoline, they tend to overestimate the reactivity of the α-naphthalene-like positions; this may be a further indication that the difference in the reactivities of the α- and β-naphthalene-like positions in these heterocycles is not as great

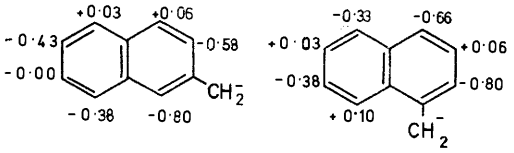


FIGURE 8 ΔL_r^+ Values (in β units) of the effect of a CH_2^- substituent on the localization energies for substitution at the positions shown

as in naphthalene itself. Use of $ArCH_2^+$ as a model for the transition state rather than the Wheland intermediate (*i.e.* calculation of delocalization energies [4]) gives no improvement; quite the reverse in fact the order becoming 5 > 8 > 4 > 7 > (phenyl) > 1 > 3 > 6. For quinoline the delocalization model [giving 8 > 5 > 6 > 3 > (phenyl) > 7 = 4 > 2] showed some improvement over the localization model [giving 8 > 5 > 4 > 6 > 3 > 7 > (phenyl) > 2] and it is evident by inspection that the main difference in the two techniques is to diminish the reactivity of the position '*para*' to the nitrogen in the delocalization model.

One very satisfactory theoretical prediction of reactivity is obtained by considering the effect of a CH_2^- substituent upon the localization energy for substitution at the remaining positions in naphthalene. This gives then a measure of the conjugative interaction between

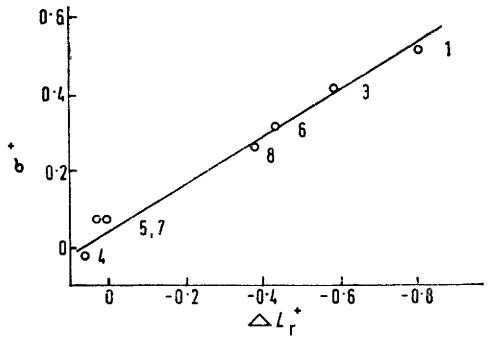


FIGURE 9 Correlation of the effect of a methylene anion on the localization energies for substitution at the other positions in naphthalene, with the reactivity (in σ units) of the corresponding positions in isoquinoline

substituent and reaction site in naphthalene-like molecules. If one plots the values (shown in Figure 8) against the positional reactivities an excellent correlation is obtained (Figure 9). However it should be remembered that the observed reactivities should relate to the *total* localization energy and *not* the amount by which this is altered by the CH_2^- substituent. The logical implication of this is again that the intrinsic relative reactivities of the α- and β-naphthalene-like positions in isoquinoline are not as great as in naphthalene. A curious feature of this result is that the order of conjugative interactions comes out to be the same as the overall π-electron density of the position in conjugation with CH_2^- substituent.

The corresponding data for quinoline do not give such a good correlation, the biggest discrepancy being the large 1,5-interaction which is predicted contrary to observation, an explanation for which has been noted [(v)]. Again the interaction model gives exactly the same order as the π-electron density model (using an auxillary inductive parameter of <0.06).

Correlation of the Electrophilic Reactivity of Isoquinoline in the Gas Phase with Electrophilic Substitutions in Solution.—Electrophilic substitution of isoquinoline under acidic condition produces predominantly the 5- and 8-isomers.[13] For example, nitration with nitric acid–sulphuric acid gives *ca.* 90% 5- and 9% 8-nitro derivatives [14] and rate profiles show that nitration does not take place upon the free base.[15] The respective partial rate factors are 9.0×10^{-6} and 1.0×10^{-6} so that σ^+ values are +0.77 and +0.92. Our results confirm therefore that these must relate to reaction of the conjugate acid since the values are so much more positive than the gas-phase values. Sulphonation also gives mainly the 5-acid with 8-sulphonic acid as byproduct; the latter is formed in higher yield with increasing temperature.[13] Hydrogen exchange of the conjugate acid of isoquinoline take place at the 5- and 8-positions,[16] and bromination under strongly acidic conditions gives mainly the 5-bromo-derivative.[17]

It is clear that 5-substitution is predominant under acidic conditions and indeed, calculations predict that this should be so; [11] the 5- and 7-positions are the most remote non-conjugating positions relative to the nitrogen, but the former is α-naphthalene-like, a factor likely to be of much greater importance in substitution of the conjugate acids when the transition state will more nearly resemble the Wheland intermediate.

Electrophilic substitution of isoquinoline under 'neutral' conditions, *i.e.* conditions insufficiently acidic to protonate the nitrogen presents a different picture. Bromination by bromine in carbon tetrachloride,[18] iodination,[13] mercuriation with mercuric acetate,[19] and hydrogen exchange under weakly acidic or neutral conditions [16] all produce reactions principally at the 4-position. For the latter reaction the rate-determining formation of a covalent hydrate was considered to lead to 2-substitution, but for the other reactions the substi-

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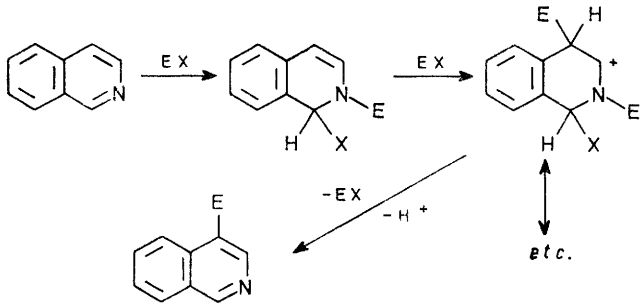
tution pattern, believed to be anomalous [13] has been interpreted in terms of the mechanism given in the Scheme.[11]



SCHEME

1,2-Addition of the electrophilic reagent EX is followed by attack of a second electrophilic molecule at the 4-position; elimination of EX and rearomatisation leads eventually to the 4-derivative. The scheme is thus analogous to that which has been proposed to account for the 3-substitution in nitration of pyridine *N*-oxide by nitric acid in acetic anhydride [20] and which we have dismissed partly on account of the requirement of bimolecularity in electrophilic reagent.[21] For isoquinoline such a scheme is clearly no longer necessary; substitution takes place at the 4-position because it is the most reactive towards electrophiles.

EXPERIMENTAL

All the esters (with the exception of the 7-isomer, see below) and intermediates were indicated to be >99% pure by g.l.c. analysis; the esters gave the expected i.r. spectra which also confirmed the absence of any alcohol or ketone precursors.

Fractional distillations were carried out using a 75 × 1 cm Vigreaux column of approximately eight theoretical plates. All esters (with the exception of the 8-isomer which was very pale yellow) were colourless viscous oils.

1-(1-*Isoquinolyl*)*ethyl Acetate*.—Isoquinoline (78 g, 0.605 mol) was converted by the method of Weinstock and Boeckelheide [22] *via* 2-benzoyl-1-cyano-1,2-dihydroisoquinoline (53%), m.p. 128—130° (lit.,[22] 125—127°) and thence 2-benzoyl-1-cyano-1-methyl-1,2-dihydroisoquinoline (67%), m.p. 118—120° (lit.,[22] 120—122°) into 1-methylisoquinoline (80%), b.p. 65—68° at 0.4 mmHg (lit.,[22] 81° at 1 mmHg).

A slurry of selenium dioxide (21 g, 0.19 mol) in dry dioxan (200 ml) was added during 1 h to a stirred solution of 1-methylisoquinoline (22.3 g, 0.156 mol) and the mixture heated for a further 4 h. Dioxan was removed by distillation from the filtered reaction product; steam distillation of the residue and condensation of the distillate at 0° gave after filtration and air drying under suction, crystalline 1-formylisoquinoline (12.8 g, 52%), m.p. 55—57° (lit.,[23] 55—55.5°).

Coupling of the Grignard reagent prepared from methyl iodide (0.14 mol) with 1-formylisoquinoline (11.7 g, 0.075 mol) followed by normal work up gave, after fractional distillation, 1-(1-*isoquinolyl*)*ethyl alcohol* (5.5 g, 42%), b.p. 98° at 0.4 mmHg (Found: C, 75.8; H, 6.7; N, 8.0. $C_{11}H_{11}NO$ requires C, 76.2; H, 6.4; N, 8.1%). Acetylation of this alcohol with acetic anhydride and pyridine gave after normal work-up and fractional distillation ,1-(1-*isoquinolyl*)-*ethyl acetate* (3.8 g, 55%), b.p. 108° at 0.2 mmHg, n_D^{20} 1.5749 (Found: C, 72.4; H, 6.2; N, 6.5. $C_{13}H_{13}NO_2$ requires C, 72.5; H, 6.1; N, 6.5%).

1-(3-*Isoquinolyl*)*ethyl Acetate*.—3-Methylisoquinoline (64.5 g, 0.45 mol) was heated to 160° and selenium dioxide (50 g, 0.45 mol) added in small portions during 1 h, the temperature being maintained below 200°. After further heating during 15 min the mixture was allowed to cool to 50° and extracted three times by refluxing with ether (200 ml each time). Concentration of the ethereal extract followed by fractional distillation gave 3-formylisoquinoline (16.1 g, 23%), b.p. 118—120° at 1.5 mmHg, m.p. 45° (lit.,[24] b.p. 151° at 10 mmHg, m.p. 47°).

Coupling of the Grignard reagent prepared from methyl iodide (0.15 mol) with 3-formylisoquinoline (12 g, 0.076 mol) followed by normal work-up and recrystallisation (from ethanol) gave 1-(3-*isoquinolyl*)*ethyl alcohol* (6.34 g, 47%), m.p. 107—109° (Found: C, 76.0; H, 6.7; N, 8.1%). Acetylation of this alcohol with acetic anhydride and pyridine gave, after normal work-up and fractional distillation, 1-(3-*isoquinolyl*)*ethyl acetate* (5.9 g, 75%), b.p. 112° at 0.2 mmHg, n_D^{20} 1.5704 (Found: C, 72.1; H, 6.2; N, 6.5%).

1-(4-*Isoquinolyl*)*ethyl Acetate*.—Isoquinoline was converted in 51% yield to 4-bromoisoquinoline, m.p. 38—39° (lit.,[25] 39—40°), by the method of Bergstrom and Rodda.[26] 4-Bromoisoquinoline (9 g, 0.043 mol) was added in small portions to freshly prepared n-butyl-lithium (0.1 mol) in a mixture of dry tetrahydrofuran (250 ml) and diethyl ether (250 ml) at −70° under dry nitrogen. The mixture was stirred during 45 min and a solution of dimethylformamide (36.5 g, 0.5 mol) in tetrahydrofuran (75 ml), cooled to −70°, added quickly, the whole being stirred during a further 15 min. After addition of ethanol (50 ml), the mixture was allowed to attain room temperature and then decomposed with a saturated solution of ammonium chloride. Normal work-up followed by recrystallization from ethanol gave 4-formylisoquinoline (3.02 g, 45%), m.p. 106—107° (lit.,[26] 101.5—103°).

Coupling of the Grignard reagent prepared from methyl iodide (0.12 mol) with 4-formylisoquinoline (8 g, 0.0051 mol), obtained from a number of batch preparations given above, yielded after normal work up and crystallization from benzene, 1-(4-*isoquinolyl*)*ethyl alcohol* (5.1 g, 57%), m.p. 115—116° (Found: C, 76.0; H, 6.7; N, 8.2%). Acetylation of this alcohol with acetic anhydride and pyridine gave, after normal work-up and fractional distillation, 1-(4-*isoquinolyl*)-*ethyl acetate* (5.4 g, 85%), b.p. 126° at 0.3 mmHg, n_D^{26} 1.5746 (Found: C, 73.0; H, 6.4; N, 6.6%).

1-(5-*Isoquinolyl*)*ethyl Acetate*.—Isoquinoline was converted in 65% yield to 5-nitroisoquinoline, m.p. 111—113°

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(lit.,[27] 110°), according to the literature method[27]. Several methods of reduction of 5-nitroisoquinoline *viz.* with tin and hydrochloric acid,[28] with iron in acetic acid,[29] catalytic reduction by Raney nickel (W2) grade, and reduction using palladium and charcoal as catalyst according to the literature method [29] were attempted. However none of these gave a product which could be satisfactorily recrystallized. The following modification of the last technique was however satisfactory. 5 Nitroisoquinoline (12.5 g, 0.072 mol) was dissolved in ethanol (300 ml) and hydrogenated under 6 atm. during 5 h in a Parr hydrogenator using 10% palladium on charcoal (1.25 g) as catalyst. The filtered solution was evaporated to dryness to give a light brown free-flowing powder, 5-aminoisoquinoline (10 g, 83%), m.p. 120—122° (lit.,[30] 121—123°); this product was used without further purification owing to its tendency to undergo atmospheric oxidation.

5-Aminoisoquinoline (10 g, 0.061 mol) was dissolved in 48% hydrobromic acid (35 ml), the solution diluted with water (30 ml), and filtered to remove any undissolved material. The cooled filtrate was diazotized with sodium nitrite (5.2 g) in water (50 ml), allowed to warm to 15°, and added to a solution of freshly prepared copper(I) bromide (15 g) in 48% hydrobromic acid (20 ml) at 50°; stirring was continued during a further 8 h. Normal work-up and steam distillation yielded 5-bromoisoquinoline (10.4 g, 82%), m.p. 83—85° (lit.,[31] 82—84°).

5-Bromoisoquinoline (14.2 g, 0.067 mol), obtained from two batch preparation as above, was ground with freshly prepared copper(I) cyanide (21 g) and heated at 250° during 45 min. The reaction flask was fitted with a 4 cm Vigreaux column and a Claisen head and 5-cyanoisoquinoline (6.5 g, 63%), m.p. 135° (lit.,[32] 139°), was distilled out of the reaction mixture at 1 mmHg pressure.

5-Cyanoisoquinoline (21 g, 0.136 mol) was heated in a sealed Carius tube at 150° for 8 h with concentrated hydrochloric acid (190 ml). The reaction mixture was evaporated to dryness, the solid redissolved in water, and the solution neutralized with ammonia to give a precipitate of isoquinoline-5-carboxylic acid (12 g, 51%), m.p. 276—279° (lit.,[32] 280—282°); this acid was used without further purification which is more easily effected at a later stage.

Isoquinoline-5-carboxylic acid (12 g, 0.069 mol) was esterified with an excess of concentrated sulphuric acid and absolute alcohol with heating under reflux during 3 days. Normal work-up gave crude ethyl isoquinoline-5-carboxylate (9.5 g, 68%).

A solution of ethyl isoquinoline-5-carboxylate (9.5 g, 0.047 mol) in ethyl acetate (27 g) and toluene (50 ml) was added to a freshly prepared suspension of sodium ethoxide (0.3 mol) in toluene, and the whole heated under reflux during 8 days. During this period the disappearance of the ester was monitored by g.l.c. analysis; formation of the condensation product is very slow at the *peri*-naphthalene-like positions. The crude sodium enolate obtained after removal of the solvent was decomposed by heating under reflux with 20% sulphuric acid (200 ml). The aqueous layer was neutralized and continuously extracted with ether; the crude ketone obtained was contaminated with unchanged ester. The latter was removed by heating with sodium hydroxide under reflux followed by a continuous ether extraction to isolate the ketone. After removal of the ether the crude product was recrystallized from ethanol at −70° to give *5-acetylisoquinoline* (2.9 g, 36%), m.p. 52—54° (Found: C, 76.7; H, 5.4; N, 8.2. $C_{11}H_9NO$ requires C, 77.2; H, 5.3; N, 8.2%).

5-Acetylisoquinoline was reduced with sodium borohydride to crude 1-(5-isoquinolyl)ethyl alcohol which was acetylated as above to give 1-(*5-isoquinolyl*)*ethyl acetate* (1.2 g, 32% based on ketone), b.p. 138° at 1.0 mmHg, n_D^{20} 1.5742 (Found: C, 71.9; H, 6.3; N, 6.4%).

1-(*6-Isoquinolyl*)*ethyl Acetate*.—Preparation of this compound was extremely difficult because of the low overall yield obtained in the first step, the preparation of 6-bromoisoquinoline from 4-bromobenzaldehyde. Cyclization catalysed by phosphoric acid [33] or by boron trifluoride–trifluoroacetic anhydride complex [34] gave no improvement over the method using sulphuric acid and phosphorus pentoxide.[32] This latter was preferred for convenience and in this way a total of 21 g of 6-bromoisoquinoline, m.p. 88—89°, was prepared in overall average yield of 7% based upon the starting material 4-bromobenzaldehyde.

6-Bromoisoquinoline (21 g, 0.10 mol) was heated with freshly prepared copper(I) cyanide as for the 5-isomer and work up gave 6-cyanoisoquinoline (6.9 g, 45%), m.p. 149—150° (lit.,[32] 152°). Hydrolysis as for the 5-isomer gave isoquinoline-6-carboxylic acid (7 g, 91%), m.p. 352—356° (lit.,[32] 355—360°).

Isoquinoline-6-carboxylic acid was converted to ethyl isoquinoline-6-carboxylate and thence to 6-acetylisoquinoline (2.1 g, 29% based on the acid) obtained as a crude solid by the methods described for the 5-isomer.

6-Acetylisoquinoline (2.1 g, 0.012 mol) was reduced with sodium borohydride to 1-(6-isoquinolyl)ethyl alcohol which was acetylated as above to give 1-(*6-isoquinolyl*)*ethyl acetate* (0.9 g, 38% based on ketone), b.p. 120° at 0.2 mmHg, n_D^{20} 1.5733 (Found: C, 72.9; H, 6.2; N, 6.5%).

1-(*7-Isoquinolyl*)*ethyl Acetate*.—3-Bromobenzaldehyde was condensed with aminoacetal and cyclized with sulphuric acid and phosphorus pentoxide to give 7-bromoisoquinoline (62% average overall yield from a number of preparations), m.p. 69—70°. Tyson reported [32] that 5-bromoisoquinoline was formed as a byproduct, but in later work [30] it was claimed that this was not so; this latter was apparently supported by g.l.c. analysis of all subsequent products and the m.p. of the derived carboxylic acid. Our work however shows that this claim is incorrect, since by comparison with the authentic sample of the 5-isomer already produced we were able to show by g.l.c. analysis that the 7-isomer *was* contaminated with the 5-isomer which was largely removed by careful fractional distillation.

7-Bromoisoquinoline (35 g, 0.168 mol) was heated with freshly prepared copper(I) cyanide as for the 5-isomer and hydrolysis of the intermediate 7-cyanoisoquinoline gave isoquinoline-7-carboxylic acid (12 g, 59%), m.p. 287—290° (lit.,[32] 295—297°; m.p. of mixed 5- and 7-acids 240—242°).

Isoquinoline-7-carboxylic acid (12 g, 0.069 mol) was con-

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verted *via* ethyl isoquinoline-7-carboxylate, treated with a five-fold excess of sodium ethoxide and ethyl acetate as above, into the crude ketone. Recrystallization from ethanol at −70° gave *7-acetylisoquinoline* (4.2 g, 35% based on the acid), m.p. 44—46° (Found: C, 77.3; H, 5.5; N, 8.1%).

Reduction of 7-acetylisoquinoline (4.2 g, 0.024 mol) with sodium borohydride and acetylation of the crude 1-(7-isoquinolyl)ethyl alcohol with pyridine and acetic anhydride gave, after work up involving careful fractional distillation, *1-(7-isoquinolyl)ethyl acetate* (0.9 g, 12% based on ketone), b.p. 110° at 0.15 mmHg, n_D^{20} 1.5675 (Found: C, 72.9; H, 6.2; N, 6.6%). G.l.c. analysis of this product showed it to contain 93% 7- and 7% 5-isomer. This would have interfered significantly with our kinetic study were it not for the fact that the 5-isomer gave rates indistinguishable from the above mixture which itself gave excellent first-order kinetics. It is evident therefore that the 5- and the 7-isomers have identical reactivities within experimental error.

1-(8-Isoquinolyl)ethyl Acetate.—2-Bromobenzaldehyde was condensed with aminoacetal and cyclized with sulphuric acid and phosphorus pentoxide to give an average yield of 31%, from a number of batches, of 8-bromoisoquinoline, m.p. 79—81° (lit.,[35] 80.5°).

8-Bromoisoquinoline (9 g, 0.043 mol) was added in small portions to freshly prepared n-butyl-lithium (0.1 mol) in a mixture of dry tetrahydrofuran (250 mol) and diethyl ether (250 ml) at −70°. The reaction was stirred during 45 min, a cooled (−70°) mixture of acetaldehyde (10 ml) in tetrahydrofuran (25 ml) quickly added, and the whole stirred during 15 min. Work-up gave crude *1-(8-isoquinolyl)ethyl alcohol* which, acetylated as above, gave after work-up and fractional distillation, *1-(8-isoquinolyl)ethyl acetate* (1.4 g, 16% based on 8-bromoisoquinoline), b.p. 124° at 0.2 mmHg, n_D^{20} 1.5675 (Found: C, 72.4; H, 6.4; N, 6.2%).

The apparatus and kinetic technique have been described in a previous Part.[35] The esters in the present study, being viscous liquids, were injected into the reactor as solutions in chlorobenzene, the latter being inert under the reaction conditions. Kinetic studies were carried out over a 50° range for each compound and, with the exception of the 1- and 3-isomers, each compound gave excellent first-order kinetic plots with linearity to >97% of reaction. The 1- and 3-isomers showed a tendency for the infinity pressure to decrease with time and this is due to polymerization of the styrene reaction product. From the rate of this polymerization the true infinity pressure could be determined; we stress that this polymerization was slight and could not have produced a significant error in the derived rate coefficients. As we have noted before, this polymerization has a lower activation energy than the elimination and so becomes less important at higher temperatures. What we now draw attention to is the fact that polymerization has been detected in pyrolysis not only with the 1- and 3-isoquinolyl esters but also with the 8-quinolyl ester [5] and the furan-2-yl,[36] 2-thienyl,[36] selenophen-2-yl,[37] and tellurophen-2-yl [37] esters. In each case a heteroatom is adjacent to the vinyl substituent produced in the elimination, so presumably a σ- or π-lone pair of electrons on the heteroatom plays a role in accelerating the polymerization.

Calculations of π-electron densities and localization energies were performed on the University of Sussex 1905 computor using the parameters described.

We thank the S.R.C. for a studentship (to E. G.).

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